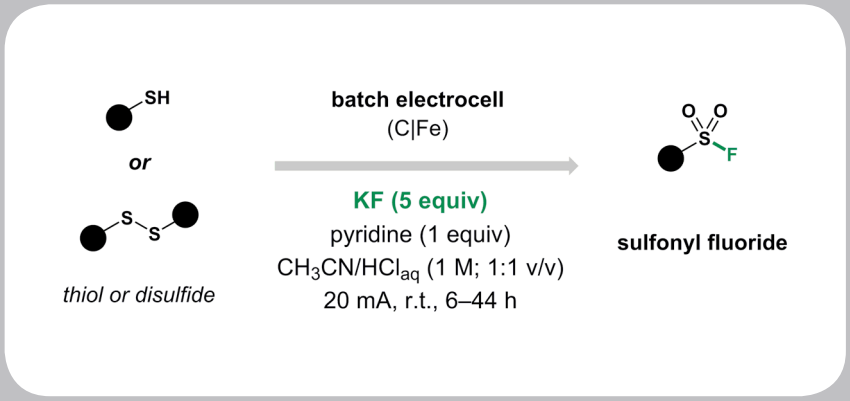
Synform

People, Trends and Views in Chemical Synthesis

2019/11

Sulfonyl Fluoride Synthesis through Electrochemical Oxidative Coupling of Thiols and Potassium Fluoride

Highlighted article by G. Laudadio, A. de A. Bartolomeu, L. M. H. M. Verwijlen, Y. Cao, K. T. de Oliveira, T. Noël



Contact
Your opinion about Synform is welcome, please correspond if you like:
marketing@thieme-chemistry.com

Thieme

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

Dear Readers,

This new issue of SYNFORM could not be further from the grey and dull atmosphere of November! It is actually quite glittering and thoroughly enjoyable, besides being informative. The first article deals with a classic of organic chemistry, namely the total synthesis of (–)-morphine and (–)-codeine, but in this case it is a catalytic stereoselective version developed by Y.-Q. Tu (P. R. of China). The second article is a Young Career Focus interview with O. Gidron (Israel) who describes his research and aims. The third article – a Name Reaction Bio – is a truly amazing and thorough report on a crucial chapter in the history of organic chemistry: the Markovnikov and Hofmann rules and the role of the trailblazers who made and rationalized those textbook discoveries on the addition and elimination reactions, and their regiochemistry. The issue is closed by the electrochemical breakthrough in the preparation of sulfonyl fluoride synthesis recently reported by T. Noël (The Netherlands).

I am sure you will enjoy your reading!!!

In this issue

Literature Coverage
Catalytic Asymmetric Total Syntheses of (–)-Morphine and (–)-Codeine A164

Young Career Focus
Young Career Focus: Dr. Ori Gidron (The Hebrew University of Jerusalem, Israel) A169

Name Reaction Bio
Reaction Regiochemistry – Markovnikov, Zaitsev and Hofmann A172

Literature Coverage
Sulfonyl Fluoride Synthesis through Electrochemical Oxidative Coupling of Thiols and Potassium Fluoride A180

Coming soon A183

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

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

Catalytic Asymmetric Total Syntheses of (–)-Morphine and (–)-Codeine

Nat. Commun. **2019**, *10*, 2507

(–)-Morphine (**1a**, Figure 1) is one of the most important and efficient analgesic drugs in the clinic and has been continuously ranked among the World Health Organization (WHO) model lists of essential medicines since 1977. Architecturally, (–)-morphine possesses a synthetically challenging pentacyclic framework containing five contiguous stereocenters. Therefore, (–)-morphine and several related alkaloids have attracted a considerable amount of research interest from the synthetic and pharmaceutical communities, and more than 30 total or formal synthetic routes have been reported. However, the catalytic and enantioselective total synthesis of (–)-morphine has not been extensively explored yet and the asymmetric construction of the crucial all-carbon quaternary stereocenter remains a major challenge. Professor Yong-Qiang Tu from Lanzhou University (P. R. of China) explained: "The existing catalytic asymmetric syntheses of (–)-morphine exhibit common drawbacks, including: (1) long synthetic routes, (2) low overall yields and unsatisfactory enantioselectivity, and (3) the lack of direct and catalytic asymmetric construction of the key chiral quaternary carbon or AEC ring system from racemic starting materials. Thus, we felt that a concise and efficient catalytic enantioselective total synthesis of (–)-morphine was much needed."

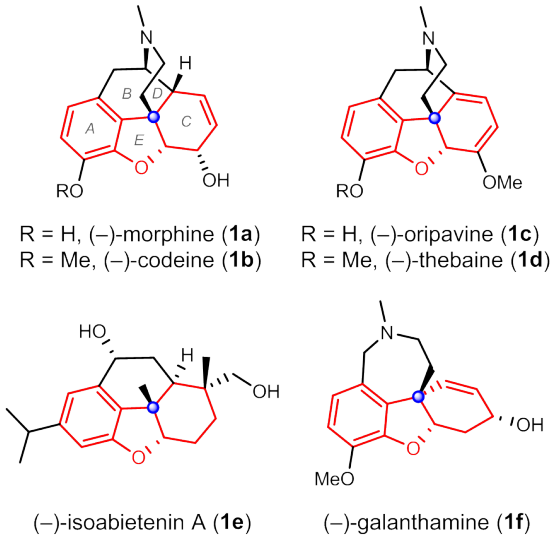


Figure 1 Morphine and several structurally related natural products

Recently, Professor Tu and Professor Fu-Min Zhang, also at Lanzhou University, reported the catalytic asymmetric total syntheses of (–)-morphine and (–)-codeine *via* a highly enantioselective Robinson annulation. "Since 2010 our group has focused on the design and preparation of novel chiral ligands or catalysts based on spirocyclic pyrrolidine (SPD) and spirocyclic amide (SPA) backbones. And these catalysts have successfully facilitated several asymmetric reactions (*Chem. Commun.* **2015**, *51*, 9979–9982; *Org. Lett.* **2017**, *19*, 6618–6621; *J. Am. Chem. Soc.* **2018**, *140*, 10099–10103)," said Professor Tu. He continued: "As a continuation of this research subject for further expanding the application of our SPD catalysts, the asymmetric total synthesis of (–)-morphine was undertaken."

The designed enantioselective Robinson annulation reaction was initially investigated by the graduate student Qing Zhang, who found that some commonly used secondary amine catalysts could not catalyze this reaction. However, the intramolecular Michael adduct **3** could be isolated (Scheme 1). "The asymmetric synthesis of such functionalized hydrobenzofuran bearing a quaternary carbon center has rarely been reported, and, importantly, the enantioselectivity of the Michael addition is vital for obtaining the enantioenriched tricyclic product **4**. Therefore, an extensive investigation of this asymmetric Michael reaction was carried out," Professor Tu explained.

Under the guidance of Professor Fu-Min Zhang, Qing Zhang screened a number of catalysts and additives. "We found that the steric hindrance of the substituents at C2 and C6 positions of benzoic acid derivatives had a significant capacity to improve the enantioselectivity of the Michael addition. Among them, the more sterically bulky additive 2,4,6-triisopropylbenzoic acid (**A1**) in the presence of our developed SPD catalyst (**Cat.1**) gave the best result (96% ee)," commented Professor Zhang. He added: "As a matter of fact, in asymmetric aminocatalysis it is extremely rare to observe such an intriguing substituent effect in an additive." Subsequently, a series of structurally varied substrates were explored in the SPD-catalyzed Michael addition. Excellent enantio- and diastereoselectivities (up to 96% ee and >20:1 dr) as well as good to high yields (up

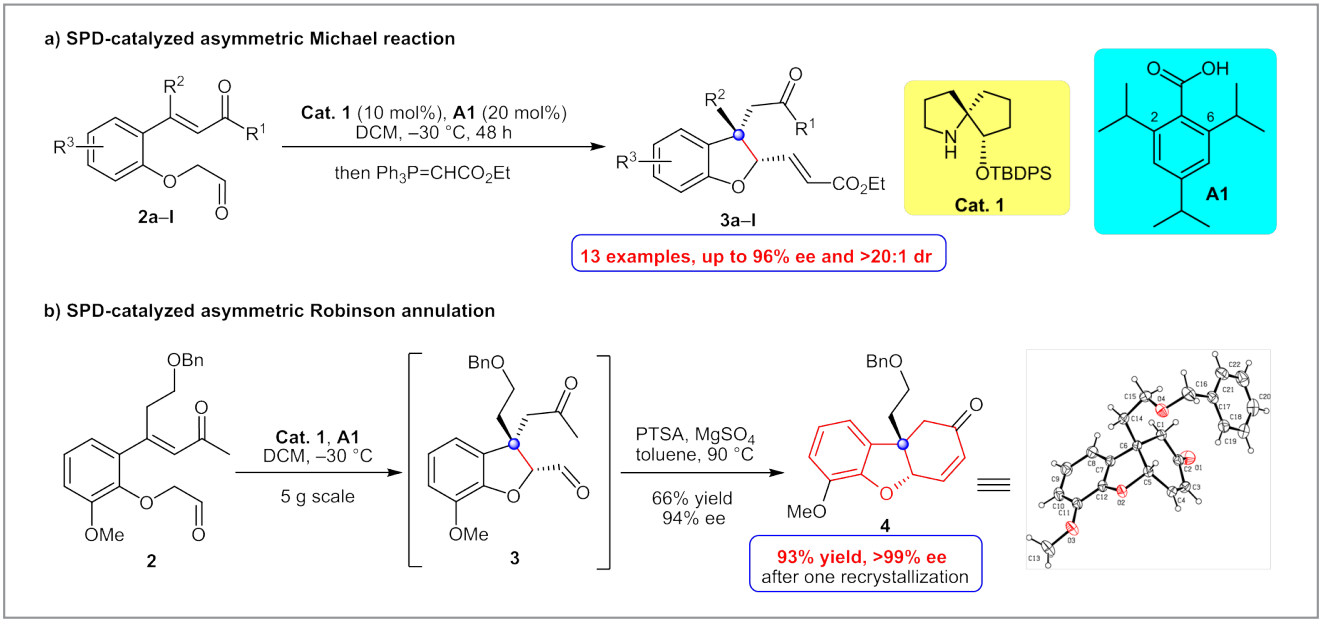
This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

to 87% yield) were obtained (Scheme 1, a). "This work represents an important advance in utilizing the SPD catalysts. It also demonstrates that our developed SPD catalysts possess unique catalytic properties for the asymmetric construction of the synthetically challenging all-carbon quaternary stereocenter," Professor Tu remarked.

After developing the SPD-catalyzed intramolecular Michael reaction, Qing Zhang successfully achieved the one-pot enantioselective Robinson annulation and further increased the enantiopurity (>99%) of the tricycle product **4** by recrystallization (Scheme 1, b). Professor Tu explained: "This key Robinson annulation reaction can efficiently construct the highly functionalized *cis*-hydrodibenzofuran framework bearing two contiguous stereocenters, including an all-carbon quaternary center, in a one-pot chemical manipulation." He continued: "Notably, the current asymmetric transformation may be applied in the syntheses of a series of structurally related bioactive natural products, such as abietane diterpene (–)-isoabietenin A (**1e**) or clinical drugs, such as (–)-galanthamine (**1f**) (Figure 1)."

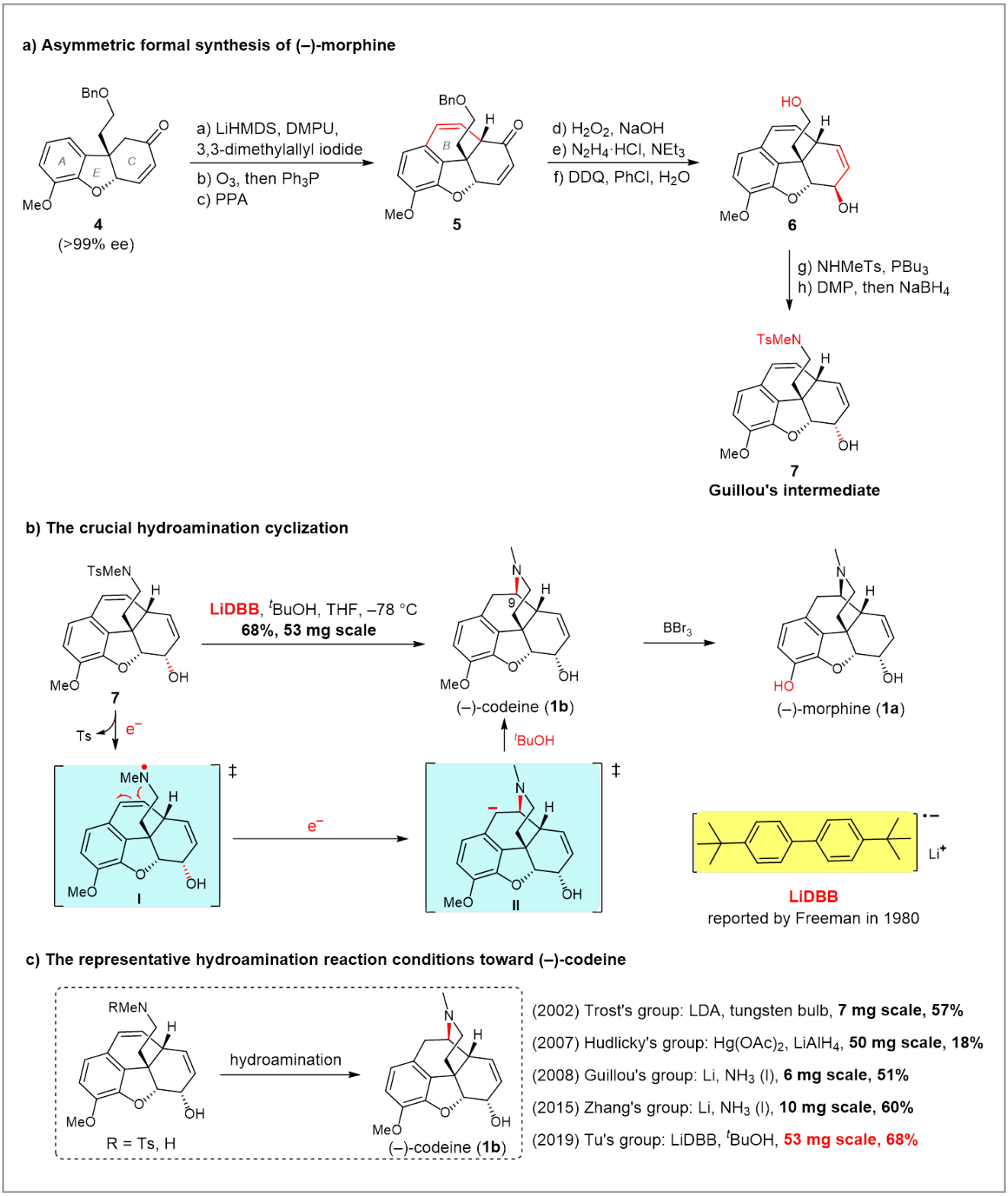
Having efficiently assembled the AEC ring system of (–)-morphine, the authors turned their attention on accomplishing the total synthesis of the target molecule **1a** (Scheme 2, a). "After screening a number of reaction conditions, we successfully constructed the B ring of (–)-morphine by Friedel–Crafts reaction over three steps. Subsequently, the transformation of tetracyclic enone **5** to allylic alcohol **6** was achieved by a Wharton reaction. Finally, a highly regioselective Mitsunobu reaction of compound **6**, followed by the inversion of configuration of the allylic alcohol, produced Guillou's intermediate **7**," remarked Professor Tu. He added: "Actually, at this point, we had completed the asymmetric formal synthesis of (–)-morphine."

In the final effort towards (–)-morphine, Professor Tu and his co-workers explored an alternative approach to the efficient construction of the C-9 stereocenter. "Mechanistically, this ring-forming reaction probably proceeds through a single-electron reduction of the sulfonamide unit to produce a nitrogen radical, which undergoes a subsequent radical addition/reduction/protonation sequence to generate (–)-codeine (**1b**) (Scheme 2, b). We speculated that after the formation of an active nitrogen radical, the next regio- and stereoselective intramolecular ring-closing procedure should readily occur in view of the annular strain and the conformational features of the morphine scaffold," Professor Tu explained. He continued: "Therefore, we considered that the mild and readily available free radical initiator, lithium 4,4′-di-*tert*-butylbiphenylide (LiDBB) (*J. Org. Chem.* **2016**, *81*, 10707–10714) might be a suitable reagent to initiate this transformation. As we expected, the crucial hydroamination cyclization proceeded well, which efficiently provided the desired (–)-codeine (**1b**) in higher yield (68%)." Professor Tu remarked: "Notably, in comparison to the previously reported results (Scheme 2, c), this novel methodology exhibited a remarkable superiority



Scheme 1 SPD-catalyzed enantioselective Michael reaction and Robinson annulation

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.



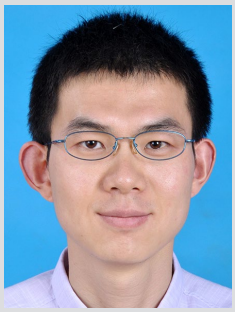
Scheme 2 The asymmetric total syntheses of (–)-codeine and (–)-morphine

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

in terms of higher chemical yield, larger synthetic scale, and better reproducibility." Finally, (–)-codeine (**1b**) was easily converted into (–)-morphine (**1a**) *via* demethylation with BBr_3 in high yield.

Professor Tu concluded: "In summary, the concise and catalytic asymmetric total syntheses of (–)-codeine and (–)-morphine were accomplished from commercially available but-3-yn-1-ol over 15 and 16 steps, respectively. The highly efficient SPD-catalyzed enantioselective Robinson annulation is not only able to construct the AEC tricyclic nucleus of the target molecules, but also showcases the excellent catalytic properties of our developed SPD catalysts. Additionally, the current study provides the first example of the synthesis of (–)-morphine through direct and catalytic asymmetric construction of the synthetically challenging all-carbon quaternary stereocenter. Finally, this asymmetric synthetic route constitutes an effective approach to the preparation of (–)-morphine and its analogues. Further synthetic applications of this methodology and significant exploration of the SPD-catalyzed tandem reaction are currently in progress in our labs."

About the authors

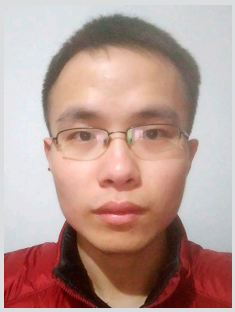


Q. Zhang

Qing Zhang is from Dezhou, Shandong Province, P. R. of China. He obtained his B.S. degree from Shandong Normal University (P. R. of China) in 2013. Then he joined Professor Yong-Qiang Tu's group at Lanzhou University (P. R. of China) as a PhD candidate. Now his research interests mainly focus on asymmetric catalysis and total syntheses of natural products.

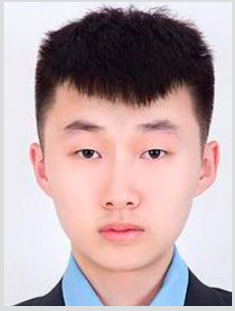
Prof. F.-M. Zhang

Fu-Min Zhang received his MS (2001) and PhD (2006) degrees from Lanzhou University (P. R. of China) under the supervision of Professor Xuan Tian and Professor Yong-Qiang Tu, respectively. He worked as a postdoctoral fellow at the Mayo Clinic (USA) with Professor Yuan-Ping Pang (2007–2008). He returned to Lanzhou University as a lecturer and was then appointed as an associate professor in 2009 and a full professor in 2014. Currently, he is interested in the total syntheses of natural products and relative synthetic methodology.



C.-S. Zhang

Chang-Sheng Zhang was born in Jiangxi Province, P. R. of China. He received his Bachelor's degree from Zhengzhou University (P. R. of China) in 2016. He then moved to Lanzhou University (P. R. of China) for his Master's degree under the supervision of Professor Yong-Qiang Tu. His research interests focus on developing new SPD-type ligands and applying them to new asymmetric reactions.



S.-Z. Liu

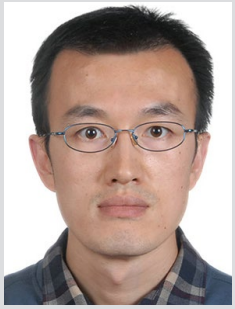
Si-Zhan Liu was born in Hebei Province, P. R. of China. He received his Bachelor's degree from Lanzhou University (P. R. of China) in 2018. Now he is studying for his Master's degree under the supervision of Professor Shao-Hua Wang at the School of Pharmacy, Lanzhou University. Currently, his research interests involve the development of novel synthetic methodologies.

Dr. J.-M. Tian

Jin-Miao Tian received his PhD from Lanzhou University (P. R. of China) in 2016 under the supervision of Professor Yong-Qiang Tu and then moved to Shanghai Jiao Tong University (P. R. of China) as a postdoctoral associate with Professor Yong-Qiang Tu. There his research focused on developing new SPD-type ligands and organocatalysts and applying them in asymme-

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

tric catalysis. Currently, he is a research associate at the Institute of Molecular Medicine (IMM), Renji Hospital, Shanghai Jiao Tong University School of Medicine. His research now focuses on aptamer-based biological applications.



Prof. S.-H. Wang

Shao-Hua Wang obtained his PhD in organic chemistry from Lanzhou University (P. R. of China) with Professor Yong-Qiang Tu in 2006. From 2006 to 2011, he was a postdoctoral associate in Professor Yuan-Ping Pang's group at the Mayo Clinic (USA). In 2011, he was appointed as an associate professor at the School of Pharmacy, Lanzhou University. His current research interests involve the development of synthetic methodologies and their application in the syntheses of natural products, and medicinal chemistry.

Dr. X.-M. Zhang

Xiao-Ming Zhang studied chemistry at Lanzhou University (P. R. of China) where he received his BS in 2007. He then joined the research group of Professor Yong-Qiang Tu and completed his PhD at Lanzhou University in 2013. Currently, he is a lecturer at the Department of Chemistry, Lanzhou University. His research mainly focuses on total syntheses and biomimetic syntheses of natural products.

Prof. Y.-Q. Tu

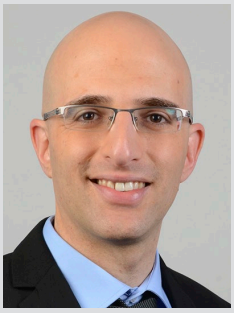
Yong-Qiang Tu received his BS and MS degrees from Lanzhou University (P. R. of China) in 1982 and 1985, respectively. He obtained his PhD in organic chemistry in 1989 from Lanzhou University under the supervision of Professor Yao-Zu Chen. After spending three years (1993–1995) as a postdoctoral fellow in W. Kitching's group at Queensland University, Australia, he was appointed to a full professor position at Lanzhou University in 1995 and became Director of the State Key Laboratory of Applied Organic Chemistry from 2001 to 2010. In 2009, he was elected as Academician of the Chinese Academy of Sciences. His current research interests mainly center on the development of novel chiral ligands or catalysts, and their application to new asymmetric reactions, as well as the total syntheses of bioactive natural products.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

Young Career Focus: Dr. Ori Gidron (The Hebrew University of Jerusalem, Israel)

Background and Purpose. SYNFORM regularly 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. Ori Gidron (The Hebrew University of Jerusalem, Israel).

Biographical Sketch



Dr. O. Gidron

Ori Gidron received his M.Sc. in chemistry from the Weizmann Institute of Science (Israel) in 2007 under the supervision of Professor M. van der Boom. He then joined the group of Professor M. Bendikov at the Weizmann Institute of Science and received his Ph.D. in 2012, for which he was awarded the Dov-Elad Prize for Excellence in Chemical Research. In June 2013, he accepted a Marie Curie (IEF) Postdoctoral Fellowship to work in the group of Professor F. Diederich at ETH Zurich (Switzerland) on supramolecular assemblies of carbon-rich materials. In 2015, he became an assistant professor at the Hebrew University of Jerusalem (Israel). In 2019, he received an ERC Starting Grant for his research on the topic of helically locked π-conjugated materials. His main interests are chiral organic semiconductors, curved aromatic systems, and furan-containing materials for organic electronics.

INTERVIEW

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

Dr. O. Gidron Our research activity aims to synthesize and study new functional π-conjugated materials for applications in organic electronics. In that context, our current main project studies how twisting aromatic molecules affects their properties. The performance of organic electronic materials is strongly dependent on their conformation. Twisting these materials out of planarity induces chirality and generates new electronic, magnetic, optical, and chiroptical properties. Materials possessing valuable new properties are desired for application in non-linear optical devices, spin filters, chiroptical devices and magneto-optical devices. However, the effect of twisting is poorly understood, and twisting is often achieved at the expense of π-conjugation, resulting in inferior device performance. We have recently introduced helically locked twisted acenes, which allow us to systematically study the effect of twisting on various electronic, optical, chiroptical, and magnetic material properties.[1]

SYNFORM *When did you get interested in synthesis?*

Dr. O. Gidron Growing up, one of the most influential books on my career was "*The Periodic Table*" by Primo Levi. The love for chemistry portrayed in his book influenced my career path and convinced me to start my undergraduate studies in chemistry. My fascination with organic synthesis began during my bachelor studies, where I was first exposed to the power of synthetic organic chemistry from the story of the discovery of conducting polymers. It amazed me that synthetic organic chemists have the power to engineer the color and conductivity of organic materials by synthetic modification. In addition, I found great satisfaction in synthetic labo-

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

© Georg Thieme Verlag Stuttgart • New York – Synform **2019/11**, A169–A171 • Published online: October 18, 2019 • DOI: 10.1055/s-0037-1612203

ratory work, in general, and particularly in obtaining a new molecule that was never previously synthesized.

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

Dr. O. Gidron Synthetic organic chemistry is more relevant today than ever, with new synthetic methodologies enabling breakthroughs, such as the recent synthesis of the first carbon nanobelts, or synthetic supramolecular assemblies that constitute molecular machines. As new applications emerge for electronic, optical, and spintronic devices comprising organic molecules, the development of new methodologies to obtain these targets is crucial. The introduction of automated processes, such as automated flash chromatography and the emergence of flow chemistry, have already greatly improved efficiency, enabling chemists to focus on more complex synthetic challenges. In addition to classical synthetic methods, the recent introduction of on-surface synthesis and STM characterization techniques enable the synthesis of large graphene nanoribbons and other carbon allotropes that were previously inaccessible, mostly because of their low solubility and low yields.

SYNFORM *Could you tell us more about your group's areas of research and your aims?*

Dr. O. Gidron Our group focuses on the development of new functional π-conjugated materials for organic electronics, and on understanding the relationship between structure (planarity, different heteroatoms, etc.) and material properties. For this purpose, we combine computational chemistry, organic synthesis, and materials characterization techniques.

In addition to the abovementioned study of helically locked twisted acenes, we also focus on three other major projects (Figure 1):

(i) *The development of conducting polymers with strong emission in the visible and near infrared (NIR) spectral region*: Although many conjugated polymers display strong emission in the visible spectral range, obtaining such emission in the NIR spectral region is a significant challenge. While oligo- and polyfurans emit considerably stronger fluorescence than their thiophene analogues, they are yet to display fluorescence in the NIR. In addition, oligofurans suffer from low stability, which limits their application. We have recently developed a new building unit, the bifuranimide, which is significantly more stable than its furan analogues. Oligomers and polymers containing bifuranimide display strong fluorescence from the blue to red spectral region.[2]

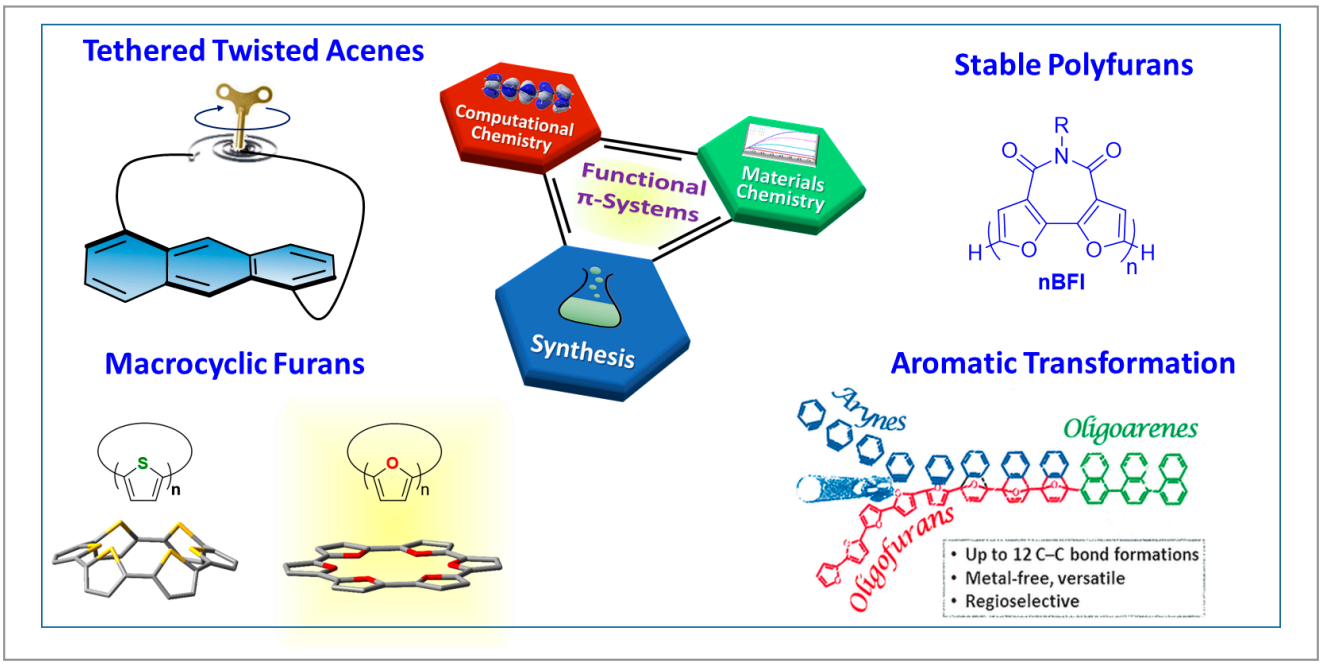


Figure 1 Main projects currently being studied in the Gidron group. Reprinted with permission from references 1a and 3, copyright (2018) American Chemical Society, and from reference 4, copyright (2017) Wiley-VCH.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

(ii) *Investigation of new macrocyclic systems*. We are investigating new oligofuran-based macrocyclic systems for organic electronics. In a computational study, we found that replacing thiophene with furan should significantly decrease the strain energies for small macrocycles. Calculations indicate that the macrocyclic ring should show a low ionization potential, small reorganization energies, and small HOMO–LUMO gaps, rendering them excellent candidates for organic semiconductors.[3]

(iii) *Development of new methodologies for the synthesis of conjugated backbones*. Although conjugated oligomers such as oligophenylenes are important active materials in organic electronics, their synthesis can be challenging. We recently introduced a regioselective transformation of oligofurans to oligoarenes using multiple Diels–Alder cycloadditions.[4]

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

Dr. O. Gidron Our introduction of the first helically locked twisted acenes is our most important scientific achievement to date. It is also the starting point toward achieving our next goal, namely, synthesizing intrinsically chiral and conjugated organic materials with tunable twist. We hope to embed our materials in conducting polymers and study the effect of helicity on performance. In this way, our goal is to obtain a better understanding of the conformational factors that govern the Chiral Induced Spin Selectivity (CISS) effect, and the performance of magneto-optical materials among other effects.

REFERENCES

(1) (a) A. Bedi, L. J. W. Shimon, O. Gidron *J. Am. Chem. Soc.* **2018**, *140*, 8086–8090. (b) A. Bedi, O. Gidron *Chem. Eur. J.* **2019**, *25*, 3279–3285. (c) A. Bedi, R. Carmieli, O. Gidron *Chem. Commun.* **2019**, *55*, 6022–6025.
(2) S. V. Mulay, B. Bogoslavky, I. Galanti, E. Galun, O. Gidron *J. Mater. Chem. C* **2018**, *6*, 11951–11955.
(3) O. Dishi, O. Gidron *J. Org. Chem.* **2018**, *83*, 3119–3125.
(4) S. Gadakh, L. J. W. Shimon, O. Gidron *Angew. Chem. Int. Ed.* **2017**, *56*, 13601–13605.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

Reaction Regiochemistry – Markovnikov, Zaitsev and Hofmann

In previous columns in this series, the focus has been on name reactions in organic chemistry. But two of the oldest synthetic reactions – addition and elimination – are also associated by name with empirical rules proposed by the pioneering chemists who observed their regiochemical and stereochemical outcomes. These named rules are a major part of the teaching of these reactions in introductory organic chemistry courses.

Additions: Markovnikov's Rule

On November 6, 1869, Aleksandr Mikhailovich Butlerov (1828–1886), newly appointed as Professor at the St. Petersburg Medical-Surgical Academy, read a paper by his former student and colleague at Kazan, Vladimir Vasil'evich Markovnikov (1837/8–1904),[1] to the meeting of the Russian Chemical Society. This paper, which appeared in the November issue of Volume 1 of the Journal of the Society,[2] contained the first disclosure of the empirical rule for predicting the outcome of addition reactions that has borne Markovnikov's name since.

Top row (left to right): Butlerov, Markovnikov; bottom row (left to right): Kittary, Kolbe

Markovnikov was born into the Russian nobility near Nizhnii Novgorod in December, but sources vary as to the year and village of his birth.[3,4] His father, Vasilii Vasil'evich, was a Lieutenant in the Belevskii Jaeger Regiment; shortly after his son was born, he retired from his military post and took his family to the estate near Knyaginino that he had procured as part of the dowry of his wife, Lyubov Nikolaevna. Markovnikov was first taught to read by the village priest, and he read so voraciously that by the time he left home at 10 years old, he could read both French and German. At 10 years of age, he was sent to the Nizhnii Novgorod Alexander II Nobles Institute to complete his secondary education. In 1856, he entered the Juridicial Faculty of the Imperial Kazan University as a student in cameral (economic) science.

At that time, Russia was implementing the German cameral system in an attempt to educate government workers better qualified to deal with new technologies. Part of the cameral course of study was a requirement that all cameral students take two years of science. Markovnikov had come in contact early with Modest Yakovlevich Kittary (1825–1880), the Professor of Chemical Technology, and Kittary's lectures captivated him. However, before he could take chemical technology for his required science, Kittary had left for Moscow. As a consequence, Markovnikov came under the influence of Aleksandr Mikhailovich Butlerov (1828–1886), whom we encountered in an earlier column in this series.[5] This was a fortuitous happenstance for both men. When Markovnikov took his first course in organic chemistry (1859–1860), Butlerov was the teacher, and Markovnikov not only took notes in the course, but also published them by the lithographic process.[6] By the end of that year, the two men were firm friends; in fact, Markovnikov became a regular visitor to Butlerov's home. Upon his graduation with the *Diplom*, Butlerov immediately seconded him to train for the professoriate.

Four months later, Markovnikov submitted his dissertation, on the subject of aldehydes, for the degree of *kandidat*.[7] Note the spelling of his name – he changed it to the modern form during his graduate studies.[8] This degree permitted him to be appointed to a salaried position as a laboratory assistant. He immediately began work for his *Magistr Khimii* degree, the

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

© Georg Thieme Verlag Stuttgart • New York – Synform **2019/11**, A172–A179 • Published online: October 18, 2019 • DOI: 10.1055/s-0037-1612204

minimum qualification that would permit him to take a faculty position at a university. In 1865, he successfully defended his dissertation, on the topic of isomerism.[9]

After completing his *M. Khim*., Markovnikov was sent abroad for further study and research. Beginning in Berlin, he traveled through Heidelberg to Leipzig, where he began work in the laboratory of Hermann Kolbe (1818–1884). As a student with a graduate degree already, Markovnikov was allowed considerable latitude is deciding what his project should be (Kolbe addressed him as 'Herr Doktor'). In 1867, he returned to Kazan, to a position as Extraordinary (Associate) Professor of Chemistry. He immediately set to completing his *Dr. Khim*. work and passing the required examinations. In the dissertation,[10] he furthered his study of isomerism, and began to consider the reasons why certain reactions (especially free-radical substitution of hydrogen by chlorine and bromine) exhibited predictable regiochemistry.

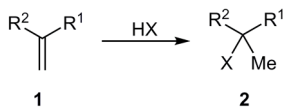
One important part of the dissertation was devoted to studies designed to demonstrate that the unsatisfied valences in alkenes were on adjacent carbon atoms. During this part of his work, when he was attempting to locate the unsatisfied affinities by adding hydrogen halides to unsymmetrically substituted alkenes (1-butene, 1-pentene and isobutylene; Scheme 1) he discovered the empirical rule that now carries his name.

The Russian Chemical Society had been organized in 1868, and it published the first volume of its journal, the *Zhurnal Russkago Khimicheskago Obshchestva*, in 1869. Markovnikov published his Rule in the inaugural volume of the *Zhurnal*,[2] based on the research in his *Dr. Khim.* dissertation. The following year, he published the more widely cited paper containing his rule in *Liebigs Annalen der Chemie*.[11]

The year after becoming *Dr. Khimii*, Markovnikov was promoted to Ordinary (Full) Professor, replacing his mentor, Butlerov, who had moved to St. Petersburg. Markovnikov continued at Kazan until 1872, when he, along with six colleagues, resigned from Kazan University to protest the treatment of Professor Pyotr Frantsevich Lesgaft (1837–1909), who had been barred from teaching physiology and denied promotion to Ordinary (Full) Professor because of his criticism of the unscientific methods used.

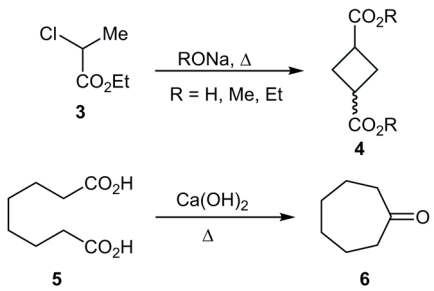
Markovnikov was not out of work long, however. Two weeks later, he received the call to Novorossiisk University in Odessa (now in the Ukraine) as Professor of Chemistry. In 1875, he accepted the call to Moscow, where he took a moribund program and built it into one of the best in Russia. At Moscow, he began research into the compositions of the Caucasus oils that led to the founding of the field of petrochemistry in Russia. In the course of this work, he was instrumental in developing the chemistry of the cycloalkanes (which he called 'naphthenes'). He became the first to synthesize derivatives of cyclobutane,[12] by the serendipitous reaction between ethyl α-chloropropionate and base (Scheme 2). He also prepared suberone (**6**) by the pyrolysis of the calcium salt of suberic (octanedioic) acid (Scheme 2),[13] and demonstrated its identity with cycloheptanone. This made Markovnikov the first organic chemist to make cyclic compounds with less than five and more than six atoms in the ring.

In 1893, twenty-five years after his first faculty appointment at Kazan, Markovnikov's enemies orchestrated his ouster from his Professorship using an arcane provision of the University Statute. He was replaced by Nikolai Dmitrievich Zelinskii (1861–1953), and although he retained his laboratory, he was evicted from the professorial apartment. He continued research until his death in 1904.[1b] His legacy was enhanced by his students from Moscow, who included Nikolai Matveevich Kizhner (1867–1935),[14] Nikolai Yakovlevich Dem'yanov (1861–1938),[5] and Aleksei Yevgen'evich Chichibabin (1871–1945),[15] all of whom have their own eponymous reactions. In 2017, Lomonosov Moscow State University established the Markovnikov Medal (Figure 1) in honor of the great chemist.[1a]



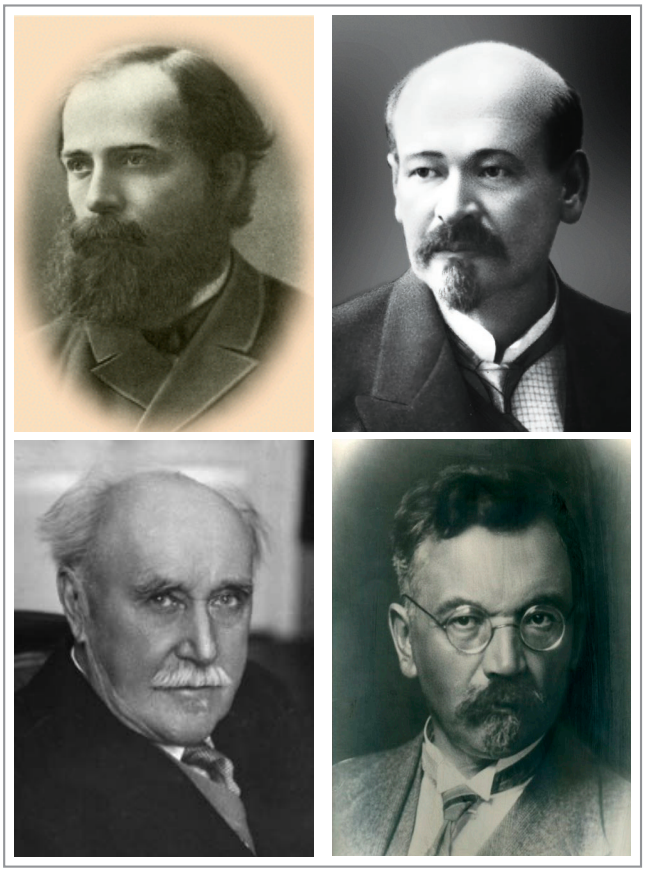
R^1 = Me, R^2 = H, X = I
R^1 = Me, R^2 = Me, X = I
R^1 = Pr, R^2 = H, X = I
R^1 = Me, R^2 = H, X = OH
R^1 = Me, R^2 = Me, X = OH

Scheme 1 Addition reactions carried out by Markovnikov



Scheme 2 Markovnikov's syntheses of the first cyclobutene derivative (**4**) and suberone (**6**)

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

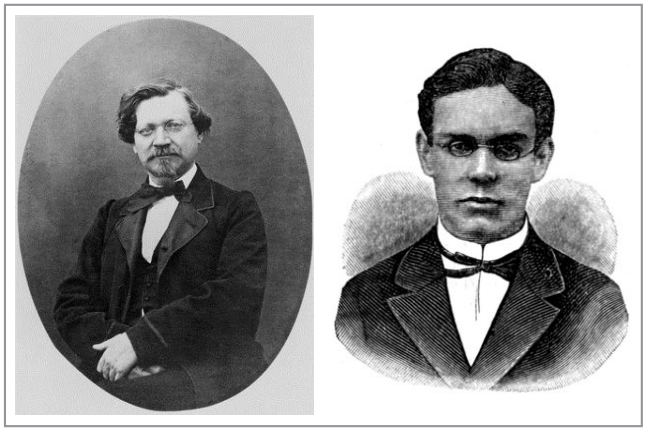


Top row (left to right): Zelinskii, Kizhner. Bottom row (left to right): Dem'yanov, Chichibabin

Figure 1 The Markovnikov Medal

Eliminations: The Zaitsev and Hofmann Rules

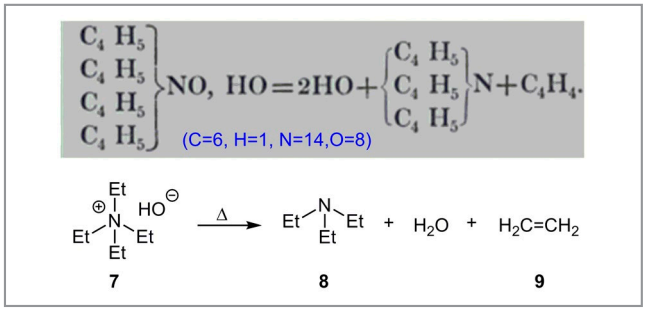
The two empirical rules that we associate with elimination reactions were first proposed by August Wilhelm (von) Hofmann (1818–1892) and Aleksandr Mikhailovich Zaitsev (Saytzeff, 1841–1910). Hofmann's biography has appeared in an earlier column in this series, describing the Hofmann rearrangement of *N*-haloamides with base.[16]



Hofmann (left) in the late 19th century, and Zaitsev (Saytzeff, right) in 1871

The Hofmann Elimination

In his early research on amines, Hofmann had prepared quaternary ammonium salts for the first time by the reaction between alkyl iodides and tertiary amines. He then found that conversion of these salts into the hydroxide and heating the hydroxide salt gave triethylamine and ethylene (Scheme 3 shows Hofmann's original and its modern interpretation).[17] This elimination, which carries his name, provides the least-substituted possible alkene as the major product of the reaction.[18]



Scheme 3 Hofmann's original elimination and its modern interpretation

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

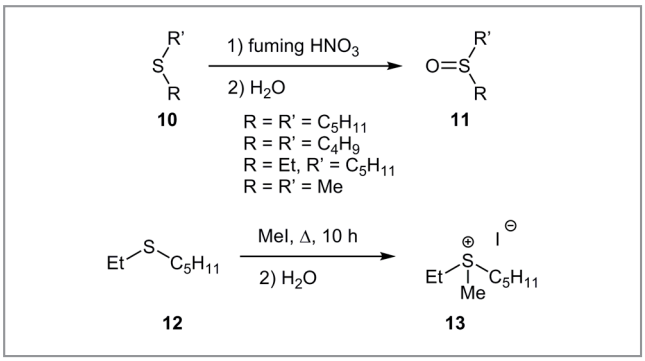
The Zaitsev Elimination

The alternative regiochemistry for elimination – giving the most substituted alkene as the major product – was reported by Zaitsev in 1875 for the eliminations of alkyl iodides by base.[19]

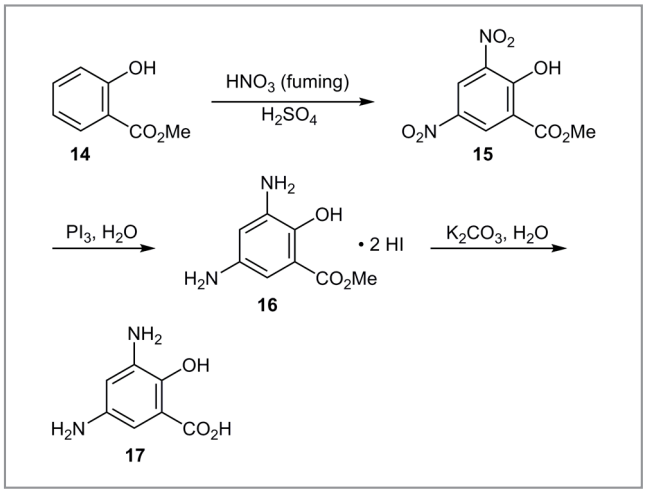
Zaitsev was born into a family that had held a prominent place in the trading guilds in the city of Kazan following the conquest of the Kazan khanate by Ivan IV ('The Terrible'). Zaitsev's father, Mikhail Savvich, had intended that his son enter the guilds after completing his studies at the Gymnasium, as his family had done for generations. Zaitsev, however, was determined to take another path. He entreated his maternal uncle, the astronomer Mikhail Vasil'evich Lyapunov (later Professor at Kazan University), to persuade his father to permit him to enter the university. Mikhail Savvich acquiesced to his brother-in-law's request, but only on the condition that Aleksandr enter the Cameral division of the Juridicial faculty; in 1858, Zaitsev entered Kazan University as a cameral student.[20]

As with Markovnikov before him, this decision brought him under the influence of Butlerov, who ultimately changed the course of his career… but not before some serious misadventures after his graduation with the *diplom* that came about because he flouted tradition. Zaitsev left Kazan immediately after receiving his *diplom*, using his inheritance (his father had died shortly before his graduation), to follow his older brother Konstantin Mikhailovich (born 1840) to the Marburg laboratory of Hermann Kolbe. He did not wait to complete the degree of *kandidat*, which was the minimum qualification for obtaining a salaried position at a Russian university.

In Marburg, Zaitsev worked with organic sulfur compounds (Scheme 4). In the process, he became the first to prepare both the sulfoxides (**11**)[21] and the sulfonium salts (**13**),[22] compounds that were to become useful compounds in organic synthesis.[23] During the 1864–1865 academic year,



Scheme 4 Zaitsev's sulfur chemistry



Scheme 5 Zaitsev's preparation of diaminosalicylic acid

Zaitsev worked in the Paris laboratory of Adolphe Wurtz; there he prepared diaminosalicylic acid (**17**) and its derivatives (Scheme 5).[24] At the end of this year, Kolbe had accepted the call to Leipzig, but Zaitsev had by then run out of money, so he could not follow; he returned to Russia.

As early as 1863, Zaitsev had come to the realization that he would need the degree of *kandidat* to return to a salaried position in Russia. He tried to rectify the situation by submitting a 76-page, handwritten dissertation '*The Theoretical Views of Kolbe on the Rational Constitution of Organic Compounds and Their Relationship with Inorganic Compounds*' for the degree.[25] The fact that he wrote a dissertation whose views were diametrically opposed to those of Butlerov, and submitted it *to Butlerov* (!) for examination is, in my opinion, indicative of two things. First, he failed to see the fundamental differences between Butlerov's and Kolbe's views on structure, and second, he was not particularly committed to Butlerov's structural theory at the time. It certainly brought the usually placid and gentlemanly Butlerov to a paroxysm of rage, which he made clear by his notes in the margin. Unsurprisingly, the degree was not awarded.

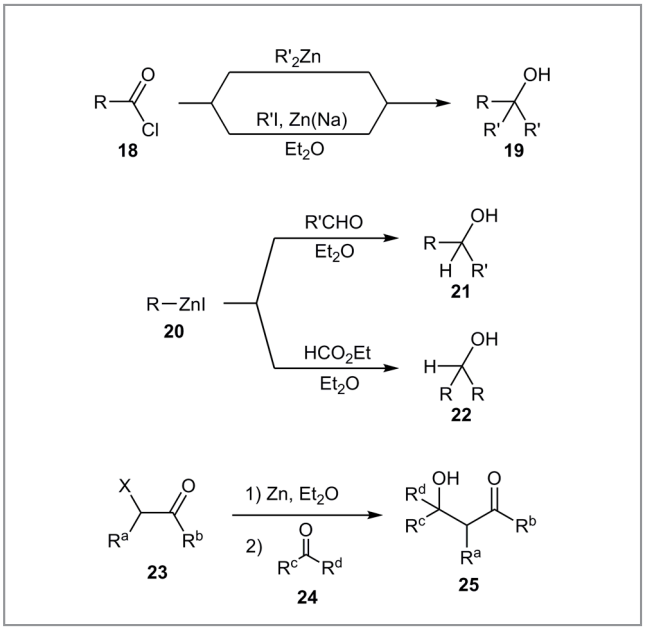
Having returned to Russia without the degree of *kandidat*, he could not occupy a salaried position at a university, but this master of ingratiation applied to Butlerov 'as a private (i.e., unsalaried) person.' Butlerov, who recognized the master synthetic chemist in this poor theoretician, accepted his offer, and immediately set him to work to submit his Paris work for the degree of *kandidat*.[26] This time, the degree was awarded, and he became a salaried Assistant in the Agronomy laboratory.

In order to become a professor, Zaitsev needed the degree of *Magistr Khimii* (*M. Khim.*), which was conferred by the

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

Physics-Mathematics Faculty. As a cameralist, he was not eligible to submit his dissertation to this Faculty, but by obtaining a doctoral degree from a western university he might become eligible. Markovnikov had relied on Butlerov's intercession, but Zaitsev was much more impatient. He submitted his work from Marburg to Kolbe at Leipzig, and was awarded the Ph.D. there in 1866. Even so, it still took Butlerov's intercession for him to receive permission to submit his dissertation for the *M. Khim*. He wrote up his work on sulfur compounds from Germany[27] and submitted it in 1867; he was awarded the degree in 1868. In 1869, he was promoted to Extraordinary Professor of Chemistry. In 1870, he successfully defended a dissertation for the *Dr. Khim.* degree,[28] containing work on the reduction of acid chlorides with sodium amalgam in ether buffered with carbon dioxide, and was promoted to Ordinary Professor.

As a Professor at Kazan, Zaitsev focused his research on the synthesis of alcohols by means of organozinc reagents. His own work had extended the work of Butlerov[29] to the use of alkylzinc iodides as nucleophiles with acid chlorides. This reaction gives tertiary alcohols with two identical alkyl groups (**19**; Scheme 6, top) provided that the alkyl group on the alkylzinc halide is methyl, ethyl or allyl.[30] With his students Innokentii Ivanovich Kanonnikov (1854–1902)[31] and Yegor Yegorovich Vagner (Georg Wagner, 1849–1903),[32] Zaitsev expanded the reaction to the synthesis of secondary alcohols by replacing the acid chloride with an aldehyde or formate ester (Scheme 6, middle). Zaitsev's next student to gain his own eponymous reaction was Sergei Nikolaevich Reformatskii (1860–1934). Reformatskii replaced the alkene π bond in the allylic iodide with a carbonyl group, thus using an α-halocarbonyl compound as the nucleophile (Scheme 6, bottom).[33]

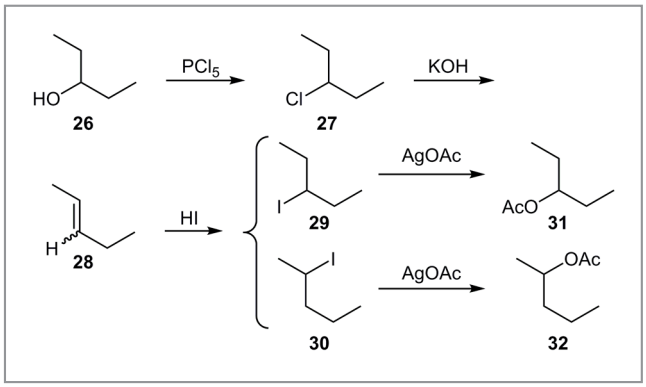


Scheme 6 Organozinc syntheses by Zaitsev and his students

Left to right: Kanonnikov, Wagner (Vagner), Reformatskii

On October 12, 1875, a series of papers from Zaitsev's Kazan laboratory were received by the Editor of *Justus Liebigs Annalen der Chemie*, and published in the last part of that journal for 1875.[19a,b] On November 6, the same year, the same series of papers were read by A. M. Butlerov and Ye. Ye. Vagner before the Russian Physical-Chemical Society, and appeared as the final articles published in volume 7 (1875) of the *Zhurnal Russkago Fiziko-Khimicheskago Obshchestva*.[19c] A reading of these papers confirms that the German papers are verbatim translations of the Russian.

The first paper in each language[19a,e] is largely a theoretical consideration of eliminations from unsymmetrical, straight-chain secondary halides. Zaitsev begins with Markovnikov's Rule, and then examines Markovnikov's experiments. From this, he reasoned that the elimination from a secondary or tertiary halide could give just one alkene only if all the alkyl groups attached to the halogen-bearing atom are identical,



Scheme 7 Conversion of 3-pentanol into 2-pentanol

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

and should also give more than one alkene if the alkyl groups are not identical. In the paper by Vagner and Zaitsev, the conversion of 3-pentanol to 2-pentanol is described.[19b,c,34] The sequence used is summarized in Scheme 7.

This work confirmed Zaitsev's summary of the literature precedents in terms of the most substituted alkene being the major product of the elimination.

Manipulating Regiochemistry

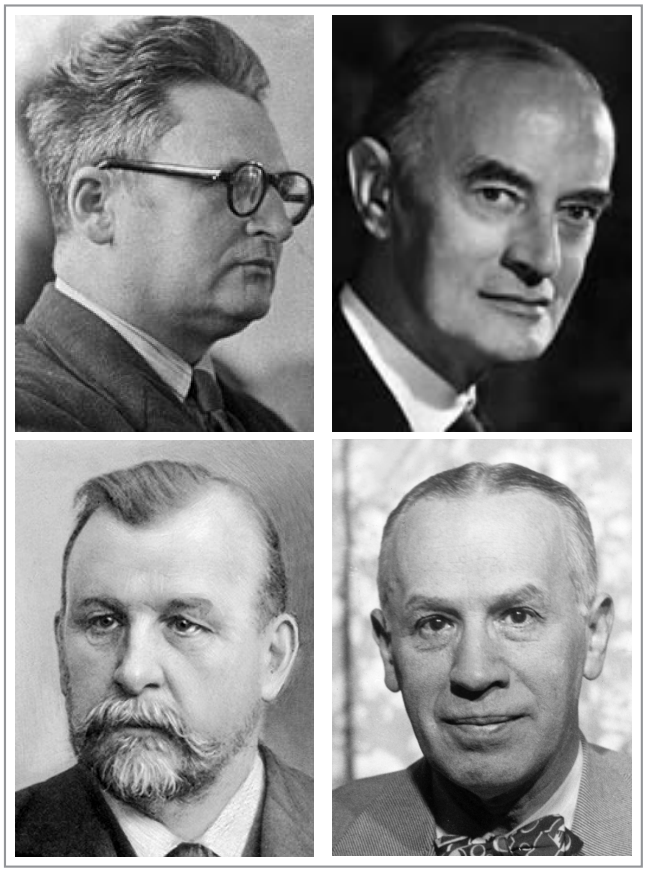
As organic synthesis entered the twentieth century, chemists moved to exert regiochemical control over reactions, over what had been the main emphasis of the nineteenth, chemoselectivity. Following the Lewis theory of bonding, this ultimately led to the intense research into the mechanisms of organic reactions by E. David Hughes (1906–1963) and Sir Christopher Kelk Ingold (1893–1970). Prior to these two giants of physical organic chemistry, it was Nikolai Aleksandrovich Menshutkin (1842–1907) who had first begun the systematic study of the effects of structure on reactivity. Although Hofmann had prepared quaternary ammonium hydroxides, it was Menshutkin who noted that the structure of the amine and the alkyl halide both had a major influence on the rate of the quaternization reaction. It was during these studies that he made the (for the time) profound observation that the solvent, which had theretofore been viewed as a non-participant in the reaction, had a dramatic effect on the rate of quaternization.[35] This solvent effect was to play an important part in the studies of substitution and elimination by Hughes and Ingold two decades later.[36]

Among the substantial early studies of elimination reactions investigated by Hughes and Ingold, the origin of the Hofmann regiochemistry occupies an important part.[37] Based on their observations, Hughes and Ingold proposed a rationalization of the Hofmann orientation (although this was later shown to be too simplistic).

Markovnikov himself recognized that his empirical rule was not universally applicable, because he, himself, had observed that the regiochemistry of the addition of hydrogen bromide to alkenes was not consistent. The origin of this phenomenon was eventually clarified by Morris Selig Kharasch (1895–1957), who coined the term 'peroxide effect' and quantitated it.[38] The inversion of regiochemistry is now attributed to the change in mechanism from ionic to radical.

Negative Interpersonal Dynamics

We cannot leave the discussion of the Markovnikov and Zaitsev rules without considering the relationship between the two young Kazan men. Zaitsev and Markovnikov overlapped at Kazan, but they were far from friends. In fact, there was an intense antipathy – to the point that despite the prolific work of photographers recording the chemists of the Russian Empire, I have never seen a single photograph where both chemists are in the same frame. This feud lasted until Markovnikov's death. The possible origins of this feud have been discussed,[39] but the question of why the feud arose is still open to interpretation.[40]



Top row (left to right): Hughes, Ingold. Bottom row (left to right): Menshutkin, Kharasch. (Image of Kharasch from University of Chicago Photographic Archive [apf1-03193])

And Now?

Unfortunately for organic chemistry, H. C. Brown ignored the mechanism of addition when he termed the regiochemistry of hydroboration, 'anti-Markovnikov'. This has led to Markovnikov's rule becoming a source of controversy,[41] because Brown's designation assumes that the hydrogen atom in the reagent is electrophilic.[42] In borane, it is not. Nevertheless, the term is now in almost universal use. The regiochemistry of hydrometallation and carbometallation reactions that

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

are frequently key steps in a catalytic cycle is usually anti-Markovnikov, so the anti-Markovnikov regiochemistry has become a key target for synthetic chemists.[1a]

In similar fashion, the preference for Zaitsev regiochemistry in E1 eliminations, and in E2 eliminations from conformationally flexible halides and sulfonates, has spurred research to obtain the Hofmann regioisomer from a precursor lacking an ammonium or sulfonium leaving group. The simplest method for doing this was shown by Hughes and Ingold to be simply using a sterically hindered base. Sterically hindered alkoxide bases such as potassium *tert*-butoxide, sterically hindered strong amide bases (e.g., LDA and similar amide bases), and non-nucleophilic amidine bases (e.g., DBN and DBU) have all been used to increase the percentage of the Hofmann regioisomer of the alkene in the product mixture.

REFERENCES

(1) (a) I. P. Beletskaya, V. G. Nenajdenko *Angew. Chem. Int. Ed.* **2019**, *58*, 4778–4789. (b) D. E. Lewis *Angew. Chem. Int. Ed.* **2019**, *58*, 3694–3705.
(2) (a) V. Morkovnikov *Zh. Russ. Khim. O-va.* **1869**, *1*, 242–247. This paper has been translated into English:
(b) D. E. Lewis *Bull. Hist. Chem.* **2018**, *43*, 21–23.
(c) D. E. Lewis *Bull. Hist. Chem.* **2018**, *43*, 24–26.
(3) December 13(25) 1838, village of Chernorech'e:
(a) I. A. Kablukov *Zh. Russ. Fiz.-Khim. O-va.* **1905**, *37*, 247–303.
(b) N. Kizhner *The Lomonosov Collection*; Moscow, **1901**, 114. [*The Lomonosov Collection*, which deals with the history of chemistry in Russia, was published in 1901 on Markovnikov's initiative.] (c) Autobiographical data: V. V. Markovnikov *Biographical Dictionary of the Professors and Teachers of the Imperial Kazan University: For the Hundred Years (1804–1904)*; N. P. Zagoskin (Ed.); Tipo-lit. Imp. Univ.: Kazan, **1904**; 424–428.
(4) December 10(22) 1837, village of Knyaginino: (a) A. F. Platé, G. V. Bykov, M. S. Eventova *Vladimir Vasil'evich Markovnikov, An Essay on his Life and Works*; Izd. Akad. Nauk SSSR: Moscow, **1968**. (b) K. Manolov *Vladimir Vasil'evich Markovnikov (1837–1904)*, In *Great Chemists In Two Volumes*; Vol. 2; Izd-vo. 'Mir': Moscow, **1986**.
(5) D. E. Lewis *Synform* **2019**, A121–A127.
(6) *Organic chemistry compiled from the lectures of Ord. Prof. A. M. Butlerov by student Vl. Morkovnikov*; Kazan lit.: Kazan, **1859–1860**. A copy of this dissertation is kept in the Rare Manuscripts Collection of the Lobachevskii Scientific Library of Kazan Federal University under No. 5595.
(7) Vl. Morkovnikov *On aldehydes and their relationship to alcohols and ketones. Kandidat Dissertation*, Kazan University: Russia, **1860**.
(8) According to the original version by A. Klyuchevich and G. V. Bykov, "on admission to the university, he was named just Morkovnikov on the passport. He later corrected it to 'Markovnikov,' *but* Butlerov did not always remember about this." A. S. Klyuchevich, G. V. Bykov *Aleksandr Mikhailovich Zaitzev (1841–1910)*; Kazan University Press: Kazan, **1980**, 18.
(9) V. Markovnikov *On the isomerism of organic compounds. M. Khim. Dissertation*, Kazan University: Russia, **1865**.
(10) Vl. Markovnikov *Materials on the question of the mutual influence of atoms in chemical compounds. Dr. Khim. Dissertation*, Kazan University: Russia, **1869**.
(11) W. Morkownikoff *Justus Liebigs Ann. Chem.* **1870**, *153*, 228–259.
(12) W. Markownikoff, A. Krestownikoff *Justus Liebigs Ann. Chem.* **1881**, *208*, 333–349.
(13) (a) V. Markovnikov *Zh. Russ. Fiz.-Khim. O-va.* **1893**, *25*, 364–378. (b) V. Markovnikov *Zh. Russ. Fiz.-Khim. O-va.* **1893**, *25*, 547–564.
(14) D. E. Lewis *Synform* **2017**, A208–A212.
(15) D. E. Lewis *Angew. Chem. Int. Ed.* **2017**, *56*, 9660–9668.
(16) D. E. Lewis *Synform* **2018**, A107–A110.
(17) (a) A. W. Hofmann *Philos. Trans. Roy. Soc.* **1851**, *141*, 357–398. (b) A. W. Hofmann *Ann. Chem. Pharm.* **1851**, *78*, 253–286. (c) A. W. Hofmann *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 5–23. (d) A. W. Hofmann *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 109–131.
(18) For a summary of regiochemistry in the Hofmann elimination, see the chapter on *Olefin-forming Eliminations. In Structure and Mechanism in Organic Chemistry*; C. K. Ingold (Ed.); Bell: London, **1953**.
(19) (a) A. Saytzeff *Justus Liebigs Ann. Chem.* **1875**, *179*, 296–301. (b) E. Wagner, A. Saytzeff *Justus Liebigs Ann. Chem.* **1875**, *179*, 302–313. (c) E. Wagner, A. Saytzeff *Justus Liebigs Ann. Chem.* **1875**, *179*, 313–325. (d) N. Grabowsky, A. Saytzeff *Justus Liebigs Ann. Chem.* **1875**, *179*, 325–338. (e) A. Zaitsev *Zh. Russ. Fiz.-Khim. O-va.* **1875**, *7*, 289–293. (f) Ye. Vagner, A. Zaitsev *Zh. Russ. Fiz.-Khim. O-va.* **1875**, *7*, 293–302.
(g) Ye. Vagner, A. Zaitsev *Zh. Russ. Fiz.-Khim. O-va.* **1875**, *7*, 302–317. (h) A. Grabovskii, A. Zaitsev *Zh. Russ. Fiz.-Khim. O-va.* **1875**, *7*, 317–328.
(20) For biographies of Zaitsev, see: (a) S. Klyuchevich, G. V. Bykov *Aleksandr Mikhailovich Zaitzev (1841–1910)*; Kazan University Press: Kazan, **1980**. (b) D. E. Lewis *Bull. Hist.*

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

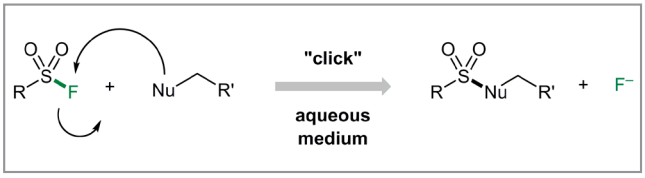
Chem. **1995**, *17/18*, 21–30. (c) D. E. Lewis *Angew. Chem. Int. Ed.* **2011**, *50*, 6452–6458.
(21) (a) A. Saytzeff *Justus Liebigs Ann. Chem.* **1866**, *139*, 354–364. (b) A. Saytzeff *Justus Liebigs Ann. Chem.* **1867**, *144*, 148–156.
(22) A. Saytzeff *Justus Liebigs Ann. Chem.* **1867**, *144*, 145–148.
(23) (a) E. J. Corey, M. Chaykovsky *J. Am. Chem. Soc.* **1962**, *84*, 867–868. (b) E. J. Corey, M. Chaykovsky *J. Am. Chem. Soc.* **1965**, *87*, 3782–3783. (c) E. J. Corey, M. Chaykovsky *Tetrahedron Lett.* **1963**, *4*, 169–171. (d) E. J. Corey, M. Chaykovsky, *J. Am. Chem. Soc.* **1965**, *87*, 1345–1353. (e) D. Kaiser, I. Close, R. Oost, J. Neuhaus, N. Maulide *Chem. Rev.* **2019**, *119*, 8701–8780. (f) M. M. Heravi, S. Asadi, N. Nazari, B. M. Lashkariani *Curr. Org. Synth.* **2016**, *13*, 308–333. (g) V. K. Aggarwal, C. L. Winn *Acc. Chem. Res.* **2004**, *37*, 611– 620.
(24) (a) A. Saytzeff *Ann. Chem. Pharm.* **1865**, *133*, 321–329. (b) A. Saytzeff *Bull. Soc. Chim. Paris* **1865**, *3*, 244–250.
(25) A. M. Zaitsev *The Theoretical Views of Kolbe on the Rational Constitution of Organic Compounds and Their Relationship with Inorganic Compounds; Kand. Dissertation*, Kazan University, **1863**.
(26) A. M. Zaitsev *O diamidosalitsylovoi kislote [On diamidosalicylic acid]*; *Kand. Dissertation*, Kazan University, **1866**.
(27) A. M. Zaitsev *On the action of nitric acid on certain organic compounds of divalent sulfur and on a new series of organic sulfur compounds obtained from this reaction*; *M. Khim. Dissertation*, Kazan University, **1867**.
(28) A. M. Zaitsev *A new method for converting a fatty acid into its corresponding alcohol. Normal butyl alcohol (propyl carbinol) and its conversion to secondary butyl alcohol (methyl ethyl carbinol)*; *Dr. Khim. Dissertation*, Kazan University, **1870**.
(29) (a) A. Boutlerow *Bull. Soc. Chim. Paris* **1863**, 582–594. (b) A. Boutlerow *Bull. Soc. Chim. Paris Nouv. Sér.* **1864**, *2*, 106–116. (c) A. Boutlerow *Bull. Soc. Chim. Paris Nouv. Sér.* **1866**, *5*, 17–33.
(30) (a) A. Zaitsev *Zh. Russ. Fiz.-Khim. O-va.* **1875**, *7*, 302–312. (b) A. Zaitsev, *Zh. Russ. Khim. O-va. Fiz. Ova.* **1876**, *8*, 290–308. (c) M. Saytzeff, A. Saytzeff *Justus Liebigs Ann. Chem.* **1877**, *185*, 151–169. (d) A. Saytzeff *Justus Liebigs Ann. Chem.* **1877**, *185*, 175–183. (e) A. Saytzeff *J. Prakt. Chem.* **1885**, *31*, 319–320.
(31) (a) J. Kanonnikoff, A. Saytzeff *Justus Liebigs Ann. Chem.* 1875, *175*, 374–378. (b) I. Kanonnikov, A. Zaitsev *Zh. Russ. Fiz.-Khim. O-va.* **1874**, *6*, 308–312. (c) J. Kanonnikoff, A. Saytzeff *Justus Liebigs Ann. Chem.* **1877**, *185*, 148–150. (d) I. Kanonnikov, A. Zaitsev *Zh. Russ. Khim. O-va. Fiz. O-va.* **1876**, *8*, 359–363.
(32) (a) G. Wagner, A. Saytzeff *Justus Liebigs Ann. Chem.* **1875**, *175*, 351–374. (b) Ye. Vagner, A. Zaitsev *Zh. Russ. Fiz.-Khim. O-va.* **1874**, *6*, 290–308.
(33) (a) S. Reformatskii *Zh. Russ. Fiz.-Khim. O-va.* **1890**, *22*, 44–64. (b) S. Reformatsky *Ber. Dtsch. Chem. Ges.* **1895**, *28*, 3262–3265. (c) S. Reformatsky *Ber. Dtsch. Chem. Ges.* **1895**, *28*, 2842–2847. (d) S. Reformatsky *J. Prakt. Chem.* **1896**, *54*, 469–477. (e) L. Andres *Zh. Russ. Fiz.-Khim. O-va.* **1896**, *28*, 283–293. (f) I. Kukulesko *Zh. Russ. Fiz.-Khim. O-va.* **1896**, *28*, 293–299. (g) S. Reformatsky *J. Prakt. Chem.* **1896**, *54*, 477–481. (h) S. Reformatsky, B. Plesconosoff *Ber. Dtsch. Chem. Ges.* **1895**, *28*, 2838–2841.
(34) Ye. Vagner, A. Zaitsev *Zh. Russ. Fiz.-Khim. O-va.* **1875**, *7*, 302–312.
(35) (a) N. Menschutkine *Z. Phys. Chem.* **1890**, *6*, 41–57. (b) N. Menshutkin *Zh. Russ. Khim. O-va.* **1890**, *22*, 346–358.
(36) K. A. Cooper, M. L. Dhar, E. D. Hughes, C. K. Ingold, B. J. MacNulty, L. I. Woolf *J. Chem. Soc.* **1948**, 2043–2049.
(37) (a) E. D. Hughes, C. K. Ingold, G. A. Maw, L. I. Woolf *J. Chem. Soc.* **1948**, 2077–2083. (b) M. L. Dhar, E. D. Hughes, C. K. Ingold, A. M. M. Mandour, G. A. Maw, L. I. Woolf *J. Chem. Soc.* **1948**, 2093–2119. (c) E. D. Hughes, J. Wilby *J. Chem. Soc.* **1960**, 4094–4101.
(38) M. S. Kharasch, F. R. Mayo *J. Am. Chem. Soc.* **1933**, *55*, 2468–2496.
(39) D. E. Lewis *Bull. Hist. Chem.* **2010**, *35*, 115–124.
(40) In a private communication in 2017, Prof. Dr. A. Zakharov suggested that Zaitsev's antipathy was based on the fact that Zaitsev was intimidated by the brilliant Markovnikov.
(41) Representative papers: (a) G. Jones *J. Chem. Educ.* **1961**, *38*, 297–300. (b) E. E. Gooch *J. Chem. Educ.* **2001**, *78*, 1358–1359. (c) P.-P. Ilich *J. Chem. Educ.* **2007**, *84*, 1109–1109. (d) R. C. Kerber *J. Chem. Educ.* **2007**, *78*, 1109–1109. (e) N. Isenberg, M. Grdinic *J. Chem. Educ.* **1969**, *46*, 601–605. (f) P. Hughes *J. Chem. Educ.* **2006**, *83*, 1152–1154.
(42) P.-P. Ilich, L. S. Rickertsen, E. Becker *J. Chem. Educ.* **2006**, *83*, 1681–1685.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

Sulfonyl Fluoride Synthesis through Electrochemical Oxidative Coupling of Thiols and Potassium Fluoride

J. Am. Chem. Soc. **2019**, *141*, 11832–11836

Sulfonyl fluorides are emerging as important reagents in chemical biology, owing to their capacity to undergo 'click'-type reactions – i.e. Sulfur(VI) Fluoride Exchange (SuFEx) (Scheme 1) – with nucleophilic functions of biopolymers, such as peptides and proteins, in water or aqueous media.[1]



Scheme 1 The Sulfur(VI) Fluoride Exchange (SuFEx) reaction

The group of Dr. Timothy Noël at the Eindhoven University of Technology (The Netherlands) was carrying out investigations towards the development of an electrochemical synthesis of sulfonamides[2] and found that, using an electrolyte with BF_4 counterion, traces of the sulfonyl fluoride product were observed in the GC-MS (Scheme 2). One of the two first authors, Gabriele Laudadio, remarked: "This observation gave us the confidence that by tweaking the sulfonamide reaction conditions, we probably could steer product formation selectively to sulfonyl fluoride."

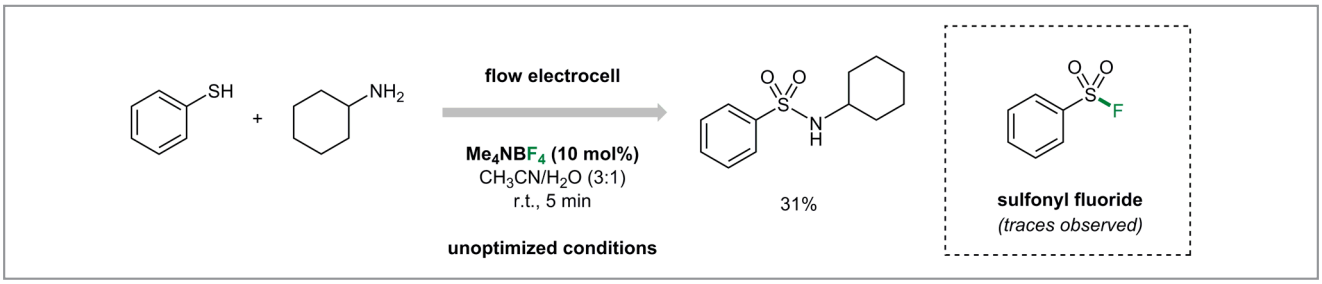
Dr. Noël, who was obviously aware of the importance of sulfonyl fluorides, especially within the realm of SuFEx click chemistry – the use of which is curbed by the fact that most methods for their preparation are rather cumbersome[1] – said: "As soon as Gabriele told me about the formation of the sulfonyl fluoride as a trace byproduct, I became really excited. In view of how important sulfonyl fluorides are for SuFEx click chemistry and the need for a simple way to prepare them, we decided that this project was a priority in our group." At that point, Aloisio de Andrade Bartolomeu, a visiting PhD student from the de Oliveira group at the Universidade Federal de São Carlos (Brazil), joined the group for a year and Dr. Noël decided he should join the sulfonyl fluoride team.

Aloisio, who is co-first author of the published paper, recalled: "When Tim asked me to join the sulfonyl fluoride team I was both excited and cautious, as I had no experience with electrochemistry. But upon seeing the interesting proof-of-concept results, I did not hesitate a single moment and I grabbed this opportunity with both hands."

Aloisio set to work with Gabriele and the pair rapidly found that potassium fluoride was the most convenient 'F' source (Scheme 3). Gabriele remarked: "This was an important finding as KF is an inexpensive, abundantly available and safe fluoride source. We found that we had to add about 5 equivalents of KF to obtain optimal results. Most of the fluoride was, however, used as a cheap supporting electrolyte."

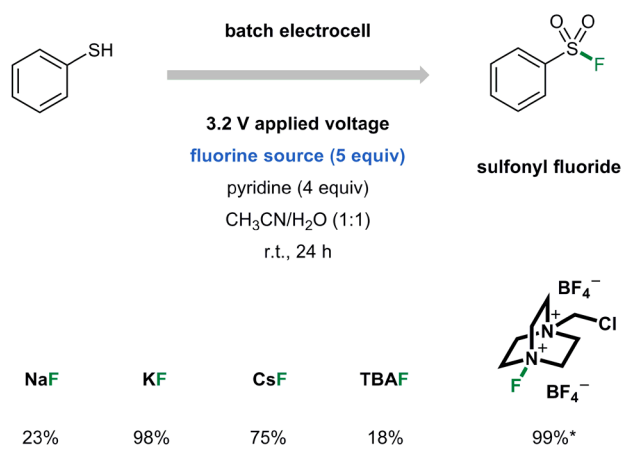
Once the optimal reaction conditions had been obtained, Gabriele and Aloisio set out to explore the scope of the method with various aromatic and aliphatic thiols (Scheme 4). Aloisio said: "Mostly, we obtained good to high yields. Some volatile sulfonyl fluorides were more challenging to isolate but we converted those immediately into the corresponding and heavier sulfonate through reaction with phenol."

Dr. Noël remarked: "During the substrate scope activities, we carried out several mechanistic experiments in parallel.



Scheme 2 Traces of sulfonyl fluoride observed in the electrochemical synthesis of sulfonamide

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

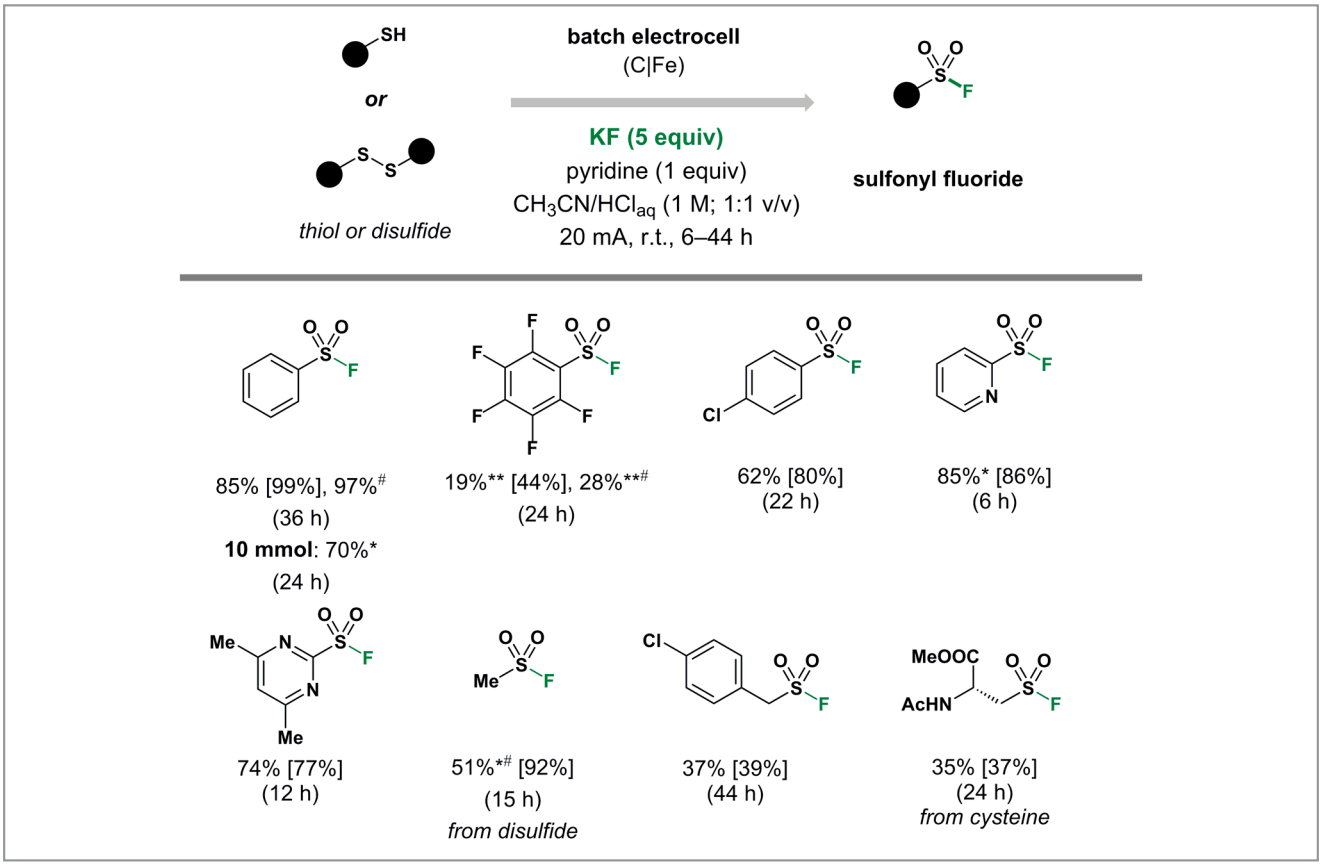


Scheme 3 Different fluorine sources tested in the electrochemical methodology. * 1.5 equiv of Selectfluor.

Kinetic experiments revealed that the thiol is quite rapidly converted into the corresponding disulfide. This observation opens up opportunities to use disulfides directly as less-smelly substrates."

In these kinetic experiments, a pseudo zeroth order was observed for the formation of the sulfonyl fluoride, which indicates the presence of mass-transfer limitations in the batch experiments. Gabriele commented: "Using a continuous-flow reactor with a 250 µm interelectrode gap, we could accelerate the reaction from more than six hours in batch to only five minutes in flow." Aloisio added: "The disulfide is subsequently fluorinated and undergoes a double anodic oxidation towards the corresponding sulfonyl fluoride (Scheme 5)."

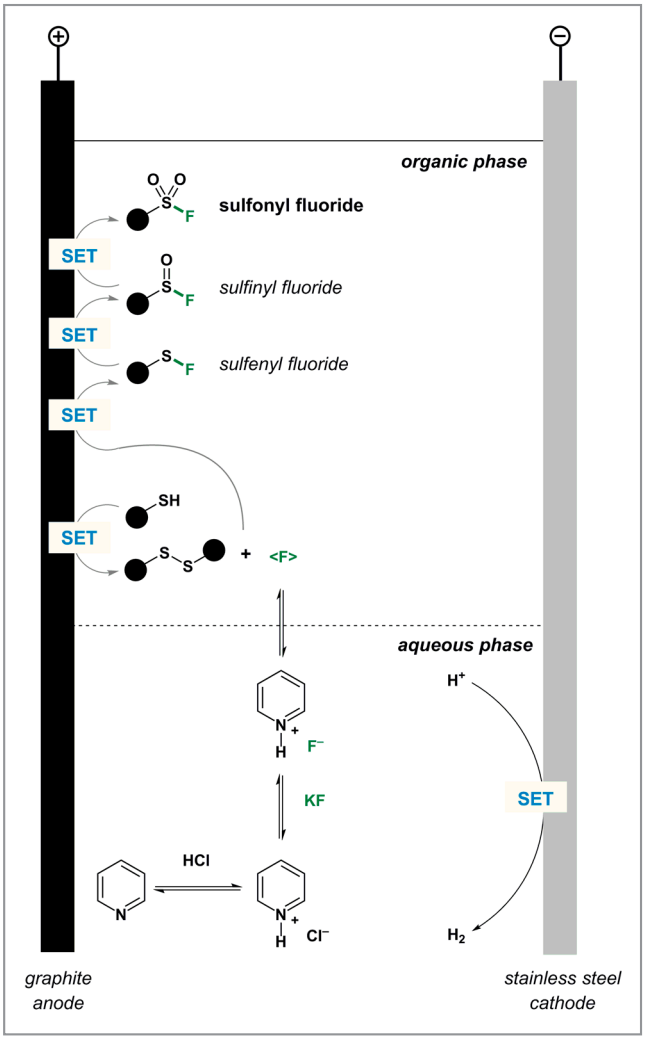
Dr. Noël concluded: "The advantage of this method is that it only uses simple starting materials, such as thiols or disulfides and KF, and does not require additional oxidants or catalysts. Meanwhile we are working on some other electrochemical methods, which display some synthetic advantages



Scheme 4 Selection of sulfonyl fluorides obtained with the electrochemical methodology. Yields between [brackets] are those referring to ^{19}F NMR yields calculated with $PhCF_3$ as internal standard. * 3.2 V applied potential. ** 4.0 V applied potential. # Isolated as phenyl sulfonate derivative through reaction with phenol.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

over other established approaches. While there are similarities with photoredox catalysis, we have found in our work that electrochemistry provides unique synthetic opportunities and often uses extremely simple reaction conditions."



Scheme 5 Plausible mechanism

REFERENCES

(1) J. Dong, L. Krasnova, M. G. Finn, K. B. Sharpless *Angew. Chem. Int. Ed.* **2014**, *53*, 9430–9448.

(2) G. Laudadio, E. Barmpoutsis, C. Schotten, L. Struik, S. Govaerts, D. L. Browne, T. Noël *J. Am. Chem. Soc.* **2019**, *141*, 5664–5668.

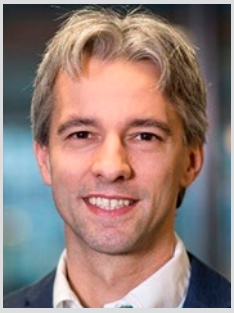
About the authors

G. Laudadio

Gabriele Laudadio was born in 1991 near Pescara, Italy. In 2016 he received his M.Sc. degree in organic chemistry at the University of Pisa (Italy). His Master's thesis was conducted under the supervision of Professor A. Carpita. He is currently a Ph.D. student at Eindhoven University of Technology (The Netherlands) in the group of Dr. Timothy Noël. His research interests focus on novel synthetic methodologies combining continuous-flow microreactor technology with electrochemistry and photochemistry.

A. A. Bartolomeu

Aloisio de Andrade Bartolomeu, born 1982 in Cabrália Paulista (Brazil), received his B.Sc. degree in chemistry from UNESP (São Paulo State University, Brazil) in 2012. In 2015, he obtained his M.Sc. degree in science and technology of materials from the same university under the supervision of Prof. Luiz Carlos da Silva Filho. Currently, he is a Ph.D. student at UFSCar (Federal University of São Carlos, Brazil), under the supervision of Prof. Kleber Thiago de Oliveira, and is a visiting Ph.D. student with a FAPESP fellowship at the Eindhoven University of Technology (The Netherlands), under the supervision of Associate Professor Timothy Noël. His current research interests are photocatalysis and electrocatalysis.



Dr. T. Noel

Timothy Noël currently holds a position as Associate Professor at Eindhoven University of Technology (The Netherlands). His research interests range from organic chemistry to chemical engineering and encompasses more specifically flow chemistry, organic synthesis and synthetic catalytic methodology development. His work has been recognized with several awards, including most recently the VIDI award (2015), the Thieme Chemistry Journals Award (2016) and the DECHEMA prize (2017).

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

Coming soon

Literature Coverage

Rhodium-Catalyzed Atroposelective C–H Arylation: Efficient Synthesis of Axially Chiral Heterobiaryls

Literature Coverage

Organocatalytic, Enantioselective Dichlorination of Unfunctionalized Alkenes

Conference Report

Thieme Chemistry Editorial Board Meeting 2019

Further highlights

Synthesis **Review: Synthesis of ^{13}C-Labeled Steroids**
(by J. Lebreton and co-workers)

Synlett **Account: Recent Advances in the Synthesis of Thiadiazoles**
(by J. Cheng and co-workers)

Synfacts **Synfact of the Month in category "Peptide Chemistry": Synthesis of Cyclic and Bicyclic Peptides**

For current SYNFORM articles, please visit www.thieme-chemistry.com
SYNFORM issue 2019/12 is available from November 18, 2019
at www.thieme-connect.com/ejournals

Impressum

Editor
Matteo Zanda, Chair in Biomolecular Imaging, Centre for Imaging Science, Department of Chemistry, School of Science, Loughborough University, Leicestershire, LE11 3TU, UK
and
C.N.R. – Istituto di Chimica del Riconoscimento Molecolare
Via Mancinelli, 7, 20131 Milano, Italy
Editorial Assistant: Alison M. Sage
synform@outlook.com; fax: +39 02 23993080

Editorial Office
- Managing Editor: Susanne Haak, susanne.haak@thieme.de, phone: +49 711 8931 786
- Scientific Editors:
  Stefanie Baumann, stefanie.baumann@thieme.de, phone: +49 711 8931 776
  Selena Boothroyd, selena.boothroyd@thieme.de
  Michael Binanzer, michael.binanzer@thieme.de, phone: +49 711 8931 768
  Giuliana Rubulotta, giuliana.rubulotta@thieme.de, phone: +49 711 8931 183
  Kathrin Ulbrich, kathrin.ulbrich@thieme.de, phone: +49 711 8931 785
- Senior Production Editors:
  Thomas Loop, thomas.loop@thieme.de, phone: +49 711 8931 778
  Thorsten Schön, thorsten.schoen@thieme.de, phone: +49 711 8931 781
- Production Manager: Sophia Hengst, sophia.hengst@thieme.de, phone: +49 711 8931 398
- Production Assistant: Tobias Brenner, Tobias.brenner@thieme.de, phone: +49 711 8931 769
- Editorial Assistant: Sabine Heller, sabine.heller@thieme.de, phone: +49 711 8931 744
- Marketing Director: Julia Stötzner, julia.stoetzner@thieme.de, phone: +49 711 8931 771
- Postal Address: Chemistry Journals, Editorial Office, Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany,
- Homepage: www.thieme-chemistry.com

Publication Information
Synform will be published 12 times in 2019 by Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany, and is an additional online service for Synthesis, Synlett and Synfacts.

Publication Policy
Product names which are in fact registered trademarks may not have been specifically designated as such in every case. Thus, in those cases where a product has been referred to by its registered trademark it cannot be concluded that the name used is public domain. The same applies as regards patents or registered designs.

Ordering Information for Print Subscriptions to Synthesis, Synlett and Synfacts
The Americas: Thieme Publishers New York, Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA.
Via e-mail: customerservice@thieme.com
Via website: www.thieme-chemistry.com
Phone: +1 212 760 0888; Fax: +1 212 947 1112
Order toll-free within the USA: +1 800 782 3488

Europe, Africa, Asia, and Australia: Thieme Publishers Stuttgart, Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany.
Via e-mail: customerservice@thieme.de
Via website: www.thieme-chemistry.com
Phone: +49 711 8931 421; Fax: +49 711 8931 410

Current list prices are available through www.thieme-chemistry.com.

Online Access
The online versions of Synform as well Synthesis, Synlett, Synfacts and SynOpen are available through www.thiemeconnect.com/products/ejournals/journals) where it is also possible to register for a free trial account. For information on multi-site licenses and pricing for corporate customers as well as backfiles, please contact our regional offices:

The Americas: esales@thieme.com, phone: +1 212 584 4695
Europe, Africa, Asia, and Australia: eproducts@thieme.de, phone: +49 711 8931 407
India: eproducts@thieme.in, phone +91 120 45 56 600
Japan: brhosoya@poplar.ocn.ne.jp, phone +81 3 3358 0692

Manuscript Submission to Synthesis, Synlett, and SynOpen
Manuscript submissions will be processed exclusively online via http://mc.manuscriptcentral.com/synthesis, http://mc.manuscriptcentral.com/synlett and http://mc.manuscriptcentral.com/synopen, respectively. Please consult the Instructions for Authors before compiling a new manuscript. The current version and the Word template for manuscript preparation are available for download at www.thieme-chemistry.com.

Copyright
This publication, including all individual contributions and illustrations published therein, is legally protected by copyright for the duration of the copyright period. Any use, exploitation or commercialization outside the narrow limits set by copyright legislation, without the publisher's consent, is illegal and liable to criminal prosecution. This applies to translating, copying and reproduction in printed or electronic media forms (databases, online network systems, Internet, broadcasting, telecasting, CD-ROM, hard disk storage, microcopy edition, photomechanical and other reproduction methods) as well as making the material accessible to users of such media (e.g., as online or offline backfiles).

Copyright Permission for Users in the USA
Authorization to photocopy items for internal or personal use, or the internal or personal use of specific clients, is granted by Georg Thieme Verlag KG Stuttgart · New York for libraries and other users registered with the Copyright Clearance Center (CCC) Transactional Reporting Service, provided that the base fee of US$ 25.00 per copy of each article is paid directly to CCC, 22 Rosewood Drive, Danvers, MA 01923, USA, 0341-0501/02.

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.