anti-Selective Aldol Reactions of SF$_5$-Acetic Acid Esters with Aldehydes Mediated by Dicyclohexylchloroborane

Highlighted article by F. W. Friese, A.-L. Dreier, A. V. Matsnev, C. G. Daniliuc, J. S. Thrasher, G. Haufe

First asymmetric approach of boron-mediated aldol reaction

1. Et$_3$N, Cy$_2$BCl, $-78$ °C, CH$_2$Cl$_2$  
2. 4-FC$_2$H$_4$CHO, $-78$ °C to r.t., 17 h  

$\text{anti/syn} = 99:1$  
$d.r.$ for $\text{anti} = 84:16$

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Dear Readers,

July is summer holiday time for many, and I am no exception to the rule as in this period I usually enjoy having a change of scenery and habits. Even though I do not like to remain completely inactive for long – in fact I never completely stop working for more than a couple of days – in this period I really need to go back to Italy for a full immersion in sunshine, gastronomy and good books for recharging my batteries. My editorial work for SYNFORM never really stops, not even during these two weeks of holiday, but it’s a real pleasure to edit an article outside on the terrace while sipping a cold drink in these hot summer nights. It’s paradise here! Wait a minute… ouch… what was that? It’s sore now… and swollen too… Oh no, hordes of blood-thirsty mosquitos attracted by the light… I hate them... I am back in the house now, I’ve locked all the windows and doors, but I am melting without air conditioning and I have the feeling that I am not even alone here... those flying vampires must have found their way inside... I am already missing so much Scotland and those cold, rainy and misty summers without mosquitos!!! OK, let’s try to focus now and have a look at the content of the July issue of SYNFORM.

The facile use of keteniminium ions for the synthesis of tetrahydropyridines and piperidines from ynamides as described by G. Evano (Belgium) is the topic of the first contribution. In the second, G. Haufe (Germany) takes us through a very useful method recently developed in collaboration with J. S. Trasher (USA) for achieving the stereoselective synthesis of α-SF₅β-hydroxy esters. The third article is an account of the recent method published by W. F. Bailey (USA) for oxidizing primary amines to nitriles, which is generally considered a challenging transformation. The issue is completed by a report on a novel method for achieving the N-monoacylation of sulfonimidamides recently published in SYNTHESIS by Y. Chen (Sweden). OK, now I am going to make an improper use of a printed version of SYNFORM: there is another mosquito on the wall...

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
Keteniminium ions are important reaction intermediates in organic chemistry. Their electrophilic heterocumulene nature has been exploited rather extensively for inter- and intramolecular cycloaddition reactions.

“While the reactivity of keteniminium ions is well understood and has been elegantly exploited for years, notably after the pioneering work of my Belgian colleague Léon Ghosez in this area, little was known about the behavior of their activated analogues bearing an electron-withdrawing group on the nitrogen atom,” said Professor Gwilherm Evano at the Université libre de Bruxelles (Belgium). He added: “We became interested in the reactivity of such species, for which we felt an untapped potential, in continuation of our studies on the chemistry of ynamides.” After spending quite some time on the development of various efficient methods for their preparation and with some of these building blocks now commercially available, the group started exploring the reactivity of keteniminium ions and their use in chemical synthesis. Professor Evano said: “If the study of the anionic chemistry of ynamides was rather straightforward and easy to predict, their cationic chemistry, and especially their use as precursors of activated keteniminium ions, was much more problematic. This was really frustrating at the beginning since we felt that these highly reactive and electrophilic intermediates clearly held a great potential and might be able to react with any nucleophile, even the poorest ones.” He continued: “To be completely honest, we didn’t think right away about their use for the activation of C–H bonds, which was actually discovered by pure serendipity while looking at the hydrofluorination of ynamides.”

Upon treatment of o-tolyl-substituted ynamides with a strong acid to promote the generation of the desired keteniminium ion, the authors noted a rather unexpected cyclization in which the key step, which triggered the cationic cyclization, was a [1,5]-sigmatropic hydrogen shift involving the keteniminium ion and an activated benzylic C–H bond. This reaction was then studied in detail. “With these results in hand, we next wondered if activated keteniminium ions would be
Scheme 2

Reaction scope

Double and triple cyclizations

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reactive enough to promote a [1,5]-hydride shift from unactivated C–H bonds. In this case, we could potentially use this activation to promote a cyclization between the newly generated enamides and a carbocation, a simple concept that was at the onset of our project,” said Professor Evano. “All it takes to make the reaction work is a talented and highly motivated PhD student, and I was lucky enough to have Morgan Lecomte working, all by himself, on this project,” commented Professor Evano. “Morgan was clearly not afraid to spend a lot of time studying the scope and limitations of the reaction in detail, which involved preparing all the starting materials and going to the complex examples that demonstrated the synthetic potential of this cyclization. I was actually concerned that one might argue this was just another synthesis of piperidine derivatives, which would be a fair comment although some piperidines are still challenging to prepare in an efficient and straightforward manner, including most of the ones that can be accessed through our keteniminium ion initiated cyclization,” remarked Professor Evano. He continued: “The main advantages of this reaction are clearly the availability of the starting ynamides as well as the operational simplicity and efficiency of the cyclization. Moreover, depending on the substitution pattern of the starting ynamide, spirocyclic and bicyclic piperidine derivatives are easily obtained and double and triple cyclizations are also found to be quite efficient, enabling an access to nitrogen heterocycles that are otherwise difficult to prepare.”

Morgan Lecomte commented: “The key factor for this transformation is actually the acid used for the generation of the activated keteniminium ion. If a weak acid is sufficient to protonate the triple bond of the starting ynamide, the main problem is actually due to the nucleophilicity of the conjugated base which needs to be as low as possible to make sure it won’t trap the keteniminium ion before the hydride shift can occur. Triflic acid was therefore found to be the best acid to trigger the cyclization and the corresponding tetrahydropyridines are formed within minutes (basically the time it takes to check the reaction) at –60 °C.”

Morgan continued: “In order to increase the molecular complexity of the products, we wondered if the intermediate cyclic iminium ion could be trapped by an external nucleophile, which would enable the formation of polysubstituted piperidines instead of tetrahydropyridines.” The authors revealed that for this reaction to be successful, the order of addition of the reagents turned out to be critical. Indeed, if the nucleophile was added at the beginning of the reaction, it reacted with the keteniminium ion before the [1,5]-hydride shift could occur. However, by simply adding the nucleophile after the cyclization (which was shown to stop at the cyclic iminium ion, the elimination to tetrahydropyridine occurring during the workup only), a set of polysubstituted piperidines was formed, in most cases in a highly diastereoselective manner. In addition, by using triethylsilane, the iminium ion could be readily reduced to the corresponding piperidine in good yields.

According to the authors, in addition to the synthetic usefulness of the reaction in heterocyclic chemistry, this study demonstrates the remarkable potency and the unique reactivity of activated keteniminium ions, the activation of C–H bonds being especially difficult to achieve. “There is clearly an enormous potential with these species which still deserves to be explored and we hope to be able to capitalize on their unique reactivity for the design of other processes,” said Professor Evano. “Right now, and in direct connection with this aspect,” said Professor Evano. “Right now, and in direct connection with this aspect,” said Professor Evano.
project, we are trying to extend the scope of this reaction by replacing the acid used for the generation of the keteniminium ion by an electrophile, which is not as easy as initially anticipated, and to extend the cyclization to the preparation of other heterocycles starting from oxygen-, sulfur- and phosphorus-substituted alkynes instead of ynamides.”

Morgan Lecomte concluded: “Unfortunately, the use of an internal nucleophile has met with little success so far, this nucleophile being intercepted by the keteniminium ion before the hydride shift or, when this is not the case, the reaction being too messy.”

Morgan Lecomte was born in Arlon (Belgium) in 1988 and studied chemistry at the Université libre de Bruxelles (Belgium). In 2012, he joined the Laboratory of Organic Chemistry as a Master’s student working under the supervision of Professors Ivan Jabin and Gwilherm Evano on the use of hetero-substituted alkynes for the selective functionalization of calixarenes. He obtained an F.R.I.A. PhD fellowship in 2013 to work in the group of Professor Gwilherm Evano and his research focuses on the study of the reactivity of ynamides and activated keteniminium ions, and on the development of new reactions and processes from these building blocks.
Metal-Free Oxidation of Primary Amines to Nitriles via Coupled Catalytic Cycles


Although the oxidation of primary amines would be, in principle, a straightforward and atom-economical entry to nitriles, the reaction is not conventionally used because of the difficulties connected with controlling the many different oxidation pathways that can originate from amines. Recently, the group of Professor William F. Bailey at the University of Connecticut (USA) has described a novel efficient strategy for accomplishing this challenging transformation.

"For the past ten years or so, my research group has been collaborating with my close friend and colleague, Professor Emeritus Dr. James M. Bobbitt, exploring the oxidation chemistry of 4-acetamido-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate (1). The salt, which we and others colloquially refer to as 'Bobbitt's salt' (the systematic name is quite a mouthful), as well as its nitroxide precursor (2) were developed by Jim (Professor Bobbitt) in the 1990s," said Professor Bailey (Figure 1). He continued: "While both the nitroxide (4-acetamido-TEMPO, ACT, 2) and Bobbitt's salt (1) are commercially available, it is far more cost-effective to prepare the salt from 4-amino-2,2,6,6-tetramethylpiperidine, via the nitroxide, than it is to purchase it: 1 may be prepared in a few simple steps, on a multi-mole scale in water, for < US$ 1 per gram; the nitroxide precursor, 2, is significantly less expensive to prepare."

The group's initial ventures in oxoammonium chemistry involved exploration of the mechanism of alcohol oxidation and the reactions of Bobbitt's salt with alcohols, aldehydes, ethers, and alkenes. "More recently, prompted by Jim's prescient suggestion that we consider the implications of a 1983 report by Martin Semmelhack, 1 we became interested in the potential of oxoammonium cations to provide a selective and mild method for oxidation of amines to nitriles," explained Professor Bailey. The seminal Semmelhack–Schmid publication disclosed that generation of the oxoammonium cation by electrochemical oxidation of TEMPO in the presence of a primary amine afforded a mixture of nitriles, imines, and aldehydes in variable proportions. Professor Bailey said: "At the time we began our investigations in 2013, the conversion of an amine into a nitrile (formally a double dehydrogenation) was a non-trivial transformation. Amines are, of course, quite easy to oxidize with a host of reagents: the difficulty is controlling the process to give only the desired product."

He continued: "Shannon Stahl beat us to the punch with his mid-2013 report of a catalytic method to accomplish the RCH₂NH₂ → RCN conversion (Scheme 1). This beautiful piece of chemistry, which, the authors noted, involved 'extensive screening of ligands and bases', set a high bar for us."

Professor Bailey explained that the major difficulty identified by Stahl in the oxidation of RCH₂NH₂ to a nitrile is the unexpectedly rapid formation of homocoupled imines by condensation of the amine starting material with the aldimine generated in the first oxidation step (Scheme 2). Professor Bailey's group had also already encountered this difficulty.

"At the outset of our investigation of amine oxidations we were interested in the development of a method for oxidation of amines to nitriles that would not involve a metal and associated ligand for the process," said Professor Bailey. They began by first exploring the use of a stoichiometric quantity of Bobbitt's salt (1) as the oxidant. The solution to the rapid

Figure 1

Scheme 1 Catalytic approach by Kim and Stahl (2013)
formation of imine in the oxidation of primary amines was a simple, operational one: they slowly added a 0.5 M solution of the amine in dichloromethane (15–20 mL/h using a syringe pump) to a stirred slurry of slightly more than the stoichiometric quantity of oxoammonium salt and an excess of pyridine as base in dichloromethane at room temperature. Professor Bailey explained: “We reasoned that the slow addition of amine allowed the oxidation of the aldimine intermediate to proceed to completion before excess amine could react to give unwanted imine. It worked. Reaction mixtures were stirred at room temperature overnight, and a simple extractive workup afforded pure nitriles in good yield (85–95%).” The report of this chemistry was submitted in November of 2014 and published in December of that year.5 The paper also demonstrated that the mechanism of the oxidation involves a hydride transfer from the amine to the oxygen atom of 1 as the rate-limiting step.

Scheme 3 summarizes the approach. The scheme also illustrates a major limitation of this method for the preparation of larger quantities of nitriles: a stoichiometric quantity of oxoammonium salt is a full 4 molar equivalents of the reagent. This is a consequence of the fact that, in the presence of base, 1 and the hydroxylamine syn-proportionate to give 4 molar equivalents of nitroxide 2.

“Clearly, as all the reviewers of our Org. Lett. article properly noted, a catalytic method for the oxidation of amines to nitriles would be far superior to this stoichiometric process for the preparation of nitriles on scale,” commented Professor Bailey. At first, the group estimated that development of a catalytic procedure for the transformation of an amine to a nitrile would take no more than a few weeks, reasoning that there are any number of ways to oxidize alcohols to aldehydes and ketones using a catalytic quantity of TEMPO and a terminal oxidant. “We should have remembered Robert Burns’ admonition: ‘The best laid schemes o’ mice an’ men/Gang aft a-gley’,”6 laughed Professor Bailey. Indeed; it took almost a year to reduce the chemistry to practice.
Professor Bailey continued: “The credit belongs to my co-author, Kyle Lambert. An exceptionally talented chemist and one of the most technically accomplished graduate students that I have had in my long career, Kyle finally cracked the problem.” The difficulty was in identifying a suitable terminal oxidant to generate the active oxoammonium salt without negatively impacting the sensitive amine substrate. “Kyle tried many approaches; the solution, detailed in the Chem. Eur. J. account, involved adaptation of several, pH-dependent catalytic cycles to create a catalytic cascade using a catalytic amount of Bobbitt’s nitroxide (ACT, 2), pyridinium bromide, oxone as a terminal oxidant, and an excess of pyridine as base in dichloromethane solution at room temperature,” explained Professor Bailey, continuing: “Once again, slow addition of the amine was required to prevent formation of the imine. Simple filtration of the product mixture through a small bed of silica gel, and removal of the solvent, afforded pure nitrile products; no chromatography needed. The procedure is a robust one. All manner of primary amines are converted into nitriles in good to excellent yield.” Scheme 4 provides an overview of the process and a few representative yields of isolated products.

Professor Bailey acknowledged that the undergraduate co-authors, Sherif A. Eldirany, Liam E. Kissane, Rose K. Sheridan, Zachary D. Stempel, and Francis H. Sternberg, participated materially in the development of the chemistry presented in the account. “They prepared, purified, and characterized many of the amine substrates used in the study and checked the oxidation procedure to ensure reproducibility. Significantly, this was the first taste of independent chemical research for many of the undergraduate students,” concluded Professor Bailey.

REFERENCES

(6) ‘Gang aft a-gley’ can be translated from Scottish as ‘often go awry’.

Scheme 4 Catalytic oxidation of amines to nitriles
Bill Bailey was born and raised in Jersey City, NJ (USA), and received his B.S. degree in chemistry in 1968. He worked with Ernest Eliel at the University of Notre Dame (IN, USA) investigating conformations of saturated heterocycles and the stereochemical dependence of C-13 shifts and obtained his Ph.D. in 1973. After a two-year postdoc with Kenneth Wiberg at Yale (USA), Bill joined the faculty at the University of Connecticut (USA) where he is currently Professor of Chemistry. A major focus of Bill’s research is development of new synthetic methodology using novel main-group organometallic chemistry.

Jim Bobbitt was born in Charleston, WV (USA) in 1930. He received his B.S. degree in chemistry at the University of West Virginia (USA) and then obtained his Ph.D. at Ohio State University (USA) where he worked on natural products and periodate oxidation of sugar derivatives with M. L. Wolfrom. Following postdoctoral studies with Carl Djerassi at Wayne State University (USA) on alkaloid structure determination, Jim was appointed in 1956 to an instructorship in chemistry at the University of Connecticut in Storrs (USA). He rose through the ranks at the University of Connecticut (USA) and served as department head from 1976–1982. His research included structure elucidation of natural products, heterocyclic chemistry, and electrooxidation of alkaloids and similar materials. In 1985, he encountered oxoammonium chemistry in his electrochemical work and has worked in that field since. He formally retired in 1992, but has continued to do bench chemistry himself and with a number of colleagues and their graduate students.

Kyle Lambert graduated summa cum laude from the University of New Haven (USA) in 2012 with dual B.S. degrees in chemistry and forensic science. He is currently a fourth-year graduate student working with Bill Bailey at the University of Connecticut (USA). Kyle’s doctoral research involves exploration of oxoammonium salts as selective oxidants as well as conformational studies of saturated heterocycles. In his spare time he enjoys coaching track and field at a local high school and plans to pursue an academic position upon completion of his graduate studies.

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**anti-Selective Aldol Reactions of SF₅-Acetic Acid Esters with Aldehydes Mediated by Dicyclohexylchloroborane**

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The aldol reaction is one of the most powerful and reliable C–C bond-forming processes in organic synthesis, and the resulting β-hydroxy carbonyl structural motif is present in many important natural and bioactive compounds. Even though this reaction has been known for more than 140 years, the fundamental studies by Wittig using preformed enolates made the reaction usable for the construction of more complex molecules. Progress in understanding the mechanism of these transformations led to the development of mild and highly selective reaction conditions useful for the construction of natural products such as polyketides and macrolides. In addition to Mukaiyama’s silicon-based methodology, the boron-mediated variant has also been developed as one of the most powerful tools of modern aldol chemistry. Both silicon- and boron-Mukaiyama’s aldol reactions involve highly diastereo- and enantioselective, and even catalytic, protocols.¹

The group of Professor Günter Haufe located at the University of Münster (Germany) is active in the development of new synthetic tools for the preparation of fluorinated compounds with the final aim of biomedical applications. Professor Haufe commented: “A couple of years ago we used intermediately formed ester enolates in Ireland–Claisen-type rearrangements to prepare α-fluoro- and α-trifluoromethyl carboxylic acid derivatives.² Now, in a fruitful cooperation with the group of Professor Joseph S. Thrasher, Clemson University in South Carolina (USA), not only fluorinated carbon centers but also sulfur-containing groups [SF₅(CF₂)ₓ (n = 0–2)] are being investigated³ in order to achieve a better understanding of the intrinsic physicochemical properties of those groups.” Among them, the fairly uncommon pentafluorosulfonyl (SF₅) group has gained much attention recently.⁴ The sheer size, comparable to that of a tert-butyl group, and the strong electron-withdrawing power are responsible for the strong steric and electronic effects exerted by the SF₅ group,⁵ making it a candidate for drug design studies, as well as an interesting functionality for agrochemicals and materials. “While the chemistry of aromatic SF₅ compounds has been improved significantly due to recent progress in large-scale preparation of these compounds,” explained Professor Haufe, “the incorporation of the SF₅ group into aliphatic positions has lagged considerably behind. It is commonly achieved by the radical addition of SF₅Cl-type reagents to C–C multiple bonds. In this way, 2-(pentafluorosulfonyl)acetic acid became readily available recently⁶ and was identified as a convenient starting material. We have been able to successfully use it in the preparation of α-SF₅ carboxylic acid derivatives by Ireland–Claisen rearrangements of allylic SF₅ acetates,” continued Professor Haufe, who added: “For the first time, intermediately formed SF₅-substituted

**Scheme 1** Synthesis of α-SF₅-β-hydroxy esters by a boron-mediated aldol reaction via a Zimmerman–Traxler-like transition state

1. Et₃N (3.5 equiv), Cy₂BCl (2.5 equiv) –78 °C, CH₂Cl₂, 4 h
2. RCHO (1.0 equiv), –78 °C to r.t., 17 h

Selected examples:

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silicon enolates were established by low-temperature NMR spectroscopy. This observation led us to speculate whether enolates of alkyl SF₅ acetates might be useful in aldol reactions.”

Professor Haufe told SYNFORM that the present work indeed profited from the power of the boron-mediated aldol reaction of (E)-enolates, formed highly selectively from alkyl SF₅ acetates to produce targeted aldols using dicyclohexylchloroborane/triethylamine. This system was previously used by Ramachandran for the enolization of α-trifluoromethyl carbonyl compounds. “Just like we hoped for, treatment of octyl SF₅ acetate with an excess of Cy₂BCl and Et₃N at –78 °C and subsequent addition of various aromatic and aliphatic aldehydes led to the formation of the anti-3-hydroxy-2-(pentfluorosulfanyl)alkyl esters almost exclusively,” remarked Professor Haufe. The anti-configuration of the hitherto unknown SF₅ aldols was established by X-ray structural analysis. Furthermore, the different conformations of para- and ortho-monosubstituted phenyl products on the one hand versus ortho,ortho’-disubstituted phenyl products on the other hand were elucidated by NMR spectroscopy and DFT calculations, again emphasizing the strong steric impact of the SF₅ group.

“Being aware of the stereochemical outcome of the reaction, we proposed a Zimmerman–Traxler-like transition state,” said Professor Haufe. “A strong interference of the SF₅ group with the rather bulky borane within the formed (E)-enolates might be the key for the high selectivity observed, but this is also creating the instability of these intermediates above –40 °C.”

As a result of the broad applicability, Professor Haufe and co-workers strived forward towards asymmetric approaches. “As a first success, a norephedrine-based auxiliary provided an anti/syn-selectivity of 99:1 and a dr of 84:16 for one of the anti-diastereomers while keeping a good level of conversion,” he said.

The usefulness of this type of aldol reaction has been shown independently by Carreira and co-workers in a practical synthesis of a number of six-membered nitrogen SF₅ heterocycles following a similar protocol, although the achieved stereochemistry was lost during subsequent transformations.

Professor Thrasher explained: “I truly believe that only because of our collaborative effort have we been able to come up with as many exciting results as those in this review and our recent papers. Perhaps no single research group in the world would be able to meet all of the scientific goals that we set, especially at the beginning of our project, funded jointly by the U.S. National Science Foundation (NSF) and the German Deutsche Forschungsgemeinschaft (DFG). Only via cooperation could the complementary expertise of both groups guarantee the success of our project. Unfortunately for us, the U.S. NSF has archived their International Collaboration in Chemistry (ICC) Program from which we obtained part of the funding.”

Professor Haufe concluded: “We believe that, based on our and others’ results, aldol reactions will help to integrate SF₅ compounds into many fields of contemporary research. Application of alternative auxiliaries allowing milder deprotection conditions and catalytic approaches being under investigation will give rise to feasible asymmetric variants. Our preliminary results applying Mukaiyama’s silicon-based aldol chemistry proved the approach to the other stereochemical series.”

REFERENCES

(b) P. R. Savoie, J. T. Welch Chem. Rev. 2015, 115, 1130.  

About the authors

**Florian W. Friese** was born in Hamm (Germany) in 1990 and received his M.Sc. in chemistry from the University of Münster (Germany) under the supervision of Professor Günter Haufe. In 2016, he joined the group of Professor Armido Studer as a Ph.D. student. His future work will mainly focus on the development of new radical chain reactions.

**Anna-Lena Dreier** was born in Münster (Germany) in 1986. After obtaining her Diploma degree in 2011, she worked on her Ph.D. thesis under the supervision of Professor Günter Haufe. She was mainly focused on the synthesis and characterization of new (pentfluorosulfanyl)-substituted compounds. After her graduation in 2015, she joined the German automotive supplier and tire manufacturer Continental.

**Andrej V. Matsnev**, a native Ukrainian, is a Research Scientist at Halocarbon Products Corporation and an Adjunct Assistant Professor at Clemson University (USA). He also serves as Vice-Chair Secretary of the American Chemical Society (ACS) Division of Fluorine Chemistry. In 2004, he obtained his Ph.D. from the Institute of Organic Chemistry of the National Academy of Sciences of Ukraine in Kiev (IOCh NASU), where he worked under the supervision of Professor Lev M. Yagupolskii. In 2008, he joined the research group of Professor Norio Shibata at the Nagoya Institute of Technology (Japan). In 2010, he transferred to the research group of Professor Joseph S. Thrasher at the University of Alabama (USA) and moved with the group to Clemson University (USA) in 2012.

**Constantin G. Daniliuc** earned his Diploma degree from the University ‘Al. I. Cuza’ in Iasi (Romania) in 2002. As a recipient of an Erasmus Scholarship, he completed his Master thesis at the Technical University of Braunschweig (Germany) in collaboration with InnoChemTech Company (Germany). He received his Ph.D. from the same university in 2008 under the supervision of Professor W.-W. du Mont, and started there as a crystallographer in cooperation with Professors P. G. Jones and M. Tamm in 2009. Since 2012, he is Head of the Crystallographic Laboratory within the Organic Chemistry Institute, University of Münster (Germany).

**Joseph S. Thrasher** received his B.S. and Ph.D. degrees at Virginia Tech (USA) prior to carrying out postdoctoral research at the Freie Universität Berlin (Germany) with Professor Konrad Seppelt and at Clemson University (USA) with Professor Darryl DesMarteau. In 1984, he started his independent career at The University of Alabama (USA), where he served as Director of Graduate Studies (1995–2002) and Department Chair (2002–2007). In the fall of 2011, Dr. Thrasher returned to Clemson University to overlap with and follow Professor DesMarteau. He has served as Chair of the American Chemical Society (ACS) Division of Fluorine Chemistry (1994), co-chaired two ACS Winter Fluorine Conferences (1993 and 1995), and was lead organizer of the 19th International Symposium of Fluorine Chemistry (2009). Additionally, he became Regional Editor for the Americas for the Journal of Fluorine Chemistry in 2016.
Günter Haufe graduated from the University of Leipzig (Germany) with a Diploma degree in 1972 and a Dr. rer. nat. in 1975 both with Professor Manfred Mühlstädt. After basic military service he started his independent scientific career and did a Habilitation and venia legendi in Leipzig (1985). In 1986, he worked as a Research Fellow of Centre National de la Recherche Scientifique (CNRS) with André Laurent at the Université Lyon I (France), and as a visiting scientist with Jakko Paasivirta at the University of Jyväskylä (Finland). From 1988–1991 he was an Associate Professor (Docent) of Bioorganic Chemistry at the University of Leipzig before he was appointed to his present position as a Professor of Organic Chemistry at the University of Münster (Germany). Guest professorships have led him to Lyon (France), Poznan (Poland), Rouen (France), Valencia (Spain), Nagoya (Japan) and to the University of Florida, Gainesville (USA) as a Paul Tarrant Visiting Professor. He was awarded with the ‘Friedrich-Wöhler-Preis’ in 1985 and elected as a member of the European Academy of Sciences in 2015. From 2008–2010 he served as a Chair of the group of German fluorine chemists within the German Chemical Society. He published a book on ‘Alicyclic Chemistry’ together with Gerhard Mann (1989) and edited a monograph ‘Fluorine and Health’ together with Alain Tressaud (2008). He was an Associate Editor of ‘Advances in Fluorine Science’ and is a Regional Editor of the Journal of Fluorine Chemistry since 2008.
In recent years, N-alkylation, N-acylation and N-arylation of sulfonamides have proven useful in organic chemistry and medicinal chemistry for producing bioactive compounds and drug candidates. Sulfonimidamides (SIAs), the aza analogues to sulfonamides, have been introduced as an interesting but underexplored area of chemistry. Functionalization of SIAs has been conducted in medicinal chemistry programs; however, an interesting challenge for functionalization of an unprotected primary SIA is that both the sulfonamidic nitrogen and the imidic nitrogen can be functionalized. Recently, Dr. Yantao Chen of AstraZeneca Innovative Medicines Cardiovascular and Metabolic Diseases (Mölndal, Sweden) published in Synthesis a convenient synthetic method to produce monoacylated SIA products from TBS-protected starting materials, using a stoichiometric acylating reagent which was prepared by mixing an acyl chloride with one equivalent of pyridazine. Dr. Chen explained: “Under the reaction conditions, monoacylated products were obtained. Moreover, the TBS protecting group was removed during the reaction course. The paper also demonstrated one example of further functionalization on the second nitrogen starting from a mono-acylated product.”

“Following our first publication (RSC Advances 2015, 5, 4171), TBS-protected SIAs can be prepared on a large scale as starting materials for further chemical exploration,” said Dr. Chen. This paper demonstrates an easy chemical process for the synthesis of N-acylated SIAs. “Through tautomerization, the achieved product is converted into the N(imidic)-acylated product, in which the amidic nitrogen is still free for another functionalization,” continued Dr. Chen. He concluded: “Looking forward, we believe that this step-by-step functionalization provides us a method for performing more versatile functionalizations of the target substrates. For instance, when the first nitrogen in an SIA is acylated (i.e., protected), then the other one is free for other functionalization, such as acylation, alkylation, arylation, etc.”
Yantao Chen was born in LaiZhou, ShanDong (P. R. of China), in 1969. He received his B.S. in chemistry from ShanDong Normal University (P. R. of China) in 1991. Then he moved to Beijing and started his journey as an organic synthesis chemist. Under the supervision of Professor Wenting Hua, he explored and patented a novel synthetic approach of Ramipril – an angiotensin-converting enzyme (ACE) inhibitor, and obtained his M.S. from Peking University (P. R. of China) in 1994. During 1994–1997, he focused on the synthesis of chiral macrocycles and received his Ph.D. in 1997 under the supervision of Professor Wenting Hua. Then he spent two years at the Institute of Chemistry, Chinese Academy of Sciences (Beijing), as a postdoctoral scholar under Professor Duanfu Xu. In 1999, he moved to Linköping University (Sweden) for his postdoctoral research in the area of antimalaria under the supervision of Dr. Åsa Rosenqvist, Professor Ingemar Kvarnström and Professor Bertil Samuelsson. In July 2001, he was employed as a senior research scientist at Thin Film Electronics AB (Sweden), where he was trained to work in a clean-room lab. His work focused on the design and safety evaluation of polymerization reactors, polymer characterization by NMR and DSC, and surface modification chemistry. In 2003, he joined AstraZeneca R&D Mölndal (Sweden), and started his career as a senior research scientist. Over the last 13 years, he has been working in the Medicinal Chemistry Department at the Innovative Medicines of Cardiovascular and Metabolic Diseases (CVMD iMed), and contributed to both lead generation and lead optimization projects. Over the years he has supported numerous projects by designing new ideas for SAR study, exploring new synthetic routes, and being a project coordinator with outsourcing partners. As a member of the Compound Collection Enhancement (CCE) panel, he has designed several libraries for lead identification and lead optimization projects. He was rewarded for his contributions of bringing the awareness of ‘Synthetic Reagent Initiatives’ (AZ SRI) to the department, leading, managing, supporting SRI in the department, and communicating with SRI members and CRO partners. It is noteworthy that AstraZeneca offers chemists great computational tools and platforms that enabled him to become a competitive and skilled organic and medicinal chemist. Recently, he has focused on the chemistry of sulfonamides, sulfonimidamides, and sulfoximines, etc., trying to provide this underexplored chemistry more room in drug discovery. So far, he has designed and published two papers about sulfonimidamides.
Coupling Catalyzed by Chiral N-Heterocyclic Carbenes

One-Step Catalytic Asymmetric Synthesis of All-syn Deoxypropionate Motif from Propylene: Total Synthesis of (2R,4R,6R,8R)-2,4,6,8-Tetramethylenecanoic Acid

Enantioselective Intermolecular Enamide–Aldehyde Cross-Coupling Catalyzed by Chiral N-Heterocyclic Carbenes

Further highlights

**Synthesis** Review: Recent Advances in the Synthesis of Sulfones (by G. Manolikakes and co-workers)

**Synlett** Account: Playing Around with the Size and Shape of Quinolizinium Derivatives: Versatile Ligands for Duplex, Triplex, Quadruplex and Abasic Site-Containing DNA (by H. Ihmels and co-worker)

**Synfacts** Synfact of the Month in category “Metal-Catalyzed Asymmetric Synthesis and Stereoselective Reactions”: Gd-Catalyzed Photocycloaddition of Aryl Cyclopropyl Ketones with Alkenes