

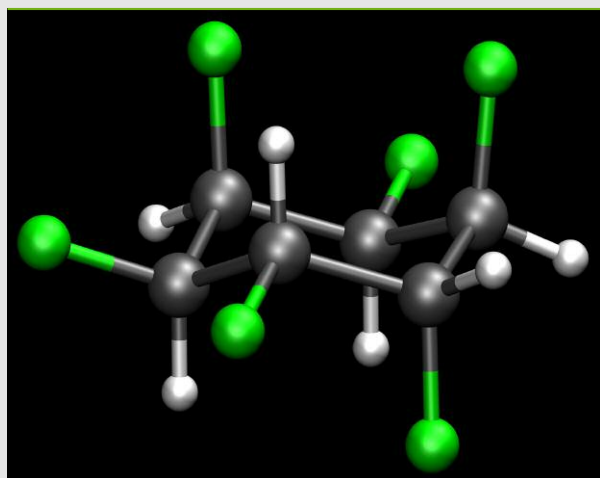
# SYNFORM

People, Trends and Views in Synthetic Organic Chemistry

2013/01

## SYNSTORIES ■ ■ ■ ■

■ The Synthesis of  $\eta$ -1,2,3,4,5,6-Hexafluorocyclohexane (Benzene Hexafluoride) from Benzene



■ Iron-Catalyzed Asymmetric Oxyamination of Olefins

■ Selective Transformations of Complex Molecules Enabled by Aptameric Protective Groups

■ Young Career Focus: Dr. Olga García Mancheño (Westfälische Wilhelms-Universität Münster, Germany)

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Dear readers,

This first 2013 issue of **SYNFORM** marks two important facts: (1) **SYNFORM** enters its 7th year of publication (we started in 2007!) and (2) it goes back to the original four-articles-per-issue format. In fact,

during the previous six years of **SYNFORM** we published ca. 600 pages of information on the exciting, cutting edge research developed in many of the top organic chemistry laboratories around the world, integrating the data published in the scientific literature with the stories of the scientists who carried out the research, revealing anecdotes, behind-the-scenes, and curiosities which are normally not available elsewhere. Now, we are back with more articles, four per issue, as **SYNFORM** used to publish until 2009, when I moved to Scotland and my diary became overwhelmingly busy, so busy, that I had to reduce my editorial activity. Now that Alison has joined the **SYNFORM** team we are back stronger and more motivated than ever, with an agenda full of exciting articles and new features, which will be gradually revealed. But let's start having a look at the first four **SYNSTORIES** of this first 2013 issue. We start with a new oxyamination of olefins developed by Prof. Yoon (USA), and we continue with the groundbreaking use of aptamers as supramolecular protecting groups envisioned by Prof. Herrmann (Germany). The third **SYNSTORY** reports on the synthesis of a textbook molecule, 1,2,3,4,5,6-hexafluorocyclohexane, achieved by Prof. O'Hagan (UK). Last but not least, the issue is closing with a Young Career Focus on Dr. García-Mancheño (Germany).

Enjoy your reading!

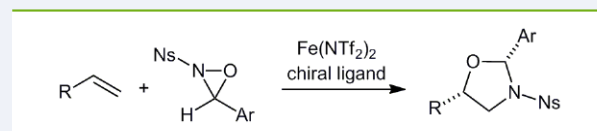
**Matteo Zanda**

Editor of **SYNFORM**

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If you have any questions or wish to send feedback, please write to Matteo Zanda at: [Synform@chem.polimi.it](mailto:Synform@chem.polimi.it)

## NEWS AND VIEWS ■ ■ NEWS AND VIEWS ■ ■ NEWS AND VIEWS ■ ■

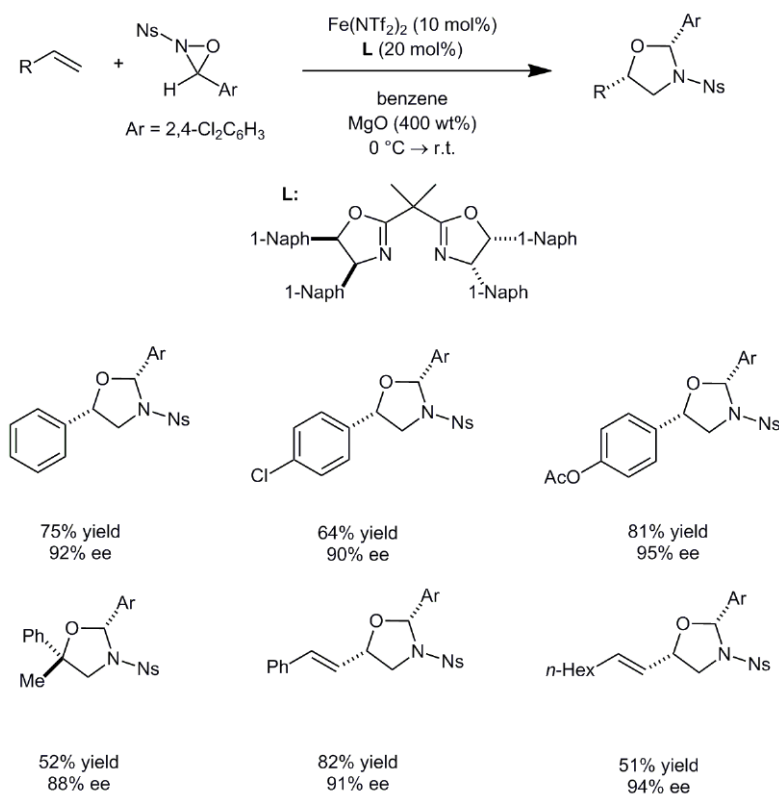
## Iron-Catalyzed Asymmetric Oxyamination of Olefins

*J. Am. Chem. Soc.* **2012**, *134*, 12370–12373

■ Since the discovery by Professor Tehshik P. Yoon, Kevin S. Williamson, and others from the Department of Chemistry at the University of Wisconsin-Madison (USA) that copper and iron catalysts promote the regioselective aminohydroxylation of olefins with *N*-sulfonyl oxaziridines (*Tetrahedron* **2009**, *65*, 5118 and references therein), the long-standing goal of Professor Yoon's group for the project has been to translate these systems into asymmetric methods. The Sharpless asymmetric aminohydroxylation (AA) reaction remains the state-of-the-art approach for the direct conversion of simple alkenes into amino alcohols; however, the use of toxic and expensive osmium salts and the poor regioselectivity observed for certain substrate classes leaves room for complementary approaches. "A number of impressive contributions utilizing other metals have been reported over the past decade, but

asymmetric aminoxygenation methods have been more elusive," said Professor Yoon. "To date, only two intramolecular examples utilizing copper (S. R. Chemler and co-workers *J. Am. Chem. Soc.* **2008**, *130*, 17638) and hypervalent iodine (T. Wirth and co-worker *Angew. Chem. Int. Ed.* **2012**, *51*, 3462) have achieved high stereocontrol. The development of our asymmetric iron reaction represents the first intermolecular example of a highly regio- and stereoselective addition of nitrogen and oxygen across olefinic bonds that does not require osmium."

He continued: "During the early development of this reaction, we quickly identified the bis(oxazoline) framework as a suitable ligand partner for the iron salt due to its oxidative stability and rich history of delivering high levels of stereoselectivity in a wide range of synthetic transformations. While we



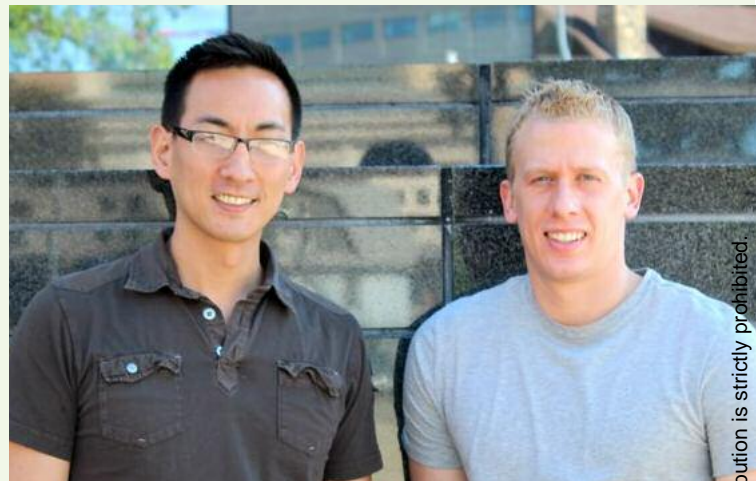
obtained >90% ee in some of the first screens we performed, these reactions were plagued with poor yields.” Professor Yoon noted that a key observation for moving the method forward was the realization that competitive rearrangement of the oxaziridine to its respective amide was outcompeting the desired transformation. This side reaction arises from one-electron reduction of the N–O bond and is well established with electron-rich iron(II) salts. “By changing the counter ion on the iron to make the catalyst less electron-rich, we were able to mitigate this side reaction and focus on developing a ligand framework that delivered high selectivity,” he explained. “To this end, we developed the tetranaphthyl-substituted bisoxazoline ligand and achieved high ee.”

Professor Yoon said that reaching high selectivities for the amination products was very exciting, due to the large number of biologically interesting natural products that contain the amino alcohol structural moiety. These range from the side chain of paclitaxel and the macrocycle of vancomycin to a number of simple beta blockers currently in clinical use. “In looking to apply our method to biologically relevant targets, one of our current goals is to develop a more robust catalyst system without significantly sacrificing selectivity,” he said. “As with many asymmetric oxidative iron-catalyzed transformations, our catalyst loadings are relatively high due to the limited lifetime of the active species under the highly oxidizing conditions. A key to applying this system to scales relevant to targeted syntheses will be improving the catalyst turnover by developing a catalyst system that is more stable towards oxidation.”

An additional synthetic goal for the oxaziridine project is to improve the stereoselectivity for the complementary copper system. “The exploration of alternative catalyst systems is currently under way,” concluded Professor Yoon. ■

*Matteo Zanda*

### About the authors



From left: Prof. T. P. Yoon, K. S. Williamson

## Selective Transformations of Complex Molecules Enabled by Aptameric Protective Groups

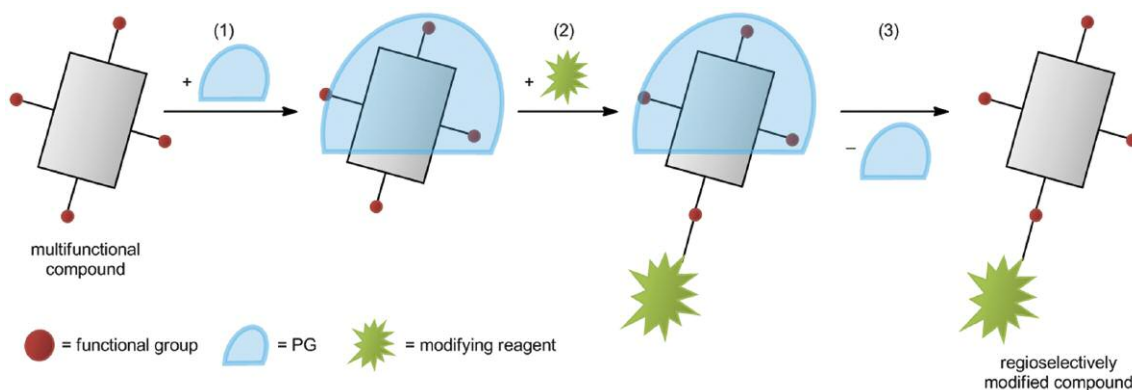
*Nature Chem.* **2012**, *4*, 789–793

Most natural products and therapeutics exhibit several functional groups, such as hydroxy, amino, olefin, carboxy, keto and sulfhydryl groups. These functionalities are known to be essential for biological activity and they are often targets for specific modification for the development of new active substances, with the aim of overcoming drug resistance, increasing drug efficiency or decreasing toxicity.<sup>1,2</sup> However, the chemical derivatization of complex scaffolds is not an easy task. Simple functionalization without protective groups results in inseparable mixtures of products because functional groups tend to show similar reactivity towards derivatization reagents. The only alternative is represented by a laborious partial or total synthesis of the modified target molecule, which often requires many synthetic steps.

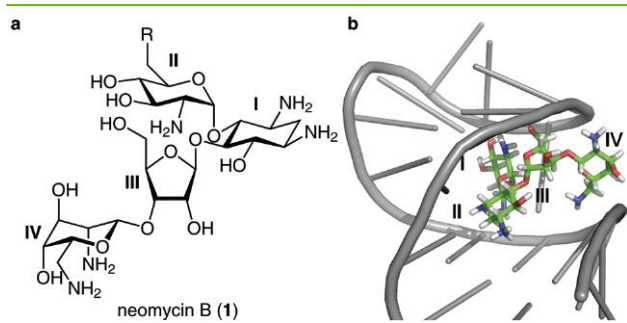
Professor Andreas Herrmann's group in the Zernike Institute for Advanced Materials at the University of Groningen (The Netherlands) recently proposed an intriguing solution to this dilemma. Instead of building up complex structures step by step, employing covalent protective group schemes, his research group employed supramolecular interactions to block the reactivity of functional groups. In the study recently published in *Nature Chemistry*, short RNA aptamers were utilized as a non-covalent protective group (PG) to shield several functionalities by non-covalent interactions while other groups not in contact with the aptamer were regioselectively converted (Scheme 1).

“With this work we have entered new grounds,” stated Professor Herrmann. His research group is known for their work on nucleic acid hybrid materials, especially the combination of DNA and synthetic polymers.<sup>3</sup> “When it comes to the synthesis of new materials we frequently rely on methods from molecular biology combined with chemical techniques to achieve new structures,” said Professor Herrmann. “Previously, we employed the polymerase chain reaction as a preparatory tool in polymer chemistry to fabricate DNA block co-polymer architectures with extended nucleic acid segments.”<sup>4,5</sup>

In their most recent work, Herrmann and co-workers relied on an RNA structure that was generated by another molecular biology tool, namely a SELEX experiment (Systematic Evolution of Ligands by EXponential Enrichment).<sup>6</sup> This RNA aptamer binds the aminoglycoside antibiotic neomycin B (**1**) that contains six amino and seven hydroxyl groups (Figure 1). Andreas Bastian, the PhD student working on the aptameric protective group project, mentions: “After searching the literature for suitable aptamers for our new approach, I immediately realized that this was the right one. The three-dimensional structure of the aptamer target complex was solved by NMR spectroscopy<sup>7</sup> and the functionalities at ring IV of the aminoglycoside were exposed to the solvent while the other rings of the molecules were buried deep inside the RNA scaffold.”



**Scheme 1** Site-specific modification of a multifunctional compound employing non-covalent protective groups (PG): introduction of protective group (1), regioselective transformation (2), mild removal of protective group (3)



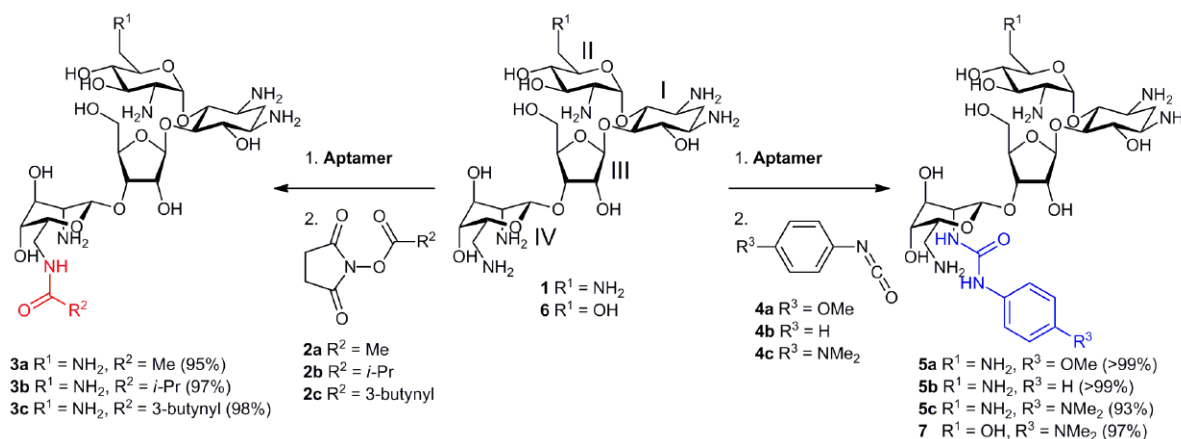
**Figure 1a** Structure of aminoglycoside antibiotic neomycin B (**1**); **b**: RNA aptamer selectively protecting neomycin B<sup>7</sup> (color coding: white – hydrogen; green – carbon; red – oxygen; blue – nitrogen)

With this 23mer RNA sequence as the starting point, neomycin B could be selectively modified at the amine group at the C6 position of ring IV with various activated esters **2a–c** to form the corresponding amide derivatives **3a–c** with regioselectivities ranging from 95–98% (Scheme 2, left). Interestingly, the aptamer even acted as an efficient shield against non-selective functionalization when DMF was added as a co-solvent to solubilize the hydrophobic activated esters.

“Now, the next step was to show that we can transform the antibiotic at a different position,” remarked Professor Herrmann. “Luckily, Andreas found that aromatic isocyanates **4a–c** exclusively react at the amino group at the C2 position of ring IV when the aptamer is employed as supramolecular protective group (Scheme 2, right).” An explanation for urea formation taking place at a different position than the amide bond

formation is the following: first, the planar aromatic isocyanates are considerably less sterically demanding than the succinimide ester. Therefore, isocyanates **4a–c** can react with the partially protected amino group in C2 position of antibiotic ring IV, while activated succinimide esters **2a–c** show no reactivity in this position. Second, amines attached to secondary carbons of neomycin B have lower  $pK_a$  values compared to amines at primary carbon atoms. For this reason, the amino group in C2 position is more likely to be in a deprotonated state, thus exhibiting higher reactivity in aqueous solution with isocyanates **4a–c**. “This reactivity difference was confirmed in a control experiment,” stated Professor Herrmann. “When neomycin B was reacted with the aromatic isocyanates without the aptameric protective group we obtained a mixture of one- to four-fold modified products according to mass spectrometry. In contrast, the application of activated ester for the transformation of neomycin B in the absence of an aptamer yielded a mixture of one- to six-fold reacted derivatives.” Additionally, the low half-life time<sup>8</sup> (seconds to minutes) of isocyanates in aqueous solution prevents the subsequent urea bond formation in C6 position of neomycin B. Thus, the antibiotic is converted in C2 position into urea derivatives **5a–c** with high regioselectivities of up to >99%.

“After successful proof-of-concept we needed to show the general applicability of the approach,” explained Andreas Bastian. In this regard, first the structurally related antibiotic paromomycin (**6**) was converted into the corresponding urea derivative **7** at the same position as neomycin B (**1**) (Scheme 2), meaning that a single aptamer could act as a supramolecular



**Scheme 2** Chemo- and regioselective transformation of neomycin B **1** in C6 position of ring IV using 30 equiv of succinimide ester **2a–c** (left) and amino group in C2 position of aminoglycosides **1** and **6** employing 15 equiv of isocyanates **4a–c** (right). Modifications of antibiotics **1** and **6** were performed in 10 mM sodium phosphate buffer at pH 6.9 containing 6.7 vol% DMF in the presence of 1.5 equiv of aptamer (24 hours). Numbers in brackets indicate the regioselectivity obtained for the corresponding antibiotic derivative.



protective group for structurally related molecules. Furthermore, two other RNA sequences evolved in the same SELEX experiment proved to act as efficient aptameric protective groups although they were only 21mers and thus two nucleotides shorter than the previous sequence. The successful experiments with three different aptamers show that SELEX experiments frequently generate nucleic acid sequences that are suited for regioselective modification by supramolecular protection.

After the successful demonstration of the broad scope of aptameric protective groups, Alessio Marcozzi, a biologist in the interdisciplinary group of Professor Herrmann, tested the new antibiotic derivatives for their antimicrobial activities against an *Escherichia coli* strain that is a standard for evaluating the efficiency of antibiotics. It turned out that several of the new antibiotic derivatives were highly active, indicating that the attachment of large residues at ring IV does not impair the antimicrobial activity.

Professor Herrmann said: "It is always rewarding to see if a compound synthesized in the lab shows a particular function," and he continued with a wink, "especially if you made a compound in a single reaction that would otherwise require more than 20 synthetic steps." But in the next breath he qualified his statement: "But you need to run a SELEX experiment first."

Professor Herrmann concluded: "In the future, we will establish aptameric protective groups as a new tool in organic and medicinal chemistry. Therefore, new reactions need to be identified that are compatible with the presence of nucleic acids. Equally important is to make our technology less costly. When RNA as aptameric protective group is replaced by DNA one could save approximately 90% of the fabrication costs. Finally, our group will work on selection protocols for the generation of aptameric protective groups that allow site-specific modification at a predefined position in a complex molecule. With these tools in hand, such protective groups will allow the fabrication of natural product derivatives that were previously almost impossible to achieve and, therewith, this technology will be a great platform for the development of natural product based drugs." ■

Matteo Zanda

## REFERENCES

- (1) F. E. Koehn, G. T. Carter *Nat. Rev. Drug Discovery* **2005**, *4*, 206.
- (2) J. W.-H. Li, J. C. Vederas *Science* **2009**, *325*, 161.
- (3) M. Kwak, A. Herrmann *Angew. Chem. Int. Ed.* **2010**, *49*, 8574.
- (4) M. Safak, F. E. Alemdaroglu, Y. Li, E. Ergen, A. Herrmann *Adv. Mat.* **2007**, *19*, 1499.
- (5) F. E. Alemdaroglu, W. Zhuang, L. Zöphel, J. Wang, R. Berger, J. P. Rabe, A. Herrmann *Nano Lett.* **2009**, *9*, 3658.
- (6) S. Stampfl, A. Lempradl, G. Koehler, R. Schroeder *ChemBioChem* **2007**, *8*, 1137.
- (7) L. Jiang, A. Majumdar, W. Hu, T. J. Jaishree, W. Xu, D. J. Patel *Structure Fold. Des.* **1999**, *7*, 817.
- (8) W. E. Brown, A. H. Green, T. E. Cedel, J. Cairns *Environ. Health Persp.* **1987**, *72*, 5.

### About the authors



From left to right: Dr. A. A. Bastian, Prof. A. Herrmann and A. Marcozzi in front of the new life science building of the University of Groningen

**Andreas Herrmann** studied chemistry at the University of Mainz (Germany). From 1997–2000 he pursued his graduate studies at the Max Planck Institute for Polymer Research in Mainz. Then he worked as a consultant for Roland Berger Management Consultants in Munich (Germany, 2001). In 2002 and 2003 he returned to academia, working on protein engineering at the Swiss Federal Institute of Technology, Zurich (Switzerland). In 2004 he was appointed head of a junior research group at the Max Planck Institute for Polymer Research. In 2007 he moved to the Zernike Institute for

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Advanced Materials at the University of Groningen (The Netherlands), where he holds a chair for Polymer Chemistry and Bioengineering. The Herrmann group investigates engineered biomacromolecules and bioorganic hybrid materials for biomedical and technological applications. Professor Herrmann was awarded the Reimund Stadler Prize from the German Chemical Society (GDCh) in 2008 and the Dr. Hermann Schnell Prize (GDCh) in 2009. For work on nucleic acid hybrid materials, he was awarded an ERC Starting Grant from the European Commission (2009) and a VICI Grant from the NWO (2010).

**Andreas Bastian** studied biomedical chemistry at the University of Mainz from 2003–2008. His studies were funded by an excellence scholarship from the German government.

During his PhD studies, he co-invented the chemistry centered around aptameric protective groups in the group of Professor Herrmann and he successfully defended his PhD with highest distinction (cum laude) in October 2012. At the moment he works for Syncom, a contract research company in Groningen.

**Alessio Marcozzi** was born in Rome (Italy). He obtained his Masters degree in molecular biology in 2009 at the University Roma Tre. After a Masters thesis in the group of Professor P. L. Luisi on 'never born proteins' he joined the research team of Professor Herrmann for his PhD studies. Currently he works on the evaluation of new antibiotic derivatives and phage display to evolve peptide binders for various applications in biomedicine and materials science.



## The Synthesis of $\eta$ -1,2,3,4,5,6-Hexafluorocyclohexane (Benzene Hexafluoride) from Benzene

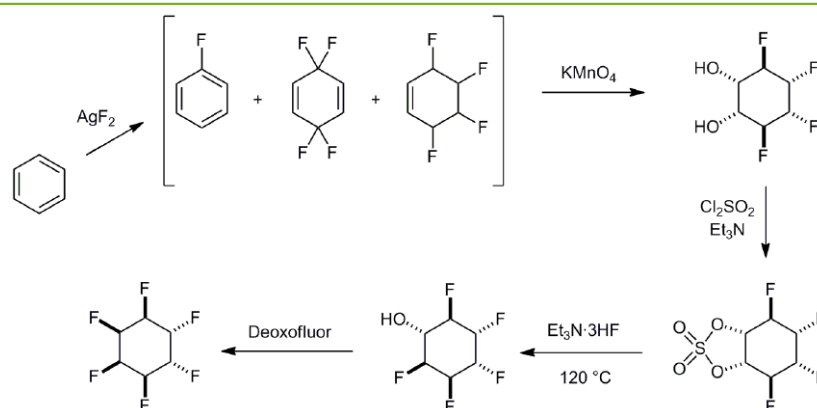
*Angew. Chem. Int. Ed.* **2012**, *51*, 10086–10088

Organic synthesis can be a form of art, and sometimes chemists are artists who pursue the synthesis of a molecule not because of its use but for its aesthetic beauty. One such molecule is 1,2,3,4,5,6-hexafluorocyclohexane, with its symmetry, structural simplicity, and the presence of one fluorine atom bound to each carbon atom. Cyclohexanes form a central structural motif in organic chemistry but until recently this fascinating cyclohexane existed only on paper and in chemists' dreams as a curiosity. Although theoretical studies have been carried out on the various isomers of this compound, a convincing synthesis of 1,2,3,4,5,6-hexafluorocyclohexane remained elusive. Recently, however, the research group of Professor David O'Hagan at the University of St Andrews (UK) has reported the first unambiguous synthesis of an isomer of this cyclohexane.

One of the goals of Professor O'Hagan's research has been to explore the consequences of placing C–F bonds adjacent to each other on carbon frameworks. Professor O'Hagan commented: "The synthesis of these molecules has proven challenging; however, this is rewarded by their analysis by X-ray crystallography and NMR spectroscopy, which allows us to explore their structures and conformation in significant detail." He continued, "We started with acyclic chains but were always attracted by the prospect of preparing a cyclohexane with a fluorine atom on each carbon; thus, we set out to synthesize at least one stereoisomer of 1,2,3,4,5,6-hexafluorocyclohexane." Representatives of the chloro and bromo family of such compounds have been known for many years.

In 1825 Michael Faraday of London prepared hexachlorocyclohexane as a mixture of stereoisomers, in a photochemical (sunlight) reaction of chlorine and benzene (*Ann. Chem. Phys.* **1825**, 274). In 1835 Eilhard Mitscherlich of Berlin generated hexabromocyclohexane, again as a mixture of stereoisomers (*Ann. Phys.* **1835**, 111, 370). This reaction used synthetic benzene produced from benzoic acid. Faraday's hexachlorocyclohexane was subsequently developed by ICI who introduced it as a global insecticide (Lindane) in 1942. However, Lindane was subsequently withdrawn due to its persistence in the ecosphere. Despite the early preparations of the bromo and chloro analogues, 1,2,3,4,5,6-hexafluorocyclohexane has remained rather obscure. The only claim of a preparatory report in the literature came from the Birmingham team of Colin Tatlow and Paul Coe in 1969, who suggested that a hexafluorocyclohexane had been formed from the reaction of benzene with  $\text{CoF}_3$ , although their characterization was tentative and a synthesis was unconfirmed (see the original paper *J. Chem. Soc. C* **1969**, 1060 for references).

"In our approach we revisited a procedure from 1980 by Arnold Zweig et al. (*J. Org. Chem.* **1980**, *45*, 3597), who reacted benzene with silver(II) fluoride to produce fluorobenzene," said Professor O'Hagan. "Two stereoisomers of 3,4,5,6-tetrafluorocyclohexene were produced as minor side products of this reaction, and these minors became the starting point for synthesizing a single stereoisomer of the hexafluorocyclohexane."



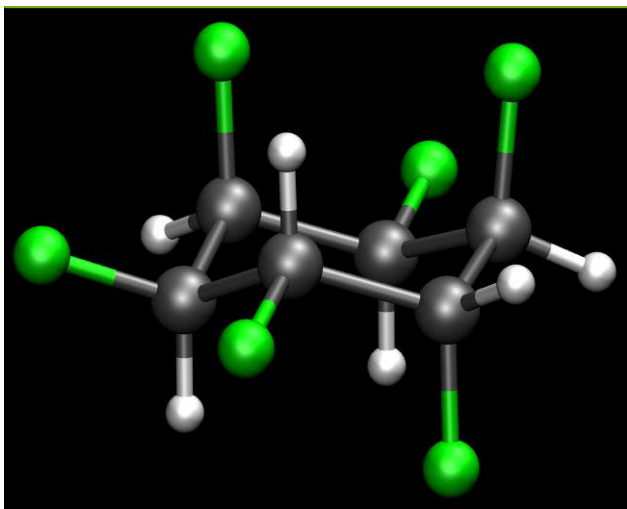


Figure 1 X-ray image of  $\eta$ -1,2,3,4,5,6-hexafluorocyclohexane

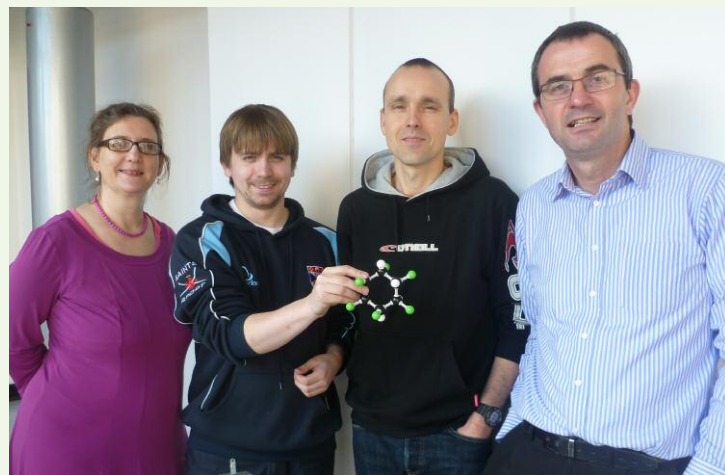
Alastair Durie, a final-year PhD student, repeated the reaction although purification was unsuccessful due to the volatile nature of the products. Therefore, the crude product was treated with potassium permanganate to give the tetrafluorocyclohexadiol as a mixture of isomers. These were cyclized with sulfuryl chloride to give the corresponding cyclic sulfates, from which a single stereoisomer was purified and the stereochemistry was established by Professor Alexandra Slawin using X-ray diffraction analysis. The cyclic sulfate was then ring-opened using Et<sub>3</sub>N:3HF at 120 °C to give the free pentafluoroalcohol and again the relative stereochemistry was established by X-ray diffraction analysis. The installation of the final fluorine was successfully achieved by treatment of the pentafluoroalcohol using Deoxofluor™ at 115 °C.

“The isomer produced was the  $\eta$ -hexafluorocyclohexane, and somewhat unexpectedly this compound was a crystalline solid,” explained Professor O’Hagan. The relative stereochemistry and solid-state conformation were shown by the X-ray structure analysis (Figure 1). “The molecule seems to be particularly polar because of the 1,3-diaxial C–F bonds on the cyclohexane framework,” said Professor O’Hagan. The room-temperature <sup>19</sup>F NMR spectrum of this compound was unusual and uninteresting, as it showed only three signals, two sharp and one very broad. However, when Dr. Tomas Lebl cooled the sample down to –80 °C, the spectrum resolved into six sharp signals as all the fluorines have a unique environment in the chair conformation, and ring interconversion is slowed down. The 1,3-diaxial fluorines show a large through-space <sup>19</sup>F–<sup>19</sup>F coupling constant in the NMR spectrum, consistent with the close proximity of these atoms across the top of the ring. “This study resulted in the first unambiguous synthesis

of a 1,2,3,4,5,6-hexafluorocyclohexane stereoisomer, and adds to the synthesis of the hexachlorocyclohexanes and hexabromocyclohexanes from Faraday and Mitscherlich, respectively,” said Professor O’Hagan. “Our challenge now is to develop methods to make this and related compounds in quantities where their properties and applications can be explored and developed.”

Matteo Zanda

### About the authors



From left to right: Prof. A. Slawin, A. Durie, Dr. T. Lebl, Prof. D. O’Hagan

**Alexandra Slawin** obtained her first degree in chemistry from Imperial College (UK) in 1983. She remained at Imperial until 1994 and then moved to Loughborough University (UK) where she initiated a single crystal lab facility. She moved to the University of St Andrews (UK) in 1999 where she is Head of the Molecular Structure Laboratory. Her research is primarily concerned with structure determination and its application to chemistry.

**Alastair Durie** was an undergraduate at St Andrews University obtaining a first class Masters in Chemistry (MChem) in 2009. He stayed at St Andrews to do a PhD with Professor O’Hagan, studying multivincinal fluorine substitution of cyclohexane rings. He is currently in his final year and will be writing his thesis soon.

**Tomas Lebl** did his first degree in chemistry from the University of Pardubice (Czech Republic) in 1995 and a PhD

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at University of Halle-Wittenberg (Germany) in 1999. After finishing his PhD he worked as a Lecturer at the University of Pardubice. His early career focused on using NMR spectroscopy to study structure and properties of organotin compounds. In 2004 he moved to the University of St Andrews where he runs the liquid state NMR facility.

**David O'Hagan** did his first degree in chemistry from the University of Glasgow (UK) in 1982 and a PhD at Southampton University (UK) in 1985. After a postdoctoral year at the Ohio State University (USA) he developed an interest in organofluorine chemistry while working as an academic at the University of Durham (UK) from 1986–2000. He moved to St Andrews University in 2000, where he is Head of Organic Chemistry, and leads a research group with broad interests in organofluorine chemistry.

## Young Career Focus: Dr. Olga García Mancheño (Westfälische Wilhelms-Universität Münster, Germany)

■ **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. Olga García Mancheño, Westfälische Wilhelms-Universität Münster, Germany.

### BIOGRAPHICAL SKETCH



Dr. O. García Mancheño

#### Olga García Mancheño

was born in 1976 in Cuenca, Spain. She graduated with a degree in chemistry from the Universidad Autónoma de Madrid (Spain) in 1999. She received her MSc (2001) and PhD (2005) in organic chemistry from

the same university under the supervision of Professor J. C. Carretero on the design of novel ferrocene ligands and their application in metal-catalyzed asymmetric reactions. During her PhD, she also carried out two three-month research stays with Professor M. T. Reetz (Max-Planck-Institut für Kohlenforschung, Germany) and Professor K. A. Jørgensen (University of Aarhus, Denmark). In September 2005, she joined the group of Professor C. Bolm at RWTH Aachen University (Germany) as a postdoctoral fellow working on iron-catalyzed nitrene transfer reactions and sulfoximine chemistry. Since October 2008 she is an independent junior group leader (Habilitation mentor: Professor F. Glorius) within the Department of Organic Chemistry at Westfälische Wilhelms-Universität Münster (Germany). Her main research interests include the development of new synthetic methods, with a special focus on catalytic approaches, and their application in the synthesis of bioactive compounds and heterocycles.

### INTERVIEW

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

**Dr. García Mancheño** | Our research is dedicated to the development, understanding and application of new synthetic methods to achieve new and more efficient organic transformations. More specifically, we are involved in both the development of mild and (enantio)selective C–H bond functionalizations for the formation of C–C and C–X bonds, with a special focus on C(sp<sup>3</sup>)–H bonds, and the development of novel non-covalent organocatalytic approaches for the synthesis of valuable small molecules.

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

**Dr. García Mancheño** | I suppose I have always been fascinated by science and chemical reactions. As a child, I enjoyed experimenting with children's chemistry kits and my interest continued throughout my schooling. When I started at university, my initial intention was to study biochemistry and genetics; however, this changed after taking the class in advanced organic chemistry given by Professor Carretero (who later became my PhD supervisor). During this time, I discovered the power of organic synthesis: designing, creating and rearranging molecules and exploiting the rich number of possible bond disconnections through organic reactions.

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

**Dr. García Mancheño** | Sometimes I have the feeling that method-development chemists are taking over the job of facing the incoming challenges in synthesis, from the identification of more sustainable processes to inventing innovative transformations. Who would have believed a decade ago that the classically considered unreactive C–H bonds could be efficiently used as functional groups to form new C–C and C–heteroatom bonds? This and many other modern transformations have started to change the way organic molecules are made; however, there are still some current synthetic problems to be solved such as efficiency, selectivity and sustainability.

**SYNFORM** | Your research group is active at the frontier of organic synthesis and catalysis. Could you tell us more about your research and its aims?

**Dr. García Mancheño** | In the last few years, we have introduced the use of TEMPO oxoammonium salts as mild and efficient oxidants for Fe- and Cu-catalyzed cross-dehydrogenative couplings (CDC). This was utilized for reactions with enolizable C-nucleophiles such as malonates,  $\beta$ -keto esters,  $\beta$ -nitro ketones and simple alkyl or  $\alpha,\beta$ -unsaturated aldehydes. Moreover, we have recently extended it to the oxidative coupling with olefins, leading to interesting heterocycles such as substituted quinolines and oxazines. These kinds of N–O oxidants have already shown a unique reactivity in some reactions compared to the classical oxidants used in dehydrogenative C(sp<sup>3</sup>)–H couplings. Therefore, we aim to further explore this chemistry towards more general and highly diastereo-/enantioselective oxidative C–C and C–X coupling reactions, as well as their application in the synthesis of other valuable compounds.

We are also involved in the development of catalytic asymmetric C–C bond-formation reactions towards the synthesis of a variety of important synthetic intermediates or bioactive five-, six-, seven- and eight-membered heterocycles by means

of non-covalent organocatalysis. Additionally, one of our programs focuses on the identification of highly efficient and easily accessible novel C–H bond based H-donor catalysts and their application in anion activation-type catalysis.

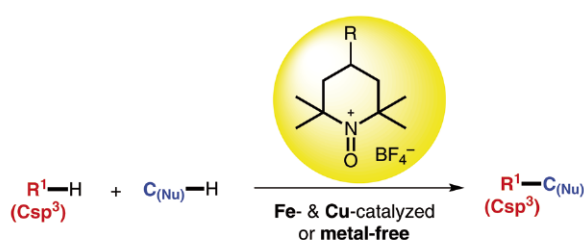
A recent goal of our lab is also the fusion of these two research lines to discover original enantioselective catalytic oxidative C–C coupling reactions.

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

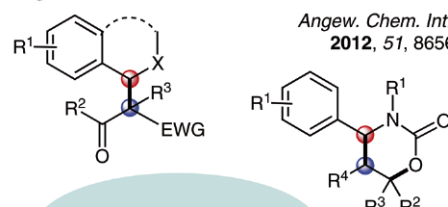
**Dr. García Mancheño** | My most important scientific achievement to date is the use of alternative, non-toxic and easy-to-handle oxidants for mild C–H bond functionalizations. Using this strategy, the synthesis of valuable bioactive heteroatom-containing compounds is much more divergent and straightforward from simple and accessible starting materials. However, this is only the beginning of a minefield of rich chemistry and, therefore, I think that our most important contribution in this area is still to be discovered: the day when selective and predictable C-H functionalizations are employed as efficient, universal tools for the synthesis of complex organic molecules. ■

Matteo Zanda

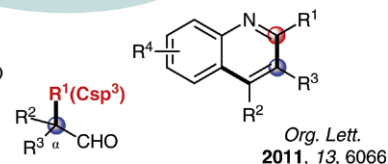
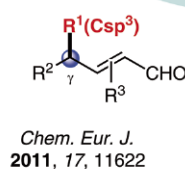
**A) C–H bond functionalizations**



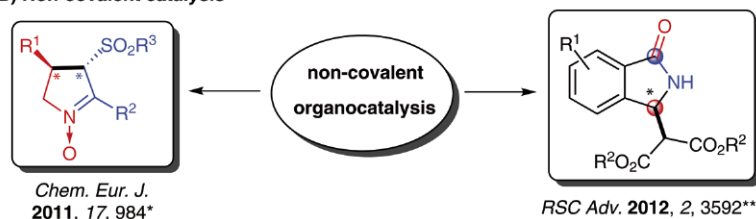
*Eur. J. Org. Chem.* **2010**, 4460



*Angew. Chem. Int. Ed.* **2012**, 51, 8656



**B) Non-covalent catalysis**



\* In collaboration with Dr. J. Alemán (Univ. Autónoma de Madrid, Spain)  
\*\* In collaboration with Dr. A. Massa (Univ. Salerno, Italy)

**Scheme 1** Recent synthetic methods developed in the García Mancheño lab



COMING SOON ►► COMING SOON ►►

# SYNFORM 2013/02

is available from  
January 18, 2013

In the next issues:

## SYNSTORIES ■ ■ ■ ■ ■

■ **Hypoiodous Acid Initiated Rearrangement of Tertiary Propargylic Alcohols to  $\alpha$ -Iodoenones**

(Focus on an article from the current literature)

■ **Synthesis of Highly Strained Terpenes by Non-Stop Tail-to-Head Polycyclization**

(Focus on an article from the current literature)

## FURTHER HIGHLIGHTS + + + +

## SYNTHESIS

**Review on: Self-Disproportionation of Enantiomers of Chiral, Non-Racemic Fluoroorganic Compounds: Role of Fluorine as Enabling Element**

(by V. A. Soloshonok et al.)

## SYNLETT

**Account on: From Commercial Enzymes to Biocatalysts Designed by Protein Engineering**

(by U. T. Bornscheuer)

## SYNFACTS

**Synfact of the Month in category "Polymer-Supported Synthesis": [Asymmetric 1,4-Addition with a Chiral Ca-Pybox Catalyst](#)**

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