

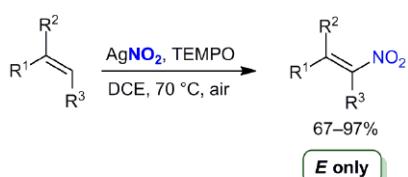
SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2013/07

SYNSTORIES ■ ■ ■ ■

■ Efficient and Stereoselective
Nitration of Mono- and Disubstituted
Olefins with AgNO₂ and TEMPO



■ N-Chlorosuccinimide, an Efficient
Reagent for On-Resin Disulfide
Formation in Solid-Phase Peptide
Synthesis

■ Young Career Focus:
Dr. AnnMarie O'Donoghue
(Durham University, UK)

■ Highly Efficient Cu(I)-Catalyzed
Oxidation of Alcohols to Ketones
and Aldehydes with Diaziridinone

CONTACT +++
Your opinion about SYNFORM is
welcome, please correspond if you like:
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Dear readers,

This issue of **SYNFORM** features three **SYNSTORIES** from three different continents. The first one comes from India and describes the very handy, efficient and stereoselective nitration of olefins developed by Professor Maiti, which represents a very attractive alternative to the well-known Henry nitroaldol reaction. The second **SYNSTORY** comes from the USA and reports on the use of diaziridinone as an oxidant for transforming alcohols into ketones and aldehydes, according to the methodology developed by Professor Shi, which is an interesting alternative to the widely used Swern reaction. The third **SYNSTORY** comes from Spain and guides us through the new protocol developed by Professor Albericio for the selective construction of disulfide bridges from cysteine-rich peptides on resin, which is an extremely valuable addition to the existing methods for the synthesis of specifically folded peptides. The issue is completed by a Young Career Focus article coming again from Europe, and specifically from the UK, where Dr. O'Donoghue is developing her research which is focused on catalysis at the interface of organic and biological chemistry.

Enjoy your reading!

Matteo Zanda

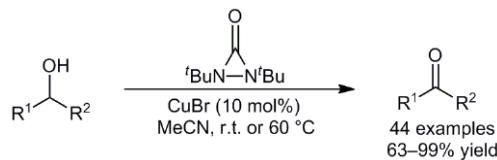
Editor of SYNFORM

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CONTACT +++

If you have any questions or wish to send feedback, please write to Matteo Zanda at:
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NEWS AND VIEWS ■■■ NEWS AND VIEWS ■■■ NEWS AND VIEWS ■■■

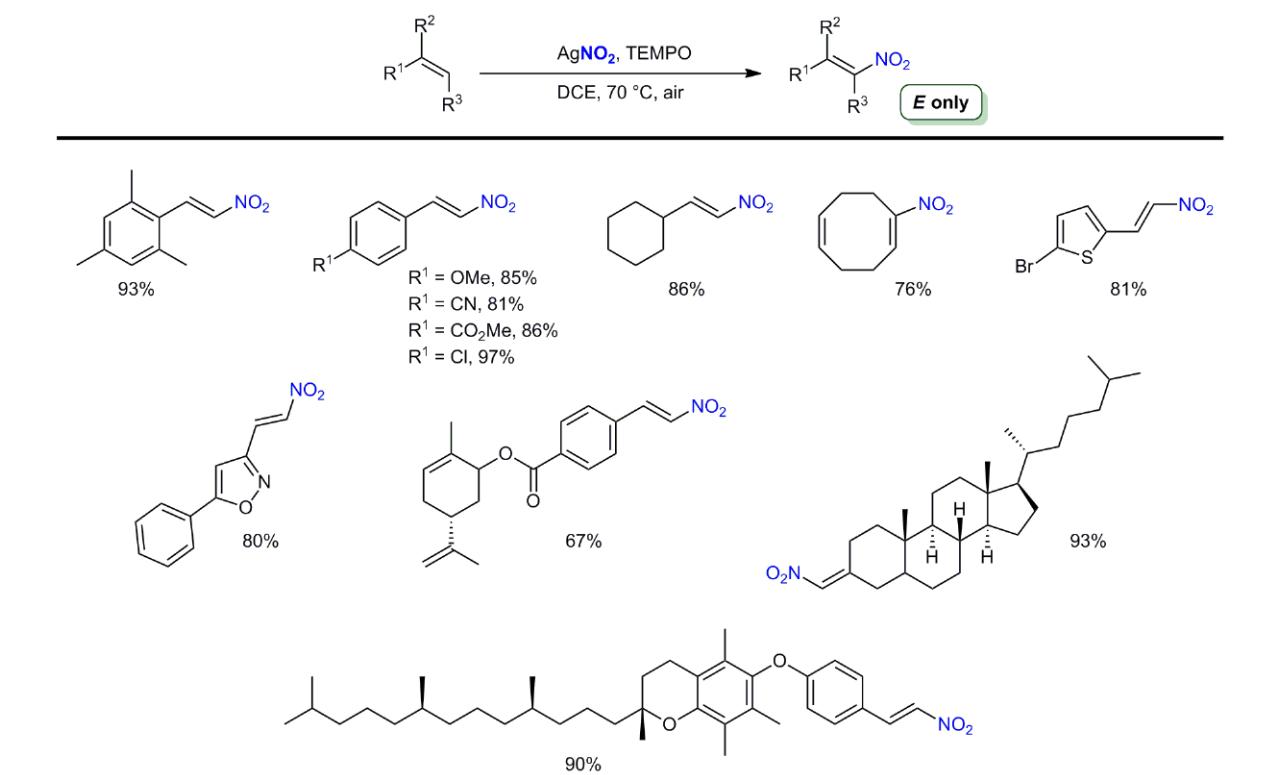
Efficient and Stereoselective Nitration of Mono- and Disubstituted Olefins with AgNO_2 and TEMPO

J. Am. Chem. Soc. 2013, 135, 3355–3358

Nitroolefins are invaluable building blocks in modern synthetic chemistry. They are used in a number of carbon–carbon bond-forming reactions including Michaeli, cycloaddition and Morita–Baylis–Hillman reactions. Conventional synthesis of nitroolefins relies upon a two-step sequence involving a base-mediated Henry reaction between nitromethane and a carbonyl compound, and subsequent dehydration of the intermediate β -nitro alcohol. However, nitration of an olefin, which can be seen as a formal replacement of an alkene hydrogen with a nitro group, is a synthetic approach that presents some potential advantages for synthesizing nitroolefins. In this regard, a number of methods for nitration of olefins have been devel-

oped using various metal-based and gaseous nitrating agents. Unfortunately, despite significant recent improvements and advances of this methodology, formation of an undesired mixture of *E/Z*-isomers, use of harsh reaction conditions and limitations in substrate scope are common traits in the previous protocols.

Recently, the research group of Professor Debabrata Maiti at the Indian Institute of Technology Bombay (Mumbai, India) has been exploring an *ipso*-nitration of arylboronic acids involving nitro radicals generated from shelf-stable metal nitrates. Professor Maiti said: “We anticipated that olefins could be nitrated under such conditions but the selection of a



Scheme 1 Scope of aromatic, aliphatic and heteroaromatic olefins

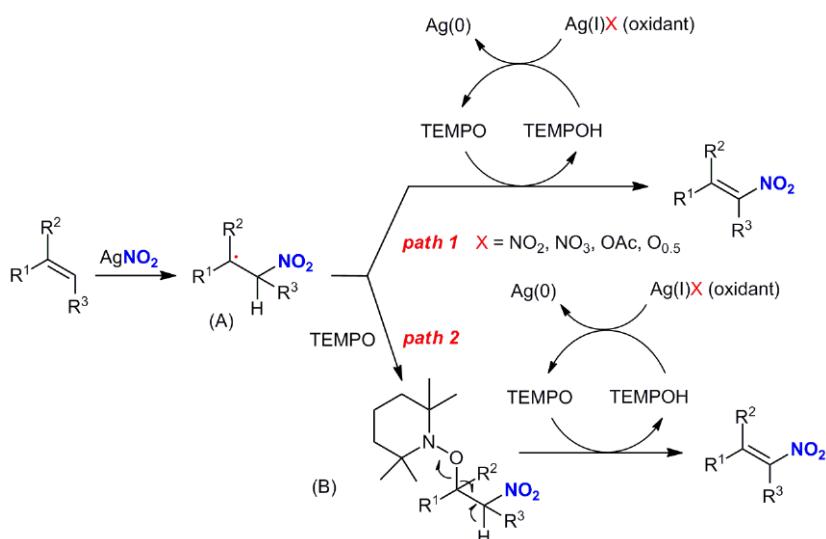
suitable oxidizing agent was absolutely crucial for the success of the reaction." The widely utilized oxyl radical TEMPO was identified as a suitable candidate reagent for performing the target reaction. Indeed, under the optimized conditions with 2–3 equivalents of AgNO_2 and 0.2–0.4 equivalents of TEMPO, a number of aromatic and aliphatic nitroolefins were synthesized in preparatively useful yields. "One significantly important aspect of our reaction is that it exhibits an unprecedented *E*-selectivity for almost all the substrates studied under our standard conditions," said Professor Maiti.

"Olefins in a complex set-up exhibited selective nitration based on slight differences in the steric and electronic environment," explained Professor Maiti. "In our study, we found that terminal olefins were selectively nitrated over internal olefins." Likewise, selective nitration of styrene was accomplished in the presence of terminal and internal olefins embedded in a natural product cavity. Olefins in the proximity of electron-withdrawing groups were considerably deactivated and such double bonds remained intact under the reaction conditions.

Preliminary investigations suggested a plausible radical pathway. An isolated TEMPO-alkane- NO_2 intermediate with norbornene further supported this proposition. Professor Maiti said: "TEMPO might be responsible for the abstraction of hydrogen from the nitroalkane radical intermediate. Silver nitrite probably has a dual role: as a nitrating agent and a terminal oxidant." The initial kinetic study conducted by the Indian researchers revealed a partial order of 0.4 with respect to TEMPO. This observation further supported the proposed mechanism.

"In conclusion," Professor Maiti said, "we have developed an efficient and stereoselective nitration of olefins with AgNO_2 as the nitrating agent in conjunction with TEMPO. Broad substrate scope, mild reaction conditions and excellent *E*-selectivity are some noteworthy features of this new nitration protocol."

Matteo Zanda



Scheme 2 Plausible mechanism of nitration of olefin

About the authors*Prof. D. Maiti*

Debabrata Maiti received his PhD from Johns Hopkins University (USA) in 2008 under the supervision of Professor Kenneth D. Karlin. After post-doctoral studies at the Massachusetts Institute of Technology (Cambridge, USA) with Professor Stephen L. Buchwald (2008–2010), he joined the Department of Chemistry of IIT Bombay (India) as an Assistant Professor in 2011. His research interests are focused on the development of new and sustainable synthetic methodologies.

*S. Maity*

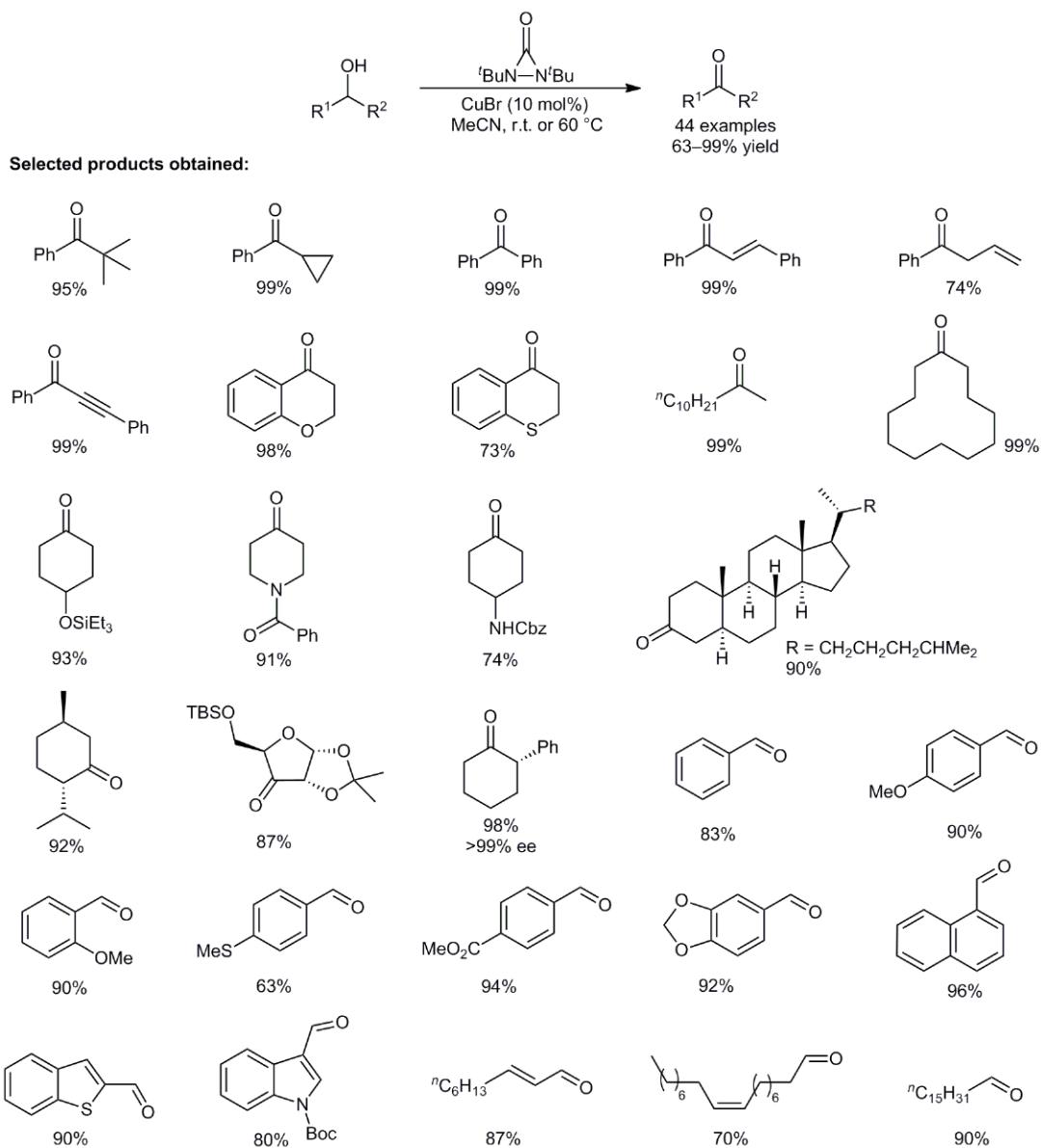
Soham Maity was born in 1988 in West Bengal (India). He studied chemistry at St. Xavier's College (Kolkata, India) and received his BSc in 2009. After completing his MSc at the University of Calcutta (India) he joined Professor Maiti's group in 2011 where he is currently a second-year PhD student.

Highly Efficient Cu(I)-Catalyzed Oxidation of Alcohols to Ketones and Aldehydes with Diaziridinone

Org. Lett. 2013, 15, 992–995

The oxidation of alcohols to aldehydes or ketones is one of the most commonly employed chemical transformations in organic synthesis. While numerous oxidation methods have been developed, only a few of them are used routinely. The development of new and efficient oxidation processes with

safe reagents under mild conditions is still highly desirable and valuable. Recently, Professor Yian Shi and co-workers at Colorado State University (Fort Collins, USA) reported a novel and efficient CuBr-catalyzed oxidation of alcohols using di-*tert*-butyl diaziridinone.



"Over the past few years, we have developed a series of Pd(0)- and Cu(I)-catalyzed diamination processes of olefins using di-*tert*-butylidiaziridinone and related analogues as nitrogen sources," said Professor Shi. "For example, we have shown that terminal olefins can be diaminated at allylic and homoallylic carbons." This diamination process likely proceeds via a diene intermediate, which is generated in situ from the terminal olefin via allylic C–H activation to a (π -allyl–Pd complex and subsequent β -hydride elimination (*J. Am. Chem. Soc.* **2007**, *129*, 7496; *J. Am. Chem. Soc.* **2008**, *130*, 8590). "In this C–H diamination process, di-*tert*-butylidiaziridinone serves as the oxidant as well as the nitrogen source," explained Professor Shi. "The intriguing reactivity displayed by the diaziridinone also prompted us to explore its utility for other synthetically useful transformations, such as the oxidation of alcohols."

"Our initial attempts on the oxidation of primary alcohols using di-*tert*-butylidiaziridinone were unsatisfactory," recalled Professor Shi. When benzyl alcohol was used as test substrate, the desired benzaldehyde was formed along with benzyl benzoate and the corresponding carbazole. These two byproducts resulted from direct oxidative esterification of benzyl alcohol and nucleophilic ring opening of di-*tert*-butylidiaziridinone with benzyl alcohol, respectively. Professor Shi said: "Our subsequent studies have shown that the formation of these two side products can be completely inhibited by using inexpensive CuBr as catalyst."

The current oxidation process is effective for a wide range of substrates bearing various functional groups. The reaction proceeds under neutral and mild conditions, which are compatible with acid- or base-sensitive substrates. The reaction is operationally simple, and requires no special precautions to exclude air or moisture. In addition, the reaction process is amenable to gram scale. "All these favorable features make this oxidation method practical and potentially useful," explained Professor Shi. He concluded: "More research is currently under way to develop other reaction processes using diaziridinones."

Matteo Zanda



About the authors



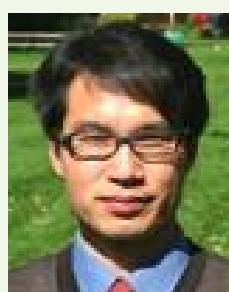
Prof. Y. Shi

Yian Shi was born in Jiangsu (P. R. of China). He obtained his B.Sc. degree from Nanjing University (P. R. of China) in 1983, his M.Sc. degree from the University of Toronto (Canada) with Professor Ian W. J. Still in 1987, and his Ph.D. degree from Stanford University (USA) with Professor Barry M. Trost in 1992. After a postdoctoral study at Harvard Medical School (USA) with Professor Christopher Walsh, he joined Colorado State University (USA) as an Assistant Professor in 1995 and was promoted to Associate Professor in 2000 and Full Professor in 2003. His current research interests include the development of new synthetic methods, asymmetric catalysis, and the synthesis of natural products.



Dr. Y. Zhu

Yingguang Zhu was born in Hunan (P. R. of China). He received his B.Sc. degree from Hunan University of Science and Technology (P. R. of China) in 2002 and his M.Sc. degree from East China Normal University (Shanghai, P. R. of China) in 2005. After two years of working at WuXi AppTec Co., Ltd. (P. R. of China) as a research scientist, he went on to obtain his Ph.D. degree from East China Normal University in 2010 under the supervision of Professors Wenhao Hu and Liping Yang. In autumn of 2010, he joined Colorado State University (USA) as a Postdoctoral Fellow with Professor Yian Shi. His current research interests include the development of novel synthetic methodologies and asymmetric synthesis.



Prof. B. Zhao

Baoguo Zhao was born in Hubei (P. R. of China). He received his Ph.D. degree from Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences (P. R. of China) in 2006 under the supervision of Professor Kuiling Ding. Then, he worked with Professor Yian Shi as a Postdoctoral Fellow for five years at Colorado State University (USA). In 2011, he joined Shanghai Normal University (P. R. of China) as a Full Professor. His current research interests include the development of new synthetic methodologies and novel chiral catalysts for asymmetric reactions.

N-Chlorosuccinimide, an Efficient Reagent for On-Resin Disulfide Formation in Solid-Phase Peptide Synthesis

Org. Lett. **2013**, *15*, 616–619

■ Cysteine-rich peptides such as conotoxins have a number of biological functions and a wide range of biological activities that depend to a great extent on the presence of topologically defined pairs of disulfide bonds that contribute strongly to the conformational stability and three-dimensional folding of these peptides. For many years, the objective of Professor Fernando Albericio's group at the University of Barcelona (Spain) has been the creation of novel tools for the formation of disulfides in peptide synthesis. The current repertoire of both Cys-protecting groups and disulfide-forming reagents are incomplete due to the lack of convenient, mild, and simple protocols.

Professor Albericio said: "In our paper we describe the use of N-chlorosuccinimide (NCS) for the on-resin formation of disulfides in solid-phase peptide synthesis (SPPS). The use of NCS stems from our previous research, where we reported the highly labile Cys-protecting group trimethoxyphenylthio (S-Tmp) as a replacement for the rather difficult to remove *tert*-butylthio (*St*-Bu) protecting group" (*Org. Lett.* **2012**, *14*, 5468).

One member of the group, the postgraduate student Tobias Postma, observed that NCS was a very convenient and rapid reagent for the formation of mixed disulfides, such as Cys-S-protecting groups. "This sparked our interest in using NCS as a potential on-resin disulfide-forming reagent in SPPS," explained Professor Albericio. Oxytocin was chosen as a well-

studied model peptide and the initial conditions were 2 equivalents of NCS in DMF for 15 minutes at room temperature. Following cleavage and total deprotection of the peptide, the authors observed quantitatively oxidized oxytocin with minimum dimerization.

"To our surprise, the initial choice of conditions turned out to be the optimal conditions for on-resin disulfide formation," said Professor Albericio. "We then utilized the same protocol in a regioselective synthesis of an α -conotoxin with two disulfide bonds." From this experiment Postma and Albericio learned that their protocol was compatible with sensitive orthogonal Cys-protecting groups, such as trityl (Trt) and methoxytrityl (Mmt), that are not compatible with harsher oxidation reagents (Figure 1).

Finally, they determined that NCS is compatible with the oxidation-prone amino acids Trp and Met. "These findings allowed us to conclude that our simple and convenient NCS method is the most versatile on-resin disulfide-forming protocol for use in SPPS," finished Professor Albericio. "We are very pleased with the performance of NCS in disulfide formation and we would like to diversify the use of NCS by investigating its potential as a bioconjugation reagent."

Matteo Zanda

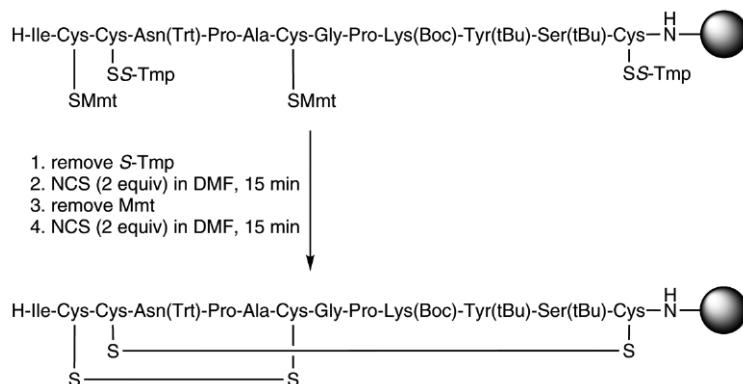



Figure 1 Regioselective synthesis of an α -conotoxin

About the authors

From left: T. Postma, Prof. F. Albericio

Tobias M. Postma was born in 1987 in 's-Hertogenbosch (The Netherlands). He received his MSc degree in 2011 from Utrecht University (The Netherlands) under the supervision of Professor Rob Liskamp. During his MSc he spent eight months at the University of Cambridge (UK) under the supervision of Dr. David Spring. In 2011, he joined the group of Professor Fernando Albericio at the Institute for Research in Biomedicine in Barcelona (Spain) where he currently is a second-year PhD student.

Fernando Albericio is Full Professor at the University of Barcelona (Spain), Group Leader at the Institute for Research in Biomedicine (Barcelona), and Honorary Research Professor at the University of KwaZulu-Natal (Durban, South Africa). His major research interests cover practically all aspects of peptide synthesis and combinatorial chemistry methodologies, as well as synthesis of peptides and small molecules with therapeutic activities. He has published over 650 papers, several review articles, more than 45 patents, and is co-author of three books. He is editor of several scientific journals and an editorial board member for several others. Recently, he was honored with a Doctorate Honoris Causa by the Universidad de Buenos Aires (Argentina) and the Vincent du Vigneaud Award by the American Peptide Society.

Young Career Focus: Dr. AnnMarie O'Donoghue (Durham University, UK)

Background and Purpose. **SYNFORM** will from time to time meet young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership. This **SYNSTORY** with a **Young Career Focus** presents Dr. AnnMarie O'Donoghue, Durham University, UK.

BIOGRAPHICAL SKETCH



Dr. A. O'Donoghue

AnnMarie O'Donoghue was born in Dublin (Ireland) in 1973. She studied for her BSc degree (Chemistry) at the University College Dublin. She remained at the same institution for her PhD studies in physical organic chemistry under the supervision of Professor Rory More O'Ferrall. Her PhD was awarded in November 1999 for her research on the formation and reactions of reactive carbocation intermediates. In 1999, she was awarded a Fulbright Fellowship to pursue postdoctoral studies in the research group of Professor John Richard at the University at Buffalo, the State University of New York (USA). There she worked on the dynamics of the proton-transfer reactions of triosephosphate isomerase. She returned to University College Dublin for a brief period in 2002 as a short-term Lecturer in Organic Chemistry. In 2003, she was awarded a Marie Curie Fellowship for postdoctoral studies on the directed evolution of proteins with Dr. Florian Hollfelder at the Department of Biochemistry, University of Cambridge (UK). From 2004–2005, she again returned to University College Dublin as a Lecturer in Organic Chemistry. In 2005 she moved to a Lectureship in Physical Organic Chemistry at the Department of Chemistry, Durham University (UK). Apart from a career break in 2008–2009 due to the birth of twins, she has since remained at Durham University as an independent researcher and was promoted to Senior Lecturer in 2012. Her research focuses on mechanistic studies of organic and biological transformations with a special interest in organocatalysis.

INTERVIEW

SYNFORM | *What is the focus of your current research activity?*

Dr. A. O'Donoghue | The focus of my current research is the study of organic and biological reaction mechanisms. Through understanding the strategies underpinning catalysis, we aim to inform the design of improved catalyst systems. We use a physical organic chemistry approach towards deciphering reaction mechanisms based on organic synthesis, reaction kinetics, isotopic labeling and structure–activity studies.

SYNFORM | *When did you get interested in synthesis?*

Dr. A. O'Donoghue | From early in my undergraduate studies, I enjoyed making molecules and it became clear that synthesis underpins all areas of organic chemistry. Physical organic chemistry has allowed me to combine my interest in synthetic chemistry with the application of physical methods for the determination of reaction mechanisms.

SYNFORM | *What do you think about the modern role and prospects of organic synthesis?*

Dr. A. O'Donoghue | In the last few decades, there have been huge developments in synthetic organic chemistry. There now exist successful methodologies for many challenging organic transformations and efficient catalyst systems for numerous synthetic processes. Given these many significant advances, the task of identifying further new organic synthetic chemistry and catalyst systems is difficult. I believe that further developments in synthetic chemistry, particularly in catalysis, will hinge upon a deeper fundamental understanding of underlying mechanisms and modes of action. Research in physical organic chemistry must keep in step with developments in synthetic chemistry.

SYNFORM | *Your research group is active at the interface of organic and biological chemistry, with a focus on catalysis. Could you tell us more about your research and its aims?*

Dr. A. O'Donoghue | Despite the large increase in the application of small molecule organocatalysts there have been few detailed studies of catalytic mechanisms. We are currently studying the mechanisms of three key classes of organocatalysts: N-heterocyclic carbenes, dimethylaminopyridine-derived and Brønsted acid/base organocatalysts. Organocatalyst systems often require higher catalyst loadings than metal-based analogues and there is significant scope for mechanism-guided improvement. Our interests in enzyme catalysis partly focus on understanding how enzymes achieve such remarkable product specificities. Significant attention has been devoted to the origin of the extraordinary rate accelerations achieved by enzymes; however, much less focus has been dedicated to the equally important factor of how enzymes suppress competing side reactions. Originating from my postdoctoral studies, we are also probing enzymatic catalysis of proton-transfer processes that are ubiquitous to many chemical transformations. The main tool that we employ in the study of enzymatic mechanism is the kinetic analysis of chemically designed ‘synthetic’ mutant substrates. As well as providing general insight into enzymatic catalysis, we also hope to translate our research into the design of small molecule catalyst systems.

SYNFORM | What is your most important scientific achievement to date and why?

Dr. A. O'Donoghue | As part of a project investigating the mechanisms of nucleophilic organocatalysis by carbenes, we have recently studied the proton-transfer reactions of a large series of N-heterocyclic carbenes (NHCs). Typically in organocatalytic applications of NHCs, the carbene is generated *in situ* by deprotonation of the conjugate acid azolium precursor by a suitable base. We have studied over 50 different NHCs, comprising several carbene classes, and have determined both kinetic acidities towards deprotonation by a common base and also pK_a values in water. Surprisingly, the kinetic acidities vary by over 10^{13} -fold and the pK_a values by 13 units within the series (Figure 1). These studies have enabled the influences of a range of structural features on fundamental NHC acid–base properties to be probed, including the effects of ring heteroatom, ring size, internal N–C–N angle, the electronic and steric nature of substituents, and linker size in bis-carbene systems.

Matteo Zanda

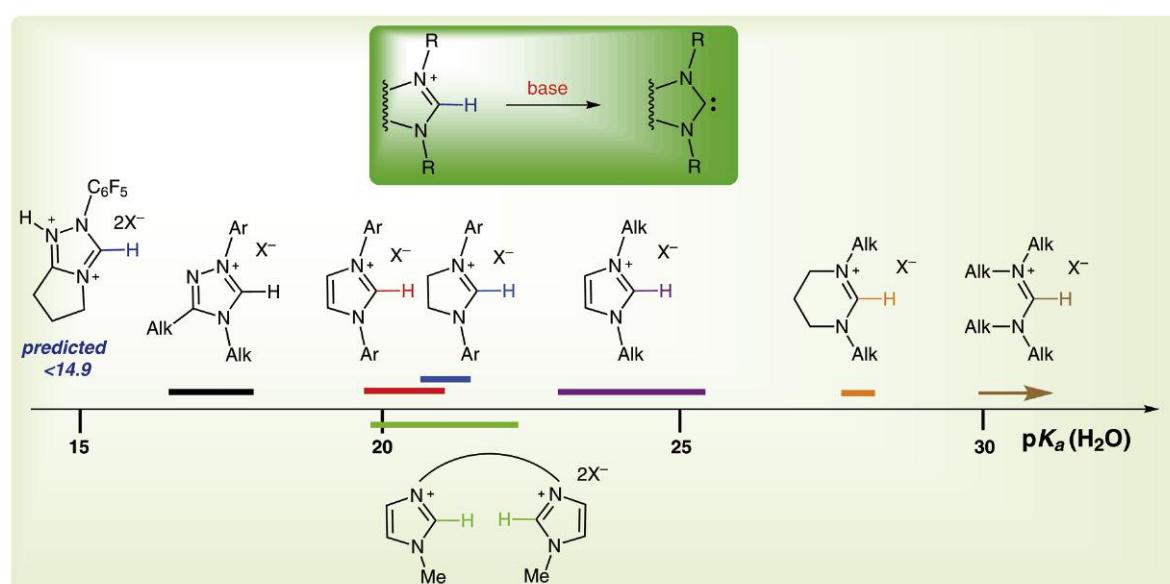


Figure 1 pK_a Scale for the conjugate acids of N-heterocyclic carbenes in water

COMING SOON ►► COMING SOON ►►**SYNFORM 2013/08
is available from July 18, 2013****In the next issues:****SYNSTORIES ■■■■****■ Copper(II) Triflate Catalyzed tert-Butylation of Anilines**

(Focus on an article presented at the 245th ACS National Meeting & Exposition, New Orleans, USA, April 2013)

■ Chiral Fluorinated Sulfoximines as New Fluoroalkylating Agents

(Focus on an article presented at the 245th ACS National Meeting & Exposition, New Orleans, USA, April 2013)

■ Hydrocupration of Terminal Alkynes: A Key Step in New Catalytic Routes for Alkyne Hydrofunctionalization

(Focus on an article presented at the 245th ACS National Meeting & Exposition, New Orleans, USA, April 2013)

■ Synthesis of 1,5-Disubstituted 3-Amino-1*H*-1,2,4-triazoles from 1,3,4-Oxadiazolium Hexafluorophosphates

(Focus on an article presented at the 245th ACS National Meeting & Exposition, New Orleans, USA, April 2013)

FURTHER HIGHLIGHTS +++**SYNTHESIS****Review on: Carbon-Sulfur Bond Formation via Metal-Catalyzed Allylations of Sulfur Nucleophiles**

(by W. Liu, X. Zhao)

SYNLETT**Account on: When Alkyne π -Activation Meets Pinacol-Type [1,2]-Rearrangement – About the Invention of Domino Reactions for the Synthesis of Carbocycles and Heterocycles**

(by K.-D. Umland, S. F. Kirsch)

SYNFACTS**Synfact of the Month in category „Metal-Catalyzed Asymmetric Synthesis and Stereoselective Reactions“: Cr/Salen-Catalyzed Nazarov Cyclization of Dienones****CONTACT +++**

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