

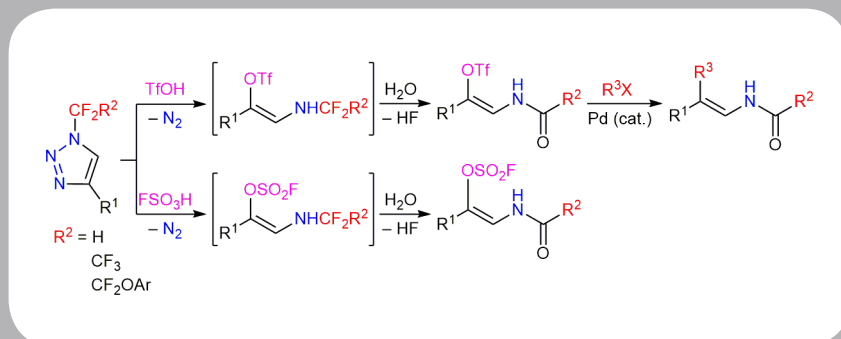
Synform

People, Trends and Views in Chemical Synthesis

2019/08

Synthesis, Stability, and Reactivity of Azidofluoroalkanes

Highlighted paper from the Spring 2019 ACS National Meeting by P. Beier



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Dear Readers,

This special issue of SYNFORM features two Conference Report articles from the Spring American Chemical Society National Meeting & Exposition held in Orlando, FL, USA, from March 31 through April 4, 2019. Sponsored by Thieme Chemistry, I had the opportunity to attend the massive event, which was attended by nearly 8,000 delegates, over 6,000 students and almost 1,000 exhibitors for a total number of 15,754 participants (<https://www.acs.org/content/acs/en/meetings/national-meeting/exhibitors/registration-statistics.html>).

With tens of parallel sessions, it is quite easy – actually, it is inevitable – to miss out on interesting lectures and events, but that is just the nature of the ACS meetings beast. And Orlando offered a particularly lively and entertaining – and noisy – environment with all of its very American tourist attractions, hotels and casinos, combined with the very nice spring weather. The scientific offer was obviously great and extremely broad, as one would expect, and among the variety of talks I had the opportunity to attend, I am pleased to thank Petr Beier (Czech Republic) and Caleb Martin (USA) who accepted to share information from their oral communications with Synform. The first ACS Conference Report article reports on the synthesis, stability, and reactivity of an intriguing class of organofluorine compounds, azidofluoroalkanes; the second on the properties and reactivity of hitherto marginally studied boron-containing heterocycles, the boroles. Moving on from the ACS meeting, I am delighted to be able to present a new chapter of the Name Reaction Bio series of articles authored by David Lewis, who accompanies us in a fascinating time-travel to the 19th century, when the discovery of carbocation rearrangements was made by true pioneers of organic chemistry, such

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

as Wagner and Demjanov. Last but surely not least, the issue presents a Young Career Focus interview with Lei Wang (P.R. of China), who shares his thoughts and research interests with our readership.

Enjoy your reading!!!

Matteo Zanda

Synthesis, Stability, and Reactivity of Azidofluoroalkanes

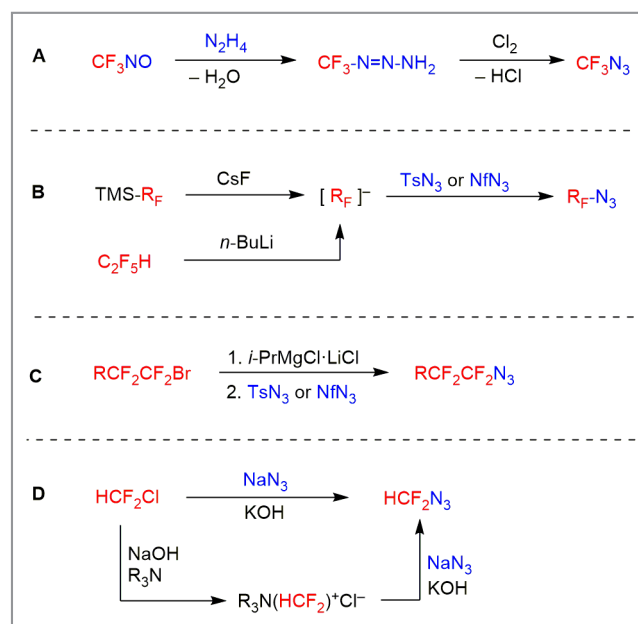
FLUO 31, Spring 2019 ACS National Meeting & Exposition, March 31–April 4, Orlando, USA

Organic azides constitute a very important class of compounds in synthetic, medicinal and biological chemistry and their preparation is often based on nucleophilic displacement of carbon-bound leaving groups starting from alkali metal azides. The synthetic utility of organic azides is very broad, encompassing reactions with electrophiles, nucleophiles (such as Staudinger reaction with phosphines), thermal or photo decomposition to nitrenes, and azide–alkyne cycloaddition to 1,2,3-triazoles. For the latter, when catalyzed by Cu(I) salts, the term ‘click reaction’ has been coined because of its reliability, high efficiency and broad substrate scope, and it has been widely used in synthetic chemistry, diversity-oriented synthesis, medicinal chemistry and materials science. Some organic azides, such as azidothymidine, even display interesting biological activities. However, a word of caution frequently appears in the literature when organic azides are described – low-molecular-weight azides are better avoided owing to their potentially explosive character.

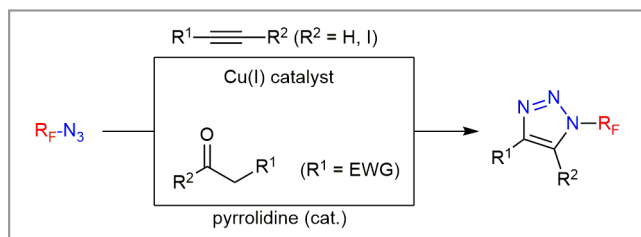
The group of Dr. Petr Beier at the Institute of Organic Chemistry and Biochemistry, Academy of Sciences, Prague (Czech Republic) has been active in the chemistry of fluorinated C1 and C2 building blocks and methodology development for some time, and recently the idea of investigating the properties and reactivity of fluorinated azides such as azidotrifluoromethane and azidodifluoromethane arose. “This chemistry was not completely new,” acknowledged Dr. Beier. “Indeed, almost 60 years ago, Makarov prepared CF_3N_3 in two steps from toxic trifluoronitrosomethane, hydrazine and chlorine, a synthesis later repeated by Christe (Scheme 1A), thereby allowing for some basic characterization of the compound to be carried out, including ^{19}F NMR, IR and Raman spectra. However, the difficult synthetic access to CF_3N_3 involving toxic and corrosive starting gases, and perhaps also a fear of its possibly explosive nature, precluded further use of this azide and investigations of its chemical reactivity.” Clearly, a new synthetic route to CF_3N_3 starting from commercial starting materials was needed. “Our initial attempts to produce CF_3N_3 from trifluoroiodomethane and sodium azide under thermal or photolytic conditions were unsuccessful. However, switching polarity of the synthons to the fluorinated carbanion derived from TMSCF_3 and an electrophilic azide (tosyl azide or nonafllyl azide) (Scheme 1B) was fruitful and allowed the preparation and full characterization (including ^{13}C NMR and high-resolution MS spectra) of CF_3N_3 and its

longer carbon chain analogues (Scheme 1B),” explained Dr. Beier. He continued: “These are all volatile compounds and were isolated by distillation as solutions in organic solvents. Importantly, their stability was found to be sufficient for safe laboratory work (in contrast to their non-fluorinated counterparts) by test-heating their solutions to $150\text{ }^\circ\text{C}$ for a prolonged time (*Angew. Chem. Int. Ed.* **2017**, *56*, 346–349). Related tetrafluoroethylene-containing azides were prepared by magnesiation of the corresponding bromides and reaction with electrophilic azides (*Org. Lett.* **2016**, *18*, 5844–5847; *Org. Biomol. Chem.* **2017**, *15*, 4962–4965) (Scheme 1C). For azidodifluoromethane, a modified published procedure based on the reaction of difluorocarbene with azide in aqueous conditions was used (Scheme 1D). The chemistry of azidodifluoromethane was also not investigated in the literature. We have fully characterized HCF_2N_3 and found that it was stable (*Eur. J. Org. Chem.* **2018**, 5087–5090).”

Click reactions of the azidofluoroalkanes with alkynes and organocatalyzed reactions with 1,3-diones or β -keto esters afforded 4-substituted and 4,5-disubstituted 1,2,3-triazoles, respectively (*Chem. Select* **2018**, *3*, 7045–7048) (Scheme 2).



Scheme 1 Synthetic approaches to azidoperfluoroalkanes and azidodifluoromethane



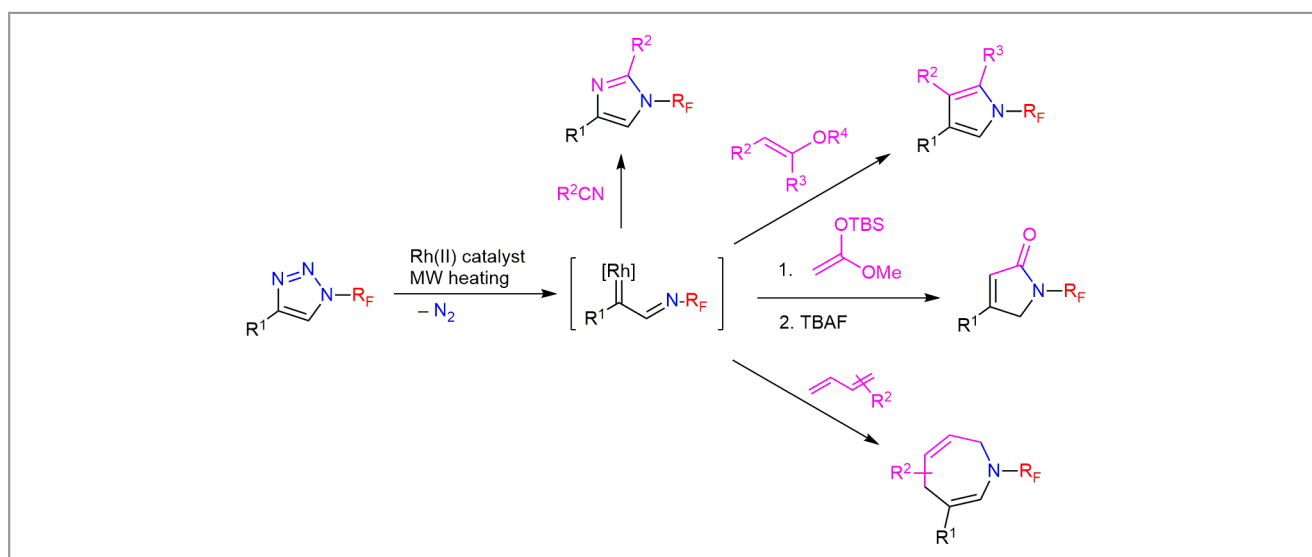
Scheme 2 [3+2] Cycloadditions with azido(per)fluoroalkanes

Dr. Beier explained that these 1-perfluoroalkylated 1,2,3-triazoles are very rare and some of them were prepared previously as mixtures of isomers. An important feature of azidofluoroalkanes when compared to azidoalkanes is their better stability and higher reactivity in click reactions with alkynes.

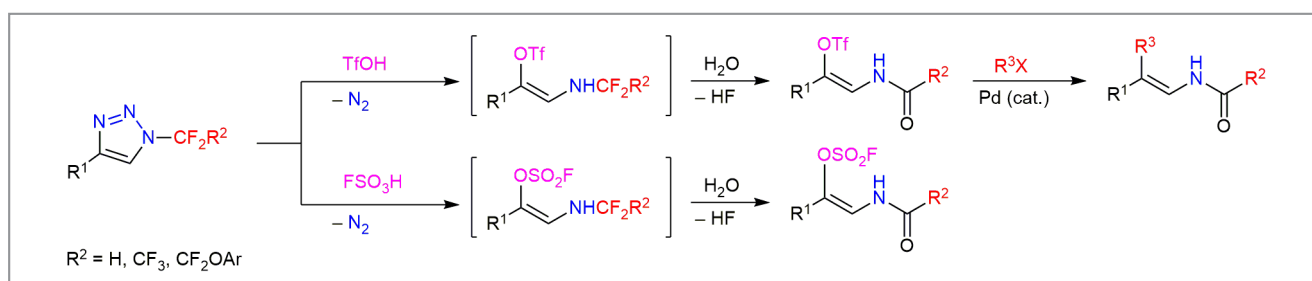
“1-Sulfonyl-1,2,3-triazoles are known to undergo rhodium-catalyzed transannulation to various nitrogen hetero-

cycles under microwave heating and we were delighted to see that the chemistry can be expanded to 1-perfluoroalkyl (but not 1-difluoromethyl) 1,2,3-triazoles, thereby allowing synthetic access to a variety of previously unknown N-fluoroalkylated nitrogen heterocycles such as imidazoles, pyrroles, imidazolones, pyrrolones (*Chem. Commun.* **2018**, 54, 3258–3261) and azepines (*J. Org. Chem.* **2018**, 83, 15195–15201) (Scheme 3),” said Dr. Beier.

He continued: “Recently we found that 1-fluoroalkylated 1,2,3-triazoles in the presence of triflic or fluorosulfonic acid undergo a cascade reaction involving triazole protonation, ring opening and loss of nitrogen to a vinyl cation intermediate which reacts stereospecifically with the conjugate base of the strong acid to enamino triflate or fluorosulfonate, respectively.” The group found that these are unstable under the reaction conditions, eliminate HF and hydrolyze to previously unreported β -enamido triflates or fluorosulfonates, respectively (Scheme 4) (*Chem. Eur. J.* **2019**, in press). “This reaction



Scheme 3 Rhodium(II)-catalyzed transannulation of N-perfluoroalkyl-1,2,3-triazoles



Scheme 4 Transformation of N-fluoroalkyl-1,2,3-triazoles into β -enamido triflates and fluorosulfonates

has a broad scope, is stereospecific, metal-free and takes place under mild conditions," said Dr. Beier. "The fluorinated group on nitrogen transforms into an amide protecting group (such as the trifluoroacetamido group) and the products are stable solids with a high synthetic utility, for example in cross-coupling reactions of the triflate group to give stereodefined enamides."

Dr. Beier concluded: "Our study shows that starting from a neglected chemical curiosity (CF_3N_3) we were able to develop a rich chemistry that afforded new products via exciting and unprecedented transformations. Physical and chemical properties of azidofluoroalkanes are currently under intensive investigation in our group."



Acknowledgment This work was financially supported by the Ministry of Education, Youth and Sports in the program INTER-EXCELLENCE (LTAUSA18037) and the Czech Academy of Sciences (RVO: 61388963).

About the author



Dr. P. Beier

Petr Beier was born in 1978 in Ostrava (Czech Republic). After his undergraduate studies at the University of Pardubice (Czech Republic) he joined the group of Prof. David O'Hagan at St. Andrews University (UK) where he received his PhD in 2004. Then he moved to the Loker Hydrocarbon Research Institute and the University of Southern California, Los Angeles (USA), where he was a postdoctoral fellow in the group of Prof. Surya Prakash. In 2007 he joined the Institute of Organic Chemistry and Biochemistry at the Academy of Sciences in Prague (Czech Republic) for a junior group leader position and since 2012 he has worked at the same institute as a senior group leader. His research interests are synthetic methodology in organofluorine chemistry and chemistry of main group elements, C1 and C2 synthons, asymmetric synthesis, and investigation of reaction mechanisms. He has received the Alfred Bader Prize for Organic Chemistry from the Czech Chemical Society (2013) and the Royal Chemical Society Fluorine Prize (2017).

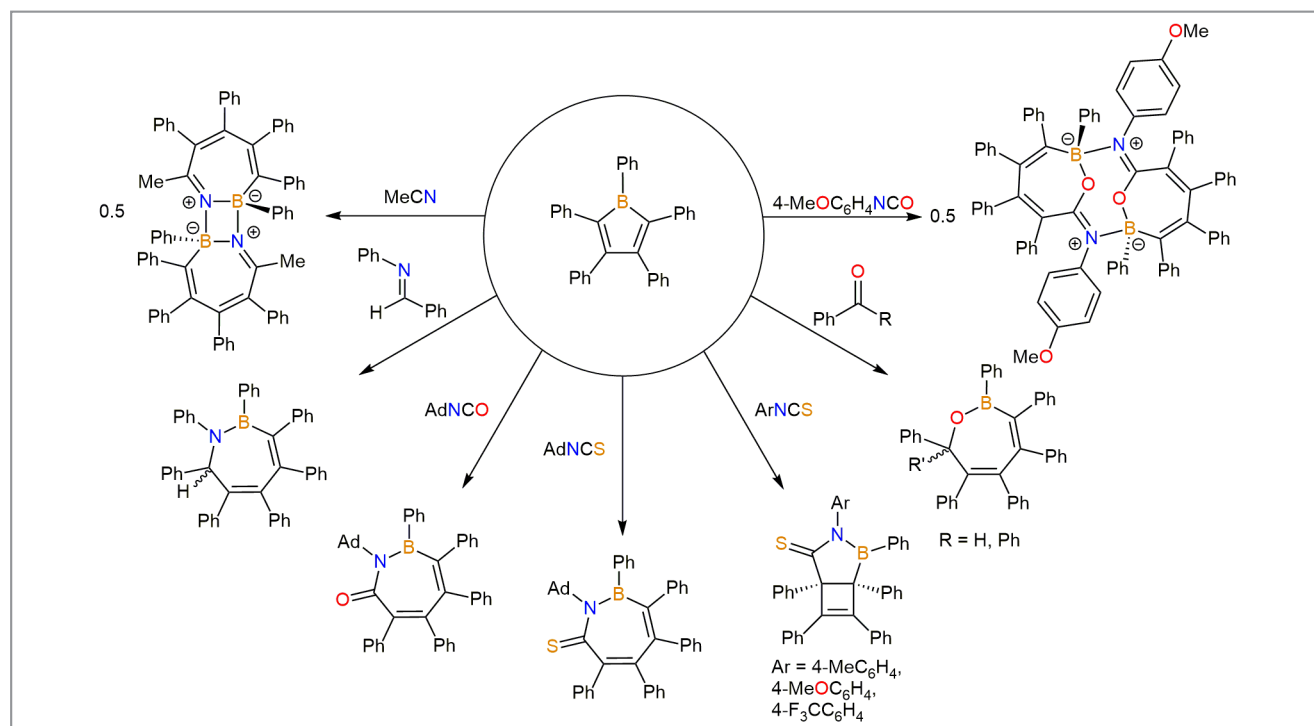
Developing the Chemistry of Boroles to Access Larger Boracycles

ORGN 298, Spring 2019 ACS National Meeting & Exposition, March 31–April 4, Orlando, USA

Boron heterocycles are emerging as an attractive class of molecules due to their promise in pharmaceuticals and electronic materials. The first drug containing a boron heterocycle approved by the US FDA was tavaborole in 2014 for the treatment of onychomycosis, a nail fungus.¹ “In regard to applications in electronic materials, when the vacant orbital on boron is in conjugation with an unsaturated system it lowers the energy of the π^* orbital in the molecule, often resulting in properties desirable for organic light emitting diodes (OLEDs) and organic photovoltaic devices (OPVs),” explained Professor Caleb Martin from Baylor University (Waco, Texas, USA). He continued: “Despite the utility of boron heterocycles, there remain challenges in accessing tricoordinate species due to their propensity to form undesirable four-coordinate compounds when nucleophiles are added. Our approach to accessing boron heterocycles is to utilize boroles, unsaturated BC_4 heterocycles, as reagents.² These compounds have diverse reactivity with a Lewis acidic boron center and diene, both of which are accentuated by the anti-aromatic state of the four- π -electron ring system.”

Although boroles have been known since 1969, Professor Martin pointed out that their reactivity had not been investigated until recently. “Our efforts have been focused on developing boroles as reagents for heterocycles via ring-expansion reactions. Unsaturated 1,2-dipolar organic molecules (nitrile, isocyanate, isothiocyanate, imine, ketone, aldehyde) insert into the endocyclic B–C bond to furnish seven-membered rings (Scheme 1)^{3–5},” said Professor Martin.

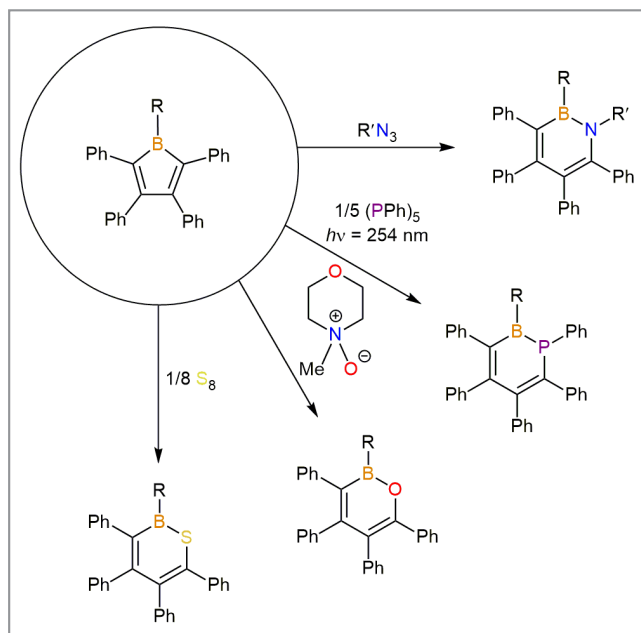
He went on to explain that – with the view of incorporating Group 15 elements – azides serve as a nitrene source and photolyzing $(PPh)_3$ acts as phosphinidene synthon to generate the corresponding 1,2-azaborine and 1,2-phosphaborine ring systems (Scheme 2).^{6,7} “Considering Group 16, the reactions of *N*-methylmorpholine *N*-oxide and elemental sulfur furnish the 1,2-oxaborine and 1,2-thiaborine heterocycles, respectively.^{8,9} In the 1,1-insertion products, incorporation of the lone-pair-bearing heteroatom adjacent to boron represents a two- π -electron substitute for a C=C unit in benzene,” remarked Professor Martin. He continued: “These systems represent hybrid inorganic/organic analogues of benzene which



Scheme 1 Insertion of unsaturated 1,2-dipolar molecules into pentaphenylborole

are planar delocalized systems, are polar, and have significant redshifts in the fluorescence emission for the central ring in comparison to their benzene relative.”

In an effort to enhance the electronic properties of the heteroarenes, the group has been investigating variants of boroles with different groups fused to the central BC_4 ring.



Scheme 2 Synthesis of heteroarenes from boroles

Professor Martin said: “9-Borafluorene is an analogue with a biphenyl backbone and this species also engages in insertion reactions to make six- and seven-membered rings, although it is not as reactive as boroles (Scheme 3).”^{10,11}

“Related to 9-borafluorenes, our group has prepared a borole derivative with a bis(*o*-carborane) framework in place of the biphenyl backbone (Figure 1)¹²,” explained Professor Martin. He concluded: “Efforts are ongoing to further develop compounds containing unsaturated BC_4 rings as reagents for the generation of boracycles that will be of interest to the inorganic, organic, and materials communities.”

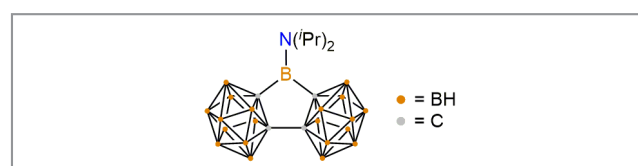
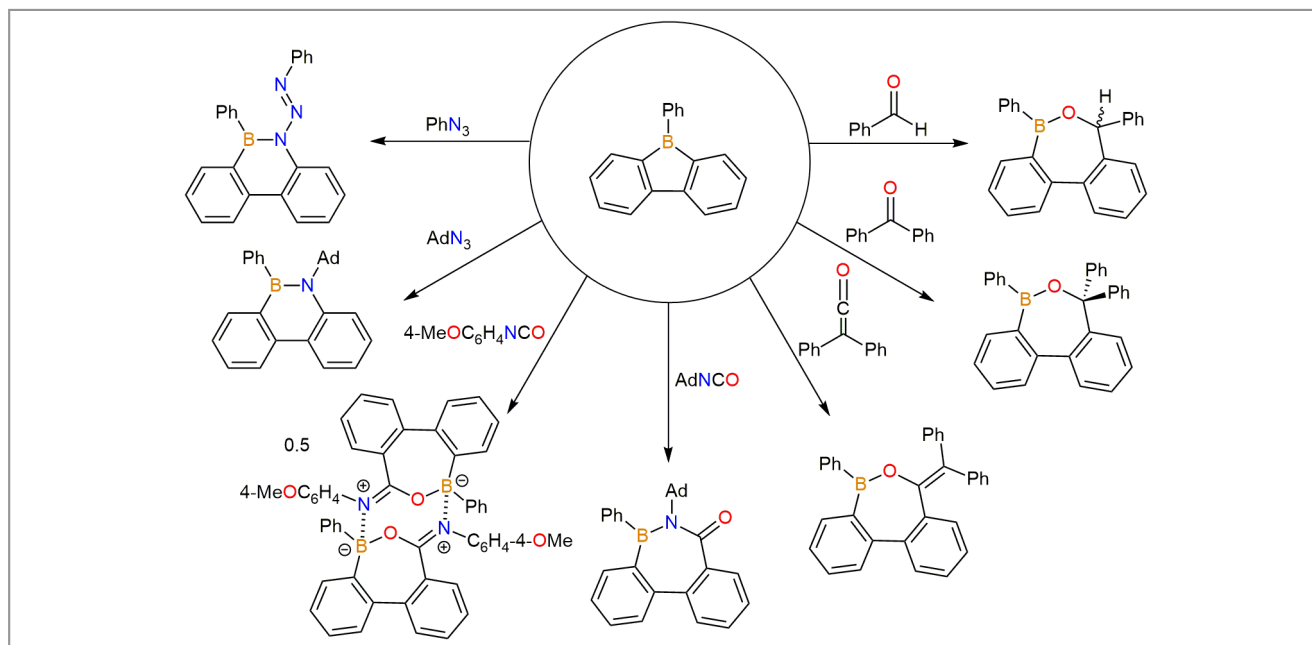


Figure 1 Analogue of 9-borafluorene with a bis(*o*-carborane) backbone

Finally, Professor Martin paid tribute to his team, saying: “The members of my group, both past and present, are thanked for their invaluable contributions since the inception of this project in 2014.”

Martin Farber

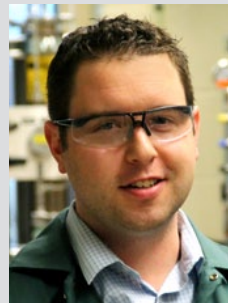


Scheme 3 Intermolecular insertion reactions of 9-phenyl-9-borafluorene

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About the author



Prof. C. Martin

Caleb Martin grew up in New Brunswick, Canada and attended Mount Allison University (Canada) for his BSc, conducting research with Glen Briand and Steve Westcott. In 2007 he moved to Western University (Canada) for his PhD, which focused on chalcogen and phosphorus chemistry with Paul Ragogna. He then moved to the USA to work for Guy Bertrand on carbene chemistry at University of California Riverside and University of California San Diego. In 2013, he accepted a position at Baylor University (Texas, USA). His research program is aimed at exploring the reactivity and properties of unusual boron compounds.

Carbocation Rearrangements: The Pinacol, Wagner–Meerwein, Demjanov, and Tiffeneau–Demjanov Rearrangements

The Pinacol Rearrangement

The first carbocation rearrangement to be observed and characterized was the pinacol rearrangement, discovered by German chemist Rudolph Fittig (1835–1910, Figure 1);^{1,2} an excellent account of the history of this reaction has been given by Berson.³ Fittig prepared pinacol (**2**) by the reaction of acetone (**1**), previously purified through its bisulfite addition product, with sodium metal, and he then prepared pinacolone (**3**) by dehydrating the pinacol with sulfuric acid (Scheme 1). Both syntheses were accomplished before atomic weights had been settled, and barely after Kekulé and Couper had proposed their versions of the structural theory of organic chemistry (in 1858).⁴

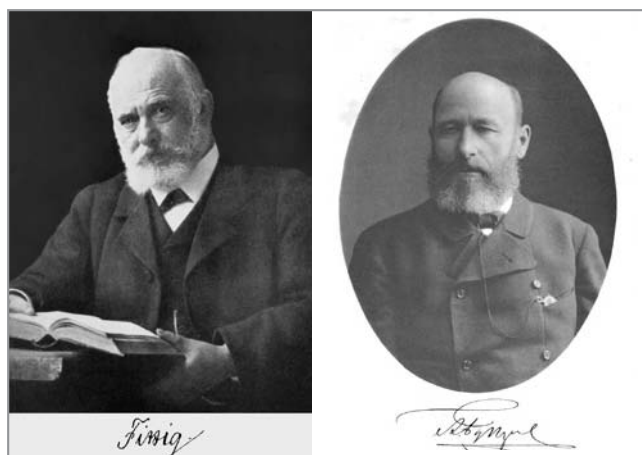
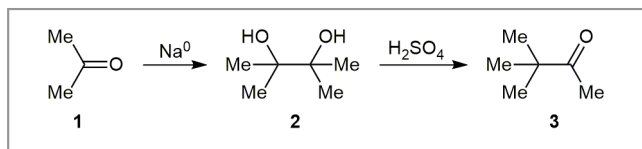


Figure 1 Fittig (left) and Butlerov (right)

The key to this reaction actually awaited the work of Aleksandr Mikhailovich Butlerov (1828–1886; Figure 1), the Russian professor of chemistry at Kazan Imperial University, and the pioneer of and ardent advocate for structural theory.

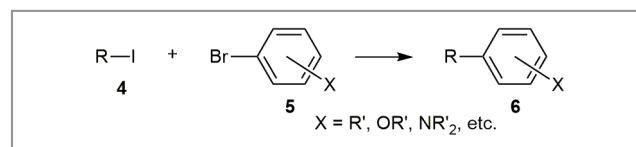


Scheme 1 Synthesis of pinacol and pinacolone

He was responsible for first proposing the correct structure of both pinacol and its acid rearrangement product.⁵

Fittig was born in Hamburg, and educated in Göttingen, where he took his Ph.D. under Heinrich Limpricht and Friedrich Wöhler. Following his graduation, Fittig remained at Göttingen, rising through the academic ranks (Assistant to Wöhler in 1858, Docent in 1860, Extraordinary (Associate) Professor in 1870). In 1870, he was appointed Ordinary Professor at Tübingen, and in 1876 he moved to Strasbourg as Professor. Here, the chemistry laboratories were constructed from his plans. He stayed at Strasbourg for the remainder of his life.

In addition to the synthesis and rearrangement of pinacol, Fittig reported a modification of the Wurtz coupling of alkyl halides⁶ with sodium, by replacing part of the alkyl halide with an aryl halide. The reaction, now known as the Wurtz–Fittig reaction,⁷ gives the corresponding alkylbenzene **6** (Scheme 2) by a cross-coupling pathway. Typically, the alkyl halide is an alkyl iodide, and the aryl halide is an aryl bromide.



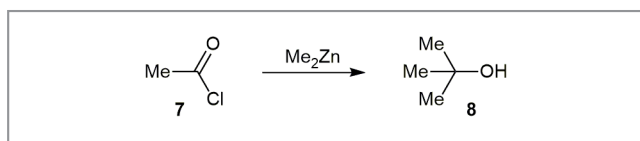
Scheme 2 Fittig's modification of the Wurtz coupling

Butlerov was born into the minor Russian nobility in Chistopol and educated at Kazan University in Russia. As a student at Kazan, he had been strongly influenced by Nikolai Nikolaevich Zinin (1812–1880), the discoverer of the reduction of nitrobenzene to aniline, and the subject of a later column in this series. Although Butlerov had begun his study of chemistry under Karl Karlovich Klaus (1796–1864, the discoverer of ruthenium), Klaus was a strong adherent of Berzelius's dualistic theory, and young Butlerov soon gravitated to Zinin with his more modern perspectives. In 1847, Zinin moved to the St. Petersburg Medical-Surgical Academy, and Butlerov reverted to entomology, his first love.

Following Zinin's departure, Kazan University needed a chemist, so, despite his personal preference for entomology, Butlerov was moved into chemistry as Klaus's assistant. He was quickly pushed through his *Magistr Khimii* (*M. Khim.*) and

Doktor Khimii (*Dr. Khim.*) degrees to allow him to be appointed as Extraordinary Professor of Chemistry. Neither his *M. Khim* nor his *Dr. Khim.* dissertation was more than marginally acceptable (his *Dr. Khim.* dissertation was failed when he presented it at Kazan); neither presaged the brilliant theoretician who would be developed by a *komandirovka* in Western Europe after his appointment as Extraordinary Professor.

Shortly after his return to Russia, he developed his own version of Structural Theory,⁴ thus becoming one of the young organic chemists at the forefront of the science. Unlike Couper and Kekulé, Butlerov used his theory to predict the existence of new compounds, *which he then prepared*. With his student Vladimir Vasil'evich Markovnikov (1838–1904), Butlerov took structural theory from an avant-garde theory to conventional wisdom.⁵ Structural theory, as modified by van't Hoff and Le Bel's stereochemical deductions, was critical to the study of rearrangement reactions. One of Butlerov's earliest successes was his synthesis of *tert*-butyl alcohol (Scheme 3).



Scheme 3 Butlerov's synthesis of *tert*-butyl alcohol

The Wagner–Meerwein Rearrangement

Carbocations and their rearrangements are almost ubiquitous in the biosynthesis of terpenoids and steroids and they are responsible for a dizzying array of natural products. Figure 2 shows representative monoterpenes [geraniol (**7a**) and fenchone (**8**)] and sesquiterpenes [farnesol (**9a**), nootkatone (**10**), modhephene (**11**), and isocomene (**12**)]. All of the cyclized terpenoids in Figure 2 are derived from the acyclic precursors [geranyl pyrophosphate (**7b**) and farnesyl pyrophosphate (**9b**)] by cationic cyclizations followed by one or more rearrangements in the biosynthetic pathway.

By far the most commonly encountered carbocation rearrangements are Wagner–Meerwein rearrangements.⁸ The first such rearrangement characterized, was reported by the Russian organic chemist, Yegor Yegorovich Vagner (1849–1903; Figure 3), who is better known in the west by the German form of his name, Georg Wagner. Towards the end of his career, Wagner had turned his attention to the structures of the bicyclic monoterpenes. In the course of this research, he was able to determine the relationship between the pinane, bornane and camphane ring systems (Figure 4).⁹ The lower

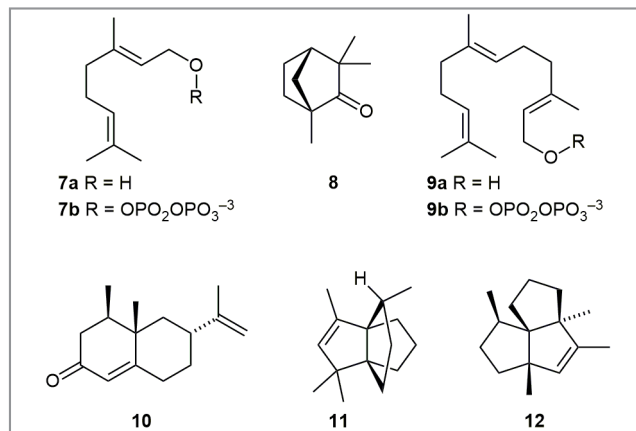


Figure 2 Representative terpenes with rearranged carbon skeletons

diagram in Figure 4 (in parentheses) clarifies the structural sequence in the original.

In 1914, Hans Lebrecht Meerwein (1879–1965, Figure 3) undertook a systematic study of carbocation rearrangements, publishing the first papers that established the link between the pinanes, camphanes and bornanes.¹⁰ The 1914 paper^{10a} is titled “Über den Reaktionsmechanismus der Umwandlung von Borneol in Camphen,” and it establishes the pattern of the 1,2- shift observed in the bicyclic terpenes. Only in 1922 did Meerwein and van Emster explicitly invoke a carbocation (Figure 5).¹¹

Wagner's family originated in East Prussia, but Wagner himself used the name ‘Yegor,’ a derivative of ‘Georgii’ that emphasized his Russian nationality. Wagner's father was a government official whose job entailed a great deal of traveling, so Wagner was entrusted to the care of his maternal grandparents after his mother died. When his grandfather died, he was sent to boarding school in modern Latvia, approximately 1700 km (1050 miles) west of Kazan.



Figure 3 (left to right) Vagner (Wagner), Meerwein and Zaitsev

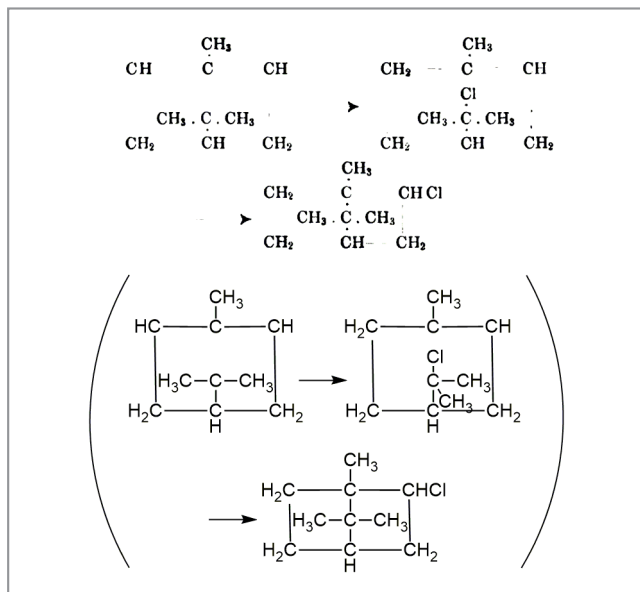


Figure 4 Wagner's description of the relationship between the pinane, camphane and bornane monoterpenes

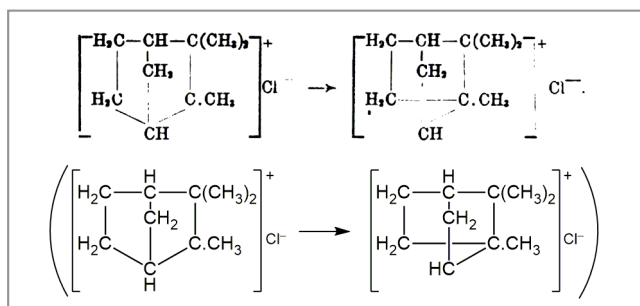
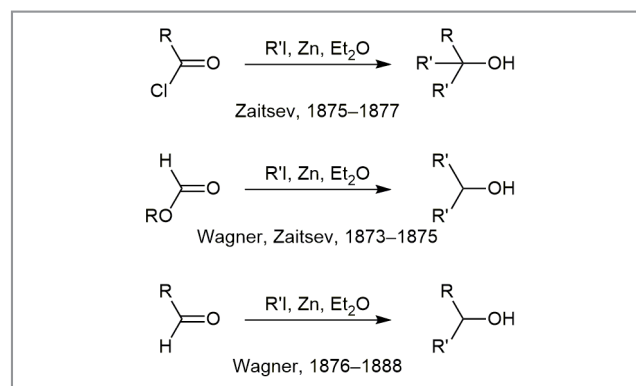


Figure 5 Meerwein and van Emster, 1922

He did not enjoy being at school, and he ran away to return to Kazan before graduating. He had enough money to cover only the first two thirds of the trip by train, so he completed the last 600 km (375 miles) on foot, begging for food along the way. Intensive home-schooling after his return permitted him to enter Kazan University in 1867. He entered the university as a student in law, but in 1869 (after his first classes in chemistry) he petitioned for a transfer to the Physics–Mathematics Faculty. The petition was granted, but at the cost of beginning his course of study from scratch.

As a student in chemistry, Wagner came under the influence of Aleksandr Mikhailovich Zaitsev (1841–1910, Figure 3). Zaitsev, who had continued the work of his own mentor, Butlerov, in the synthesis of alcohols from organozinc reagents,¹² oversaw Wagner's chemical research at Kazan.

Butlerov had prepared tertiary alcohols by the reaction between acid chlorides and dialkylzinc reagents,¹³ and Zaitsev had modified the procedure by using zinc metal and an alkyl (especially allyl) iodide (an alkylzinc iodide prepared *in situ*).¹⁴ Wagner's contribution was to substitute the acid chloride in the Zaitsev synthesis by aldehydes and formate esters, thus allowing the synthesis of symmetrical and unsymmetrical secondary alcohols.¹⁵ These developments in the organozinc synthesis of alcohols are summarized in Scheme 4.



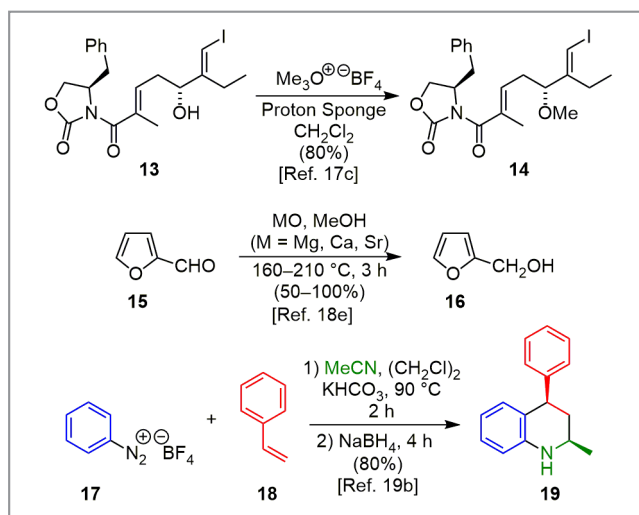
Scheme 4 Wagner's contributions to the synthesis of alcohols using organozinc compounds

Wagner graduated from Kazan in 1874 with the degree of *kandidat*. The next year, he was sent to St. Petersburg to study with Butlerov and Menshutkin as a salaried student. Following his move to Novo-Aleksandriya (now Puławy, Poland), Wagner turned his attention to the oxidation of alkenes with potassium permanganate, demonstrating that the oxidation with dilute permanganate solution ($\leq 2\%$) would give the diol without further oxidation. In Russia, this reaction is known as the Wagner oxidation. Later in his career, at Warsaw, he began the study of terpenes that led him to his description of the rearrangement that bears his name. One of his key deductions was the correct structure for α - and β -pinene,¹⁶ an achievement that brought Adolf Baeyer to concede that his own structure was incorrect, and to describe Wagner as 'a marvelously sharp-witted chemist.' Unfortunately for organic chemistry, Wagner died at 53 years of age due to complications of surgery for colorectal cancer.

The second chemist associated with this eponymous reaction, Hans Lebrecht Meerwein, was born in Hamburg and educated at the Fresenius University of Applied Sciences in Hesse. In 1900, he moved to the University of Bonn, where he eventually took his Ph.D. under Kekulé's student, Richard Anschütz. After a short term at Berlin, Meerwein became

Professor at Bonn in 1914, and then Professor of Organic Chemistry at the University of Königsberg until 1922. In 1922, he moved to Marburg as Professor, and he remained there until his retirement in 1953. He continued his research until his death twelve years later. Between 1948 and his death, Meerwein was nominated for the Nobel Prize in Chemistry twenty-seven times.

In addition to his work on rearrangement reactions, Meerwein also made other eponymous contributions to organic chemistry, including Meerwein's salt,¹⁷ the Meerwein-Ponndorf-Verley reduction,¹⁸ and the Meerwein arylation reaction.¹⁹ Some typical examples are gathered in Scheme 5: Meerwein's salt was used to effect methylation of alcohol **13** in the synthesis of nannocystin A analogues,^{17c} Group 2 oxides (MgO, CaO and SrO) catalyzed the reduction of furfural by methanol, which has the potential to be applied in the treatment of biomass,^{18e} and the Meerwein arylation of styrene **18** by diazonium ion **17** (which gives the aryl radical) and trapping of the resultant reactive intermediate provided a one-pot, metal-free, three-component assembly of aryltetrahydroquinolines such as **19**.¹⁹



Scheme 5 Applications of some of Meerwein's contributions to the field of organic chemistry

The Demjanov and Tiffeneau–Demjanov Rearrangements

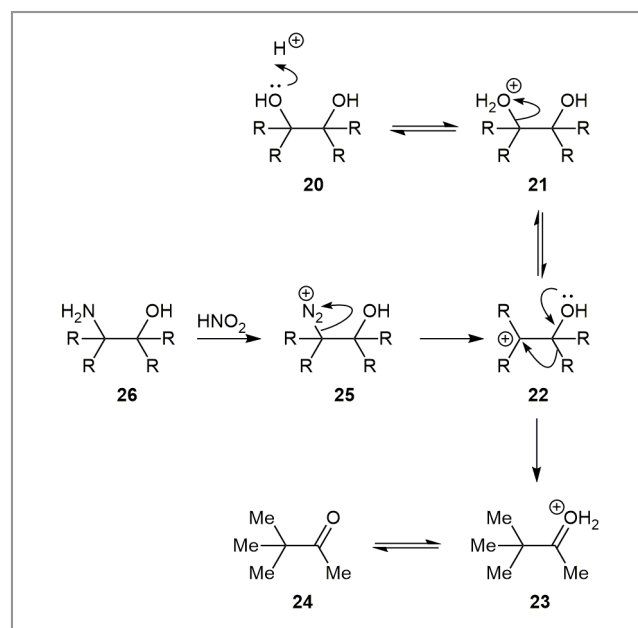
In 1903, Nikolai Yavkovlevich Dem'yanov (1861–1938; Figure 6) and his student, Mikhail Alekseevich Lushnikov, published the first paper describing the rearrangement of the cyclobutylcarbinyl system to the cyclopentyl system by the treat-

ment of (cyclobutylmethyl)amine with nitrous acid.²⁰ This was followed, four years later, by three papers in the *Zhurnal Russkago Fiziko-Khimicheskago Obshchestva*,^{21a-c} and three in the *Berichte der deutschen chemischen Gesellschaft* in which he expanded his studies to the cyclopropylcarbinyl and cyclobutyl systems.^{21d-f} In 1937, French chemist Marc Émile Pierre Adolphe Tiffeneau (1873–1945; Figure 6) published a paper with his students in which he described the rearrangement of 1-(aminomethyl)cyclohexanol to cycloheptanone by treatment with nitrous acid.²² This reaction, now known as the Tiffeneau–Demjanov rearrangement, has mechanistic elements of both the Demjanov and pinacol rearrangements (Scheme 6).

Nikolai Yavovlevich Dem'yanov was born in the city of Tver, northwest of Moscow, to Yakov Ivanovich Dem'yanov,



Figure 6 (left to right) Dem'yanov, Tiffeneau and Gustavson



Scheme 6

who was a member of the local nobility. Yakov Ivanovich died when his son was just three years old, and Nikolai was raised by his mother on their estate in Dievo, approximately 100 km north of the city. Dem'yanov was home-schooled until 11 years of age, and then he entered the prestigious 4th Moscow Classical Gymnasium. Little is known of this part of his life. He was an excellent student up to the 5th grade, but after that he found himself absorbed by physics and mathematics—much more so than by ancient languages; entering the 8th grade, he dropped out of the Gymnasium by request before graduating. He immediately applied to Moscow University as a volunteer, but he was denied admission for two years, while he completed his secondary education at the Tver Gymnasium.

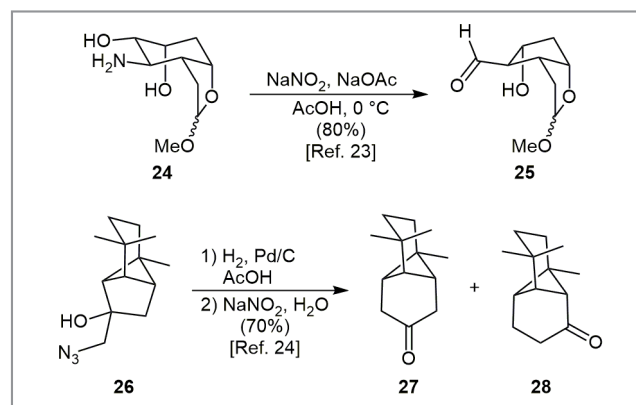
At the university, he quickly devoted himself to the intense study of chemistry. He showed an aptitude for research early on, and quickly became a student of Vladimir Vasil'evich Markovnikov (1838–1904), the great organic chemist who had built his research laboratory into one of the best in Europe. In 1886, Dem'yanov graduated from Moscow with the degree of 'authenticated student' and received an invitation from Markovnikov to remain with him for further training; he declined. Instead, he spent two years studying chemical technology and agronomic chemistry. He received a second diploma, in the physical sciences, for a report "On dextrins." This was not a *kandidat* degree.

In 1887, he was appointed Assistant in Inorganic and Analytical Chemistry at the Petrovskaya Academy of Agronomy and Forestry. Here, he met the organic chemist Gavriil Gavriilovich Gustavson (1842–1908; Figure 6), who was to become his mentor and friend. Under Gustavson's mentorship, Dem'yanov defended his dissertation for the *M. Khim.* degree at St. Petersburg in 1895, and for his *Dr. Khim.* at Moscow in 1899. In 1891, Gustavson retired from the Petrovskaya Academy, and accepted an appointment as Professor at the Higher Women's Courses (also known as the Moscow University for Women; now the Moscow State Pedagogical University). Gustavson's departure led to Dem'yanov's appointment to Extraordinary Professor, despite him being an *M. Khim.* student and not a graduate. In 1894, Dem'yanov became Head of Organic Chemistry at the Academy; he held this position until his death. In 1924, Dem'yanov was elected a Corresponding Member of the USSR Academy of Sciences, and in 1929 he was elected a Full Member.

Marc Tiffeneau was born in Mouy, 85 km north of Paris, and after leaving school he was apprenticed to an apothecary in Pont Sainte-Maxence, and a year later he moved to Paris, where he qualified as a pharmacist at the École de Pharmacie de Paris in 1899. After working as a pharmacy intern in several Paris hospitals, he was appointed head pharmacist at

the Hôpital Boucicaut in 1904; in 1927, he became head pharmacist at the Hôtel Dieu. Tiffeneau continued his graduate education after joining the Hôpital Boucicaut, and graduated Dr. ès Sciences in 1907 and obtained his degree in medicine in 1910. In 1924, he was elected to a Chair of Chemistry at the Hôtel Dieu, and two years later, to a Chair of Pharmacology and materia medica at the Sorbonne. In 1937, he became Dean of the Faculty of Medicine in the University of Paris. He was elected to the Académie de Médecine in 1927, and in 1939 he was elected to the Institut de France. He was elected Chevalier (1923) and Officier (1938) of the Légion d'honneur, and received the Prix Jecker twice: in 1911 (in part) and 1923 (full prize). At the time of his death, Tiffeneau was President of the Société chimique de France.

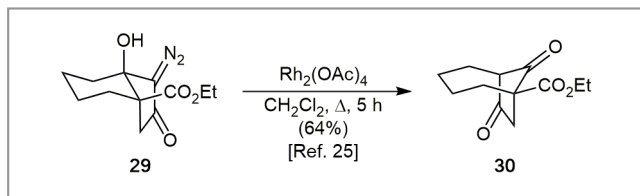
The Tiffeneau–Demjanov rearrangement has been used in synthesis for many years, as in Woodward's synthesis of prostaglandin $F_{2\alpha}$,²³ and Miyashita and Yoshikoshi's synthesis of longipinene²⁴ (Scheme 7).



Scheme 7 Applications of the Tiffeneau–Demjanov rearrangement

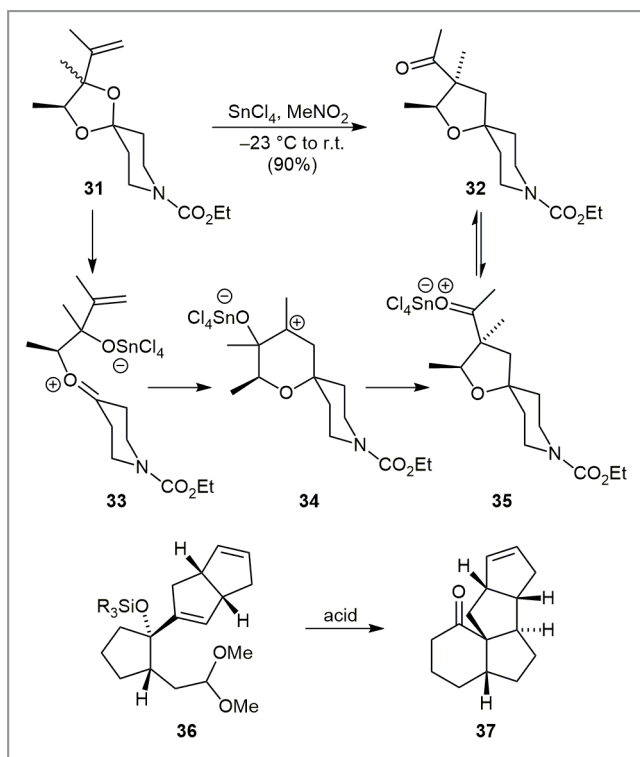
In the Woodward synthesis, the cyclopentane of the prostaglandin is assembled with the correct relative stereochemistry by the regioselective Tiffeneau–Demjanov ring contraction of cyclohexylamine derivative **24** to give cyclopentane **25**. The reverse operation, the Tiffeneau–Demjanov ring expansion of the tricyclic aminoalcohol obtained by reduction of azide **26**, gave a 95:5 mixture of the regioisomeric ketones **27** and **28**, respectively.

More recently, alternative methods for the formation of the deaminated carbocation have been developed. Several of these methods involve using a singlet carbene substitute as a carbocation surrogate, as illustrated by the rhodium–carbene complex formed from the fused-ring α -diazo ketone **29**, which rearranges into bridged-ring diketone **30** (Scheme 8).²⁵



Scheme 8 Rearrangement of fused-ring α -diazo ketone **29**

Recent applications of the pinacol rearrangement are provided by the pinacol-terminated Prins reaction shown in Scheme 9. Overman and Rishton²⁶ used the reaction for the stereospecific synthesis of spirotetrahydrofuranone derivative **32** from ketal **31**, and Overman and Pennington used the reaction to close the tetracyclic ring system of ketone **36** from acetal **37**.²⁷



Scheme 9 Recent applications of the pinacol rearrangement by Overman and co-workers

The use of carbocation rearrangements is of long standing in organic synthesis, and it is still likely that new carbocation rearrangement reactions will be developed in the future. I am one chemist who looks forward to seeing what that future holds.

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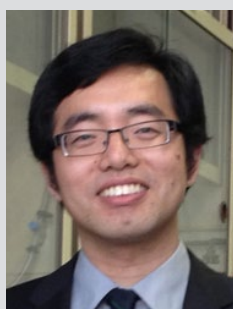
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Young Career Focus: Dr. Lei Wang (Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences and Peking Union Medical College, P. R. of China)

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. Lei Wang (Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences and Peking Union Medical College, P. R. of China).

Biographical Sketch



Dr. L. Wang

Lei Wang was born in Anhui (P. R. China). He received his B.S. degree in traditional Chinese medicine from the Jilin Agricultural University (P. R. China) in 2005. Then, he started his studies in natural product chemistry and obtained an M.S. degree in 2008 from the Institute of Materia Medica, Chinese Academy of Medical Sciences & Peking Union Medical College (CAMS & PUMC, P. R. China) under

the guidance of Professors Ruoyun Chen and Dequan Yu. He received his Ph.D. in organic and medicinal chemistry in 2013 at the National University of Singapore (Singapore) with Prof. Jian Wang. During his Ph.D. studies, he focused his research on C–H activations and enamine chemistry and developed a series of novel reactions to synthesize heterocycles which included coumarins, benzazepines, pyrazoles, and 1,2,3-triazoles. Then he began postdoctoral research at the RWTH–Aachen University (Germany) in Prof. Dieter Enders's group, where he worked on NHC catalysis, supported by the Alexander von Humboldt Foundation. After working as a senior research fellow at the National University of Singapore, he joined the Institute of Medicinal Plant Development, CAMS & PUMC as an associate professor in 2017. Currently, Dr. Wang focuses his research on asymmetric catalysis, medicinal chemistry and natural product chemistry. He was awarded the Natural Science Prize of Ministry of Education of China (Second Class) in 2013 and the Alexander von Humboldt Scholars from Germany in 2016. In 2019, he received the Thieme Chemistry Journals Award.

INTERVIEW

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

Dr. L. Wang The goal of my group is to develop novel synthetic transformations via organocatalysis/transition-metal catalysis and apply these methods to bioactive complex molecule synthesis and late-stage functionalization of natural products and marketed drugs. The ultimate goal is to establish efficient synthetic pathways to assemble bioactive molecule derivatives and to increase the probability of success in clinical trials. Additionally, we are interested in developing synthetic methodologies to construct axially chiral compounds, which are widespread in biologically active molecules.

SYNFORM *When did you get interested in synthesis?*

Dr. L. Wang I became interested in organic synthesis during my Bachelor's studies at Jilin Agricultural University. I was captivated by the story of the discovery of artemisinin and the assembly of artemisinin derivatives via organic synthesis to reduce the mortality rates for patients suffering from malaria. I was so curious about why natural products could play a magic role in curing diseases and how synthetic chemistry could enhance the curative effects. Then in my Master's studies at the Institute of Materia Medica, CAMS & PUMC, I was fortunate to work on natural product chemistry to further understand the magic role of natural products in drug discovery, nutrition, cosmetology, and applied chemistry. During this period, I was also attracted by Prof. Dequan Yu's seminar about bioactive natural product structure modifications and derivative synthesis, which helped me to understand the importance of organic synthesis in drug discovery. Thus, I chose to perform my Ph.D. research in organic and medicinal chemistry at the National University of Singapore, where I devel-

oped synthetic methods to construct versatile novel bioactive molecules via C–H activations and enamine catalysis. Then I moved to RWTH–Aachen University for postdoctoral studies under the supervision of Prof. Dieter Enders, where I focused on the construction of chiral bioactive molecules using various organocatalysts.

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

Dr. L. Wang I believe that organic synthesis belongs to the fundamental science lying between physics and biology. Organic synthesis, the art and science of constructing novel substances, plays a central role in materials science, agricultural chemistry, environmental science, especially in medicinal chemistry and pharmaceutical industry. Organic synthesis, in some sense, forms the bottleneck of the construction of new valuable bioactive molecules. Thus, I think one important continuing role is to explore atom- and step-economic methods for bioactive molecule synthesis, together with the construction and development of novel lead compounds. Within the rapidly growing realm of organocatalysis, domino/cascade reactions from simple substrates for the construction of bioactive complex molecules have emerged as important routes to achieve sustainable synthesis. Another goal of organic synthesis is to develop novel and simple synthetic methods that are suitable for mass production, with the lowest cost possible. The potential methods for mass production should be scrutinized for both safety and environmental considerations, and involve multi- and trans-disciplinary collaborations incorporating organic syntheses, bioassays, and clinical trials.

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

Dr. L. Wang Inspired by Nature's success in generating bioactive molecules in an efficient and environmentally friendly way, one major focus of my research is to synthesize bioactive molecules with environmental friendliness and operational simplicity. We employed organocatalysis for this purpose from the start of my independent academic career in 2017. Recently, we have developed some green methodologies to assemble heterocycles that were suitable for mass production with the lowest cost possible and optimization of lead compounds. We have also employed NHC catalysis to synthesize a series of heterocycles embedded with an oxindole moiety together with using the diversity-oriented synthetic strategy as a tool for the discovery of novel biologically active

small molecules for further clinical development. Moreover, transdisciplinary collaborations to achieve hit compounds among our organic syntheses with bioassays and clinical trials are also continuing in my lab.

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

Dr. L. Wang Our recent progress in organocatalysis with environmental friendliness and operational simplicity is something I consider so important (*Commun. Chem.* **2019**, *2*, 69). This triazene–alkyne cycloaddition produces reactive triazene intermediates, which readily participate in the cycloaddition reactions with terminal/internal alkynes, thus assembling densely substituted 3-trifluoromethylpyrazole scaffolds with high efficiency (Figure 1). The cycloaddition strategy is also extended to enable late-stage functionalization of pharmaceuticals, such as anti-cancer drug (erlotinib), anti-HIV drug (efavirenz), and antihypertensive drug (pargyline). The protocol also exhibits a remarkable broad scaffold diversification scope to embed 3-trifluoromethylpyrazole into various kinds of bioactive compounds, ranging from pharmaceutically relevant molecules and natural products to a panel of bioactive heterocycles, such as paclitaxel, hydroxycamptothecin, fluorouracil, flavonoids, coumarins, alkaloids and so on. Considering the important role of COX inhibition in antiplatelet therapy, we also developed the synthesis of a novel drug-like platelet aggregation inhibitor using this protocol on a ten-gram scale without erosion of the yield. Due to its ease of operation, high efficiency, and environmental friendliness, this synthetic strategy will significantly accelerate the efficiency of related lead-compound and drug-discovery processes.



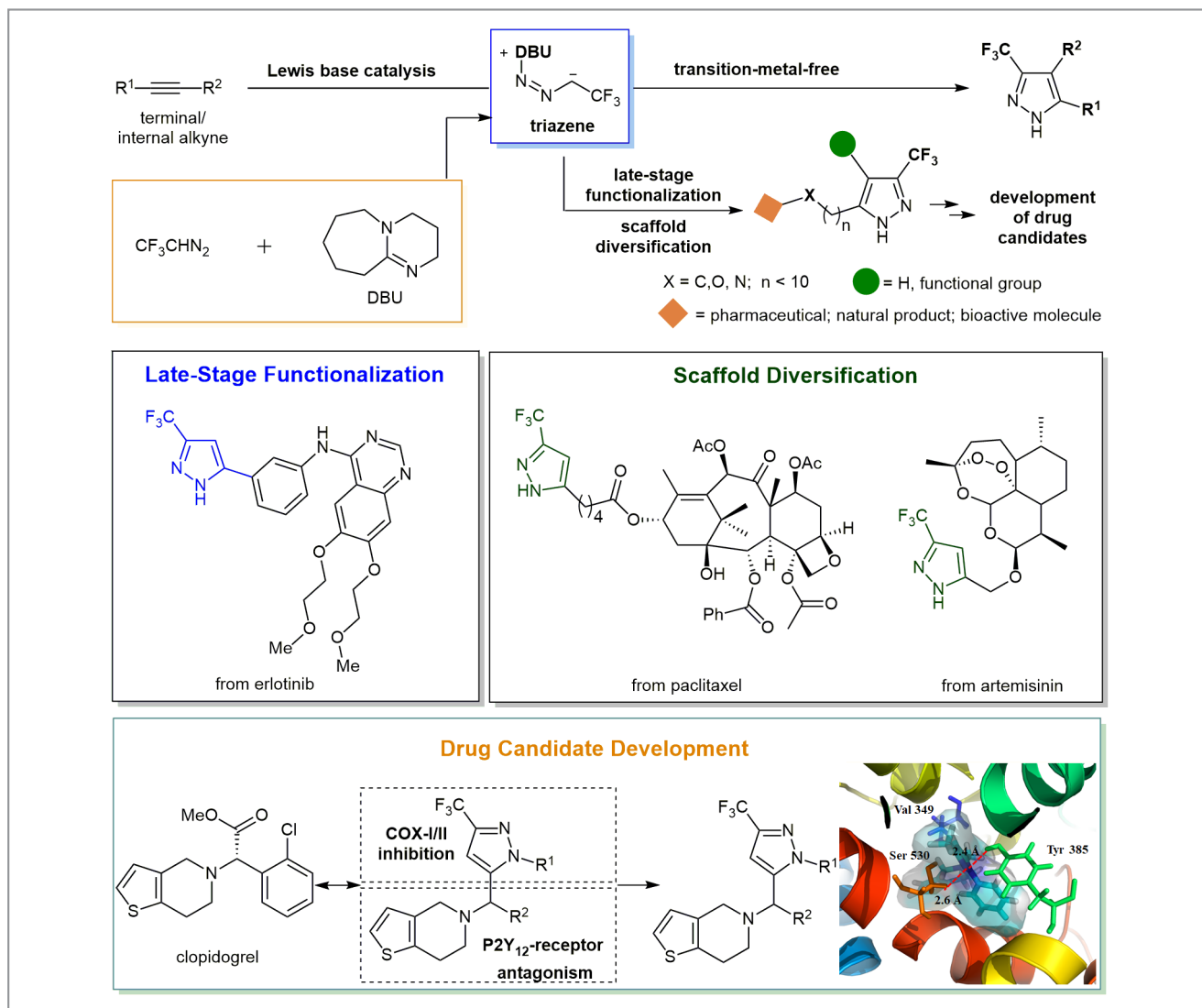


Figure 1 Triazene–alkyne cycloaddition for the assembly of 3-trifluoromethylpyrazoles, late-stage functionalization, scaffold diversification, and novel drug candidate development

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Site-Selective Enzymatic C–H Amidation for Synthesis of Diverse Lactams

— Literature Coverage

Asymmetric Synthesis of Tetrazole and Dihydroisoquinoline Derivatives by Isocyanide-Based Multicomponent Reactions

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Synthesis of Eight-Membered Lactams through Formal [6+2] Cyclization of Siloxy Alkynes and Vinylazetidines

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