SYNSTORIES

- A Chiral Cagelike Copper(I) Catalyst for the Highly Enantioselective Synthesis of 1,1-Cyclopropane Diesters
- Catalytic Enantioselective Allylic Amination of Unactivated Terminal Olefins via an Ene Reaction/[2,3]-Rearrangement
- Taming of Fluoroform: Direct Nucleophilic Trifluoromethylation of Si, B, S, and C Centers
- Young Career Focus: Professor Matthias D’hooghe (Ghent University, Belgium)
Dear readers,

I know that my impression is based on very partial and subjective data, and I am well aware that such things as global warming and the greenhouse effect are scientifically proven and (unfortunately) absolutely true, but judging from the weather we’ve had in the last few weeks I would rather say that we are heading towards a new glacial era here in Scotland... High winds, snow blizzards, ice and only a few minutes of sunshine in the last few weeks... Normally I am not a big fan of warm weather, but recently I have been dreaming of a tropical beach, or even better the wonderful sea of my beloved Sardina in a hot summer... Just a dream unfortunately, still several months ahead before such things may materialize. Let's be realistic then, and think about the good things we have right here, right now. A new issue of SYNFORM for example, what else!! We have an outstanding first SYNSTORY on the use of an industrial by-product, fluoroform, for performing trifluoromethylation reactions according to the methodology developed by Professor S. Prakash and the Nobel laureate Professor G. Olah (USA). The second SYNSTORY brings us into the realm of catalytic enantioselective amination of terminal olefins, in the new version developed by Professor U. K. Tambar (USA). The third SYNSTORY covers the enantioselective synthesis of 1,1-cyclopropane diesters discovered by Professor Y. Tang (P. R. of China). Last but not least, the issue is completed by the Young Career Profile on Professor M. D’hooghe (Belgium).

Enjoy your reading!

Matteo Zanda
Editor of SYNFORM
The trifluoromethyl group is a key structural element present in a large number of pharmaceuticals, agrochemicals and materials. Nucleophilic trifluoromethylation is one of the most commonly used methods to introduce a trifluoromethyl group into an electrophilic substrate utilizing (trifluoromethyl)trimethylsilane, TMS-CF₃, the Rupper–Prakash reagent developed in 1989. This reagent is currently synthesized from CF₃Br (a gas) and its use is highly regulated in the western world due to the Montreal protocol on ozone-depleting CFCs. Hence, production of this important reagent is becoming difficult and expensive and is only taking place in countries such as Ukraine and P. R. of China. The recent Science paper by Professor G. K. Surya Prakash and co-workers as well as Professor George Olah of the Loker Hydrocarbon Research Institute, University of Southern California (USA), appears to crack this important and long-standing problem. In fact, the new article discloses a novel synthetic route for the synthesis of TMS-CF₃ and related (trifluoromethyl)silanes as well as many other trifluoromethylated boron, sulfur and carbon derivatives in a single step using an equivalent amount of fluoroform (CF₃H, a cheap and abundant source of the trifluoromethyl group). A Perspective by Professor Günther Haufe (University of Münster, Germany) was also published in the same issue of Science (Science 2012, 338, 1298) expounding the importance of the work.

“Fluoroform is a potent and stable greenhouse gas (with an atmosphere life-time of 250 years). It has an estimated global warming potential 11,700 times greater than CO₂ and the amount residing in the atmosphere is projected to be about 24.3 kilotons by 2015,” said Professor Prakash. Current fluoroform mitigation methods have economical and operational limitations. Professor Prakash explained that fluoroform is a by-product (produced in the range of 22,000 to 25,000 tons per year) during the manufacture of Teflon, PVDF, foaming agents, and fire retardants from chlorodifluoromethane, CIF₂H, HCFC-22. Concurrent with increasing production of Teflon, large quantities of fluoroform are also available in storage. Its disposal by incineration is also quite tedious. The ideas for developing fluoroform chemistry came from Professor Prakash himself, who has been convinced for the past 20 years that fluoroform can be deprotonated under the right conditions, and Nobel laureate Professor George Olah has been genuinely supportive of the fluorine chemistry work carried out in Professor Prakash’s group.

Professor Prakash said: “Our work not only resolves a major problem associated with the storage of greenhouse gas, but it also provides a practical outlet for this unwanted ‘by-product’ to make synthetically very useful reagents.” He continued: “The methodology developed for silanes was extended to make trifluoromethylated boron derivatives, which are also
promising synthons. The same methodology was also extended to synthesize a vital bulk chemical such as trifluoromethanesulfonic acid (triflic acid, CF₃SO₃H), but this currently requires further optimization.” Triflic acid, a non-oxidizing superacid (100 times stronger than 100% sulfuric acid) has found wide use in catalysis and synthesis. The triflate anion is also a very efficient leaving group.

“For synthetic chemists, the work sheds light on the much-debated ‘instability’ of the purported trifluoromethyl anion in the absence of polar solvents such as dimethylformamide (DMF),” continued Professor Prakash. “It has been claimed repeatedly in the literature that the trifluoromethyl anion derived from fluoroform needs to be stabilized as the hemiaminolate, which is the de facto source of the trifluoromethyl anion.” However, Professor Prakash reports that under such conditions, trifluoromethylation of silicon centers did not take place. “Grushin has recently developed elegant CF₃Cu chemistry based on fluoroform, which seems to work only in the presence of DMF,” he said. Following a quote from Professor Prakash “In real estate everything is ‘location, location, location’; in chemistry it is ‘conditions, conditions, conditions’.” Parag Jog, since 2008 a research scientist in Professor Prakash’s group, who has worked continuously on this challenging project since then, with the assistance of Patrice Batamack, another research associate who has been at the Loker Institute since the late 1990s, systematically explored various common aprotic organic solvents such as THF, toluene and diethyl ether for the generation of trifluoromethyl anion from fluoroform using a variety of bases at various temperatures. By trial and error, nitrogen- and oxygen-centered bases were found to give good results. In particular, KHMDS and t-BuOK were the bases of choice. Sodium- and lithium-centered bases did not work at all. Professor Prakash recalled that introducing molar equivalents of a low-boiling gas such as CF₃H was particularly challenging and required the use of customized equipment such as mass flow controllers, low temperature glass wares, etc., which were all fabricated in house. Professor Prakash concluded: “The work provides chemists a huge opportunity to extend the chemistry of fluoroform, thus trifluoromethylation chemistry, giving it a huge boost.”
Chiral amines represent an important sub-class of medicinally relevant nitrogen-containing molecules, and nitrogen-containing chemical structures are ubiquitous in functional materials. Furthermore, nitrogen-containing moieties are key components of a number of FDA-approved pharmaceutical drugs. Most enantioselective methods for the synthesis of chiral amines are dependent on the pre-functionalization of hydrocarbons, including olefins, into reactive electrophiles, such as allylic halides and alcohols. It is therefore not surprising that the direct conversion of olefins into chiral amines through an enantioselective allylic amination reaction has remained an important goal in chemistry for many years. In particular, the direct allylic amination of unactivated olefins represents a highly practical, economically efficient, and en-
Unsaturated hydrocarbons are ideal substrates for chemical synthesis, because they are inexpensive and abundant components of petrochemical feedstock. However, olefins are also challenging substrates for asymmetric catalysis, because it is difficult to selectively transform a single C–H bond into a C–N bond in the presence of several sterically and electronically similar C–H bonds.

Professor Uttam K. Tambar and Hongli Bao at the University of Texas Southwestern Medical Center (Dallas, USA) recently developed a catalytic enantioselective allylic amination of unactivated terminal olefins via an ene reaction/2,3]-rearrangement. This discovery is based on chemistry previously developed by the groups of Sharpless, Kresze, and others, who utilized a thermal [2,3]-rearrangement to generate racemic allylic amines from olefins.1 “In our strategy, we treated unactivated olefins 1 with a benzenesulfonyl sulfurdiimide reagent 2,” said Professor Tambar. “We then subjected the resulting zwitterionic intermediate 3 to a chiral palladium catalyst. This two-step process produced chiral allylic sulfonamide products 4 in greater than 90% enantiomeric excess.”

For many years, it was widely believed that the [2,3]-rearrangement of reactive zwitterions such as 3 would proceed easily in the absence of any catalyst.5 This would preclude any possibility of stereoinduction by a chiral catalyst. Professor Tambar said: “Our lab recently challenged this belief by developing a palladium-catalyzed enantioselective [2,3]-rearrangement of amine N-oxides, another class of reactive zwitterions.”6 This process served as a blueprint for catalyzing other rearrangements of reactive zwitterions that were traditionally thought to be too thermally reactive to engage with a chiral catalyst in the context of a stereoselective transformation. Professor Tambar continued: “We utilized this mode of activating [2,3]-rearrangements to develop a practical chiral palladium catalyst that converted unactivated olefins into enantioenriched allylic amines via a tandem ene reaction/[2,3]-rearrangement. The mild reaction conditions and the absence of any directing group requirements in the olefin substrate led to a general method for converting olefins into amines that is tolerant of several functional groups, including benzyl ethers, phthalimides, nitriles, aldehydes, and alkyl chlorides.”

Professor Tambar concluded: “The chiral rearrangement products can be easily transformed into synthetically useful allylic sulfonamides and primary amines, which has enabled the conversion of terminal olefins into molecules having pharmaceutical value, such as vigabatrin, an antiepileptic drug.”

REFERENCES

Professor Brian Stoltz. After he completed his NIH Postdoctoral Fellowship at Columbia University (USA) with Professor James Leighton in 2009, he began his independent research career at UT Southwestern Medical Center in Dallas (USA). He is currently an Assistant Professor in the Biochemistry Department and a W. W. Caruth, Jr. Scholar in Biomedical Research. The Tambar lab is interested in asymmetric catalysis, natural product synthesis, and medicinal chemistry.

Hongli Bao received her B.S. degree in Chemistry from the University of Science & Technology of China (Hefei, P. R. of China) in 2002. She obtained her Ph.D. from the joint program of the Shanghai Institute of Organic Chemistry (P. R. of China) and the University of Science & Technology of China in 2008 with Professors Kuiling Ding and Tianpa You. She joined the Tambar lab in 2009, and she is interested in developing metal-catalyzed enantioselective [2,3]-rearrangements. Hongli is the recipient of the UT Southwestern Chilton Postdoctoral Fellowship in Biochemistry.
Optically active 1,1-cyclopropane diesters are valuable chiral intermediates in total synthesis due to their versatile reactivity, the presence of two geminal ester functions, and the preservation of stereochemical information in most transformations. Chiral sources or kinetic resolutions of racemic cyclopropanes are methods frequently employed to synthesize these compounds. The research group of Professor Yong Tang of the Shanghai Institute of Organic Chemistry (P.R. of China) has recently investigated an alternative method. Professor Tang said: “In comparison with other methods, asymmetric cyclopropanation of olefins with malonate-derived metallocarbenes has the potential to provide the most straightforward synthetic route.” He continued: “However, this approach proved to be quite challenging because of the lack of an enantioface differentiation in this reaction with a symmetrically substituted metal carbene.” To date, high enantioselectivity and diastereoselectivity have only been achieved with rhodium catalysts in a few examples (P. Müller, A. Ghanem Org. Lett. 2004, 6, 4347; T. Nishimura, Y. Maeda, T. Hayashi Angew. Chem. Int. Ed. 2010, 49, 7324). Professor Tang continued: “Over the last decade, we have introduced a side-arm approach for ligand design in asymmetric catalysis and successfully applied this strategy to a number of reactions. Now, we have turned our attention to further extending this approach to the asymmetric cyclopropanation of olefins in hopes of solving some remaining problems. Quite recently, we successfully developed a highly diastereo- and enantioselective catalytic system for the asymmetric cyclopropanation of both cis- and trans-1,2-substituted unfunctionalized alkenes (Angew. Chem. Int. Ed. 2012, 51, 8838).” In light of this success and the works by Müller and Hayashi, the group proposed initially that $C_1$-symmetric ligand $L_1$ might also favor stereochemical control in the cyclopropanation with the symmetric malonate-derived copper carbenes, but unfortunately
only moderate enantioselectivity was obtained. “However, to our great pleasure,” said Professor Tang, “C2-symmetric ligand L2 (Figure 1) surprisingly showed an excellent enantioselectivity in the cyclopropanation reactions over a wide range of styrenes and cis-disubstituted olefins (Scheme 1).”

To gain some insight into the asymmetric induction in this reaction, the group developed a single crystal of the L2/Cu(I) complex from toluene–THF under an atmosphere of nitrogen in a glove box. “X-ray crystallography revealed that the complex is not a C2-, but a C1-symmetric cage-like molecule, in which the bond angle of N3–Cu–N1 is distinctively larger than that of N3–Cu–N2, and the Cu–N1 bond is shorter than that of Cu–N2 due to the non-symmetric weak interaction between C–H of the benzene ring on the oxazoline and benzene ring of the side arm (Figure 2),” explained Professor Tang. “Consequently, this non-symmetric effect probably enhances the control of the conformation of the two ester groups in the transition state, thus providing a better chiral pocket to discriminate the two prochiral faces of the incoming olefin.”

Professor Tang concluded: “Now that we have achieved high enantioselectivity for 1,1-cyclopropane diesters using cheap copper catalysts and readily available ligands, our next goal is to find a solution to improve the reaction efficiency as well as the selectivity, in particular for aliphatic and trans-1,2-substituted olefins.”

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**Figure 2** X-ray crystal structure of [Cu(CH3CN)L2]+ (Unless labeled, hydrogen atoms and PF6– are omitted for clarity.)

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**About the authors**

Yong Tang received his B.Sc. from Sichuan Normal University (P. R. of China) and his Ph.D. degree from the Shanghai Institute of Organic Chemistry (P. R. of China) before becoming a postdoctoral fellow with Professor Yian Shi at Colorado State University, Fort Collins (USA) and Professor A. Kozikowski at Georgetown University (USA). He moved back to the Shanghai Institute of Organic Chemistry in 1999, where he was appointed as an Associate Professor, and promoted to Research Professor in 2000. His research interests include organometallic chemistry centering on olefin polymerization, ylide chemistry in organic synthesis, and asymmetric catalysis.

Li-Jia Wang was born in Fuxin, Liaoning (P. R. of China). She received her B.Sc. in 2004 and Ph.D. in 2009 from Sichuan University (P. R. of China) under the supervision of Yong Tang.
Professor Xiao-Ming Feng. She was a postdoctoral fellow with Professor Keiji Maruoka at Kyoto University (Japan) from 2009–2011. Then, she moved to the Shanghai Institute of Organic Chemistry in 2011, where she was appointed as an Associate Professor in Professor Yong Tang’s group. Her research interest is in the area of developing new methodologies in asymmetric catalysis.

Chao Deng obtained his B.S. degree in chemistry from Shanxi Normal University (P. R. of China) in 2005. He received his M.S. degree in physical chemistry from Sichuan University under the supervision of Professor Yi Ren in July 2008, where he studied computational chemistry concerning organic reaction mechanisms. In August 2008, he joined Professor Yong Tang’s group at the Shanghai Institute of Organic Chemistry, working on some computational chemistry and asymmetric catalysis. In January 2013, he obtained his Ph.D.

Jun Zhu obtained his B.S. degree in pharmacy from the College of Pharmacy, Wuhan University (P. R. of China) in 2010. Then, he joined the research group of Professor Yong Tang for his Ph.D. studies at the Shanghai Institute of Organic Chemistry. Currently, his work focuses on asymmetric catalysis.
Young Career Focus: Professor Matthias D’hooghe
(Ghent University, Belgium)

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 Professor Matthias D’hooghe, Ghent University, Belgium.

INTERVIEW

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

Prof. M. D’hooghe | The focus of our research work is two-fold. On the one hand, we are involved in heterocyclic synthesis with the objective to study the reactivity and appli-
cability of a variety of systems, particularly focusing on
small-ring azaheterocycles such as aziridines, azetidines and β-lactams. Within this context, it is our ambition to explore new synthetic strategies and their application toward the con-
struction of novel heterocyclic frameworks. On the other
hand, we devote considerable attention to the preparation of
new organic molecules with certain biological activities,
such as antimalarial, antiviral, antibacterial and antifungal
agents and HDAC inhibitors. This work is situated at the
interface of organic and medicinal chemistry, and provides
input to the early stages of drug design and discovery.

SYNFORM | When did you get interested in synthesis?

Prof. M. D’hooghe | During the last year of high school, when I discovered the tremendous potential of organic synthesis (albeit only on paper) and its impact on our society. Shortly thereafter, I had the chance to perform organic syn-
theses in a laboratory course at the university, which con-
vinced me to pursue a degree in organic chemistry and related
disciplines. I conducted scientific research for both my
Master’s thesis and my Doctoral dissertation in the group of
Professor Norbert De Kimpe, who introduced me to the fa-
cinating chemistry of small-ring azaheterocycles and who
guided me through the early steps of my career.

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

Prof. M. D’hooghe | Although many interesting new
approaches and techniques have emerged in recent years, the
main objective of organic synthesis will never change: the
construction (or better, the creation) of new organic com-
ounds. Nonetheless, it is clear that these emerging methods
have a profound impact on the way organic synthesis is per-
formed and, in that respect, I believe that the implementation

BIOGRAPHICAL SKETCH

Professor Matthias D’hooghe was born in Kortrijk, Belgium, in 1978. He received his Master’s diploma in 2001 and obtained a PhD degree in 2006, both from Ghent University (Belgium). In 2007, he became Assistant Professor in the group of Professor N. De Kimpe, and in 2009 he performed a short postdoctoral stay with Professor D. Vogt at Eindh-
oven University of Technology (The Netherlands) in the field of homogeneous catalysis. In October 2010, he was promoted to Associate Professor at the Department of Sustainable Organic Chemistry and Technology, Faculty of Bioscience Engineering, Ghent Uni-
versity, Belgium. His main research interests include the
chemistry of small-ring azaheterocycles, with a special
focus on aziridines, azetidines and β-lactams, and the syn-
thesis of bioactive target compounds. He is the author of
90 publications in international peer-reviewed journals.
of sustainable strategies such as the application of energy-efficient techniques, renewable resources and (bio)catalysis will continue to attract an increasing interest. Within that context, we recently introduced microwave-assisted transformations and particular metal- and biocatalyzed conversions into our studies in azaheterocyclic chemistry, allowing for the preparation of new types of valuable target systems.

SYNFORM | Your research group is active at the interface of organic and bioorganic chemistry. Could you tell us more about your research and its aims?

Prof. M. D’hooghe | The statement “there has been little investigation into ring openings of simple N-alkylated aziridines” (Chem. Soc. Rev. 2002, 31, 247), published in a review on aziridine chemistry during the first year of my PhD studies, prompted us to explore and unravel the peculiar reactivity of these so-called ‘non-activated aziridines’ (aziridines bearing an electron-donating group at nitrogen), and these endeavors have produced a plethora of new methods and transformations over the years. Today, we still deploy the rich chemistry of non-activated small-ring aza-heterocycles for the design of new syntheses and the formation of new classes of interesting structures. In particular, aziridines, azetidines and β-lactams continue to provide us with inspiration for new applications in heterocyclic chemistry, although we focus on other heterocyclic scaffolds as well.

Figure 1 Selection of heterocyclic scaffolds prepared through synthetic elaboration of aziridines, azetidines or β-lactams
Next to unraveling fundamental chemical aspects related to reactivity and mechanisms, we are very much interested in applying our knowledge to the synthesis of biologically relevant compounds and the evaluation of their bioactivities. In that respect, we have international collaborations with distinguished experts in the framework of various joint programs, ranging from antimalarial assessments over the study of antiviral, antibacterial, and antifungal agents to the rational design and development of new HDAC inhibitors. In this way, we aspire to bridge the gap between fundamental and applied organic chemistry, and it is particularly gratifying when a novel synthetic strategy provides a new organic scaffold associated with a pronounced bioactivity. I am convinced that synthetic organic chemists can have a major impact on the advancement of medicinal chemistry through the elaboration of novel synthetic methods leading to structural diversity and chemical novelty, which is of fundamental importance to effectively cope with major challenges in medicinal and biological sciences.

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

**Prof. M. D’hooghe |** Motivated by the above-mentioned statement on non-activated aziridines in 2002, our research has demonstrated these compounds to be extremely versatile synthons in organic chemistry. I consider the fact that I have had the opportunity to contribute to this impressive development, culminating in more than 50 SCI papers solely on aziridine chemistry, a very important achievement. In addition, we also broadened the scope of this study to other constrained ring systems such as azetidines and azetidinones, demonstrating the huge potential of small-ring azaheterocycles in organic synthesis (Figure 1). The honor of being selected as a finalist of the European Young Chemist Award 2012 (*Chem. Eur. J.* 2012, 18, 14881) and as a recipient of the Thieme Chemistry Journal Award 2013 is a further acknowledgement of the relevance and impact of our work.

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Matteo Zanda

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**SYNFORM**

**COMING SOON**

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- Regioselective Reactions of 3,4-Pyridynes Enabled by the Aryne Distortion Model
  (Focus on an article from the current literature)
- Synthesis of Fluorenones via Quaternary Ammonium Salt Promoted Intramolecular Dehydrogenative Arylation of Aldehydes
  (Focus on an article from the current literature)
- Ligand-Enabled Methylene C(sp²)–H Bond Activation with a Pd(II) Catalyst
  (Focus on an article from the current literature)

**FURTHER HIGHLIGHTS**

**SYNTHESIS**

Review on: Palladium-Mediated Total Synthesis of Bio-active Natural Products
(by K. C. Majumdar, B. Sinha)

**SYNLETT**

Account on: A New Tool in the Toolbox: Electron-Downdrawing Group Activated Ruthenium Catalysts for Olefin Metathesis
(by K. Grela et al.)

**SYNFACTS**

Synfact of the Month in category “Metal-Catalyzed Asymmetric Synthesis and Stereoselective Reactions”: Copper-Catalyzed Asymmetric Synthesis of Piperidines by a [6+3] Cycloaddition

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