

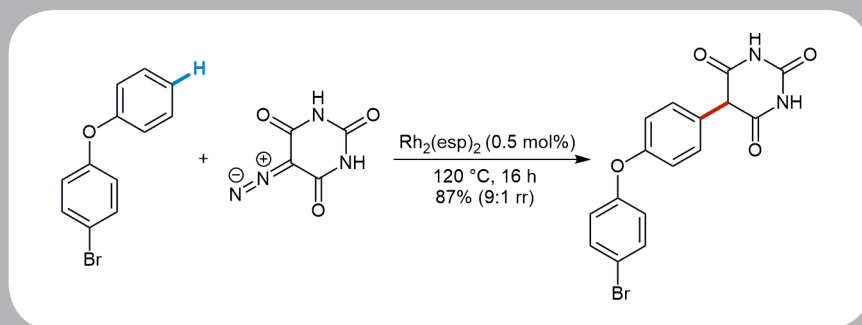
Synform

People, Trends and Views in Chemical Synthesis

2015/11

Direct Synthesis of 5-Arylbarbituric Acids by Rhodium(II)-Catalyzed Reactions of Arenes with Diazo Compounds

Highlighted article by D. Best, D. J. Burns, H. W. Lam



Contact

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Dear Readers,

Once again this Editorial comes at a very busy time, so that's me writing it during the "lunch break" (what I mean by that is swallowing a packet of oatcakes, a couple of cheese chunks and an apple while desperately typing on a keyboard, exactly what we are advised not to do by nutrition experts...) while keeping an eye on the watch because the next meeting is already looming. Tough life, isn't it? But it's still a lot of fun, as long as administration work remains a minor share and research continues to rule in my diary (hopefully the senior management won't read this Editorial, otherwise I might find myself flooded with administration from the next Monday...). Let's have a look at the content of this November 2015 issue of Synform then. A new YCF article opens the issue, featuring M. J. Fuchter (UK) who answers the usual 5 questions in a very exhaustive and entertaining manner (thanks Matthew!). The next SynStory covers a topic which is very close to my heart: the synthesis of barbiturates, a fascinating class of bio-active molecules with a long tradition in chemistry. These molecules look structurally simple, but believe me, their synthesis is not! So the new synthetic approach developed by H. W. Lam (UK) is more than welcome as it will make 5-aryl-barbiturates way more accessible. The third SynStory is absolutely fascinating and combines recent advances in synthetic methodology with intriguing aspects of the history of chemistry, expanding on a recent article published in SYNTHESIS by A. Giannis (Germany). I definitely urge you to read it! The issue is closed by a SynStory based on an interesting SYNLETT article, a contribution from the big pharma industry, presenting a new synthesis of functionalized cyclic imines developed by T. A. Moss (UK).

Lunch break is over, someone is knocking on my door...
Enjoy your reading!



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

Young Career Focus:

Dr. Matthew J. Fuchter (Imperial College London, UK)

Background and Purpose. From time to time SYNFORM meets 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 Young Career Focus presents Dr. Matthew J. Fuchter (Imperial College London, UK).

Biographical Sketch



Dr. M. J. Fuchter

Matthew Fuchter obtained his first class honors degree (MSci in Chemistry) from the University of Bristol (UK) in 2002, where he was awarded the Richard N. Dixon Prize as well as an undergraduate scholarship and several faculty commendations. In January 2006 he completed his PhD research entitled 'Synthetic Studies on Porphyrines: Biological Applications and New Preparative Methods' under the supervision of Professor Anthony G. M. Barrett, FRS FMedSci (Imperial College London, UK) and in close collaboration with Professor Brian Hoffman (Northwestern University, USA). Following a short spell as a Research Associate at Imperial College, Dr. Fuchter was appointed as a CSIRO Research Fellow at the Commonwealth Scientific and Industrial Research Organisation, Australia as well as a Visiting Fellow at the University of Melbourne (Australia), where he worked with Professor Andrew B. Holmes, AM FRS FAA FInstP. He briefly took up an independent Fellowship position in 2007 at the School of Pharmacy, University of London (UK), before being appointed as a Lecturer in Synthetic and Medicinal Chemistry at Imperial College London (UK) in July 2008. He was subsequently promoted to Senior Lecturer in July 2012, and Reader in September 2015. He is currently additionally the co-Director of the Imperial College MRes course in Drug Discovery, a Research Board member of the Imperial College Institute of Chemical Biology, an Associate Editor of the Royal Society of Chemistry (RSC) journal MedChemComm and an Appointed Member of the RSC Organic Division Council. In 2014 he was awarded the Royal Society of Chemistry's Harrison-Meldola Memorial Prize, as well as being admitted to the RSC as a Fellow. In 2015, he was selected as a Thieme Chemistry Journal Awardee by the Editorial Boards of the

Thieme Chemistry journals and received a Diploma for being the 'most meritorious runner-up' of the European Federation for Medicinal Chemistry (EFMC) Prize for a Young Medicinal Chemist in Academia (2015). The Fuchter group has a wide-ranging track record in the design, synthesis and application of organic molecules in chemistry, medicine and materials.

INTERVIEW

SYNFORM What is the focus of your current research activity?

Dr. M. J. Fuchter Broadly speaking, research in my group aims to use expertise in chemical synthesis to impact molecular science in chemistry, biology and materials. This means that while we are interested in the development and/or application of state-of-the-art organic synthetic procedures and strategies, our efforts in these areas are aligned to multidisciplinary and collaborative projects. Representative examples of research projects include the design and development of novel bioactive probes to be used in chemical biological and medicinal chemistry programs, and the design and development of novel chiral semiconducting molecules for application to unique organic electronic devices.

SYNFORM When did you get interested in synthesis?

Dr. M. J. Fuchter During my undergraduate degree in chemistry, the problem solving and creative nature of organic synthesis captivated me. The ability to design brand new molecules, even using only a basic understanding of molecular reactivity, seemed very powerful to me, and still does! I continue to be inspired by the fact that synthesis can deliver a wealth of fascinating molecular materials, which create vast opportunities for science and for society.

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

Dr. M. J. Fuchter Organic synthesis continues to deliver a whole range of wide-value products including pharmaceuticals, agrochemicals, plastics and organic electronics. The value of organic synthesis to society is therefore undeniable. Personally, I am really interested in how to design organic molecules to perform specific and unique tasks, from perturbing protein function, to modulating light signals, to conducting charge: to control molecular function via smart design. For many years, organic chemistry was concerned with the development and application of organic synthesis to better understand molecular structure. Now that we have a very good understanding of molecular structure, I think it is the turn of molecular function. Others have advocated such an idea too (for example: G. M. Whitesides, J. Deutch *Nature* **2011**, 469, 21). For me, such studies involve collaborative efforts with other scientists in physics, materials, biology and medicine. I truly believe that the ‘molecular vision’ of chemists is rather unique and so chemists can provide strong leadership in such collaborative multidisciplinary projects.

SYNFORM Your research group is active in the areas of organic synthesis, medicinal chemistry and organic materials. Could you tell us more about your research and its aims?

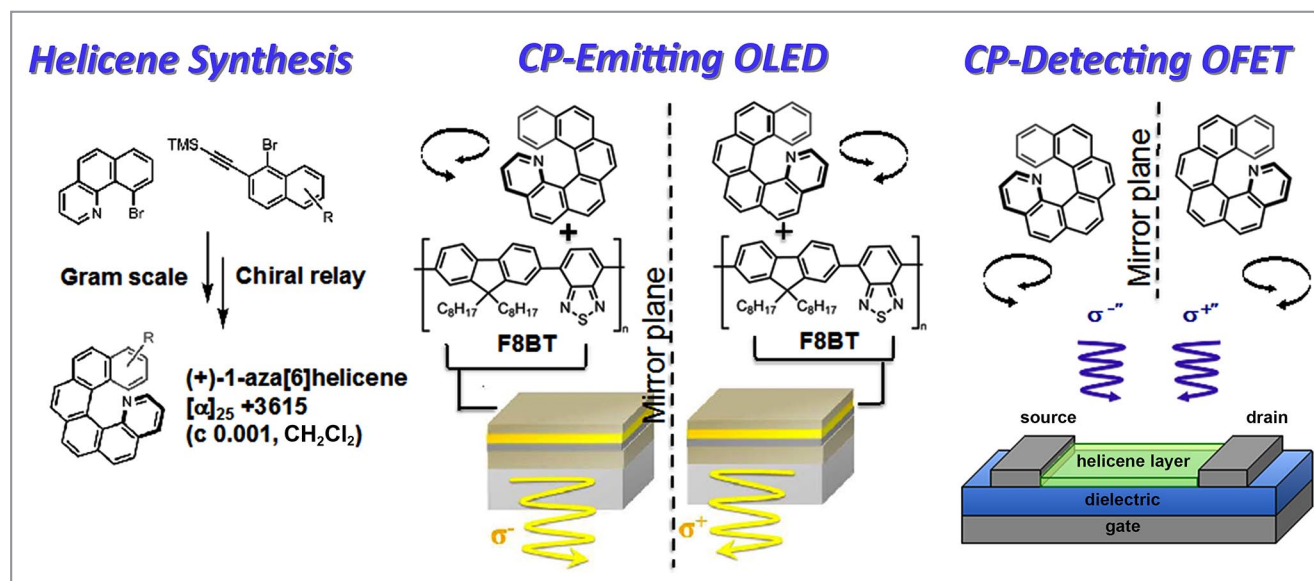
Dr. M. J. Fuchter I would like to highlight two representative areas in which my group is active. It is worth noting, though, that enabling synthetic organic chemistry underpins

all the ongoing research in the group, from natural product (semi-synthesis) to asymmetric methods to construct helically chiral aromatics. In many cases, this results in published outputs focused on synthetic methodology development (although not highlighted here).

1) Stereochemistry in chemistry, materials and devices.

Chirality is a fundamental symmetry property of elemental particles, molecules or even macroscopic objects like human hands. Chirality is a significant theme in the group and we have published novel synthetic methods to control/install a number of forms of molecular chirality including point (*Org. Biomol. Chem.* **2012**, 10, 512), axial (*Synlett* **2013**, 24, 2365; invited submission for the *EuChemS Young Investigators Workshop Special Issue*) and helical (*Org. Lett.* **2013**, 15, 1706) chirality. Such methods give us unique access to interesting chiral small molecules and polymers, which we explore in a range of applications in materials science.

A representative application area for our chiral materials is in the development of unprecedented chiroptical organic electronic devices. Circularly polarized (CP) light is central to a large range of current and future display and photonic technologies, including highly efficient LCD backlights, optical quantum information processing and communication, and optical spintronics. There is therefore high interest in constructing CP-light-emitting devices, however to date, no highly efficient and broadly applicable methods for fabricating such devices have been reported. In collaboration with Dr. Alasdair Campbell (Physics, Imperial) we were the first to



use a chiral small molecule dopant (in this case an enantiopure azahelicene) to induce solid-state circularly polarized (CP) electroluminescence from a conjugated polymer (*Adv. Mater.* **2013**, *25*, 2624). Simple blending of 1-aza[6]helicene or [7]-helicene, with a conventional (achiral) light-emitting polymer (F8BT), led to morphologically distinct thin films whose photoluminescent (PL) and electroluminescent (EL) emission was observed to become significantly circularly polarized. The sign of the CP emission was directly determined by the enantiomer of the helicene dopant, and the magnitude of the response competitive with, or better than, the state of the art. This highly translational approach allowed the fabrication of organic light-emitting diodes that directly emit CP light – a high-interest area for the preparation of energy-efficient displays.

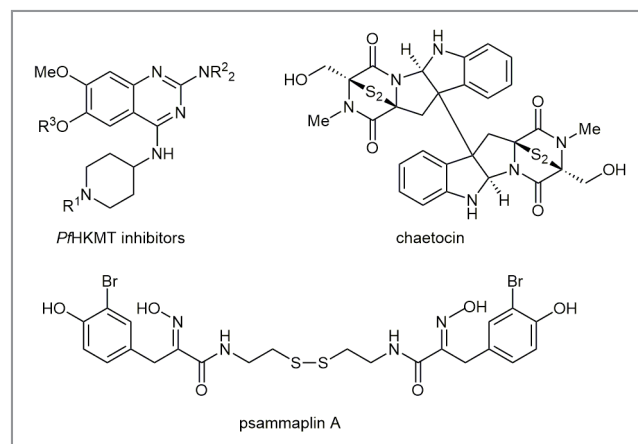
To develop CP-based technologies to their full potential would require the realization of miniature, integrated devices that are capable of detecting the chirality of CP light. Organic field-effect transistors (OFETs), in which the active semiconducting layer is an organic material, allow the simple fabrication of ultrathin, compact devices. Also together with Dr. Campbell, we have recently shown, for the first time, that OFET based on enantiomerically pure 1-aza[6]helicene can detect and differentiate CP light, acting as a CP-electrical switch (*Nature Photon.* **2013**, *7*, 634). OFETs with a semiconductor layer of helicene were solution-processible, leading to a self-organized crystalline morphology, and have well-behaved device characteristics. Critically, a highly specific and reversible photo-response to CP light was observed, which is directly related to the enantiomer of the helicene molecule. We believe this proof-of-concept device opens up a unique possibility for CP-light sensing in highly integrated photonic technologies. For example, patterning techniques available for solution-processible organic semiconductors, such as high-resolution ink-jet printing, should allow the creation of arrays of micrometer-scale CP-light-sensitive devices, as well as integration with CMOS electronics.

Aside from our interest in helicenes and related compounds, we have an active interest in stereochemical determination, particularly for natural products. Indeed, emerging from our natural product chemical biology studies on chaetocin (see below), we used state-of-the-art chiroptical methods to unambiguously establish the stereochemistry of 3,6-epidithio-diketopiperazine (ETP) desulfurization. This has led to stereochemical reassignment of the desulfurized natural product dehydrogliotoxin (*Chem. Eur. J.* **2011**, *17*, 11868) as well as a unified mechanism for the stereochemical course of this

reaction for all chiral ETP compounds (*J. Org. Chem.* **2013**, *78*, 11646).

2) The medicinal chemistry and chemical biological study of epigenetic processes in disease.

'Epigenetic' describes the heritable changes in gene expression that occur without changes in DNA sequence. Epigenetic processes underpin fundamental physiology and are implicated in the aetiology of many diseases, particularly cancer. As such, epigenetics is an exponentially growing and exciting area of interest for scientific study. Through hypothesis-driven medicinal chemistry, my group has made significant progress in the discovery of unique and unprecedented small-molecule inhibitors of epigenetic enzymes; published outputs include highly ligand-efficient HDAC inhibitors (*ChemMedChem* **2013**, *8*, 149), highly isoform-selective SIRT inhibitors (*MedChemComm* **2012**, *3*, 373; *ChemMedChem* **2015**, *10*, 69), quinazoline dual EZH2/EHMT2 HKMT inhibitors (*Clin. Epigenetics*, in press) and quinoline EHMT1/2 inhibitors (*MedChemComm* **2014**, *5*, 1821; invited submission to a special epigenetics edition).



Working closely with expert collaborators, we have used these molecules to provide novel opportunities in therapy. Perhaps the best example of this is our work targeting epigenetic pathways in malaria. This work is in collaboration with Professor Artur Scherf (Pasteur Institute, Paris, France), a leader in parasite epigenetics. Together we were the first to discover *Plasmodium* histone methyltransferase (*Pf*HKMT) inhibitors that result in blood-stage independent parasite killing (*Proc. Natl. Acad. Sci. USA* **2012**, *109*, 16708; *ChemMedChem* **2014**, *9*, 2360; *Antimicrob. Agents Chemother.* **2015**, *59*, 950). We also discovered that our inhibitors have the unprecedented ability to 'reawaken' dormant liver-stage parasites (*Nature Med.*

2014, 20, 307). Dormant and largely drug-resistant *Plasmodium* parasites (in *P. vivax*) cause recurrent malaria and are a significant and largely untreatable clinical problem; this drug-induced 'awakening' approach holds much hope for tackling such a limitation and therefore provides a potential new therapeutic option for this disease.

My group has also used enabling synthetic medicinal chemistry and biochemistry to unambiguously determine the mechanism of action of several epigenetically active natural products, including the fungal metabolite chaetocin (*Nature Chem. Biol.* **2013**, 9, 136; *J. Med. Chem.* **2013**, 56, 8616) and the marine natural product psammaphin A (*J. Med. Chem.* **2012**, 55, 1731). Based on this work, we were invited to publish a critical perspective (*Nat. Prod. Rep.* **2013**, 30, 605, cover article), which covers some of the challenges in this area.

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

Dr. M. J. Fuchter Given that I am at the earlier stage of my career, I hope there will be significant achievements to come. This is especially true in the area of medicinal chemistry: while many of our medicinal chemistry efforts are at an early stage, I hope one day at least one project will reach a stage where a clear benefit to patients is recognized. Perhaps the area I am currently most proud of is our work on chiral organic materials for organic devices highlighted above (*Nature Photon.* **2013**, 7, 634; *Adv. Mater.* **2013**, 25, 2624). For me, this project has a nice blend of fundamental and applied science, and is a technology reliant on a key enabling organic material. Furthermore, the organic material in question – a helicene – is a challenging synthetic target and so it is a project area where innovation in synthesis is a requirement for success!



Direct Synthesis of 5-Arylbarbituric Acids by Rhodium(II)-Catalyzed Reactions of Arenes with Diazo Compounds

Angew. Chem. Int. Ed. **2015**, *54*, 7410–7413

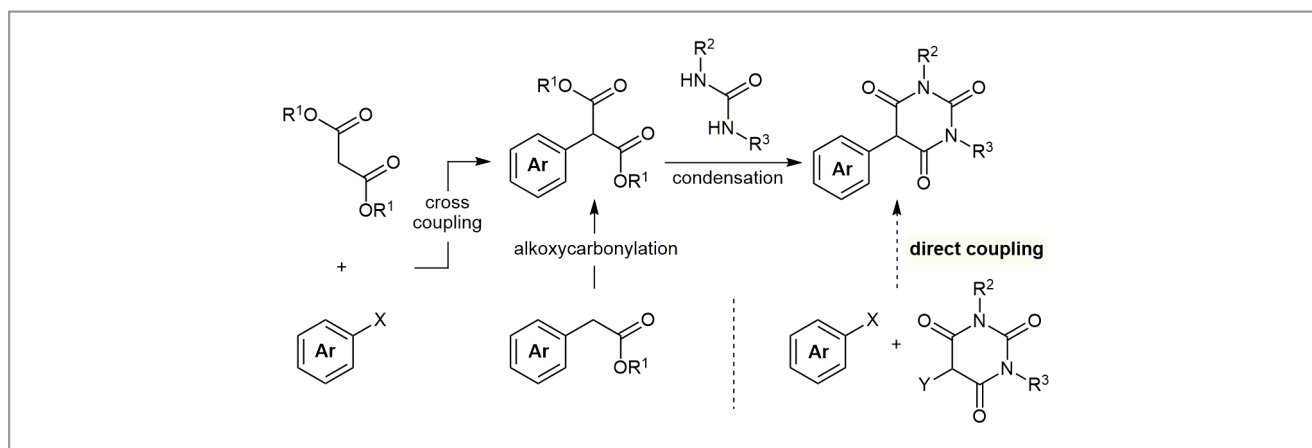
Barbiturates are central nervous system (CNS) depressants having a well-known sedative, hypnotic and anxiolytic effect. First synthesized in 1864 by Adolph von Bayer, barbiturates have been used as sedatives and anticonvulsants since the discovery of the pharmacological properties of barbital by Emil Fischer in 1903. More recently, 5-arylbarbituric acids have found use in cancer treatment and in *in vivo* imaging as matrix metalloproteinase (MMP) inhibitors. The synthesis of barbituric acids essentially relies on the base-promoted condensation of urea with substituted malonate esters, which is highly moisture-sensitive and generally suffers from low yields. Recently, the group of Professor Hon Wai Lam at the University of Nottingham (UK) has developed a conceptually novel approach to the barbiturate ring.

The use of cyclic 1,3-dicarbonyls, including barbituric acids, as directing groups for C(sp²)-H functionalization reactions has been an ongoing area of interest within Professor Lam's group.¹ Professor Lam's team said: "We recently discovered a new mode of oxidative annulation of certain 1,3-enynes with 5-arylbarbituric acids,^{1f} and with a view to investigating the scope of this reaction, a library of variously substituted 5-arylbarbituric acids was required." They continued: "Given their long history, we assumed that the straightforward synthesis of 5-arylbarbituric acid libraries would be a solved problem, but as we dug deeper into the literature, it soon became ap-

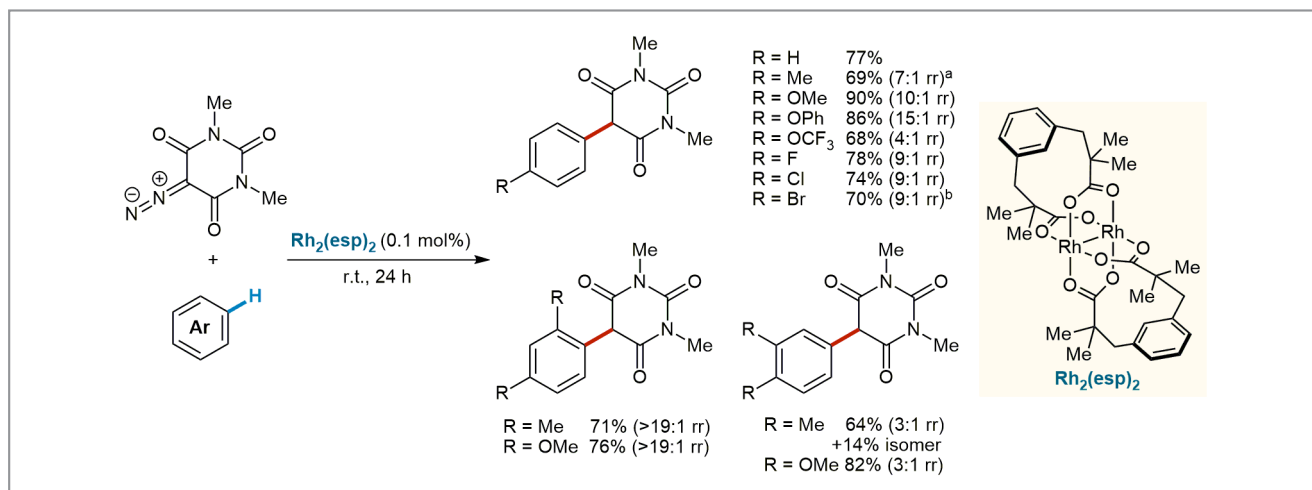
parent that this was not the case. 5-Arylbarbituric acids are conventionally prepared by the condensation of ureas with 2-arylmalonates (Scheme 1), and application of this strategy would therefore require the preparation of various 2-arylmalonates."

This strategy was explored briefly, but a number of problems were encountered. "During the attempted condensation of ureas with 2-arylmalonates bearing electron-withdrawing groups on the arene, undesired decarboxylation occurred," the team explained, continuing: "Furthermore, modern cross-coupling methods for 2-arylmalonate preparation were somewhat unreliable in our hands." A classical approach to these compounds is α -alkoxycarbonylation of 2-arylacetates, but very few 2-arylacetates are commercially available. Finally, the length and early-stage divergence of these sequences were unappealing. A more convenient strategy involving the late-stage formation of the arene–barbituric acid linkage was therefore sought.

Professor Lam's team said: "Unable to extend existing Pd- or Cu-catalyzed haloarene-malonate coupling methods to barbituric acids, we turned to α -diazodicarbonyl chemistry. The direct coupling between α -diazodicarbonyls and arenes is not so common, and the chemistry of 5-diazobarbituric acids has scarcely been explored." While the precedented Friedel–Crafts-type reactivity of α -diazocarbonyl-derived Rh(II)-car-



Scheme 1 Existing approaches to 5-arylbarbituric acids and preferable direct coupling



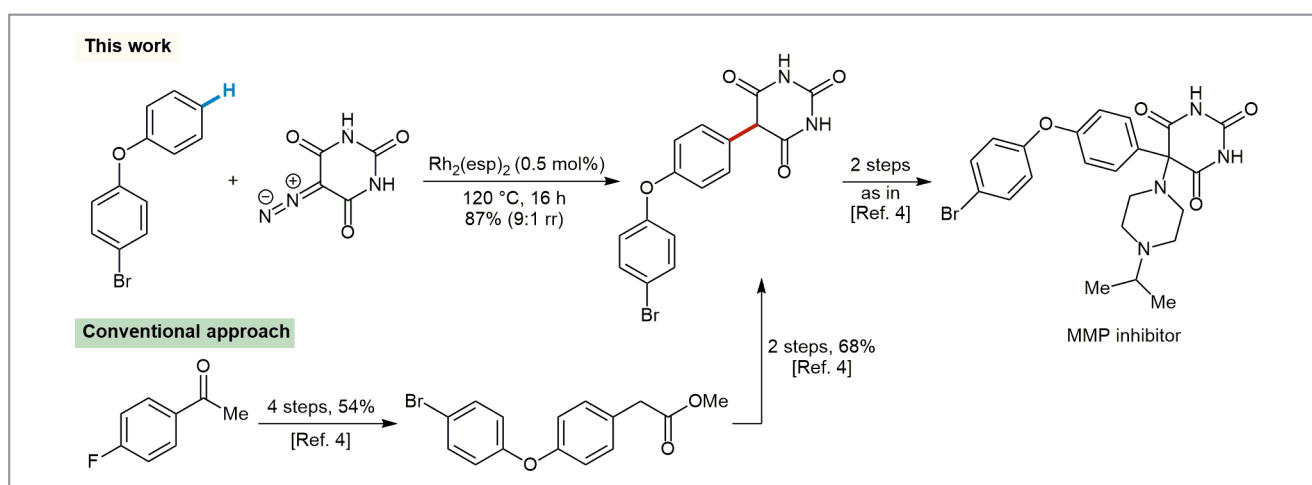
Scheme 2 Reactions of arenes with 5-diazo-1,3-dimethylbarbituric acid; rr = regioisomeric ratio of the crude reaction mixture, and products were isolated as a mixture in the same ratio after chromatography. ^a Isolated as a single regioisomer. ^b Isolated as a 10:1 mixture of regioisomers.

benoids towards arenes was encouraging for Professor Lam and his co-workers,² at the outset of their studies the only reported reactions of 5-diazobarbituric acids in this context were cyclopropanations of styrenes conducted in fluorobenzene, *with no indication of reaction with the solvent*.³

“Fortunately, we discovered that commercially available $\text{Rh}_2(\text{esp})_2$ efficiently catalyzed the direct arylation of 5-diazobarbituric acids with a variety of arenes, and, in the case of 5-diazo-1,3-dimethylbarbituric acid, did so at low catalyst loading (0.1 mol%) at room temperature (Scheme 2),” remarked Professor Lam’s team. “The scope of the reaction

is fairly broad; this type of transformation is usually limited to electron-rich (hetero)arenes, but in our case, moderately deactivating *o/p*-directors (Cl, Br, OCF_3) on the arene were also tolerated.”

Mindful of the fact that very few 1,3-dialkylated barbiturates exhibit potent biological activity, Professor Lam’s group next examined the use of 5-diazobarbituric acids bearing free N–H groups. Fortunately, elevated temperatures and increased catalyst loadings did indeed permit access to medicinally important 5-arylbarbituric acids, without complications of N–H insertion. They said: “For example, 5-[4-(4-bromophenoxy)]



Scheme 3 Direct arylation of 5-diazobarbituric acid in the synthesis of an MMP inhibitor, compared with the conventional approach

phenylbarbituric acid, previously prepared in 37% yield over six steps (Scheme 3, bottom),⁴ was easily prepared using our methodology (Scheme 3, top). The synthesis of a potent MMP inhibitor in only four steps from barbituric acid (vs eight steps from 4-fluoroacetophenone)⁴ exemplifies the advantages of our strategy.”

In summary, what began as a seemingly straightforward exercise in substrate synthesis ended up revealing a long-standing, unsolved problem in medicinal chemistry. “In response, we developed a more direct approach to 5-arylbarbituric acids that is much more convenient for library synthesis than traditional strategies,” said Professor Lam’s team. “The 5-diazobarbituric acids used are all bench-stable solids, all of the arylation reactions were performed under air atmosphere, and all reagents were used as received from commercial suppliers. This method has enabled us to explore a new mode of 1,3-enyne annulation via C(sp²)-H functionalization,^{1f} and we hope that it will find other applications (e.g., in medicinal chemistry) as well,” they concluded.

Mattes Fank

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About the authors



Dr. D. Best

Daniel Best received an M.Chem. degree from the University of Oxford (UK) in 2007, undertaking his final-year research in the laboratory of Professor George W. J. Fleet. Daniel remained in the Fleet group to conduct a D.Phil. degree, which he received in 2011. In January 2011, he moved to the University of Edinburgh (UK) to undertake postdoctoral research in enantioselective catalysis and C–H functionalization in the Lam group, and moved to the University of Nottingham (UK) with the same group in October 2013. Daniel took up a postdoctoral position at the Université de Rennes 1 (France) in January 2015 where he is currently investigating the design and synthesis of highly cytotoxic, natural-product-inspired enediyne warheads for antibody–drug conjugates.



Dr. D. Burns

David Burns was born in Newtownards (Northern Ireland, UK) in 1986. He studied for a Master’s degree at the University of Edinburgh (UK) and following the completion of his studies (2009), he moved to the University of York (UK) for his doctoral studies. David’s Ph.D. thesis was on the total synthesis of samaderine C and related quasinoinal analogues, and was completed jointly within the groups of Professors Richard Taylor and Peter O’Brien. After obtaining his doctorate in 2013, David began working in the Lam group as a postdoctoral fellow, focusing on the catalytic C–H functionalization of small molecules. His most recent work has been concerned with the development of novel processes involving catalytic 1,4-Rh(III) migration.

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Prof. H. W. Lam

Hon Wai Lam received an M.Chem. degree in chemistry from the University of Oxford (UK) in 1998. He then moved to the University of Nottingham (UK) to carry out his Ph.D. under the direction of Professor Gerald Pattenden. In January 2002, he moved to Harvard University (USA) as a GSK Postdoctoral Fellow to work with Professor David A. Evans. In October 2003, he joined the School of Chemistry at the University of Edinburgh (UK) where he became a Reader in Organic Chemistry. In October 2013, Hon took up the GSK Chair of Sustainable Chemistry at the University of Nottingham (UK). His group's research interests are based around the development of new synthetic methodology, including enantioselective catalysis and C–H functionalization chemistry.

The Mistake in Carl Bosch's PhD Thesis: A Contribution to 'Retro-Chemistry'

Synthesis **2015**, 47, 1887–1892

"It's starting to spit!" exclaimed Fritz Haber one afternoon in the laboratory of Physical Chemistry at the University of Karlsruhe sometime in the middle of the year 1909. He was greatly excited, realizing his achievement to synthesize ammonia from its elements nitrogen and hydrogen for the very first time! "This was a moment of glory not only for Haber but also for mankind and human history," acknowledged Professor Athanassios Giannis from the University of Leipzig (Germany).

The credit for the industrial production of ammonia (more than 100 megatons per year) belongs, however, to Carl Bosch (Figure 1), an expert in high-pressure technology, and Alwin Mittasch, an expert in catalyst development, both working at BASF (Germany). F. Haber and C. Bosch were each awarded the Nobel Prize in Chemistry, in 1918 and 1931, respectively. "It is estimated that the number of humans supported per hectare of arable land has increased from 1.9 to 4.3 persons between 1908 and 2008,¹ which was made possible mainly because of Haber-Bosch ammonia production," said Professor Giannis, who added: "It is calculated that every second nitrogen atom

in our body stems from the Haber-Bosch process! It is also estimated that 40% of the world's population at the end of the twentieth century was dependent on fertilizer inputs to produce food. Nitrogen fertilizers were responsible for feeding 44% of the world's population in 2008. That means the lives of about half of the human race are made possible by the Haber-Bosch process!! 'Bread out of air' is a German term used to describe these facts."

Ammonia is used not only for the production of fertilizers but also for the synthesis of drugs, dyes, fibres and a lot more. "Unfortunately, there is a dark side to ammonia: it is used in the production of explosives. The Haber-Bosch process is directly linked to about 150 million deaths in the last century," said Professor Giannis.

During the years 1998–2002 Athanassios Giannis was Professor of Organic Chemistry at the University of Karlsruhe (Germany). About that period, he recalled: "I had the opportunity every day to see the (in the meantime roasted) high-pressure steel reactor for the production of ammonia via the



Figure 1 Carl Bosch (1874–1940)

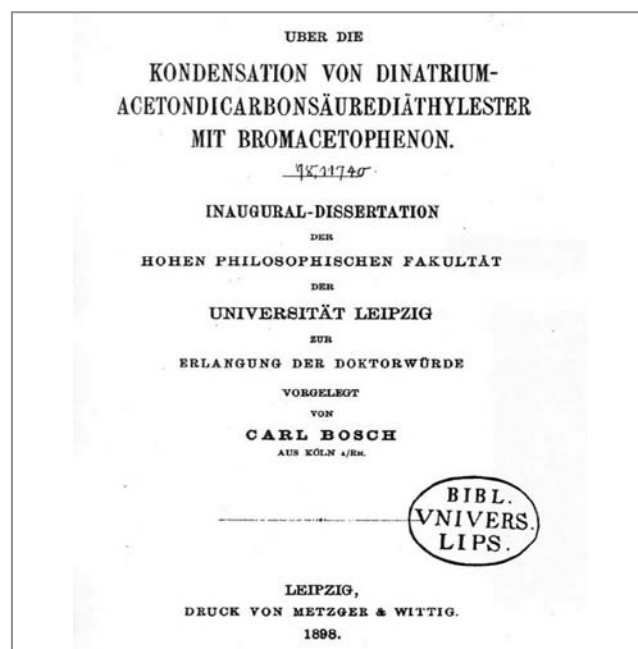


Figure 2 First page of Bosch's PhD work

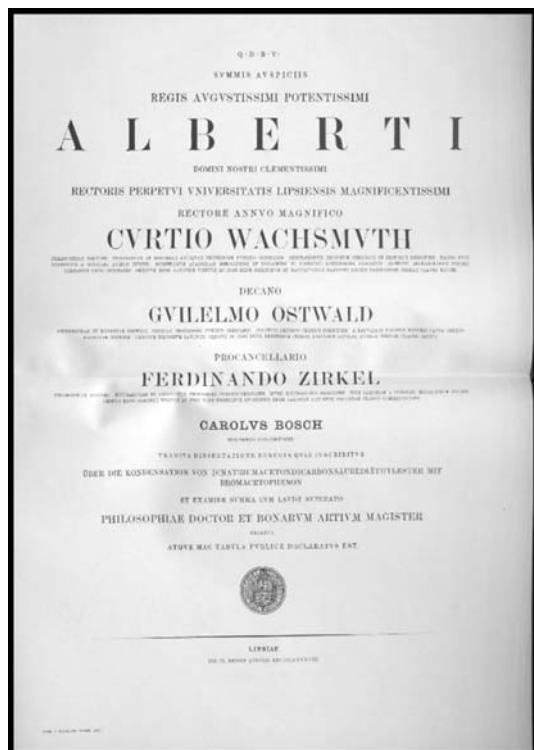


Figure 3 PhD certificate of Carl Bosch (1898)

Haber process, displayed at the beginning of the Fritz-Haber-Weg on the university campus. By a curious quirk of fate, I moved to the University of Leipzig (Germany) in 2002, where Carl Bosch had performed his PhD work under the supervision of Johannes Wislicenus.” He continued: “Last year I had a discussion with my colleague Professor Lothar Beyer, a retired Professor of Inorganic Chemistry who is deeply interested in historical aspects of the University of Leipzig. He is presently preparing the second volume of the book “Vom Doktoranden zum bedeutenden Chemiker”, Passage Verlag Leipzig, with Dr. Lothar Hennig, and in this context they asked me to help with the re-evaluation of Carl Bosch’s PhD work.”

In his thesis entitled “Über die Kondensation von Di-natriumacetoncarbonsäurediethylester mit Bromacetophenon” (undertaken in Leipzig between 1896–1898, Figures 2 and 3), Bosch envisaged the synthesis of a derivative of heptamethylene (a cycloheptane derivative). These efforts were related to the work of F. S. Kipping and W. H. Perkin,² but the young student realized that the reaction did not yield the expected product. In fact he isolated a derivative having the formula $C_{25}H_{24}O_6$ and proposed three different structures **1–3** with a preference for **2** (Figure 5). Professor Giannis said: “I was glad to meet Toni Smeilus, a smart undergraduate student who was very enthusiastic to participate in these studies. He performed the reaction and from the yellow-colored mixture (Figure 4) he isolated a main product.” Professor Giannis continued: “Subsequently, and using modern analytical methods (high-resolution mass spectrometry, NMR) as well as X-ray

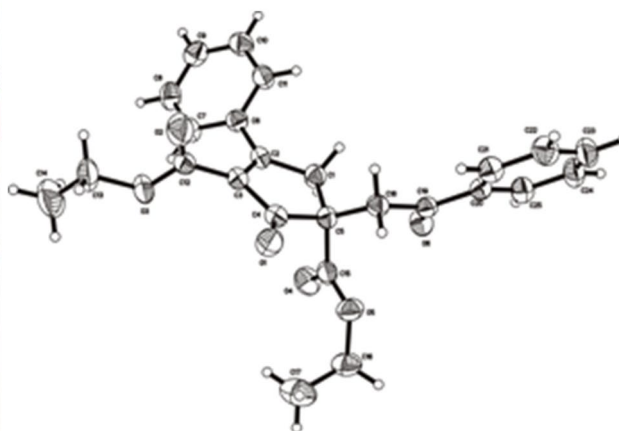


Figure 4 Reaction mixture according to the original procedure, and X-ray crystal structure of compound **4**

crystal-structure analysis (Figure 4) we were able to identify the structure of Bosch's product: It was the highly functionalized cyclopentenone with structural formula **4** (Figure 5). This reaction is generally applicable and further similar cyclopentenone derivatives were synthesized. From the mixture of the original reaction, traces of derivative **5** (mixture of isomers) were also isolated."

This method enables access to highly functionalized cyclopentenone derivatives, which occur in several bioactive natural products, as for example, in cyanthiwigin diterpenoids, aflatoxins, manamenones, cantabrenoates, or in other anti-proliferative agents like rocaglamide and silvestrol. Finally, a merger of Hünlich base³ and Bosch product **4** was successfully performed to obtain derivative **6**. Professor Giannis remarked: "By the way, Hünlich was also a PhD student at our university about 100 years ago."

Professor Giannis said: "In summary, Bosch made a mistake concerning the structure of his derivative. However, he did not have the analytical tools we now routinely use. Using these tools we were able to elucidate the structure of the unknown derivative and simultaneously open the way for the synthesis of compounds containing a highly functionalized

cyclopentenone moiety. Bosch's mistake, combined with our curiosity, disclosed new organic compounds that can serve the organic chemist working in the area of natural product synthesis."

The syntheses in this work were performed by Toni Smeilus, with NMR studies by Dr. Hennig. Professor Sieler was responsible for the X-ray crystal-structure analysis and Professor Beyer rediscovered Bosch's PhD work. Professor Giannis concluded: "I only had the pleasure to wait in my office for the nice and exciting results!"

Andreas Frenkel

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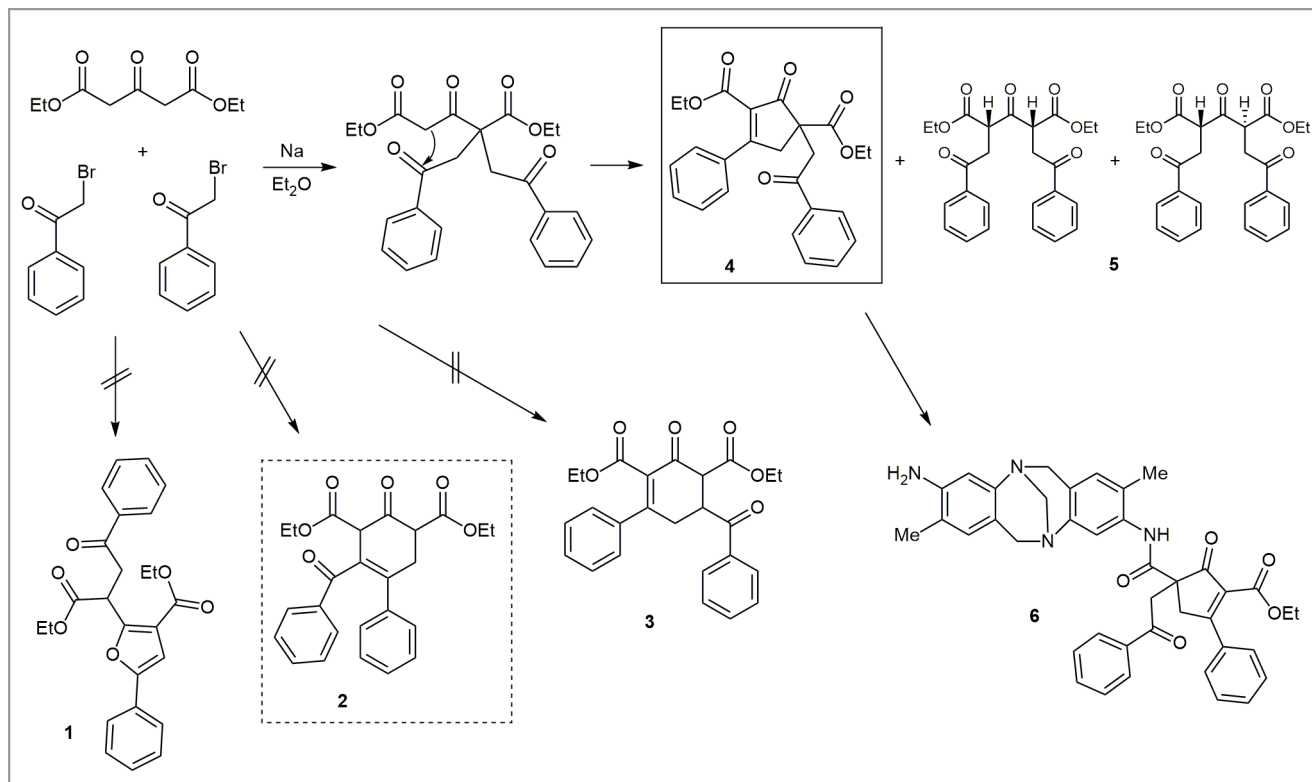


Figure 5 For details see text

About the authors



From left to right: Prof. L. Beyer, Dr. L. Hennig, Prof. J. Sieler, Prof. A. Giannis, T. Smeilus

Lothar Beyer is Professor Emeritus of Inorganic Chemistry at the University of Leipzig (Germany). He was born in 1936 in Oberwiesenthal (Germany), studied chemistry and obtained his PhD in 1965 under the supervision of Eberhard Hoyer at the University of Leipzig. He was Visiting Professor at the Chemistry Department of the University Montevideo (Uruguay) from 1970–1972 and Professor of Chemistry at the Technical University of Leipzig from 1982–1993. He was appointed as a C4-Professor at the University of Leipzig in 1993 and became Director of the Institute of Inorganic Chemistry. His research is focused on coordination and bioinorganic chemistry with sulfur ligands, the history of chemistry and the relations between chemistry and art. He has published several textbooks in inorganic chemistry and various books about the history of chemistry. He received Doctor honoris causa of the San Marcos University Lima (Perú) in 2000.

Lothar Hennig was born in Eilenburg (Germany) in 1953 and obtained his PhD in 1981 at the University of Leipzig. Since 1992 he has been the Laboratory Head of Spectroscopy within the Institute of Organic Chemistry. The main topic of his work is the structure determination of organic compounds, especially by NMR methods. He is author and co-author of more than 160 papers and collaborates with numerous national and international institutions.

Joachim Sieler was born in Markranstädt (Germany) and obtained his PhD at the University of Leipzig in 1966. He established X-ray crystal-structure analysis at the Faculty of Chemistry and is author and co-author of 216 papers in the field of solid-state and structural chemistry.

Toni Smeilus was born in Leipzig (Germany) in 1990. He received his Bachelor of Science in chemistry from the University of Leipzig in 2013 and is currently performing research under the supervision of Professor A. Giannis at the same university as a postgraduate student. His research concerns, among other topics, the synthesis of C-nor-D-homosteroids.

Athanassios Giannis is a chemist and physician. He was born in Greece in 1954 and studied chemistry from 1972–1980 and medicine from 1978–1987 at the University of Bonn (Germany). He completed his PhD in 1986 with Konrad Sandhoff and habilitated in 1992 at the University of Bonn in organic chemistry and biochemistry. From 1998–2002 he was Full Professor of Organic Chemistry and Natural Products Chemistry at the University of Karlsruhe (Germany). Since 2002 he has been a Full Professor of Organic Chemistry and Natural Products Chemistry at the University of Leipzig. His area of research is biological- and medicinal-oriented organic chemistry.

Expedient Synthesis of Highly Functionalized Cyclic Imines

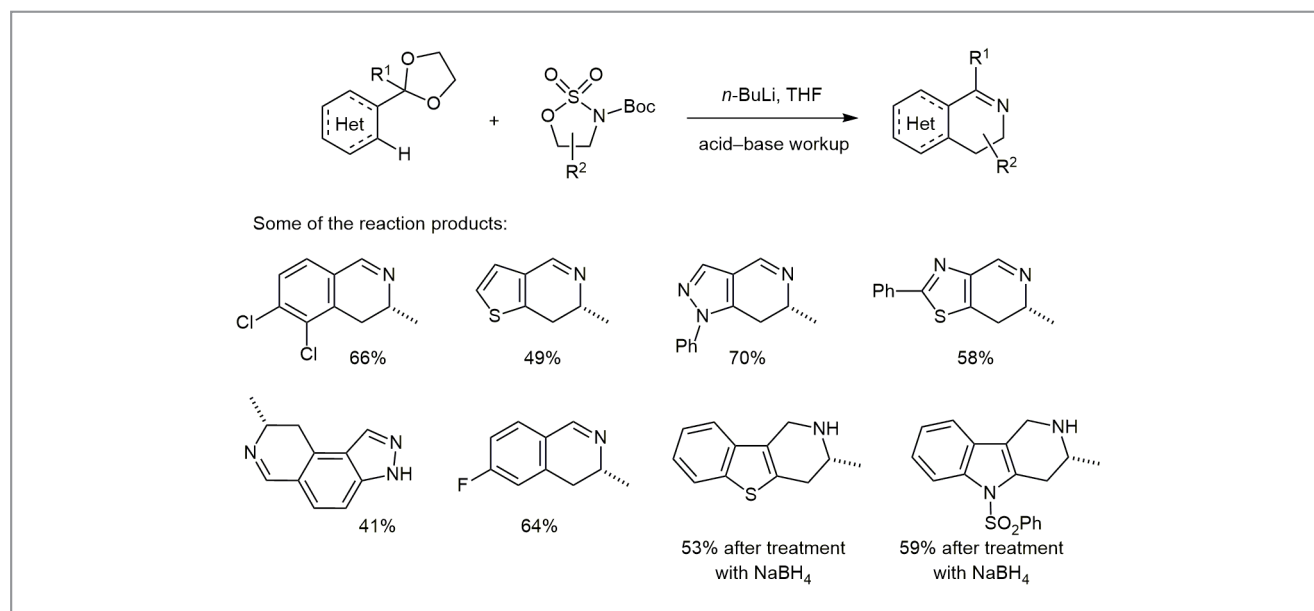
Synlett 2015, 26, 1375–1378

Cyclic imines are very important building blocks in organic chemistry, and this is particularly true for cyclic imines fused with aromatic rings. Although a number of methods are available for accessing these scaffolds, most of them are affected by significant weaknesses including low regiochemical control, substrate limitations, and harsh reaction conditions. For these reasons, the development of straightforward and efficient methods for preparing cyclic imines incorporating aromatic rings remains an active area of research in organic synthesis. Recently, Dr. Thomas A. Moss from AstraZeneca Mereside (UK) reported a new efficient route for producing highly functionalized cyclic imines.

Dr. Moss said: “Since moving to AstraZeneca, the synthesis of novel, partially saturated fragments has been of particular interest to me. The pharmaceutical industry has really begun to consider the potential benefits of ring saturation, which is becoming increasingly important as we attempt to drug more and more challenging targets.” The main challenge – according to Dr. Moss – is to develop robust methodologies which can tolerate the wide array of heterocycles that commonly appear in drug molecules. “Fortunately, AstraZeneca encourages its chemists to find new and innovative solutions to synthetic problems, which then underpins our traditional drug development programs,” he explained.

Dr. Moss was interested in synthesizing a range of heteroaryl-fused cyclic imines, since these make convenient precursors to a range of products through their diverse reactivity profile. “Surprisingly, there were very few methods out there for the synthesis of these substrates, and most of those used harsh cyclization techniques,” explained Dr. Moss, adding: “Since a carbon–carbon bond-forming cyclization would be the limiting factor in electron-deficient substrates, we changed the approach to make the bond-forming stage an intramolecular condensation reaction.”

The main challenge was to build the saturated alkyl portion. Dr. Moss said: “We favored a directed *ortho*-metalation strategy as it generally gives predictable regioselectivity. Cyclic sulfamides turned out to be the best reagents for introducing this functionality.” He continued: “We have used these substrates in a number of previous methodologies and have found them to be generally superior to aziridines – the main advantage being that you don’t need strongly activating protecting groups to get acceptable reactivity in the ring opening.” Naturally the carbonyl group had to be protected during the metalation step. The AstraZeneca researcher found that cyclic acetals were not only stable, but could be deprotected simultaneously with the N-Boc under acid conditions, which allowed him to conduct the whole reaction to the



final cyclic imines in a one-pot sequential fashion. Normally it would take several steps to build such complexity, but Dr. Moss was able to access it in a single transformation from simple starting materials.

Dr. Moss concluded: "We were pleased to find that the reaction tolerated a range of common heterocycles. Although usually the carbon–carbon bond-forming reaction occurred through a directed *ortho*-metalation, it could also be performed by lithium–halogen exchange. This gives the methodology added flexibility as you are not restricted to metalation only at the most acidic carbon."

About the authors



Dr. T. A. Moss

Thomas Moss was born in Coventry (UK) in 1983. He received his Master's degree from the University of Oxford (UK), which included a final year project in Professor David Hodgson's group. He moved to Manchester (UK) in 2006 to study for a PhD in asymmetric organocatalysis under the supervision of Professor Darren Dixon. After a postdoctoral year at Imperial College London (UK), he joined AstraZeneca in 2011. His research interests are centered around developing new methods to partially saturated ring systems.

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