

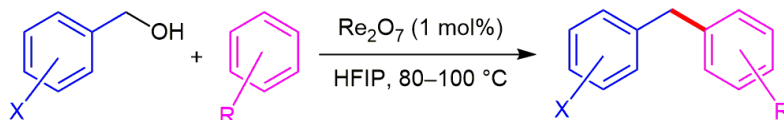
# Synform

People, Trends and Views in Chemical Synthesis

2019/04

## Diarylmethane Synthesis through $\text{Re}_2\text{O}_7$ -Catalyzed Bimolecular Dehydrative Friedel-Crafts Reactions

Highlighted article by Q. Qin, Y. Xie, P. E. Floreancig



### Contact

Your opinion about Synform is welcome,  
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## Dear Readers,

The boards of SYNTHESIS and SYNLETT have recently decided on the Best Paper Awards for 2018, which come with a €3,000 prize, a certificate and all the glory and visibility that such a prize deserves! This issue of SYNFORM is opened by an interview with the SYNLETT Best Paper Award winner, Professor James Morcken from Boston College (USA), who together with his co-workers was recognized for the paper *A Protocol for Direct Stereospecific Amination of Primary, Secondary, and Tertiary Alkylboronic Esters* (DOI: [10.1055/s-0037-1610172](https://doi.org/10.1055/s-0037-1610172)). Warmest congratulations to Professor Morcken, and we are looking forward to hosting the SYNTHESIS Best Paper Award winner in the next issue.

The second article of this highly diversified issue covers an exciting paper published by Paul Floreancig (USA) on the use of a dehydrative Friedel–Crafts reaction to access diarylmethanes. The third contribution serves as a red carpet for Professor Franziska Schoenebeck, RWTH Aachen University (Germany), who is a new Editorial Board Member of SYNTHESIS. Well done to Franziska and a warm welcome to the Thieme Chemistry family! The issue is closed by a fantastic article of the Name Reaction Biography series, authored by David Lewis, on some of the most influential Russian chemists who passed away at the beginning of the 20<sup>th</sup> century, such as Mendeleev, Beilstein and Menshutkin. Considering that 2019 is the International Year of the Periodic Table, the article could not be more timely!

Enjoy your reading!!



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### Contact

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

## SYNLETT Best Paper Award 2018: A Protocol for Direct Stereospecific Amination of Primary, Secondary, and Tertiary Alkylboronic Esters

*Synlett* **2018**, 29, 1749–1752

**Background.** Thieme Chemistry and the Editors of *SYNTHESIS* and *SYNLETT* present the ‘*SYNTHESIS*/*SYNLETT* Best Paper Awards’. These annual awards honor the authors of the best original research papers in each of the journals, considering their immediate impact on the field of chemical synthesis. James Morken and co-workers, from Boston College in the USA, are the recipients of the *SYNLETT* Best Paper Award 2018. The authors are recognized for their stereospecific approach to alkylamines. Benjamin List, Editor-in-Chief of *SYNLETT*, commented: “The team has devised a new route to highly valuable alkylamines, which are among the most important substructures in pharmaceuticals and natural products. The developed method solves an important, previously not addressable synthetic problem, which is to stereospecifically convert primary, secondary, and even tertiary boronic esters, which are readily available reagents, into the corresponding alkylamines. The protocol is practical and requires only inexpensive reagents. It should therefore be of great utility to scientists working in the area of chemical synthesis, especially in medicinal chemistry.” *SYNFORM* spoke with Prof. James P. Morken, who was happy to share some background information regarding the prize-winning paper as well as current research activities ongoing in his group.

### Biographical Sketch



Prof. J. P. Morken

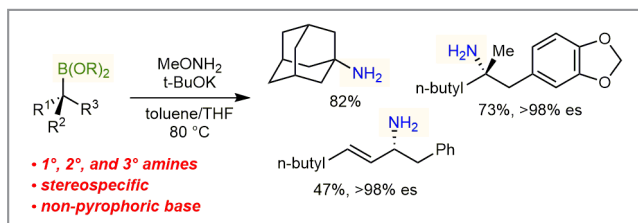
**James P. Morken** was born in Concord, California (USA) and obtained his B.S. in chemistry in 1989 from UC Santa Barbara (USA) working with Prof. Bruce Rickborn. He obtained his Ph.D. from Boston College (USA) in 1995 with Prof. Amir Hoveyda and was an NSF Postdoctoral Fellow with Prof. Stuart Schreiber at Harvard University (USA). In 1997, he became an Assistant Professor of Chemistry at the University of North Carolina at Chapel Hill (USA). He was promoted to Associate Professor in 2002 and in 2006 joined the faculty of Boston College (USA). In 2014, he was named the Louise and James Vanderslice and Family Chaired Professor of Chemistry at Boston College. Professor Morken’s research focuses on the development of transition-metal-catalyzed asymmetric processes and their use in complex molecule synthesis. He is particularly interested in the

study and development of catalytic enantioselective reactions involving organoboron reagents. Because of the broad array of reactions that are available to organoboronates, these types of process can be employed to address a number of compelling problems in the construction of organic frameworks.

## INTERVIEW

**SYNFORM** Could you highlight the value of your award-winning paper with respect to the state-of-the-art, as well as the potential or actual applications?

**Prof. James P. Morken** Over the past decade or so, there has been a tremendous surge in the development of processes, both catalytic and non-catalytic, that result in the enantioselective construction of compounds bearing boronic ester functional groups attached to stereogenic carbon atoms. While these reaction products may be oxidized to give chiral alcohols, or subjected to C–C bond-forming homologation reactions, a simple and effective amination of boronic esters in a stereospecific fashion really wasn't available. A few years ago, my group developed one protocol for accomplishing this objective, but it required the use of pyrophoric reagents and very low reaction temperatures, and was ineffective with some substrate classes, most notably tertiary alkylboronic esters. The paper selected for the SYNLETT Best Paper Award fixed all of these problems: it uses a simple base, can be conducted in the open atmosphere, and applies to primary, secondary, and tertiary alkylboronic esters (Scheme 1). With this strategy, it is now just as easy to convert an alkylboronic ester into an amine as it is into an alcohol.



Scheme 1

**SYNFORM** Can you explain the origin, motivations and strategy used for conducting the award-winning research?

**Prof. James P. Morken** The motivation for the work was pretty simple: we had developed effective new methods for the catalytic construction of tertiary boronic esters and, for synthesis reasons, really wanted to convert them into amines. We considered plausible mechanistic reasons why previous methods for amination of these substrates failed, and then we considered potential solutions. That mechanistic thinking, combined with observations we had made in previous studies about reactivity with mild bases, suggested a solution to the problem.

**SYNFORM** What is the focus of your current research activity, both related to the award paper and in general?

**Prof. James P. Morken** My group focuses on the development of catalytic methods for the enantioselective construction of organoboron compounds, and the use of these methods in natural product synthesis. Two main areas of current interest focus on the development of an organocatalytic enantioselective alkene diboration, and the development of a transition-metal-catalyzed conjunctive cross-coupling reaction. The products of both of these reactions can be transformed into useful organic building blocks by taking advantage of the many transformations available to organoboron compounds; the SYNLETT paper adds to this collection of transformations by facilitating construction of chiral amines.

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

**Prof. James P. Morken** The central role of organic synthesis in contemporary society is to provide chemical compounds that facilitate research at the frontiers of modern science. The major challenge to organic synthesis arises from asking how can we do it better. We need simpler and cheaper methods to create complex compounds from simple and abundant starting materials. Fortunately for people who are excited about fundamental science, to address these challenges requires that we develop a better understanding of the fundamental ways molecules behave, that we develop new reactivity concepts, and that we develop new strategies for chemical synthesis. It will keep us busy for a long time.

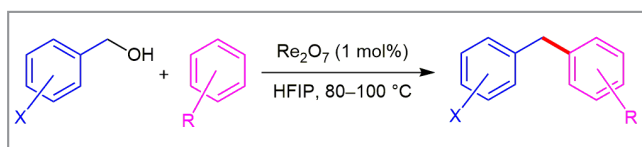
*Matthew Fenske*

# Diarylmethane Synthesis through $\text{Re}_2\text{O}_7$ -Catalyzed Bimolecular Dehydrative Friedel–Crafts Reactions

*Chem. Sci.* **2018**, *9*, 8528–8534

First-year chemistry students learn that the OH group is a very poor leaving group and nucleophilic substitution reactions involving alcohols as electrophiles require suitable activation of the hydroxy function. In this context, transient OH group activation with an electrophilic catalyst is particularly attractive for a number of reasons, including environmental and economic ones. Dehydrative coupling reactions able to produce complex organic structures from benzylic alcohols are among the most interesting emerging options in the toolbox of modern organic synthesis.

The roots of this project lie in the work that Professor Floreancig's group at the University of Pittsburgh (USA), in conjunction with Dr. Youwei Xie of Huazhong University of Science and Technology (P. R. of China) has done on  $\text{Re}_2\text{O}_7$ -mediated allylic alcohol transposition reactions.<sup>1</sup> Professor Floreancig said: "Our initial method employed electrophilic groups to trap one isomer of a mixture of transposing allylic alcohols, thereby providing a thermodynamic driving force that allowed for useful bond-forming processes. However, we noticed while using epoxide groups as electrophilic traps that increasing the level of substitution on the allylic alcohol led to an unexpected change in the product.<sup>2</sup> Further exploration revealed that the added substitution actually caused the allylic alcohol to serve as a precursor to a carbocation, causing the epoxide group to act as the nucleophile."



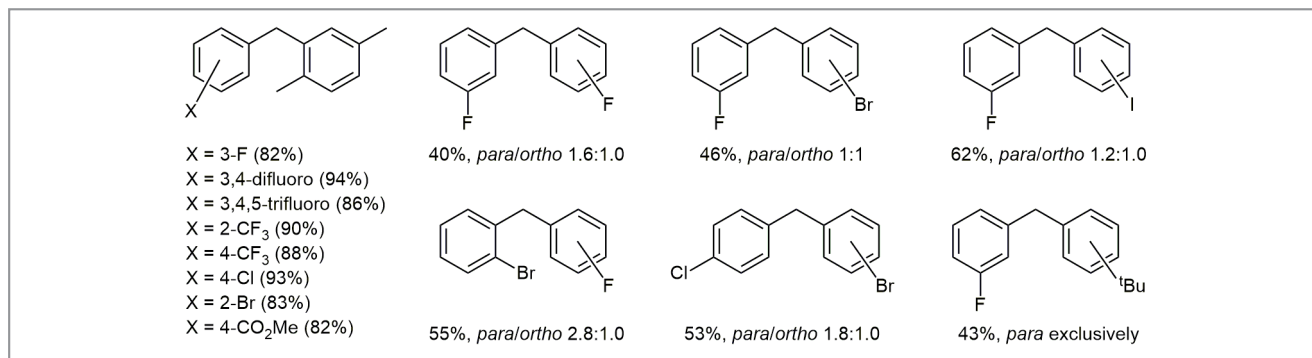
**Scheme 1** The new dehydrative Friedel–Crafts methodology

This result allowed the authors to consider alternative reaction designs in which allylic alcohols act as precursors to electrophiles that react with appended nucleophiles to form rings.<sup>3</sup> This was demonstrated through the development of a stereoselective dehydrative tetrahydropyran formation that proceeded through cation formation through  $\text{Re}_2\text{O}_7$ -mediated ionizations of allylic alcohols followed by nucleophilic addition by pendent alcohols. "The applicability of this method

to complex molecule synthesis was established by its use in a cyclization reaction that delivered a late-stage intermediate in the construction of the natural product herboxidiene," explained Professor Floreancig. He continued: "We demonstrated the superiority of  $\text{Re}_2\text{O}_7$  over Brønsted acids for allylic cation formation by comparing the efficiency of these processes with sulfonic acid catalyzed variants. This led us to postulate that the perrhenate ester, or possibly the protonated perrhenate ester, was the relevant intermediate in these reactions rather than a protonated alcohol."

Youwei Xie, who developed the early stages of the  $\text{Re}_2\text{O}_7$ -catalyzed transformations as a graduate student and was later a postdoc in Ben List's group at the Max Planck Institute (Germany), made the connection between the dehydrative cyclization chemistry and the outstanding work being done on Lewis and Brønsted acid mediated benzylic alcohol ionization by Hall<sup>4</sup> and Moran.<sup>5</sup> "These processes, which were applied to diarylmethane synthesis via Friedel–Crafts reactions, were very impressive because of their ability to generate cations from electron-deficient benzylic alcohols," remarked Professor Floreancig, continuing: "Youwei postulated that the superiority of  $\text{Re}_2\text{O}_7$  to Brønsted acids in the dehydrative cyclization reactions could be translated to benzylic alcohol ionization, leading to lower catalyst loadings and milder reaction conditions. He quickly validated his hypothesis by showing that  $\text{Re}_2\text{O}_7$  catalyzes the dehydrative coupling of pentafluorobenzyl alcohol with *p*-xylene in hexafluoroisopropyl alcohol (HFIP, a solvent that was critical to the success of Hall's and Moran's studies) to generate the corresponding diarylmethane." The reaction proceeded with low catalyst loading (1 mol%) and provided the product in very high yield. Dr. Xie examined several additional benzene derivatives and showed that their reactivity followed an expected trend based on their nucleophilicities. He was also able to show that the reaction of *p*-methoxybenzyl alcohol with *p*-xylene could be effected with as little as 0.01 mol%  $\text{Re}_2\text{O}_7$ . "At this point Youwei informed me of the results and asked if I would like to have a graduate student complete the study. I accepted this generous offer and Qi Qin, who had just completed the dehydrative cyclization study, continued with the project," said Professor Floreancig.

Mr. Qin's initial objectives were to explore the reactivity of a number of benzylic alcohols that incorporate electron-



**Figure 1** Reaction scope and regioselectivity

withdrawing groups. Professor Floreancig explained: “While he did not complete a formal Hammett plot, he was able to use Hammett parameters to show which substrates would be reactive. He also showed that certain halogenated arenes could act as nucleophiles. This will be valuable for efforts in which the products can be further diversified through cross-coupling chemistry or – in case of drug candidates – prevented from metabolic destruction by fluorine incorporation.” During this study, Mr. Qin discovered that Re<sub>2</sub>O<sub>7</sub>·SiO<sub>2</sub> could be used as an alternative to crystalline Re<sub>2</sub>O<sub>7</sub> with only a modest reduction in rate for most substrates. This agent, simply prepared by stirring Re<sub>2</sub>O<sub>7</sub> and SiO<sub>2</sub> in Et<sub>2</sub>O followed by solvent evaporation, was useful for measuring the quantities of catalyst to be used in these low-loading experiments and provided superior handling properties during a humid Pittsburgh summer. Very reasonable concerns arose in the initial review of this paper as to whether Re<sub>2</sub>O<sub>7</sub>·SiO<sub>2</sub> is a distinct catalyst or simply an agent that releases Re<sub>2</sub>O<sub>7</sub>. “Qi addressed this issue by heating Re<sub>2</sub>O<sub>7</sub>·SiO<sub>2</sub> in HFIP then filtering the solids. The filtrate was observed to be catalytically active, indicating that Re<sub>2</sub>O<sub>7</sub>·SiO<sub>2</sub> acts by releasing Re<sub>2</sub>O<sub>7</sub> into solution,” said Professor Floreancig.

Lowering the catalyst loading became Mr. Qin’s next objective. He observed that 0.1 mol% loading of Re<sub>2</sub>O<sub>7</sub>·SiO<sub>2</sub> was sufficient for promoting ionization of moderately deactivated systems, such as *m*-fluorobenzyl alcohol, but was not effective for the ionization of highly deactivated alcohols, such as *p*-trifluoromethylbenzyl alcohol. The catalyst loading to ionize activated alcohols, however, could be lowered significantly. “*p*-Methoxybenzyl alcohol couples with mesitylene in the presence of just 0.0033 mol% Re<sub>2</sub>O<sub>7</sub>·SiO<sub>2</sub>. Moreover, the concentration of this reaction could be increased to 2.5 M without consequence, and to 5.0 M with only a minimal impact on reaction efficiency” said Professor Floreancig. He continued: “This is significant because it improves the process with respect to cost and environmental impact. HFIP, despite showing

extremely useful properties, is somewhat expensive. We attributed the drop in efficiency at 5.0 M to a change in solvent properties since the relative volume of HFIP is much lower when the substrate concentrations are increased. This led us to examine the role of and need for HFIP in these processes. Qi showed that pure HFIP is required for reactions of unreactive substrates while mixtures of HFIP and 1,2-dichloroethane (DCE) can be used for more reactive substrates.” This is consistent with the high polarity of HFIP being required to generate unstable carbocation intermediates. However, the reaction with *p*-methoxybenzyl alcohol in pure DCE provided bis-*p*-methoxybenzyl ether as a significant by-product. “This suggests that HFIP plays the additional role of suppressing the nucleophilicity of the alcohols through hydrogen bonding,” explained Professor Floreancig.

He continued: “These reactions generate water as the sole by-product, and Re<sub>2</sub>O<sub>7</sub> is an anhydride. Therefore, Mr. Qin explored the possibility that perrhenic acid is the active agent in these reactions. This work showed that HOREO<sub>3</sub> can serve as a suitable alternative to Re<sub>2</sub>O<sub>7</sub> or Re<sub>2</sub>O<sub>7</sub>·SiO<sub>2</sub> for these reactions. This result was significant because HOREO<sub>3</sub> is less expensive than Re<sub>2</sub>O<sub>7</sub> while being equally reactive and can be handled as readily as Re<sub>2</sub>O<sub>7</sub>·SiO<sub>2</sub>. However, this also led to questions as to whether the reactions proceeded through a perrhenate ester, as initially proposed, or simply through Brønsted acid catalysis.”

“We had initially assumed that the reaction proceeded through a perrhenate ester since the pK<sub>a</sub> values of HOREO<sub>3</sub> and TfOH, the acid used in Moran’s studies,<sup>5</sup> differ by nearly 13, but the two agents are comparable at promoting the reactions,” said Professor Floreancig, who pointed out that other Brønsted acids that have pK<sub>a</sub> values that are similar to HOREO<sub>3</sub>, such as TFA and *p*-TsOH, are not nearly as effective at promoting the reactions. “The possibility exists, however, that an anomalous acidity enhancement is observed for HOREO<sub>3</sub> in

HFIP and none of our prior experiments could disprove that hypothesis,” said Professor Floreancig, who explained: “We addressed this initially by comparing the catalytic potencies of  $\text{Re}_2\text{O}_7$ ,  $\text{HOREO}_3$ , and TfOH in the coupling of *p*-trifluorobenzyl alcohol with *p*-xylene. We observed similar reaction rates with 1 mol%  $\text{Re}_2\text{O}_7$ , 2 mol%  $\text{HOREO}_3$ , and 10 mol% TfOH. Lowering the loading of TfOH to 2 mol% resulted in a much slower reaction. Thus, if  $\text{HOREO}_3$  acts as a Brønsted acid then the HFIP enhancement must provide >13 orders of magnitude in potency. The remarkable nature of this conclusion still does not invalidate the Brønsted acid hypothesis. We addressed this through comparing the reactivity of the alcohols, which can act through protonation or perrhenate ester formation, with acetate analogues, which can react only through protonation since the acyl group blocks perrhenate ester formation. TfOH catalyzes Friedel–Crafts alkylation reactions with the alcohols and the acetates, but  $\text{Re}_2\text{O}_7$  and  $\text{HOREO}_3$  only promote reactions with the alcohols.” This study finally dispelled the notion that  $\text{HOREO}_3$  acts solely as a Brønsted acid and supported the intermediacy of the perrhenate ester, though reactions could indeed proceed through a protonated perrhenate ester intermediate. Notably, the reactions between the acetate substrates in the presence of TfOH, while effective, proceeded slightly more slowly than the reactions of the corresponding alcohols despite the greater nucleofugacity of acetic acid in comparison to  $\text{H}_2\text{O}$ . This – according to the authors – indicates an additional role of HFIP as a desiccant in these reactions.

Professor Floreancig believes that this study is significant for multiple reasons. “From a practical perspective the use of  $\text{HOREO}_3$  as an agent for alcohol ionization provides a mild yet powerful approach to the formation of potent and important electrophiles. From a mechanistic perspective, the validation of a perrhenate or protonated perrhenate ester provides a new intermediate that can be generated in situ from readily available precursors.” Professor Floreancig concluded: “The use of perrhenate esters as progenitors to cationic intermediates should be considered as an alternative for processes that utilize strong acids to initiate ionization or that employ leaving groups that must be generated in a distinct step from an alcohol precursor.”

*Matthew Fenske*

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## About the authors



Prof. P. Floreancig

**Paul Floreancig** received his B.S. degree in chemistry from Indiana University (USA) in 1986. He moved to Yale University (USA) where he earned an M.S. degree while working for Professor Fred Ziegler. After spending two years at Eli Lilly (USA) he left for Stanford University (USA), where he earned his PhD in 1997 with Professor Paul Wender while working on the total synthesis of paclitaxel. After two years as an NIH postdoc-

toral fellow with Professor Peter Dervan at Caltech (USA), he moved to the University of Pittsburgh (USA) in 1999 as an assistant professor. He was promoted to associate professor in 2005 and to professor in 2010. His research interests include reaction design, natural product synthesis and analogue study, and drug delivery.



Dr. Y. Xie

**Youwei Xie** received his B.Sc. degree from Jilin University (P. R. of China) in 2006. He moved to the USA and received his M.Sc. degree under the guidance of Prof. Tewodros Asefa from Syracuse University (USA), and moved to the University of Pittsburgh (USA) to earn his PhD under the guidance of Prof. Paul Floreancig. In 2015, he became a Humboldt post-doctoral fellow at the Max-Planck-Institut für Kohlenforschung (Germany)

with Prof. Benjamin List. In early 2018, he joined the faculty at Huazhong University of Science and Technology (HUST, P. R. of China) where he is a professor in the School of Chemistry and Chemical Engineering.



Q. Qin

**Qi Qin** was born in Shanxi (P. R. of China). He received his B.S. degree in pharmaceutical science from Peking University Health Science Center (P. R. of China) in 2011, and his M.S. degree in chemical biology at the same school in 2013 under the guidance of Dr. Xin-shan Ye investigating stereoselective glycosylation based on pre-activation of thioglycosides. He then joined Dr. Paul Floreancig's group at the University of Pittsburgh (USA) as

a graduate student. His main research is centered around the synthesis of oxygen-based heterocycles and diarylmethane scaffolds through the use of  $\text{Re}_2\text{O}_7$  catalysis.



## Editorial Board Focus: Professor Franziska Schoenebeck (RWTH Aachen University, Germany)

**Background and Purpose.** From time to time, SYNFORM portraits Thieme Chemistry Editorial Board or Editorial Advisory Board members who answer several questions regarding their research interests and revealing their impressions and views on the developments in organic chemistry as a general research field. This Editorial Board Focus presents Professor Franziska Schoenebeck (RWTH Aachen University, Germany) who joined the Editorial Board of SYNTHESIS with effect of January 2019.

### Biographical Sketch



Prof. F. Schoenebeck

**Franziska Schoenebeck** has been a Full Professor at the Institute of Organic Chemistry at RWTH Aachen University (Germany) since the summer of 2016. Professor Schoenebeck was born and raised in Berlin (Germany). From 2001 to 2004, she studied chemistry at the Technical University of Berlin (Germany) and the University of Strathclyde in Glasgow (UK). She undertook her PhD studies in synthetic organic chemistry in the group of Prof. John A. Murphy in Glasgow (UK). In 2008, she moved to California to work with Prof. K. N. Houk at University of California Los Angeles (USA), where she was involved in computational studies of organic reactivity. In 2010, she joined the faculty of the ETH Zürich (Switzerland) as an Assistant Professor. In 2013, she was appointed Associate Professor at the Institute of Organic Chemistry at RWTH Aachen University (Germany) and promoted to Full Professor in 2016. She is the recipient of the Novartis Chemistry Lectureship (2016–2017), an ERC Starting Grant, the 2014 'Dozentenpreis' of the German Chemical Industry Fund, the 2014 ORCHEM Prize by the German Chemical Society, the 2014 Marcial Moreno Lectureship by the Spanish Royal Chemistry Society, the 2014 JPOC Award for Early Excellence in Physical Organic Chemistry and the ADUC Prize 2012.

### INTERVIEW

**SYNFORM** Please comment on your role as a Member of the Editorial Board of Synthesis.

**Prof. Schoenebeck** I will be responsible for the special topics and special issues, which are thematic collections of articles within Synthesis on relevant and exciting areas in organic chemistry.

**SYNFORM** What is the focus of your current research activities?

**Prof. Schoenebeck** Our research program is based at the interface of synthetic organic, mechanistic and computational chemistries with a strong emphasis in homogeneous metal catalysis. Our primary motivation is to uncover and develop fundamentally new reactivities as innovative solutions to pertinent research questions in relation to the preparation, properties and function of molecules.

*Mattias Fanck*

## Mendeleev, Menshutkin and Beilstein: A New Generation Takes Over

This year is the sesquicentennial of the publication of the periodic table,<sup>1</sup> and 2019 has been designated the International Year of the Periodic Table by UNESCO. Of equal (or more) importance to organic chemists, this year is also the sesquicentennial of the initial publication of Markovnikov's Rule, making 1869 a standout year for Russian chemistry. As a result, during this sesquicentennial year, the Name Reaction Bio columns will focus on Russian name reactions and rules.

The last third of the nineteenth century was a banner era in Russian organic chemistry.<sup>2</sup> In 1868, the Russian Chemical Society was founded during a meeting of the first Congress of Russian Naturalists and Physicians, making it one of the oldest chemical societies in Europe (Figure 1). During this time, Butlerov, Borodin, Markovnikov, Zaitsev, Wagner, Zelinskii,

Beilstein, Reformatskii, Menshutkin and others had contributed greatly to the growth of the discipline.

In the sixteen weeks from October 18, 1906, to February 5, 1907, three of the founding members of the Society died: Friedrich Konrad (Fedor Fedorovich) Beilstein (1838–1906; d. October 18), Dmitrii Ivanovich Mendeleev (1834–1907; d. February 2) and Nikolai Aleksandrovich Menshutkin (1842–1907, d. February 5). Their deaths followed those of Borodin (d. February 27, 1887), Wagner (d. November 27, 1903) and Markovnikov (d. February 11, 1904). This brief period also signaled the end of an era in Russian chemistry. The last of the Russian organic chemists who had achieved their zenith during the 19<sup>th</sup> century, Aleksandr Mikhailovich Zaitsev (1841–1910), died by the end of the decade.



**Figure 1** Founders of the Russian Chemical Society. Standing (left to right): F. R. Vreden, P. A. Lachinov, G. A. Schmidt, A. R. Shulyachenko, A. P. Borodin, **N. A. Menshutkin**, N. A. Sokovkin, **F. F. Beil'shtein (F. K. Beilstein)**, K. I. Lisenko, **D. I. Mendeleev**, F. H. Savchenkov. Seated (left to right): R. Yu. Richter, S. I. Kovalevskii, N. P. Nechaev, V. V. Markovnikov, A. A. Voskresenskii, P. A. Il'enkov, P. P. Alekseev, A. N. Engel'gardt. Image courtesy of Lomonosov Moscow State University.



Beilstein

Mendeleev

Menshutkin

### Mendeleev

Mendeleev was born in Tobolsk, Siberia, the youngest surviving child of seventeen. His father died when Mendeleev was a child, leaving his mother to raise her children alone. She reopened the family glass factory after her husband's death and ran it until it burned down. With that, she took her family to Moscow where she hoped to gain her son entry into the university. He was not accepted, however, so she moved the family again, to St. Petersburg, where Mendeleev was accepted into the Main Pedagogical Institute (now St. Petersburg State University), graduating in 1856. He contracted tuberculosis shortly thereafter, which forced him to move to a drier climate – Simferopol, Crimea. There he became science master at the Gymnasium, but he quickly found that he was not cut out to be a secondary school teacher. In 1857, recovered, he returned to St. Petersburg to the Chair of Chemistry at the St. Petersburg Technological Institute. He was called to the Chair in General Chemistry at St. Petersburg University in 1867 and was succeeded at the Technological Institute by Beilstein. He moved to the University of St. Petersburg, where he remained as Professor of Chemistry until 1890; he was appointed director of the Bureau of Weights and Measures in 1893 and occupied this position until his death.

In 1861, Mendeleev wrote *Organic Chemistry*<sup>3</sup> in response to his perception that there was no modern textbook for his course in organic chemistry. He wrote the book, which won the Demidov Prize of the Russian Academy of Sciences, in just two months. It was based on Gerhardt's type theory,<sup>4</sup> which was being superseded as organic chemists moved to the structural theory of organic chemistry.<sup>5</sup> Butlerov's book, *Introduction to the complete study of organic chemistry*,<sup>6</sup> published in 1864 and based entirely on structural theory, soon displaced it. Mendeleev's *Principles of Chemistry*, published in 1868,<sup>7</sup> quickly eclipsed his *Organic Chemistry* and became a major textbook of chemistry. It was while writing it that he developed his periodic table. The title pages of Mendeleev's books are given in Figure 2.



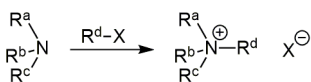
Figure 2 Title pages of Mendeleev's *Organic Chemistry* (left) and *Principles of Chemistry* (right)

His most lasting contribution to chemistry was his Periodic Law, during the development of which he proposed the existence of three then-unknown elements to fill gaps in his periodic table. Moreover, he asserted, on more than one occasion, that the accepted atomic weights for certain elements were incorrect because they did not correlate with periodic law; subsequent research proved him correct. Mendeleev did not present his proposals in person because he was absent from St. Petersburg on business for the Government Office of Weights and Measures. His paper<sup>1</sup> was read by his colleague and close friend, Menshutkin, and with Beilstein's encouragement, it was translated into German.<sup>8</sup> Mendeleev was elected a Corresponding Member of the Russian Academy of Sciences in 1876, but in 1880 he was denied the position of Professor of Technology in the Academy of Sciences by one vote (actually, an extraordinary majority was needed for election, but Mendeleev's supporters focused on the "just one vote").<sup>9</sup> He was awarded the Davy Medal of the Royal Society in 1882 (jointly with J. L. Meyer), and the Copley Medal of the Royal Society in 1905 for his work in elucidating the Periodic Law. In 1907 he missed a share of the Nobel Prize in Chemistry by a single vote (again!),<sup>10</sup> but the denial of the Professorship in the Russian Academy of Sciences was his most bitter defeat.

### Menshutkin

Mendeleev's colleague and friend Nikolai Aleksandrovich Menshutkin was a pioneer in physical organic chemistry, though he is best known for his eponymous reaction, the quaternization of tertiary amines with alkyl halides (Scheme 1). This paper appeared first in Russian,<sup>11a</sup> and then in German,<sup>11b</sup>

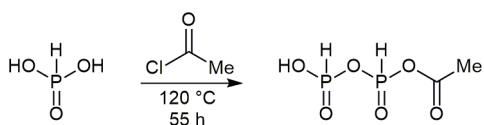
and although it has become primarily a synthetic paper, it was actually a far-reaching kinetic study of the rates of the quaternization reaction.



**Scheme 1** The Menshutkin reaction: quaternization of tertiary amines with alkyl halides

Menshutkin was born to a wealthy merchant family in St. Petersburg and attended the German School there. He graduated first in his class 1857, at age 15, but because he was underage, he was prevented from entering the university until he had passed a comprehensive examination. At the university, he came under the mentorship of two distinguished elder statesmen of Russian chemistry: Aleksandr Abramovich Voskresenskii (1809–1880), from whom he learned analytical and physical chemistry, and Nikolai Nikolaevich Sokolov (1826–1877), from whom he learned organic chemistry. Sokolov was a dedicated pedagogue, and Menshutkin idolized him.

At this time, most Russian universities seldom had more than rudimentary laboratory facilities – the chemistry laboratory at St. Petersburg, for example, consisted of two small rooms<sup>12</sup> – so as soon as Menshutkin had graduated with the degree of *kandidat* in 1862, he set off on a three-year *komandirovka* (paid study leave) in Western Europe to learn practical chemistry. He spent these three years in the Tübingen laboratory of Adolph Strecker (1822–1871), the Paris laboratory of Adolphe Wurtz (1817–1884), and the Marburg laboratory of Hermann Kolbe (1818–1884). While in Paris, he began his studies on the phosphorous acid derivative formed by the reaction between phosphorous acid and acetyl chloride (Scheme 2).<sup>13</sup>



**Scheme 2** Reaction of phosphorous acid and acetyl chloride

By the time of his return to St. Petersburg, he was ready to write up his dissertation for the degree of *Magistr Khimii*, based on his studies of phosphorous acid.<sup>14</sup> Immediately after

his graduation, he became Privatdocent in chemistry, and was quickly appointed permanent Docent (Assistant Professor) in the Chair of Chemistry. Menshutkin taught analytical chemistry (both lecture and laboratory), and a special course on alcohols. He began the research for his *Dr. Khimii* degree at the same time, and presented his dissertation, *Synthesis and properties of ureides*, in April 1869.<sup>15</sup> The formal opponents of this dissertation were Mendeleev and Butlerov, who both noted the extraordinary experimental skill of its author. Menshutkin was immediately appointed Extraordinary (Associate) Professor of Chemistry, and in 1876 he became Ordinary (Full) Professor. Beginning in 1871, he served two terms as Secretary of the Physics–Mathematics Faculty, and this was followed in 1879 by his election as Dean. He held this position until 1887, when he returned to the faculty as Professor. In 1885, he had become Head of Organic Chemistry, and in 1891 he was appointed “Honored Professor.” Two years later, in accord with the rules of the Ministry of Education, he retired from his Chair and became a “contingent” (i.e., Emeritus) Professor, but he retained his laboratory.

For much of his career, Menshutkin was an administrator, and his research output was fairly limited. He did serve as the Editor of the *Journal of the Russian Chemical Society* in 1869,

ROH		AcOH	ROH
		155 °C	
<b>Primary alcohols</b>			
Alcohol	Initial velocity	Alcohol	Initial velocity
MeOH	55.59	<sup>t</sup> PrOH	26.53
EtOH	46.81	EtCH(Me)OH	22.59
<sup>n</sup> PrOH	46.50	<sup>t</sup> PrCH(Me)OH	18.95
<sup>n</sup> BuOH	46.85	Et <sub>2</sub> CHOH	16.93
<sup>n</sup> C <sub>8</sub> H <sub>17</sub> OH	46.57	<sup>t</sup> BuCH(Et)OH	18.23
<i>i</i> -BuOH	44.36	<sup>n</sup> C <sub>6</sub> H <sub>13</sub> CH(Me)OH	21.19
H <sub>2</sub> CCHCH <sub>2</sub> OH	35.72		
HCCCH <sub>2</sub> OH	20.50		
PhCH <sub>2</sub> OH	38.64		
<b>Tertiary alcohols</b>			
Alcohol	Initial velocity		
<sup>t</sup> BuOH	1.43		
Me <sub>2</sub> C(Et)OH	0.81		
Et <sub>2</sub> C(Me)OH	1.04		
<sup>n</sup> PrCMe <sub>2</sub> OH	2.15		
<sup>t</sup> PrCMe <sub>2</sub> OH	0.86		
H <sub>2</sub> C=CHCH <sub>2</sub> CMe <sub>2</sub> OH	3.08		
<b>RCO<sub>2</sub>H</b>			
		<sup>t</sup> BuOH	
		155 °C	
		RCO <sub>2</sub> /Bu	
Acid	Initial velocity	Acid	Initial velocity
HCO <sub>2</sub> H	61.69	<sup>n</sup> C <sub>7</sub> H <sub>15</sub> CO <sub>2</sub> H	30.86
MeCO <sub>2</sub> H	44.36	<sup>t</sup> PrCO <sub>2</sub> H	29.03
EtCO <sub>2</sub> H	41.16	EtCH(Me)CO <sub>2</sub> H	21.50
<sup>n</sup> PrCO <sub>2</sub> H	33.25	<sup>t</sup> BuCO <sub>2</sub> H	8.28
<sup>n</sup> C <sub>5</sub> H <sub>11</sub> CO <sub>2</sub> H	33.08	EtCMe <sub>2</sub> CO <sub>2</sub> H	3.45

**Figure 3** Menshutkin's investigations of uncatalyzed esterification reactions

and of its successor, the *Journal of the Russian Physical–Chemical Society* from 1870 to 1900, leaving a lasting mark on the course of organic chemistry in Russia.

We have already alluded to what we now know as the Menshutkin (Menschutkin) reaction, but he was actually one of the pioneers of physical organic chemistry. In both the Menshutkin reaction and his extensive studies of the effects of structure on the rates of uncatalyzed esterification reactions, he was able to show that the structure of the alkyl group of the acid and the alcohol both affect the rate of the esterification reaction. Figure 3 gives data from one of Menshutkin's studies in which equimolar quantities of the acid and alcohol were heated together at 155 °C without any catalyst. All the reactions were carried out to the same fraction of completion (approximately 70%).<sup>16</sup> Thus, Menshutkin was one of the pioneers in the study of what we call structure–reactivity relationships.

### Beilstein

The third principal of this Name Reaction Bio is Fyodr Fyodrovich Beil'shtein, better known by the German form of his name, Friedrich Konrad Beilstein. To quote American historian Mark Gordin,<sup>17</sup> “Beilstein may be the best-known organic chemist that most organic chemists know nothing about.” Most organic chemists are familiar with *Beilsteins Handbuch der organischen Chemie*, which has gone through four supplements to the original *Hauptwerk*, and is now online (since 2009, the content has been maintained and distributed by Elsevier Information Systems in Frankfurt, under the product name “Reaxys”<sup>18</sup>).

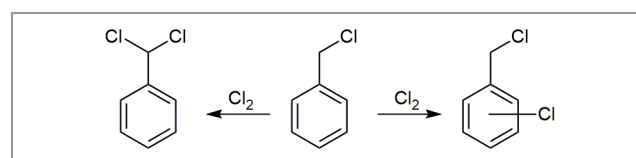
Beilstein was born to an ethnic (Baltic) German family in St. Petersburg, but his parents decided that he should receive a German education. He began his education at the St. Petersburg German School, and then, in 1853, at the age of 15, his parents sent him to Germany to complete his education. He studied first with Bunsen at Heidelberg, then he moved to Berlin in 1855, where he worked with Jolly and attended lectures by Liebig. He met Hübner and Kekulé on his return to Heidelberg in 1856 and became firm friends with both. In 1857, he moved to Göttingen, where he received his Ph.D. two days before his 20<sup>th</sup> birthday.

Beilstein spent 1858 with Wurtz in Paris, and returned to Germany in 1859 as Assistant to Löwig in Breslau. However, Beilstein chafed under the rigid rules in Löwig's laboratory, so when Wöhler offered him a position at Göttingen in 1860, he eagerly returned to his alma mater. He remained at Göttingen until 1866, when he returned to St. Petersburg after the sudden death of his father. It is interesting that he had been made an offer by St. Petersburg University in 1865 and that this had

been countered by an offer from Göttingen, but he returned to Russia to take up a position as Professor at the less prestigious St. Petersburg Technological Institute at a lower salary. A year after his return to Russia, he renounced his German citizenship to become a subject of the Tsar; at the time, this was a highly unusual action. Beilstein spent the remainder of his career at the Technological Institute.

Beilstein's research output was relatively scant (especially compared to his contemporaries, Menshutkin, Markovnikov and Butlerov), which may be surprising given the impact of his *magnum opus*. Unlike the University, the Technological Institute was not a research-focused institution, but was intended, instead, for the education of engineering students. Neither the students nor Beilstein's assistants had any interest in research, so his output rapidly dwindled to zero. This may, in fact, have been a blessing in disguise, because it gave him the time needed to write his *Handbuch der organischen Chemie*.

Beilstein's original research was involved with the preparation and reactions of organic halogen compounds. His study of the chlorination of benzyl chloride showed that the regiochemistry of the reaction was dependent on the exact reaction conditions. At low temperature, Beilstein obtained ring-substituted products, chlorobenzyl chlorides, and at high temperature, he observed the formation of the side-chain-chlorinated product, benzal chloride (Scheme 3).<sup>19</sup> During this same work, he developed the Beilstein test for halogens<sup>20</sup> (consisting of heating a copper wire in a Bunsen burner flame until all traces of blue or green were absent from the flame, cooling the wire, immersing the cold wire in the substance to be tested, and finally returning it to the flame; a green flame indicated the presence of halogen in the test material).



**Scheme 3** Beilstein's investigations into the regiochemistry of the chlorination of benzyl chloride

Like Menshutkin, Beilstein served as Editor of a chemistry journal. In Beilstein's case, the journal was the *Zeitschrift für Chemie und Pharmacie*, which he co-edited with his friend, Hübner, and Rudolf Fittig. He continued editorship of the journal following his return to Russia, and there he successfully promoted the *Zeitschrift* as a German-language outlet for Russian chemists. It was Beilstein who persuaded Mendeleev to

publish his periodic law in the *Zeitschrift*, which was probably a critical step in obtaining its widespread acceptance.<sup>21</sup>

We cannot conclude this Name Reaction Bio without recounting the events of 1880, when Mendeleev was denied the Chair of Technology in the Academy of Sciences. This event literally tore the Russian chemical community apart. The “Russian” faction in the Academy, which included Aleksandr Mikhailovich Butlerov (1828–1886), viewed Mendeleev’s rejection as a repudiation of Russian organic chemists in general. Butlerov led the major figures in writing a letter to the popular press in which they lambasted the Academy, but Beilstein did not sign the letter because he believed that the appropriate action was to censure the Academy in a lecture read before the Russian Physical–Chemical Society. This branded him as a member of the “German” faction (his actions in having become a naturalized subject of the Tsar thirteen years earlier notwithstanding) and shattered his long friendship with Butlerov. When Butlerov himself was elected to the Chair in 1882, he used the rules of the Academy to prevent Beilstein from being confirmed in that position: Beilstein became the Professor in the Chair of Chemical Technology only after Butlerov’s death.

With the loss of these three chemists, the nineteenth century era of organic chemistry in Russia came to an end, and the torch was passed on to the next generation of Russian organic chemists. Among these were Markovnikov’s students (Kizhner, Chichibabin and Dem’yanov), Zaitsev’s students (Reformatskii and Arbuzov), as well as Butlerov’s student (Favorskii) and Favorskii’s student (Ipat’ev/Ipatieff), all of whom influenced the course of organic chemistry.

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