

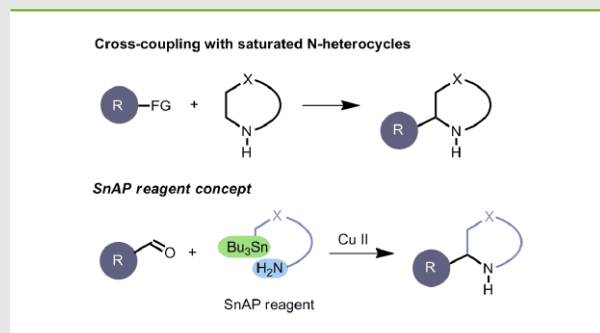
# SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2014/08

## SYNSTORIES ■ ■ ■ ■

■ **SnAP Reagents for the One-Step Synthesis of Medium-Ring Saturated N-Heterocycles from Aldehydes**



■ **Amide Synthesis by Nucleophilic Attack of Vinyl Azides**

■ **A Reagent-Controlled S<sub>N</sub>2-Glycosylation for the Direct Synthesis of β-Linked 2-Deoxy-Sugars**

■ **Young Career Focus: Dr. Kasper Moth-Poulsen (Chalmers University of Technology, Gothenburg, Sweden)**

**CONTACT ++++**

Your opinion about SYNFORM is welcome, please correspond if you like:  
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**Dear Readers,**

Three weeks ago the Thieme Chemistry Editorial Board Meeting was held in Saint-Émilion (France). It was a vibrant meeting where very important actions and implementations were discussed for all the journals and for

**SYNFORM** as well. I am very excited for the future of **SYNFORM**, and I would like to announce that important changes are looming. First and foremost, **SYNFORM** will become “eFirst”, which means that we will shortly start publishing individual **SYNFORM** articles on the new Thieme Chemistry **SYNFORM** website (<https://www.thieme.de/en/thieme-chemistry/journals-synform-54850.htm>), as soon as they are ready to go online. Furthermore, **SYNFORM** will publish News Articles specifically dedicated to the most exciting research papers published in Synlett and Synthesis, thus giving additional visibility and impact to our authors. The traditional downloadable monthly pdf format of **SYNFORM** will still be published; however, readers are encouraged to connect frequently to our new website for being the first to read the newest **SYNFORM** articles “as soon as published”!

Let’s have a look at the content of this brand new issue of **SYNFORM** now. The first **SYNSTORY** covers a conceptually new amide synthesis methodology developed by S. Chiba (Singapore), which is followed by the novel carbohydrate chemistry reported by C. Bennett (USA). The third **SYNSTORY** is dedicated to the innovative cyclization methodology developed by J. Bode (Switzerland). The issue is completed by a Young Career Profile featuring K. Moth-Poulsen (Sweden).

Enjoy your reading!

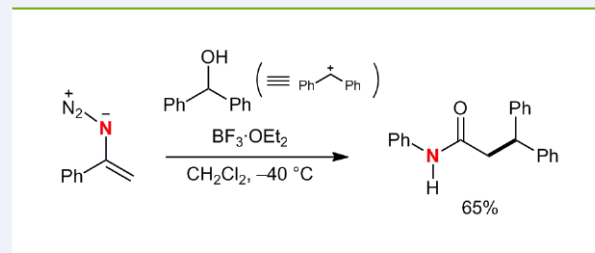
**Matteo Zanda**

*Editor of SYNFORM*

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**CONTACT + + + +**

If you have any questions or wish to send feedback, please write to Matteo Zanda at: [synform@outlook.com](mailto:synform@outlook.com)

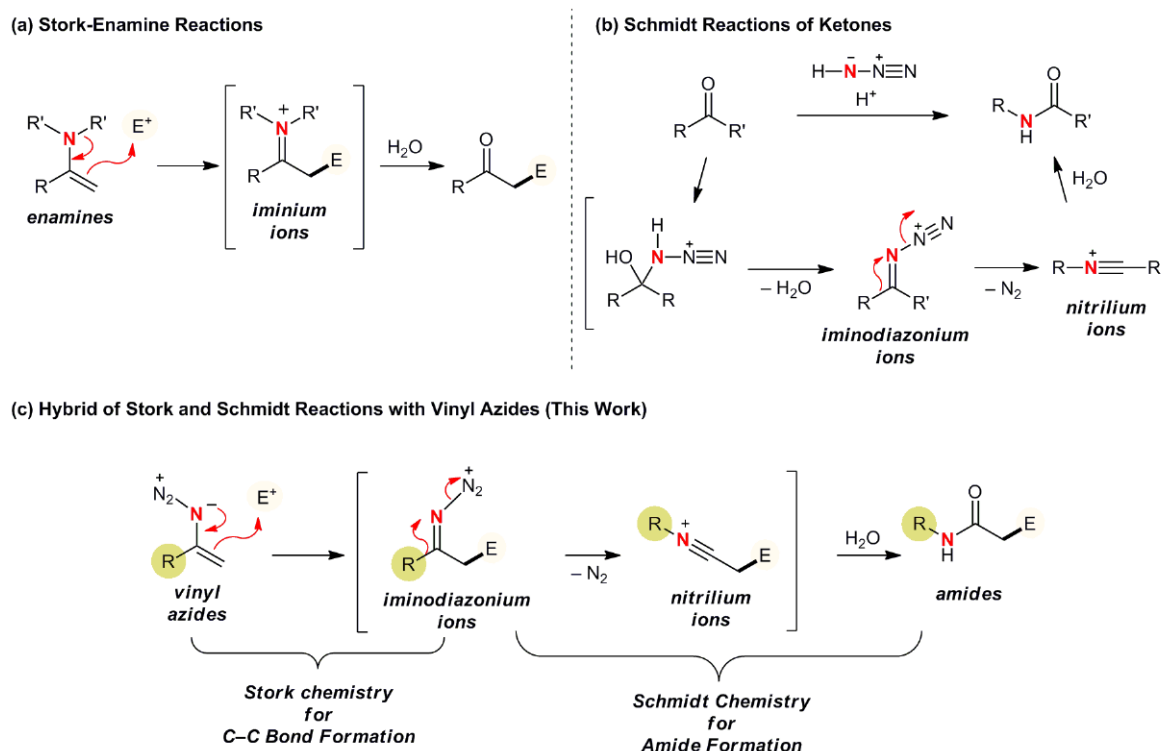
## Amide Synthesis by Nucleophilic Attack of Vinyl Azides

*Angew. Chem. Int. Ed.* **2014**, *53*, 4390–4394

■ Nucleophilic attack of enamines to carbon electrophiles ( $E^+$ ) results in the formation of a new C–C bond at their  $\alpha$ -carbon, along with the generation of an iminium ion moiety that is hydrolyzed to give a ketone carbonyl group. This process is known as the ‘Stork Enamine Reaction’ (Scheme 1-a) (for example, see: *J. Am. Chem. Soc.* **1963**, *85*, 207). On the other hand, the reaction of ketones with hydrazoic acid ( $\text{HN}_3$ ) under strongly acidic conditions leads to the formation of iminodiazonium ions that then undergo 1,2-migration of the substituent R to form nitrilium ions with concurrent elimination of dinitrogen ( $\text{N}_2$ ). Hydrolysis of the nitrilium ions produces the corresponding secondary amides. This process is called the ‘Schmidt reaction’ (Scheme 1-b) (for example, see:

*Org. React.* **2012**, *78*, *Org. React.* **1946**, *3*). Recently, a hybrid of the Stork and Schmidt reactions in one flask has been realized by treatment of vinyl azides with various carbon electrophiles in the presence of  $\text{BF}_3 \cdot \text{OEt}_2$ , enabling amide synthesis (Scheme 1-c), as reported by the group of Professor Shunsuke Chiba of Nanyang Technological University (Singapore).

Since 2007, Professor Chiba’s group has been interested in examining intriguing chemical reactivity of vinyl azides towards the synthesis of various nitrogen-containing compounds (see accounts: *Chimia* **2012**, *66*, 377; *Synlett* **2012**, *23*, 21). Professor Chiba said: “Given the structural analogy between enamines and vinyl azides, we envisioned that vinyl

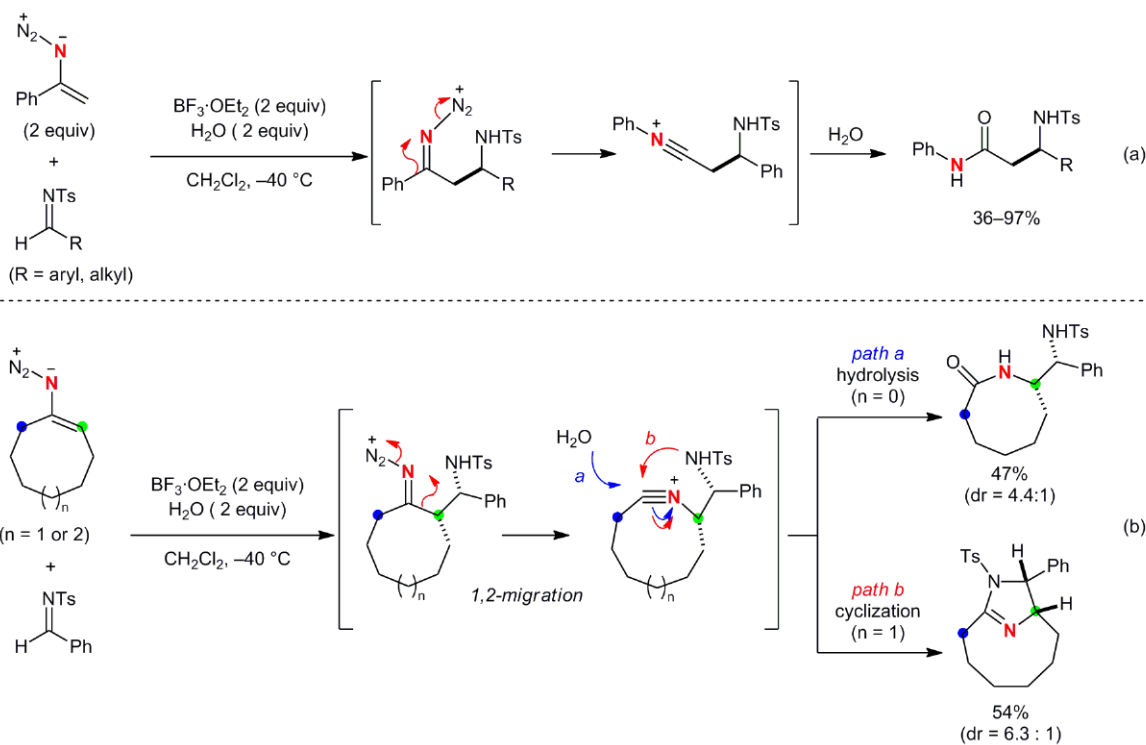


Scheme 1

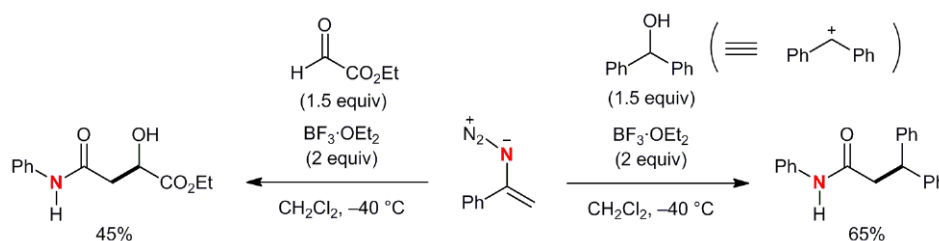
azides might undergo Stork-type nucleophilic attack towards carbon electrophiles. In this process, a new C–C bond could be constructed along with the formation of iminodiazonium ions that could subsequently be transformed into nitrilium ions via Schmidt-type 1,2-substituent migration. Hydrolysis of the nitrilium ions could finally produce the corresponding amides (see Scheme 1-c)."

With this hypothesis in mind, the Singapore-based researchers tested the reaction of vinyl azides **1** and *N*-tosyl aldimines **2**. Extensive screening of the reaction conditions revealed that the reaction proceeded smoothly at  $-40\text{ }^{\circ}\text{C}$  using

$\text{BF}_3 \cdot \text{OEt}_2$  as a Lewis acid promoter and  $\text{H}_2\text{O}$  as an additive, providing the corresponding amides in good yields (Scheme 2-a). "This protocol is viable for a variety of vinyl azides and *N*-tosyl aldimines," said Professor Chiba, who continued: "Interestingly, cyclic vinyl azides produced either a ring-expanded lactam or a bicyclic dihydroimidazole, depending on the ring size of the starting materials. Remarkably, tertiary alkyl group migration proceeds exclusively in these reactions." According to Professor Chiba, these outcomes suggest that *E*- and *Z*-configured iminodiazonium ion intermediates may be in equilibrium under the present reaction conditions,



Scheme 2



Scheme 3

which enables the selective rearrangement of the substituent with the higher migratory aptitude (i.e., aryl > alkyl, tertiary alkyl > secondary alkyl).

“This strategy with vinyl azides also allows the use of aldehydes and carbocations (which are generated in situ from alcohols), enabling the construction of the corresponding amides (Scheme 3),” he said.

“This work provides a new entry of the chemical reactivity of vinyl azides (i.e., nucleophilicity towards various carbon electrophiles), enabling hybridization of the Stork and

Schmidt reactions for amide synthesis,” said Professor Chiba, concluding: “More challenges and opportunities still remain to be addressed before this strategy can be adopted as a truly practical amide synthesis. One significant improvement would be, for example, the use of robust catalysis that would upgrade this method to a catalytic asymmetric variant.” ■

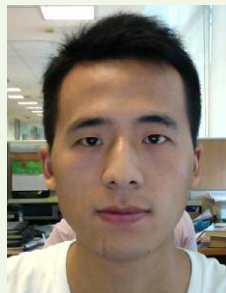
Matteo Zanda

### About the authors



F.-L. Zhang

**Feng-Lian Zhang** was born in Hebei (P. R. of China) in 1988. She received her BSc in 2011 from Nankai University (P. R. of China). She is now pursuing her PhD under the supervision of Professor S. Chiba at Nanyang Technological University (Singapore).



X. Zhu

**Xu Zhu** was born in Anhui (P. R. of China) in 1986. He obtained his BSc and MSc degrees at Soochow University (P. R. of China) in 2008 and 2011, respectively. He is currently a PhD student at Nanyang Technological University under supervision of Professor S. Chiba.



Dr. Y.-F. Wang

**Yi-Feng Wang** was born in Hunan (P. R. of China) in 1981. After he obtained his PhD from Nanyang Technological University in 2011 under the supervision of Professor K. Narasaka, he joined the group of Professor S. Chiba at the same university as a postdoctoral research fellow. In 2012, he was awarded the Lee Kuan Yew Postdoctoral Fellowship.



Prof. S. Chiba

**Shunsuke Chiba** was born in Zushi, Kanagawa (Japan) in 1978. He received his PhD in 2006 from The University of Tokyo (Japan, Professor K. Narasaka). He was appointed as a research associate at The University of Tokyo in 2005. In 2007, he moved to Nanyang Technological University as an Assistant Professor. In 2012, he was promoted to Associate Professor (with tenure) in the same university. The research focus of his

group is methodology development in the area of synthetic organic chemistry.



G. H. Lonca

**Geoffroy Hervé Lonca** was born in 1989 and received a formation as an engineer at the Ecole Polytechnique (France). From 2013 to 2014, he pursued a master's degree in the internship program at Nanyang Technological University under the direction of Professor S. Chiba, working on methodology development using vinyl azides. His work was awarded the Grand Prix du Stage de Recherche from Ecole Polytechnique.

## A Reagent-Controlled S<sub>N</sub>2-Glycosylation for the Direct Synthesis of β-Linked 2-Deoxy-Sugars

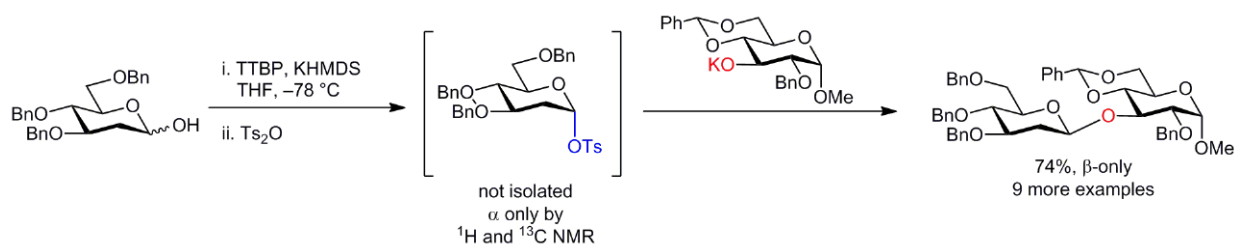
*J. Am. Chem. Soc.* **2014**, *136*, 5740–5744

■ 2-Deoxy-sugars have been shown to play a critical role in modulating the bioactivity of an array of natural products. Altering the composition of these sugars can result in molecules with dramatically improved pharmacokinetic properties and/or biological activities. The use of this approach for drug discovery has yet to find broad applicability, however, due in large part to the difficulty associated with the construction of 2-deoxy-sugar-containing oligosaccharides. This is especially true in the case of β-linked 2-deoxy-sugars, which are considered to be one of the most difficult glycosidic linkages to synthesize directly. To date, the vast majority of approaches to β-linked 2-deoxy-sugar synthesis rely on indirect synthesis (prosthetic groups or de novo synthesis), which leads to longer than optimal synthetic sequences.

This problem has been considered by Professor Clay Bennett's group at Tufts University (Medford, MA, USA). Professor Bennett said: "We envisioned that an approach that made the glycosylation reaction more S<sub>N</sub>2-like would permit the direct and stereoselective construction of β-linked 2-deoxy-sugars. To this end, we chose to examine the use of glycosyl sulfonates as donors." Professor Bennett explained that since glycosyl sulfonates exist predominantly or exclusively as α-anomers, such an approach would afford β-linked products, if ionization of the activated donor to an oxocarbenium cation could be avoided. "The reactivity of sulfonates spans several orders of magnitude," he continued, "and we reasoned that it should be possible to match the reactivity of a particular sulfonate to the intrinsic reactivity of the sugar backbone to afford a species that undergoes glycosylation through an S<sub>N</sub>2-like manifold."

Professor Bennett said: "Glycosyl sulfonates are too reactive to isolate, however. We therefore decided to generate them in situ by metalating a hemiacetal followed by trapping with an electrophilic sulfonate source. Our initial forays into this chemistry examined the use of *N*-tosyl-4-nitroimidazole as a sulfonylating agent (*Org. Lett.* **2013**, *15*, 4170)." While this reagent permitted the direct construction of 2-deoxy-sugar thioglycosides and phenolic glycosides, attempts to use nucleophilic sugar O-acceptors in the reaction provided products in low yields, accompanied by significant amounts of sulfonylated acceptor. Reasoning that a more active sulfonylating agent would permit complete conversion of the hemiacetal into the corresponding glycosyl sulfonate before addition of the acceptor, the Tufts-based researchers chose to examine *p*-toluenesulfonic anhydride (Ts<sub>2</sub>O) in the reaction. Under these conditions, both D-2-deoxy- and L-2,6-dideoxy-sugar donors reacted with sugar acceptors to afford products exclusively as β-anomers. "This result led us to posit that the reaction was proceeding through an S<sub>N</sub>2-mechanism," said Professor Bennett. "This hypothesis was further corroborated by low-temperature NMR experiments that demonstrated that treating the metalated hemiacetal at low temperature with Ts<sub>2</sub>O led to exclusive formation of a α-linked glycosyl tosylate."

Professor Bennett concluded: "These results demonstrate that it is possible to place the stereochemical outcome of a glycosylation reaction entirely under control of the glycosylation promoter. Importantly, it should be possible to match the reactivity of different sulfonates with different classes of glycosyl donors, thereby permitting the creation of a stereoselec-



tive glycosylation 'kit'. The development of such a kit and the application of this chemistry to oligosaccharide synthesis are currently under investigation in our lab." ■

**Matteo Zanda**

### About the authors



From left: J. P. Issa, Prof. C. S. Bennett

**John Paul Issa** was born in Riverside, California (USA) in 1988. After completing his secondary studies, he left home to pursue a BS in Chemistry at UC Irvine (USA), where he studied organic synthesis in the laboratory of Professor Scott D. Rychnovsky. In 2011 John Paul relocated to Tufts University in Medford, MA (USA) to carry out doctoral work under the guidance of Professor Clay S. Bennett. His PhD studies pertain to the field of complex carbohydrate synthesis and methodology development. Since joining the lab, John Paul has worked to develop methods of stereospecific glycosylation of deoxy-sugars with the ultimate goal of applying these approaches to natural product synthesis.

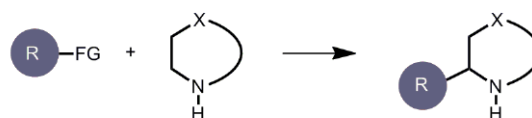
**Clay S. Bennett** received his BA in chemistry from Connecticut College (USA) in 1999. He then entered the University of Pennsylvania (Philadelphia, USA) where he studied natural products total synthesis with Professor Amos B. Smith, III. Upon obtaining his PhD in 2005 he joined the lab of Professor Chi-Huey Wong at The Scripps Research Institute (La Jolla, USA) as a Ruth L. Kirschstein Postdoctoral Scholar to study carbohydrate and glycoprotein synthesis. Since 2008 he has been an Assistant Professor in the Department of Chemistry at Tufts University. His research interests include developing new methods for carbohydrate synthesis, and their application to the construction of biologically relevant oligosaccharides.

# SnAP Reagents for the One-Step Synthesis of Medium-Ring Saturated N-Heterocycles from Aldehydes

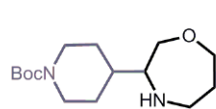
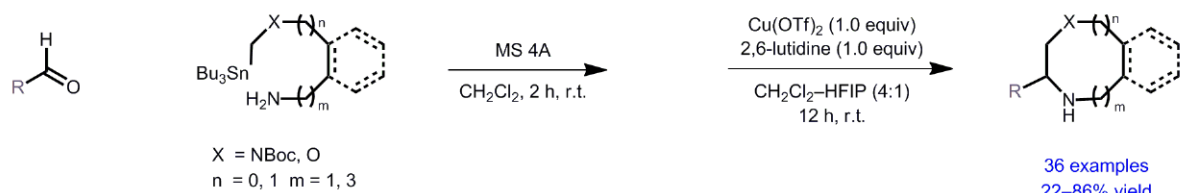
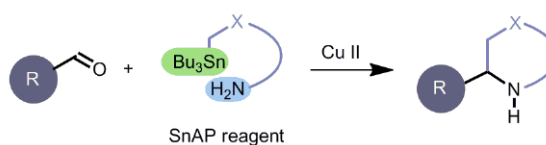
*Nat. Chem.* **2014**, *6*, 310–314

■ The remarkable success of cross-coupling reactions of aromatics and heteroaromatics has revolutionized the discovery and development of new biologically active small molecules. Limitations in the solubility, pharmacokinetics and bioavailability of functionalized aromatic scaffolds have led many medicinal chemists to favor saturated N-heterocycles. However, commercial availability of saturated N-heterocycles is lower than that of the aromatic counterparts, thus raising the need for new synthetic methods. This is particularly true considering that the functionalization of pre-formed saturated N-heterocycles is a rather laborious process not usually applicable to medium-sized rings. The majority of methods appli-

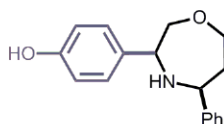
## Cross-coupling with saturated N-heterocycles



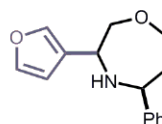
## SnAP reagent concept



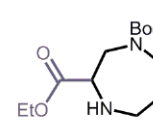
43% yield



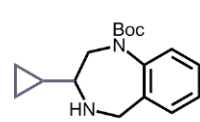
75% yield (dr = 10:1)



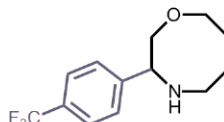
67% yield (dr > 10:1)



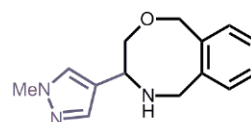
62% yield



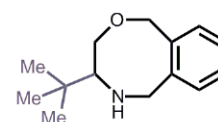
83% yield



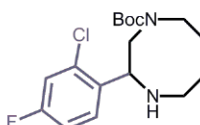
46% yield



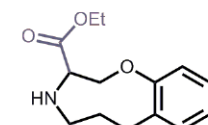
51% yield



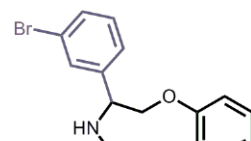
79% yield



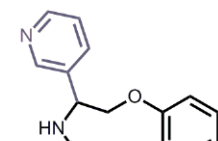
45% yield



41% yield



35% yield



22% yield



cable to the synthesis of six-membered and medium-sized saturated N-heterocycles require multiple synthetic steps wherein different substituents are introduced early on in the synthetic route and/or require protecting groups.

The research group of Professor Jeffrey Bode at the Laboratorium für Organische Chemie (ETH Zürich, Switzerland) pursued an effort to provide an alternative to cross-coupling reactions using widely available functional groups to afford unprotected N-heterocycles in a single synthetic operation, thus allowing for the rapid generation of libraries of the valuable functionalized pharmacophores.

In 2013, Bode's research group reported SnAP reagents [SnAP = tin(Sn) amino protocol] for the one-step synthesis of N-unprotected 3-thiomorpholines from aldehydes. Professor Bode said: "The success of this reaction encouraged us to further explore this approach and include different heteroatoms and ring sizes."

Despite the enthalpic and entropic penalties of forming medium-sized rings, this mild method provides unprotected substituted saturated seven-, eight- and nine-membered-ring N-heterocycles in moderate to good yields. The desired unprotected medium-sized N-heterocycles are also obtained where the SnAP reagents contain no backbone elements that favor the cyclization. Professor Bode explained: "We believe that the SnAP methodology will become an important tool in medicinal chemistry laboratories due to its mild reaction conditions, simple reaction protocol, availability of reagents, and broad scope of aldehyde substrates."

"With regard to current or future prospects and developments, we will try to get more insight into the reaction mechanism and try to render this process catalytic in copper," said Professor Bode. He concluded: "We also anticipate that the reagent design and reactions can easily be adapted to accommodate SnAP reagents with additional substituents and functional groups. Another important direction for future development is to expand the substrate scope to ketones and to develop enantioselective transformations. We are currently working to make the SnAP reagents commercially available and design reagents for the preparation of more exotic heterocycles." ■

**Matteo Zanda**

### About the authors



Dr. C.-V. T. Vo

**Cam-Van T. Vo** was born in 1981 in Gia Lai (Vietnam). She completed her undergraduate studies at the University of Medicine and Pharmacy in Ho Chi Minh City (Vietnam). She started her PhD in the research group of Professor Dr. Jeffrey W. Bode at the University of Pennsylvania (USA) in 2008 and moved to the ETH Zürich (Switzerland) in 2010 where she received her PhD in 2013.



M. U. Luescher

**Michael U. Luescher** was born in 1985 in Solothurn (Switzerland) and was trained as a medicinal chemistry laboratory technician at the Novartis Pharma AG in Basel (Switzerland). He then moved on to earn a BSc degree in chemistry in 2010 from the University of Basel, and joined Professor Dr. Karl Gademann's group for his MSc studies. He started his PhD work in Professor Dr. Jeffrey W. Bode's group at the ETH Zürich in 2012, where he is currently investigating catalytic protocols using the SnAP methodology.



Prof. J. W. Bode

**Jeffrey W. Bode** studied at Trinity University in San Antonio, TX (USA). Following doctoral studies at the California Institute of Technology (USA) and ETH Zürich and postdoctoral research at the Tokyo Institute of Technology (Japan), he began his independent academic career at UC Santa Barbara (USA) in 2003. He moved to the University of Pennsylvania as an Associate Professor in 2007 and to ETH Zürich as a Full Professor in 2010. Since 2013, he is also a Principal Investigator and Visiting Professor at the Institute of Transformative Biomolecules (WPI-ITbM) at Nagoya University (Japan).

## Young Career Focus: Dr. Kasper Moth-Poulsen (Chalmers University of Technology, Gothenburg, Sweden)

■ **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. Kasper Moth-Poulsen, Chalmers University of Technology, Gothenburg, Sweden.

### BIOGRAPHICAL SKETCH



Dr. K. Moth-Poulsen

**Kasper Moth-Poulsen** (born July 7, 1978) grew up near Copenhagen, Denmark. He studied organic chemistry at the University of Copenhagen where he obtained his Cand. Scient. (2003) and PhD (2007) degrees under the supervision of Professors J. B. Christensen and T. Bjørnholm. After obtaining his PhD, he worked as a postdoctoral researcher in the Bjørnholm lab. In early 2009, he

received a grant from the Danish Research Councils to continue his career abroad as a postdoctoral associate at the College of Chemistry at UC Berkeley (USA). At Berkeley, he worked with Professors R. A. Segalman and K. P. C. Vollhardt on developing a new solar thermal energy storage material. In 2011, Kasper was recruited to Chalmers University of Technology (Gothenburg, Sweden), where he currently holds a position as an assistant professor at the Department of Chemical and Biological Engineering. His work has been recognized by support from, among others, the European Research Commission (ERC Starting Grant), the Swedish Strategic Research Council (SSF future research leader grant) and the Swedish Research Council (young researcher grant). In 2013, he received a stipend from HM King Carl XVI Gustaf's foundation for science, technology and the environment for his work on molecular solar thermal systems. In 2014, he was awarded the Thieme Chemistry Journal Award, given to young scientists recognized as "high-potential researchers" in the field of synthetic organic chemistry.

### INTERVIEW

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

**Dr. Kasper Moth-Poulsen** | My research focuses on the synthesis of small molecules and nanoparticles for a number of applications; one area of interest is self-assembled single molecule electronics, where our long-term goal is to be able to address electronically single molecule components placed at surfaces in a well-defined way. Another topic is the design of molecular photoswitches where the switching event is associated with a large endothermic transformation – leading to stored energy that can be released on demand by reversing the process – so-called molecular solar thermal systems (MOST).<sup>1</sup> Along the lines of the energy storage project, we are also working on molecules for photon fusion (triplet–triplet annihilation photon up-conversion) which is a process that combines two low-energy photons to one high-energy photon. In my opinion, the photon fusion project is intimately linked to solar energy storage in chemical bonds, since photo-induced chemical bond breaking typically needs relatively high photon energies to occur (blue or UV light). Only a smaller part of the solar spectrum contains blue or UV photons, so photon fusion processes are a way to enhance the solar spectrum to efficiently drive the chemical processes that we are interested in.<sup>2</sup>

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

**Dr. Kasper Moth-Poulsen** | From my early school years through my time in high school, my interest in chemistry grew from curiosity to a dedicated interest. In high school I was lucky to have stimulating teachers that spurred my interests in chemistry even further. My passion for synthesis was evoked at university where I initially, through classes in organic and inorganic synthesis, laboratory courses and later through the research projects, got inspired by the predictive yet challenging experimental nature of organic and inorganic synthesis. Once again, the stimulating environment created by my dedicated teachers and fellow students played a decisive role in the development of my interest in synthesis.

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

**Dr. Kasper Moth-Poulsen** | I think that chemistry and specifically synthetic chemistry will play a very important role when trying to develop materials and solutions for the great challenges that society is facing, that being challenges with diseases, increasing world population, and a growing energy need. Meanwhile, the fossil fuel stockpiles are rapidly diminishing. We must come up with material solutions for these challenges, and in my opinion the element carbon is likely to play an important role here. Chemists have developed synthetic routes for a vast number of different structures of carbon through the last 200 years of chemical research, and I foresee that the chemists will play an equally important role in the years to come.

**SYNFORM** | Your research group is active in the area of organic chemistry and materials science. Could you tell us more about your research and its aims?

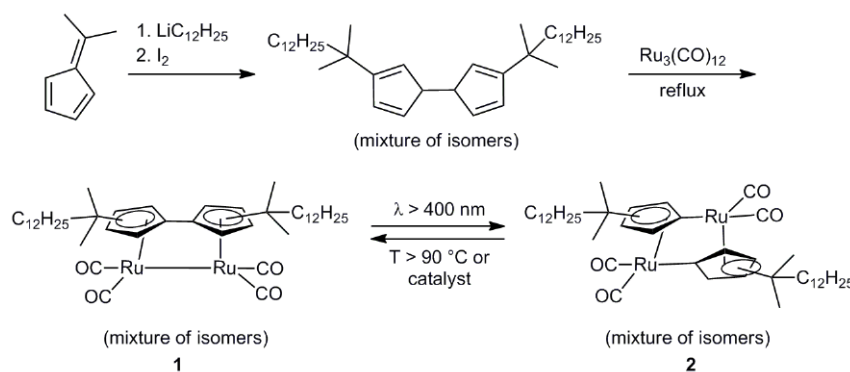
**Dr. Kasper Moth-Poulsen** | One example of our research activities is related to the development of molecules for molecular solar thermal (MOST) applications.<sup>1-4</sup> To develop an effective molecular system for this application is a challenging task, where several factors such as optical absorption (solar spectrum match), energy storage capability, quantum yield of conversion and energy storage time need to be optimized simultaneously. We are currently focusing on modifying the norbornadiene-quadracyclane system for these purposes.<sup>4</sup> With the aid of computational methods we are designing new systems that we are synthesizing in the labo-

ratory. Specifically, we are introducing electron donors and electron acceptors to the system to be able to red-shift the absorption of the systems while trying to keep the molecular weight as low as possible.

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

**Dr. Kasper Moth-Poulsen** | As a young scientist in the beginning of my career, I hope that important scientific achievements lie ahead of me. One achievement that I am proud of is the design and synthesis of a soluble version of fulvalene diruthenium intended for molecular solar thermal energy storage. Although the synthetic procedure might be considered crude in its approach, the simplicity of the method made it possible for us to synthesize enough material to be able to construct the first continuous flow device for molecular solar thermal energy storage.<sup>2</sup> The work on fulvalene diruthenium compounds for solar energy storage led by Vollhardt and co-workers is one example where chemical design plays an important role in the development of new materials with unforeseen properties and capabilities. ■

Matteo Zanda



**Scheme 1** Synthesis of soluble fulvalene diruthenium photoswitch for molecular solar thermal applications<sup>2</sup>

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