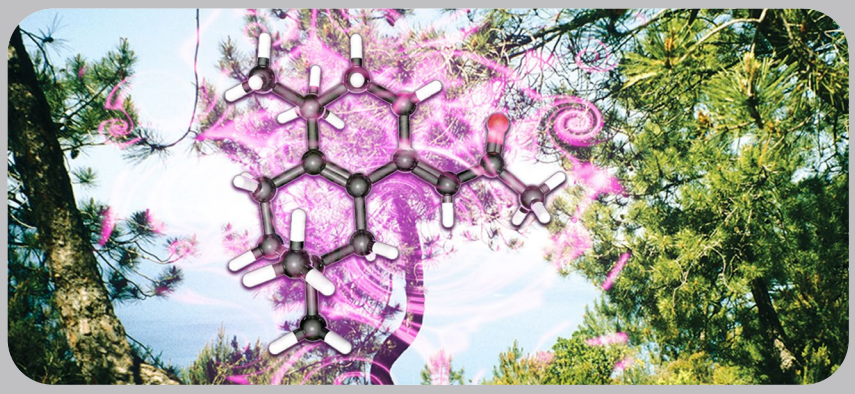
Synform

People, Trends and Views in Chemical Synthesis

2021/05

New Musks and the Molecular Modeling of Olfactory Receptors

Highlighted article by J. Liu, V. Hürlimann, R. Emter, A. Natsch, C. Esposito, S. M. Linker, Y. Zou, L. Zhou, Q. Wang, S. Riniker, P. Kraft



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Dear Readers,

One of the few positive things that came out of this pandemic is the proof that highly innovative mRNA vaccines – which are turning out to be true game changers in the war against Covid-19 – can work really well, thanks to their efficacy, safety and potential versatility against mutant viral strains. But at this point, one is entitled to wonder whether the use of mRNA (and other RNAs) can be extended to different types of vaccines or even therapies, for treating disorders such as cancer, autoimmune or genetic diseases. Trailblazer companies – such as BioNTech and Moderna – have been working on this revolutionary concept for years, although – as far as I can tell – the definitive proof that mRNA technology can actually work only came with the Covid-19 vaccines. Now there is a whole new horizon ahead: are we heading into the RNA therapeutics era? Time will tell, but certainly these are very exciting and potentially revolutionary times for biomedical research. Despite the increasingly important role of biotechnology, I am convinced that chemistry will continue to play a key role for the foreseeable future of biomedical research. Titanic research endeavours such as the ones that eventually led to the development of Covid-19 vaccines will always require an in-depth understanding of complex molecular aspects – such as the formulation of mRNA in these vaccines, which is a key aspect for their efficacy – besides being increasingly based on the cross-disciplinary work of large and international teams of scientists. Both the progress and importance of organic chemistry are witnessed also by the top-notch research presented in this new issue of SYNFORM, which starts with the 2020 SYNLETT Best Paper Award interview with the corresponding authors Q. Wang, S. Riniker and P. Kraft, which takes us into the fascinating world of fragrances and their perception. The second article covers the [3+2] (hetero)annulation of nonconjugated alkenes developed by K. M. Engle and colleagues (USA) and originally published in *Nat. Commun.* The next article is also based on ground-breaking research published in *Nat. Commun* by Z.-J. Shi (P. R. of China) for achieving the synthesis of arylamines and N-heterocycles using molecular nitrogen N2. The final article is a new chapter in the magic history of organic reactions authored by David Lewis, this time about Chichibabin and the dawn of pyridine chemistry.

Enjoy your reading!!

In this issue

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SYNLETT Best Paper Award 2020: New Musks and the Molecular Modeling of Olfactory Receptors

Synlett **2020**, *31*, 972–976

Background. Thieme Chemistry and the Editors of SYNTHESIS and SYNLETT present the 'SYNTHESIS/SYNLETT Best Paper Awards'. These annual awards honor the authors of the best original research papers in each of the journals, considering their immediate impact on the field of chemical synthesis.
Dr. Philip Kraft from the Givaudan Innovation Center Kemptthal, Switzerland, Professor Sereina Riniker from ETH Zurich, Switzerland and Professor Quanrui Wang from Fudan University, P. R. of China, are the recipients of the SYNLETT Best Paper Award 2020 for their article '*A New Family of Rigid Dienone Musks Challenges the Perceptive Range of the Human Olfactory Receptor OR5AN1*' (Figure 1). Benjamin List, Editor-in-Chief of SYNLETT, stated: "This paper describes the design and discovery of new musk odorants. These targets are accessed using equally elegant and practical chemical synthesis methods. Moreover, the paper also contains a careful QM/MM study to investigate binding of the designer scents to a human musk receptor. Overall, this is truly beautiful work encompassing scent design and evaluation, an impressive synthetic approach, and a thorough computational study."
SYNFORM spoke with Philip Kraft, Sereina Riniker and Quanrui Wang.

Biographical Sketches

Top from left: Dr. Stephanie M. Linker *(© 2018 Select Photography GmbH, Löwenstrasse 69, 8001 Zürich, Switzerland)*, Vera Hürlimann, Dr. Roger Emter, Jie Liu; **Center from left:** Prof. Sereina Riniker *(© ETH Zurich/Giulia Marthaler)*, Dr. Philip Kraft *(© Sandra Stamm Fotografie)*, Prof. Quanrui Wang; **Bottom from left:** Dr. Carmen Esposito *(© Lisa Caflisch)*, Dr. Andreas Natsch, Dr. Yue Zou, Dr. Lijun Zhou

Philip Kraft is a Research Fellow at the Givaudan Innovation Center Kemptthal (Switzerland). He studied chemistry at Kiel University, and obtained his Ph.D. with Werner Tochtermann working on macrocyclic musk odorants in collaboration with H&R. In 1996, he joined Givaudan fragrance research and was promoted to the ranks of chief chemist (2001), group leader (2008) and research fellow (2015) with a focus on rational odorant design. He has authored 97 publications including 3 books, 38 patents, invented or co-invented seven commercially successful perfumery materials and reads Fragrance Chemistry at the University of Bern (Switzerland) and the ETH Zurich (Switzerland).

Sereina Riniker is currently Associate Professor of Computational Chemistry at ETH Zurich (Switzerland). She studied chemistry at ETH Zurich and obtained her Ph.D. with Wilfred van Gunsteren in 2012 working on molecular dynamics simulations. After a postdoctoral stay at Novartis Institutes for BioMedical Research, she returned to ETH Zurich as Assistant Professor in 2014 and was promoted to Associate Professor in 2020. The mission of her laboratory is to develop new methodology for molecular computer simulations and cheminformatics, and its application to gain insights into challenging (bio)chemical questions.

Quanrui Wang is currently Professor of Organic Chemistry at Fudan University (Shanghai, P. R. of China). Following his diploma in chemistry from Henan University (P. R. of China) in 1983, he pursued his Master's degree at Northwest University (Xi'an, P. R. of China) in 1986. He then studied organic chemistry at the Universität Konstanz in Germany and obtained his Ph.D. with J. C. Jochims in 1994 working on heterocumulene chemistry. After a two-year postdoctoral study at Peking University, he joined Fudan University to begin his independent career. The mission of his group is to develop new synthetic methodologies and application of rearrangement reactions, with a special focus on biomolecular significant molecules and odorants. He has authored 120 publications and two college textbooks.

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INTERVIEW

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

Dr. Philip Kraft The core mission of fragrance research today is to provide sustainable, renewable and biodegradable ingredients. This requires innovative chemical solutions. A great opportunity in addressing these challenges is that we now have available for the first time receptor assays to generate activity data beyond odor thresholds. This opens up an exciting new era of rational design of odorants. Due to their commercial importance, musks have been amongst the first families to get investigated, and a *PNAS* paper by the groups of Block, Matsunami, O'Hagan, Batista and Zhuang had postulated the OR5AN1 receptor to be responsible for the perception of musks. Studying the perceptive range of a new family of rigid musks, we found however that the OR5AN1 receptor is only responsible for animalic aspects not primarily musky. These rigid compounds should now be of help to find the genuine musk receptor, which will then enable the rational design of potent, environmentally benign new musk odorants from sustainable resources.

Prof. Sereina Riniker This collaboration was an excellent opportunity to assess the state-of-the-art computational approaches for odor receptor modeling in a prospective real-world setting. The insights we gained provide now a direction for future developments.

Prof. Quanrui Wang The ancient Chinese book "the Shennong Ben Cao Jing" had recorded the musk's efficacy of "awakening the mind, promoting blood circulation, relieving pain and inducing labor." Musk has played an irreplaceable role in fragrance chemistry since muscone was first isolated from natural musk by Heinrich Walbaum in 1906. Our collaborative research has expanded the family of synthetic musks and provided new insights into the molecular mechanisms by which this special scent is produced.

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

Dr. Philip Kraft This research was inspired by the structural motifs that became available from combining sigmatropic rearrangements of vinyl propargyl systems with allenylic intramolecular Diels–Alder reactions, which was the topic of the PhD thesis of Jie Liu in the group of Professor Wang. We thought this tandem sequence should allow the construction of rigid systems with a backbone characteristic of the 5th and most recent class of musk odorants – that of dienone musks. Because of their rigid nature, these should be ideal candidates to characterize and challenge the proclaimed musk receptor OR5AN1 both by an *in vitro* assay and a computational model, and this led to an exciting collaboration both with our *in vitro*

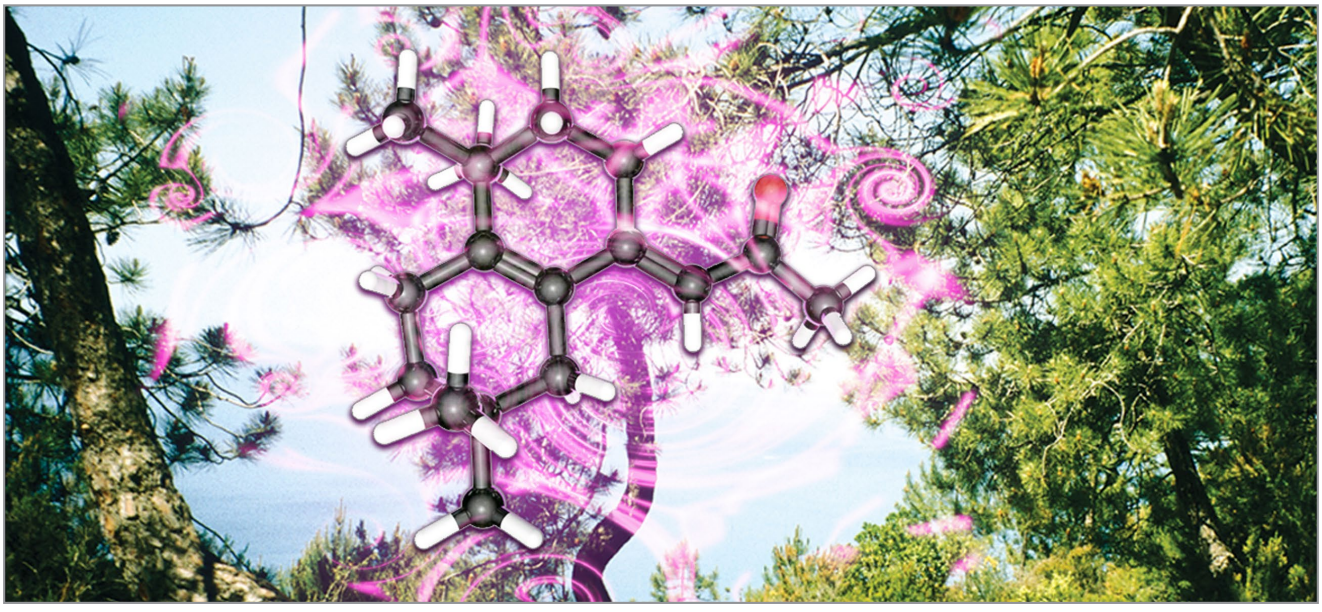

Figure 1

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molecular screening team and the ETH modeling experts of the group of Professor Riniker.

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

Dr. Philip Kraft We hope to be able to expedite our insight in the musk receptor in the design of novel and attractive musk structures that will provide characteristic signatures in perfumery. Musks are central in defining what the average person perceives as a perfume. The essence and purpose of a perfume is to enchant and delight. Having served this purpose they should discretely disappear, but also their production should be sustainable and minimize the environmental impact. Thus, high potency is desired which could be designed by complementarity to the binding pocket of the musk receptor. We feel we have taken a critical step and strive to publish a follow-up paper with the genuine musk receptor if we are able to find it with the help of this new family of dienone musks.

Prof. Sereina Riniker Computer simulations have become increasingly important in recent years to complement experimental studies by allowing insights at the atomic level into the molecular processes involved. The advances in both computer power and methodology have contributed to this. Nevertheless, there are still many challenges remaining, which trigger continued improvements of existing approaches and the development of new methods. Being able to collaborate with experimental groups and apply the available tools is essential for this process, and is also a highly valuable experience for my co-workers.

Prof. Quanrui Wang Various rearrangement reactions have been and remain attractive as synthetic methods. In recent years, we have been committed to developing new types of rearrangement reactions and the rearrangement-initiated tandem reactions to construct complex and useful molecules. We aim to demonstrate the vitality and application value of these strategies. The theoretical results derived from the study on the relationship between the molecular structure and the musk scent can be regarded as pointing out the direction of development for synthetic chemists in this field. The results from this cooperation with Givaudan are a successful example.

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

Dr. Philip Kraft Organic chemistry will play the central role in enabling a sustainable future in harmony with nature and using renewable sources is part of being a modern player in chemistry. Fragrance chemistry, in addition, creates joy and happiness by offering captivating sensory experiences. Especially in challenging times like these with the severe travel restrictions by Covid-19, perfumes can take you on a magic carpet ride and transpose you to far-away places or conjure fond memories of the distant past. Organic chemistry has fueled perfumery creativity in the past 150 years, and will continue to do so, only now more sustainable, in compliance with nature and human health, more rationally understood and designed, but as innovative as ever. Environmental sustainability is becoming the central guiding principle of organic chemistry, and this constitutes one of the biggest and most timely opportunities in a post-fossil world. Most importantly this needs well-educated, creative and inspiring organic chemists, those who likely are also readers of SYNLETT.

Prof. Quanrui Wang I hold exactly the same view as Philip. I think organic chemistry is a flourishing and also "mature" discipline. The theory of organic chemistry still needs to be further developed and innovated, and the relationship between the structure and properties of organic molecules, such as the molecular mechanism of odor perception, and the details and rules of important organic reaction mechanisms should be further illuminated. Organic chemistry should actively integrate with other disciplines such as information science, materials science, life science, environmental science, energy science, space science, and so on, to find research topics and to achieve common prosperity.

SYNFORM *What does this award mean to you/your group?*

Dr. Philip Kraft We are greatly humbled and feel honored to receive this precious award which increases the visibility of fragrance chemistry and should encourage academic researchers to engage in this fascinating domain. As two of my early research papers were published in SYNLETT (*Synlett* **1996**, 1029–1035 and *Synlett* **1997**, 600–602), I feel in addition personally attached to this journal with its informative style, its concise format and its immediacy, which I have learned to know and love throughout all my chemistry studies and career. I also much enjoyed the fast and critical crowd-review process: A great experience indeed.

Prof. Sereina Riniker This award highlights the value of interdisciplinary research and the complementary nature of experimental and theoretical studies. It is a great motivation for future work.

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Prof. Quanrui Wang This award is really a bonus for us, just in time for the Chinese New Year of the Ox. We take the great pleasure to receive this honor. To some extent, it reflects the importance of collaboration, especially for us with Givaudan, a leading company in the development of fragrances. The synthetic work has been mainly performed by my PhD student Jie Liu, the first author of this paper. It is because of the joint efforts of our co-workers that the research went deeper and more systematic. We believe we are off to a good start in the study of musk chemistry, and this is an inspiration for other related investigations. This award will also inspire us to continue our study. We look forward to presenting new achievements to SYNLETT.

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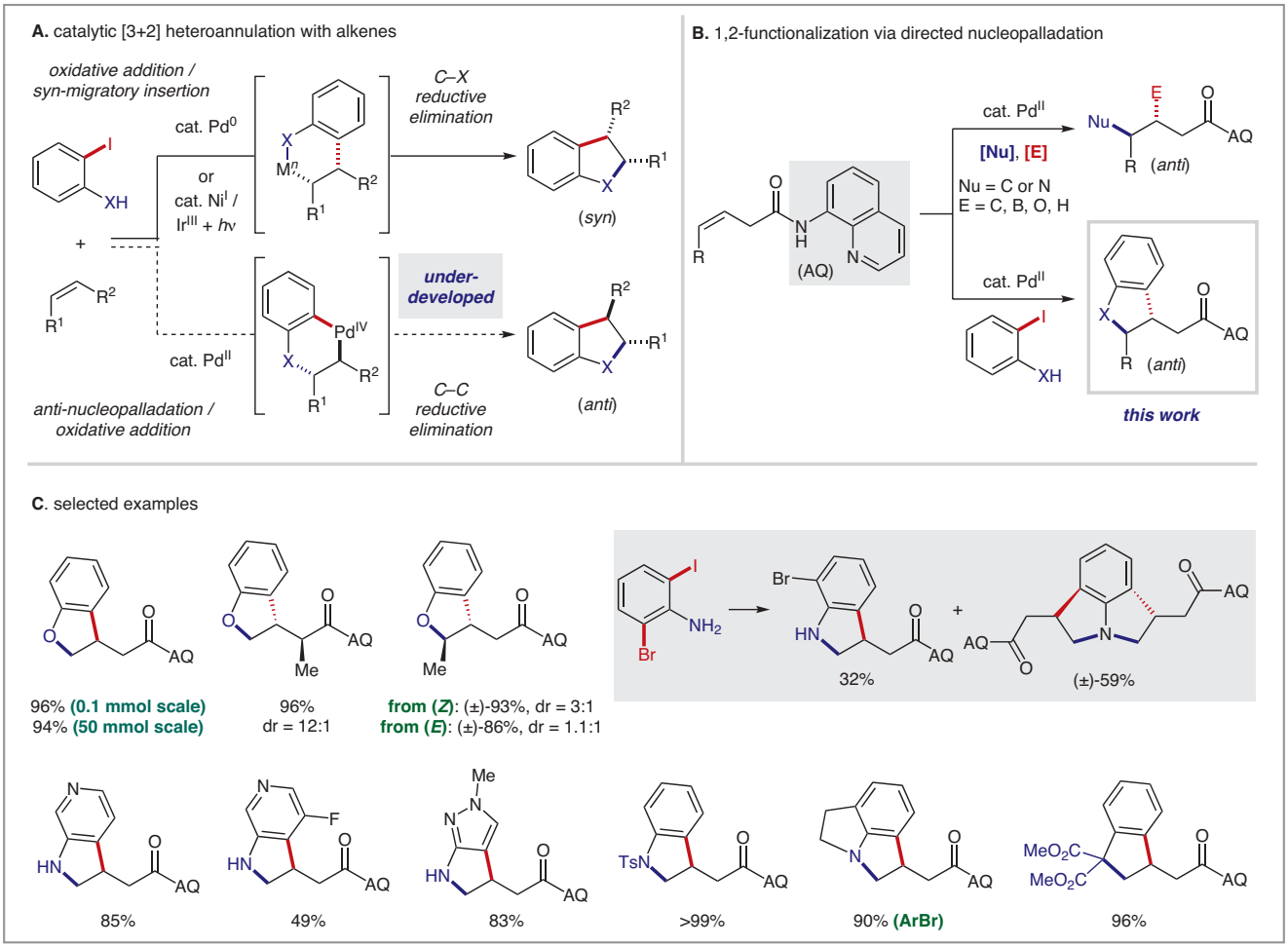
Anti-Selective [3+2] (Hetero)annulation of Nonconjugated Alkenes via Directed Nucleopalladation

Nat. Commun. **2020**, *11*, 6432; DOI: 10.1038/s41467-020-20182-4

Carbo- and heterocyclic core structures – such as 2,3-dihydrobenzofurans, indolines, and indanes – are common motifs in bioactive and therapeutic molecules, as well as in natural products. Due to their usefulness, it remains important to identify efficient routes to access these compounds easily, quickly, and inexpensively. The groups of Dr. Indrawan J. McAlpine from Pfizer Oncology Medicinal Chemistry (San Diego, USA), Professor Peng Liu from the University of Pittsburgh (USA) and Professor Keary M. Engle from the Scripps Research Institute (La Jolla, USA) collaborated on the work leading to the publication of this paper in *Nature Communications*. Professor Engle said: "Based on the development of Larock-type (hetero)annulation reactions between ambiphilic aryl halides and alkenes over the past 30 years, as well as prior work in 8-aminoquinoline (AQ)-directed alkene 1,2-difunctionalization, we sought to develop an all-encompassing annulation process that could unite non-conjugated alkenes and a diverse collection of *O*-, *N*- and *C*-based coupling partners using a mechanistic approach distinct from prior (hetero)annulations, namely one that relies on an initial nucleo-



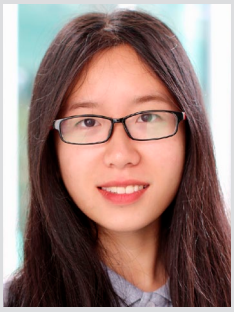
Scheme 1

palladation event, subsequent oxidative addition, and finally C(sp^3)–Ar reductive elimination, involving an overall Pd(II)/Pd(IV) redox couple."

At first, the three research groups were wary that the development of this reaction could end up facing insurmountable challenges. Professor Engle explained: "For example: (1) phenols and anilines have proven ineffective coupling partners in AQ-directed nucleopalladation reactions; (2) the strained transition states for intramolecular Pd(II)/Pd(IV) oxidative addition and reductive elimination appeared to be potentially high-energy; (3) competitive pathways arising from Heck- or Wacker-type oxidative alkene addition, hydrofunctionalization, or the alkene isomerization may diminish yield." He continued: "To our surprise and delight, however, the envisioned method was indeed viable (Scheme 1). Moreover, the substrate scope and the functional group tolerance of this reaction is impressive. In fact, this reaction system tolerates *ortho*-iodophenols, *ortho*-iodoanilines with or without protecting groups (such as *N*-acetyl, -tosyl, and -alkyl groups), various aminoiodopyridines, different carbon-based coupling partners, internal alkenes, and α-substituted alkenes." The authors found that good to excellent yields and diastereoselectivities were observed in most cases. The reaction was found to tolerate both air and moisture, and its performance did not require any special precautions. "Due to its operational convenience, the methodology can be easily scaled and gram quantities are obtained through simple work-up and purification. Unlike prior methods, where *syn*-oxy/aminopalladation is proposed to take place, in this reaction system an *anti*-nucleopalladation pathway is operative, as evidenced by single-crystal X-ray diffraction data from a representative product," remarked Professor Engle, who continued: "Importantly, the reaction tolerates both air and moisture and does not require any special precautions to perform. As a result, this methodology could be conveniently scaled up, allowing for isolation of 14.3 g of the desired product with minimal impurities after an operationally simple work-up and purification procedure."

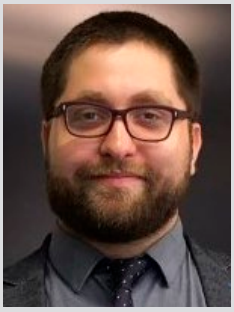
Professor Engle concluded: "Thanks to the joint efforts of three research groups, we have discovered a method that provides direct access to useful 2,3-dihydrobenzofurans, indolines, and indanes by employing ambiphilic aryl halide coupling partners and non-conjugated alkenyl amides. Mechanistic experiments and DFT studies shed light on the origins of diastereoinduction, anti-selectivity, and other fundamental aspects of this Pd(II)/Pd(IV) annulation process."

About the authors



H.-Q. Ni

Hui-Qi Ni was born and raised in Shanghai, P. R. of China. She earned her B.S. degree in 2019 from the University of Science and Technology of China, where she carried out undergraduate research under the direction of Prof. Xi-Sheng Wang. While completing her B.S., she also took two summer internships in the laboratories of Prof. Keary M. Engle (2017; Scripps Research, USA) and Prof. Neil K. Garg (2018; University of California Los Angeles, USA). She is currently pursuing a doctorate degree at Scripps Research (USA) under the tutelage of Prof. Keary M. Engle.



I. Kevlishvili

Ilia Kevlishvili was born in Tbilisi, Republic of Georgia. He obtained a B.A. degree in chemistry and mathematics at the Franklin & Marshall College (USA) in 2012. Currently, he is a member of the Prof. Peng Liu group at the University of Pittsburgh (USA) as a fifth-year doctoral student. His research interests are transition-metal-catalyzed reaction mechanisms and computation-guided catalyst design.

P. G. Bedekar

Pranali G. Bedekar was born and raised in San Jose, California (USA). In 2018, she began her undergraduate studies at the University of California, San Diego (USA) and is expected to graduate in 2022 with a B.S. in pharmacological chemistry. During this time, she began an internship at Scripps Research (USA) in 2019 under the supervision of Prof. Keary M. Engle.

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Dr. J. S. Barber

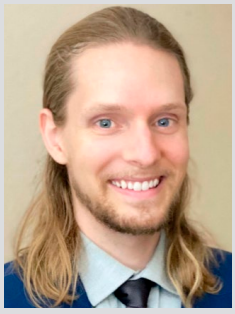
Joyann S. Barber was born and raised in southern California (USA). She received her B.S. in chemistry from Cal Poly Pomona (USA) in 2014. In 2014, she began her doctoral studies at the University of California, Los Angeles (USA) in Professor Neil K. Garg's laboratory where her research primarily focused on harnessing the reactivity of strained intermediates for the construction of heterocycles. In 2019, she graduated and moved to San Diego, CA (USA) where she currently works as a medicinal chemist at Pfizer.

Dr. S. Yang

Shouliang Yang grew up in Shandong Province, P. R. of China, and he received his B.S. from Inner Mongolia University (P. R. of China) in 2009. He pursued his graduate studies under the guidance of Professor Zhen Yang at Peking University (P. R. of China) and earned his Ph.D. in 2014. Then, he took up a postdoctoral position in the laboratory of Professor Dale L. Boger at Scripps Research (USA) and worked on total synthesis and structure modification of vinblastine. In January 2018, he joined the medicinal chemistry department at Pfizer, La Jolla (USA) and began his new career in drug discovery.

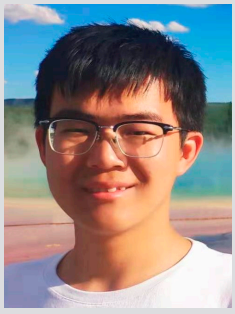
M. Tran-Dubé

Michelle Tran-Dubé was born in San Diego, California (USA). She received her B.S. at the University of California, Irvine (USA) in 2001 where her research was on nucleophilic addition to tetrahydrofuran oxocarbenium ion intermediates in Prof. Keith Woerpel's laboratory. She then received her M.S. in 2003 at Boston College (USA) in Prof. Scott Miller's laboratory researching the development of peptide-based and amino acid based asymmetric catalysts. In 2003, she returned to southern California where she currently works as a medicinal chemist at Pfizer in La Jolla (USA).



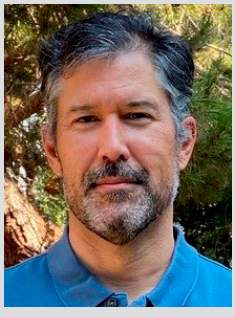
A. M. Romine

Andrew M. Romine is originally from Philadelphia, Pennsylvania (USA). He received his B.S. in chemistry and business, economics, and management in 2016 from the California Institute of Technology (USA) where he performed research supervised by Prof. G. Jeffrey Snyder (2013) and Prof. Robert H. Grubbs (2015–2016). While completing his B.S., he also attended a research program at ICIQ (Spain) under the supervision of Prof. Vladimir V. Grushin (2014). Andrew is currently an NSF fellow and fifth-year doctoral student at Scripps Research (USA) working with Prof. Keary M. Engle.



H.-X. Lu

Hou-Xiang Lu was born in Shandong, P. R. of China. He obtained a B.Sc. degree from Tsinghua University (P. R. of China) under the supervision of Prof. Bijie Li (2020). In the third year of his undergraduate studies, he participated in a summer research program at Scripps Research (USA) under the supervision of Prof. Keary M. Engle. Hou-Xiang is currently a first-year graduate student in the group of Prof. Bijie Li at the Center of Basic Molecular Science at Tsinghua University (P. R. of China).



Dr. I. J. McAlpine

Indrawan J. McAlpine was born in Chicago (USA) and grew up in the far northern suburb of Libertyville, Illinois (USA). He obtained his B.S. in chemistry in 1991 at the University of Illinois, Urbana-Champaign (USA). He obtained his Ph.D. in 1998 at the University of California, Los Angeles (USA) with Prof. Robert Armstrong. He went on to complete an NIH postdoctoral study with Prof. Stuart Schreiber at Harvard University (USA). In 2000, he then became a medicinal chemist at Agouron/Warner-Lambert (USA) which was bought out by Pfizer in that same year. He is currently a Research Fellow in Oncology Medicinal Chemistry at Pfizer in La Jolla, CA (USA).

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Prof. P. Liu

Peng Liu was born in Liaoning, P. R. of China. He obtained a B.Sc. degree from Peking University (P. R. of China), an M.Sc. degree from the University of Guelph (Canada), and a Ph.D. degree from the University of California, Los Angeles (USA). In 2014, he joined the University of Pittsburgh (USA) as an Assistant Professor and was promoted to Associate Professor in 2019. His research group uses computational tools to study the mechanisms, reactivity, and selectivity of transition-metal-catalyzed reactions.

Prof. K. M. Engle

Keary M. Engle was born and raised in western Michigan (USA). He was educated at the University of Michigan (USA), the Max-Plank-Institut für Kohlenforschung (Germany), the Scripps Research Institute (USA), the University of Oxford (UK), and the California Institute of Technology (USA). He began his independent career as an Assistant Professor at Scripps Research in 2015 and was promoted to Professor in 2020. His laboratory pursues basic science research in homogeneous catalysis with the goal of inventing useful new organic reactions.

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Synthesis of Arylamines and N-Heterocycles by Direct Catalytic Nitrogenation Using N_2

Nat. Commun. **2021**, *12*, 248, DOI: 10.1038/s41467-020-20270-5

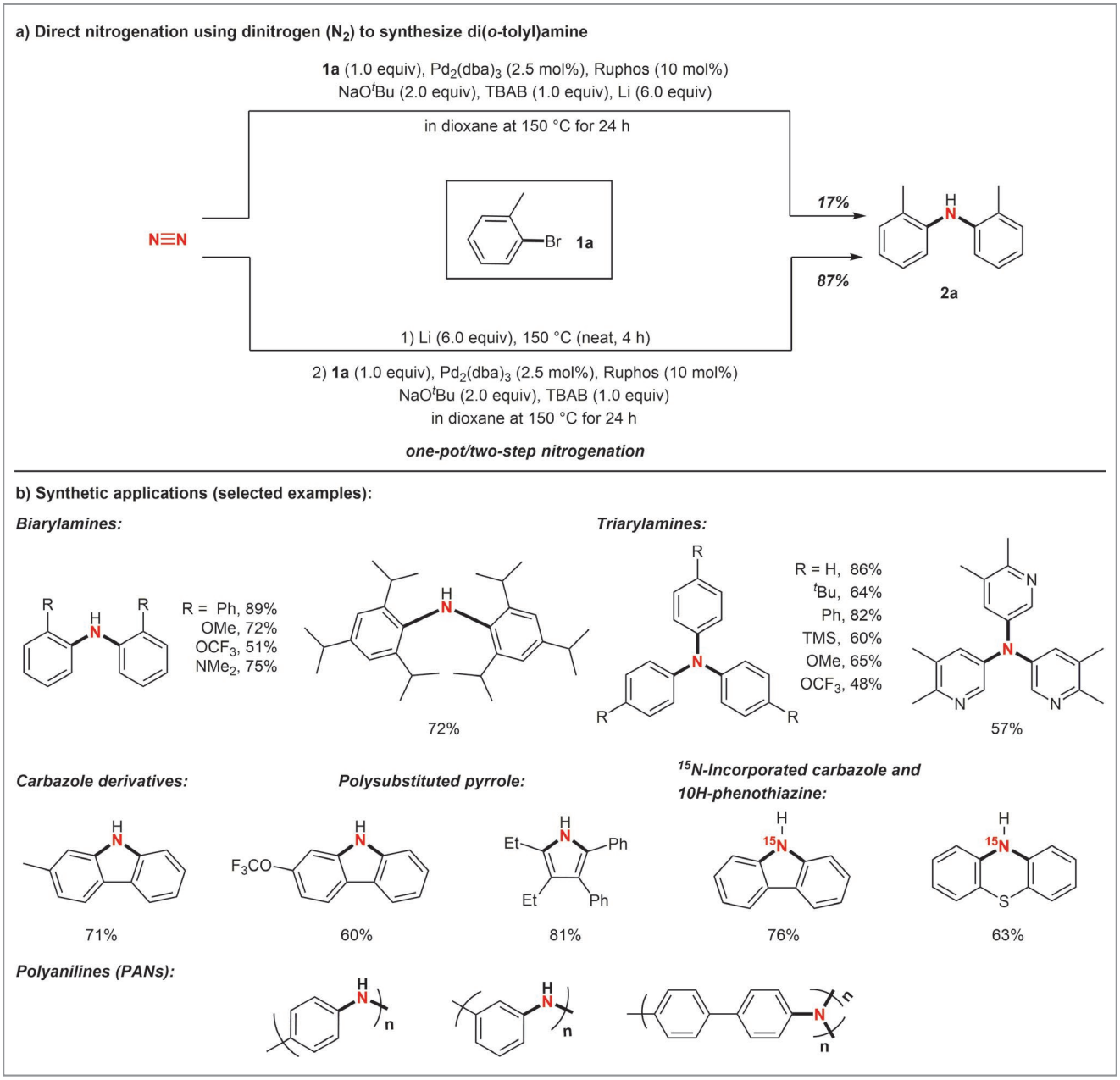
Owing to the significance of nitrogen-containing molecules, the incorporation of nitrogen atoms into organic molecules through C–N bond formation is a critically important process in organic chemistry. Due to environmental and economic reasons, it is becoming increasingly important to use more abundant, readily accessible and economic nitrogen sources. "The ideal nitrogenation process – especially from the economic viewpoint – would involve direct use of dinitrogen (N_2) as a nitrogen source to construct N-containing organic molecules, thus avoiding traditional processes based on platform chemicals such as ammonia or nitric acid," said Professor Zhang-Jie Shi at Fudan University (Shanghai, P. R. of China), who continued: "However, direct catalytic transformation of dinitrogen (N_2) into organic molecules has been a fundamental challenge, even though it has been established as an efficient method for the synthesis of ammonia." According to Professor Shi, current strategies to prepare different N-containing organic compounds are limited to stoichiometric methods, despite some striking synthetic cycles having been reported (for references see the original article). "A key way forward would be to develop efficient systems to enable the use of organo-electrophiles compatible with strong reductants."

Addressing this challenge, Professor Shi's group chose to focus on cheap and easily available alkali or alkaline-earth metals as reductants, and applied aryl halides as electrophiles to construct C–N bonds through transition-metal-catalyzed C–N coupling. "The use of lithium or magnesium as reductants for our designed direct nitrogenation is possible thanks to their high reactivity toward unreactive dinitrogen. For example, Mg can burn in pure dinitrogen to produce magnesium nitride under critical conditions. Lithium nitride (Li_3N) was also prepared from lithium and dinitrogen at 400–500 °C," explained Professor Shi.

"Based on our hypothesis, we began our investigation by using direct nitrogenation with *o*-tolyl bromide (**1a**) and dinitrogen in the presence of Li as the reductant and $Pd_2(dba)_3$ as the catalyst in dioxane. Various ligands were screened, and we found that RuPhos was effective in affording the desired di(*o*-tolyl)amine (**2a**) in 17% isolated yield (Scheme 1a). It is important to note that the valuable diarylamine was produced from dinitrogen in a catalytic manner," said Professor Shi. Further optimization efforts failed to improve the yield, and the reduced byproduct toluene was always obtained. Professor Shi and co-workers came up with the idea that the formation of the desired product proceeded through in situ generated Li_3N as a key intermediate, followed by a Pd-catalyzed C–N coupling reaction. While the kinetic reaction rate to generate Li_3N was rather slow, compared with the Li–halogen exchange between the Li solid and the substrate **1a**, toluene was produced after the protonation of aryllithium. Rational analysis of the data suggested that a one-pot/two-step protocol could be an alternative approach for dealing with the problem. After performing a solid–gas two-phase reaction in a vessel containing Li powder under an N_2 atmosphere at 150 °C for four hours, the desired product **2a** was obtained in 87% isolated yield in the subsequent Pd-catalyzed Buchwald–Hartwig amination. "It is worth noting that the simple Li_3N intermediate could be transmetalated with a palladium catalyst to construct the N–Csp2 bond. This finding convinced us that this chemistry would provide a practical method for the functionalization of nitrogen to synthesize nitrogen-containing compounds," remarked Professor Shi.

Under the conditions employed, diarylamines, triarylamines, carbazole derivatives and pyrroles with different functional groups were synthesized (Scheme 1b). Notably, this nitrogenation process was compatible with high steric hindrance. For example, 2,4,6-diisopropyl-substituted diarylamine could also be synthesized. "With this method, ^{15}N isotopes can be easily incorporated into organic molecules. We were also able to further expand the substrate scope to dibromobenzenes, for the preparation of structurally diversified polyanilines, showing great potential for materials chemistry applications," said Professor Shi, who concluded: "A one-pot/two-step protocol for direct catalytic nitrogenation, relying on the use of dinitrogen as nitrogen source, has been developed through Pd catalysis in the presence of Li as reductant, as described in our paper. This chemistry was shown to occur through Li_3N as the key platform chemical to construct C–N bonds, avoiding the traditional procedures relying on N_2–NH_3/N_2–HNO_3. However, it should be acknowledged that this chemistry still suffers from the use of relatively harsh conditions, as well as the use of Li, resulting in the competing reduction of substrates. This has spurred us to explore other mild reductants and new C-sources, in a further expansion of

the synthetic applications of this method for achieving the catalytic functionalization of N_2."



Scheme 1 (a) Direct nitrogenation using dinitrogen (N_2) to synthesize di(o-tolyl)amine. (b) Synthetic applications through one-pot/two-step nitrogenation in this work

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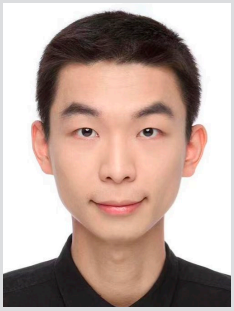

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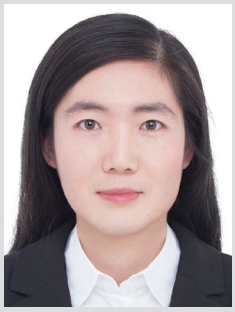

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Aleksei Yevgen'evich Chichibabin (1871–1945) and Pyridine Chemistry

Dedicated to the memory of Prof. Dr. Vladimir Ivanovich Galkin (1954–2020), Head of the Butlerov Institute of Chemistry at Kazan Federal University, Russian Federation.

The pyridine ring is viewed as a privileged structure in medicinal chemistry, and is well represented in modern pharmaceuticals, as illustrated by the antihistamine, loratadine (**1**), the antiretroviral compound, nevirapine (**2**), the acetylenic retinoid, tazarotene (**3**), used to treat skin conditions such as psoriasis, and the dihydropyridine calcium channel blockers **4**, used to treat hypertension (Figure 1). In this sesquicentennial of the birth of the great pyridine chemist, Aleksei Yevgen'evich Chichibabin (1871–1945),[1] it is appropriate that this name reaction biography focus on pyridine and its analogues.

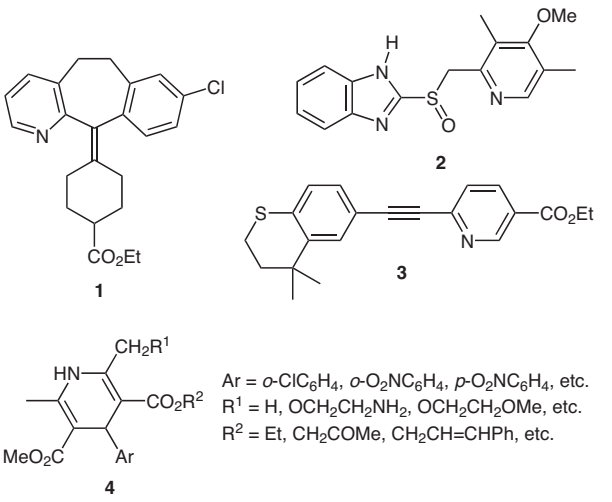
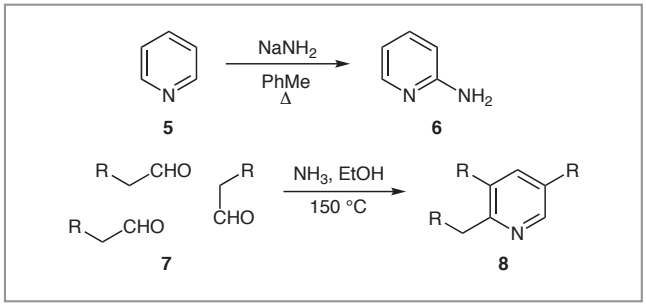


Figure 1 Representative pharmaceuticals containing the pyridine ring

Aleksei Yevgen'evich Chichibabin

Chichibabin was the first to observe an S_N^H displacement that converted the quite unreactive pyridine nucleus (**5**) into the 2-aminopyridine nucleus (**6**),[2] which is much more reactive towards electrophiles. He also developed an economical, one-pot synthesis of 2,3,5-trisubstituted pyridines **8** from ammonia and monosubstituted acetaldehydes **7**.[3] Although the yields in this reaction are low (typically 20–30%), the simplicity of the reaction, the low cost of the starting materials, and the ability to purify the product by fractional distillation, still render it an important entry into the pyridine ring system. These reactions are summarized in Scheme 1.

Aleksei Yevgen'evich Chichibabin



Scheme 1 The Chichibabin amination reaction and the Chichibabin pyridine synthesis

Choose two adjectives to describe Chichibabin's life and career, both 'tragic' and 'traumatic' must be among the top ones that come to mind.

Chichibabin was born in Kuzemino in the Poltava Oblast of the Russian Empire (now part of the Poltava Oblast in Ukraine), the eldest son of Yevgenii Savvich Chichibabin (1837–1876), a collegiate secretary. When Aleksei was three years old, his father moved the family to Lubny, where he took up an appointment as *Zemstvo* (District Council) Secretary. Within two years of this move, Yevgenii Savvich had died, leaving his widow, Natal'ya Petrovna, with six children below the age of ten.

Despite the financial hardships involved, Natal'ya Petrovna was determined that the younger children should all receive an education, and with Aleksei's older sister, Yevgeniya (b. 1867), she took on extra work to supplement their scant savings. Even so, it was often necessary for the younger children to work to help keep food on the table. In fact, the poverty that characterized his formative years stayed with him until after the October Revolution in 1917.

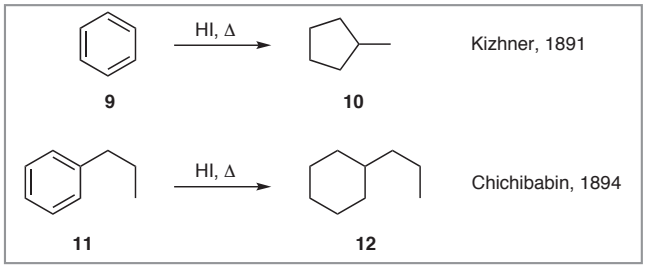
In 1879, Chichibabin entered the Men's Gymnasium in Lubny, but his attendance and performance as a student suffered due to his need to earn money by serving as a tutor. He did graduate from the Gymnasium, and in 1888 he entered the Natural Science Division of the Physics–Mathematics Faculty of Moscow University, where Vladimir Vasil'evich Markovnikov (1837–1904) had rebuilt the organic chemistry program into one of the best in Russia. Pictured are Markovnikov and a group of chemistry professors and lecturers in 1899.

Markovnikov with a group of the chemistry professors and lecturers of Moscow University in 1899

Under the University Statute of 1863, which was probably the most liberal version of the tsarist era, the universities had considerable autonomy: the majority of the power was vested in the University Councils. In 1884, the new University Statute severely curtailed this, and transferred control from the University Councils to the government, which exercised an oppressive oversight. In the spring of 1890, student demonstrations took place, protesting the reform of the Petrovskoe Agricultural Academy (now the Timiryazev Moscow State Agrarian University) to conform with the 1884 statute. Chichibabin was dismissed from the university for his participation in these demonstrations, but he was soon reinstated, and was able to complete his studies without serious interruption.

At the time of Chichibabin's entry into the University, Markovnikov was studying the composition of crude oils—foundational work for the discipline of petrochemistry. Chichibabin was soon working with Markovnikov and his privat-docent, Mikhail Ivanovich Konovalov (1858–1906).

Chichibabin's first project with Markovnikov was to study the Berthelot reduction[4] of propylbenzene with hydriodic acid in a sealed tube. Another Markovnikov student, Nikolai Matveevich Kizhner (1867–1935)[5] had carried out the same reaction with benzene itself (**9**) and found that the product was not cyclohexane, but methylcyclopentane (**10**).[6] In contrast to Kizhner's work, Chichibabin found that the reduction of propylbenzene (**11**) led to propylcyclohexane (**12**),[7] without rearrangement (Scheme 2).



Scheme 2 The Berthelot reductions of benzene and propylbenzene carried out by Kizhner and Chichibabin in Markovnikov's laboratory

Chichibabin graduated with the *diplom* in 1892, and under normal circumstances would have continued his education at Moscow forthwith. But circumstances were not normal. In 1893, the outspoken Markovnikov was ousted from his Professorship when his enemies used an arcane regulation that allowed the university to force compulsory retirement on any academic who had served 25 years since their first appointment. For Markovnikov, this came in 1893.[8]

Markovnikov's Chair was given to Nikolai Dmitrievich Zelinskii (1861–1953), who was on poor terms with Markovnikov (Markovnikov had accused him of unethical practices by carrying out research on Markovnikov's project without notifying him). Zelinskii's antipathy extended to Markovnikov's student, so Chichibabin was left without a formal research mentor. For the next three years, he lived on what he could earn as a private tutor and a journalist reporting on scientific stories. In 1895, Professor Rudnev of the Aleksandrovskii

College of Commerce invited him to become Assistant in the laboratory, but he was not approved for a permanent position and was forced to leave a year later. At the same time, he continued his scientific work, working on analytical techniques for industry, in the laboratory of the *Society for the Promotion of the Manufacturing Industry*, where he became Assistant Head of the laboratory.

Chichibabin's return to financial security came in 1896, when Konovalov was appointed to the Chair at the Moscow Agricultural Institute and made him the Head of the chemistry laboratory. In 1901, he was appointed Privat-Docent at Moscow University, where he remained until 1911. In 1905, he accepted the position of Chair of Inorganic Chemistry at Warsaw University with the rank of Extraordinary Professor, but he returned to Moscow as Director of the Moscow Agricultural Institute less than a year later because he found the facilities and atmosphere there totally incompatible with his research. In 1908, he was appointed Professor of General and Organic Chemistry at the Moscow Higher Technical School (now Bauman Moscow State Technical University), where he remained until 1930 as either Professor or Dean.

Chichibabin with his students in the laboratory of organic synthesis at the Higher Technical School, spring semester 1914

Even as a professor, Chichibabin retained the progressive ideals of his youth; in 1908, the police took note of regular meetings of anti-government individuals in his home, where they also found banned revolutionary literature. For whatever reason, his involvement was kept secret, and he retained his position. Then, in 1911, he resigned his position at Moscow University in solidarity with other progressive-minded colleagues (among them, future Academicians Kliment Arkad'evich Timiryazev (1843–1920), Pyotr Nikolaevich Lebedev (1866–1912), and Vladimir Ivanovich Vernadskii (1863–1945) who were protesting the reactionary policies of Lev Aristidovich Kasso (1865–1914), the Minister of Education. Although Chichibabin resigned from his position at Moscow University, he retained his position at the Higher Technical School.

With the advent of World War I, Chichibabin turned his attention to the nation's need for a reliable supply of pharmaceuticals. A 1904 trade agreement with Germany on coaling Russian naval vessels[9] had included a provision precluding Russia from refining coal tar.[1b] This was an important raw material for the pharmaceutical industry, giving Germany a monopoly in Russia on synthetic pharmaceuticals. With the war cutting off the supplies of these compounds from Germany, Chichibabin helped to organize the Moscow Committee for the Development of the Chemical Pharmaceutical Industry.

He also served as the first Head of the Committee. As part of his work for the committee, Chichibabin organized pilot plant laboratories for the isolation of alkaloids—morphine, codeine, atropine and caffeine—at both the Higher Technical School and the Shanyavskii People's University in Moscow, and during this time he also taught at both institutions.[10] In addition, he organized the manufacture of synthetic analgesics and antipyretics such as salicylic acid, aspirin, phenacetin, and phenyl salicylate. His efforts were credited with saving the lives of thousands of Russian soldiers during the war.

Two revolutions took place in Russia during 1917: the February Revolution, which led to the abdication of the Tsar, and the October revolution (the Bolshevik revolution), which began the Soviet era of Russian history. It was followed by a bloody civil war that did not end until 1923, five and a half years later. Chichibabin's loyalties were to Russia, and not to any political party, so he had no problem shifting his allegiance to the new regime. He continued his efforts to build the Russian pharmaceutical industry of the State Board of Chemical and Pharmaceutical Plants and headed the Chemical–Pharmaceutical Institute. By the time Chichibabin left Russia, his efforts and foresight had assured that Russia had fully functional chemical and pharmaceutical manufacturing industries.

During the civil war, shortages of such essentials as food, shelter and clothing became endemic in Russia after almost a decade of continuous warfare. During this time, Chichibabin wrote his textbook, *Osnovnye nachala organicheskoi khimii* [*Fundamentals of Organic Chemistry*],[11] trading a few pages at a time to the publisher in return for additional ration cards for food. This book became the dominant organic chemistry textbook in Russia, going through seven Russian editions, and was eventually translated into seven other languages.

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By 1925, Chichibabin had become an elder statesman of organic chemistry—especially synthetic pharmaceutical chemistry—in Russia. That year, he won the Greater Butlerov Prize of the USSR Academy of Sciences, and in 1926 he received the first Lenin Prize for chemistry. In 1927, he was elected a Corresponding Member of the USSR Academy of Sciences, and a Full Member (Academician) in 1929. In 1927, he and Vladimir Nikolaevich Ipatieff (1867–1952) were among the Russian scientists invited to participate in 'Russian Science Week' in Berlin.

In 1910, at the age of 39 years, Chichibabin became father to a daughter, Natal'ya Alekseevna (Natasha, 1910–1929), pictured here. He doted on his daughter, who chose to follow her father's footsteps into chemistry. As a student at the Technical Institute, she was required to obtain practical training in industry. She was working at the Dorogomilovskii chemical plant in Moscow, where naphthalenesulfonic acids for the dye industry were produced by the sulfonation of naphthalene with oleum at 180 °C. She had been assigned a task for which she had not been trained, operating a sulfonating autoclave. Thanks to the incompetence of the apparatchik supervising her work, there was an explosion that left her severely burned. She spent the next two days in agony before dying of her injuries.[12] Chichibabin dedicated the third edition of his *Osnovnye*, published in 1931, to his deceased daughter (Figure 2).

Chichibabin with his daughter, Natasha

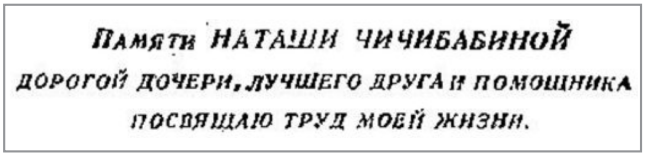


Figure 2 The dedication in the third edition of the *Osnovnye*. It reads „In memory of Natasha Chichibabina, dear daughter, best friend and helper, I dedicate the work of my life."

Natasha's death devastated her parents and made it impossible for them to remain in Moscow, where the accident had happened because of the incompetence of her supervisor. Her mother, Vera Vladimirovna, drifted into a deep depression. In 1930, Chichibabin was awarded a *komandirovka* (paid study leave) in Paris, where he worked with Tiffeneau. He and his wife left Russia for good in 1930.

Chichibabin spent his first two years in Paris in the laboratory of Marc Tiffeneau at the Hôtel-Dieu. At the same time, Vera Vladimirovna underwent psychiatric treatment to help her cope with the deep depression caused by her daughter's death. After two years, Chichibabin was placed in charge of a special research laboratory in the French pharmaceutical and dye company, the Établissements Kuhlmann. At the same time, he became a consultant to the German pharmaceutical company, Schering AG, and to Roosevelt and Company of New York. In 1931, he was offered a small laboratory in the Collège de France, and here he spent the remainder of his career.

Chichibabin's time in Paris was not always happy. He was homesick for Russia, but the political situation there made him wary of returning, despite the many letters he received from high-ranking Soviet scientists begging him to return and assuring him of his welcome. Stalin's purges of the late 1930s suggest he was right. Chichibabin never returned to Russia, and in 1936 he was stripped of his Soviet citizenship and his membership in the USSR Academy of Sciences, with six members dissenting. With the outbreak of World War II, foreigners were denied permission to work in France, so once again Chichibabin fell into straitened circumstances. He died in Paris the day the war ended. In 1990, one of the last acts of the USSR Academy of Sciences was to reinstate Chichibabin to Full Membership.

Chichibabin Pyridine Synthesis

In 1896, Chichibabin began his research into the chemistry of pyridine and its derivatives, culminating in seven papers in Russian (*Zh. Russ. Fiz.-Khim. O-va.*)[13] and five in German[14] by 1902. In 1902, he submitted his dissertation for the *Magistr Khimii* (Figure 7) on the reactions of pyridine and quinoline with alkyl halides and the products of thermolysis of the resultant quaternary ammonium ions to give mixtures of α- and γ-alkylpyridines and -quinolines.[15]

Although he submitted his M. Khim. dissertation in 1902, scheduling its defense was problematical in the face of opposition by Zelinskii and his allies. When the defense was finally scheduled (in 1903), Zelinski wrote a negative examiner's report; the comment by Aleksander Pavlovich

Sabaneev (1843–1923), an organic chemist who was Dean of the faculty, is also illustrative of the atmosphere: when Chichibabin rose to defend his dissertation, Sabaneev mocked him as being a 'self-taught man'. At the time, not being associated with a recognized school was a reason to demean, rather than congratulate the student for completing his work despite the absence of a formal research mentor. His relationship with his old mentor had become cold, so even Markovnikov did not give his approval of the work. Chichibabin revised and resubmitted the dissertation, and the degree was finally awarded in 1904. The atmosphere at Moscow in the aftermath of his defense was truly toxic, so six months later he accepted the appointment to the University of Warsaw.

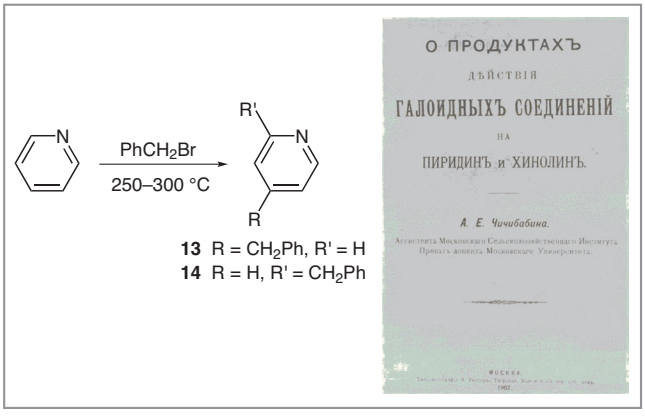
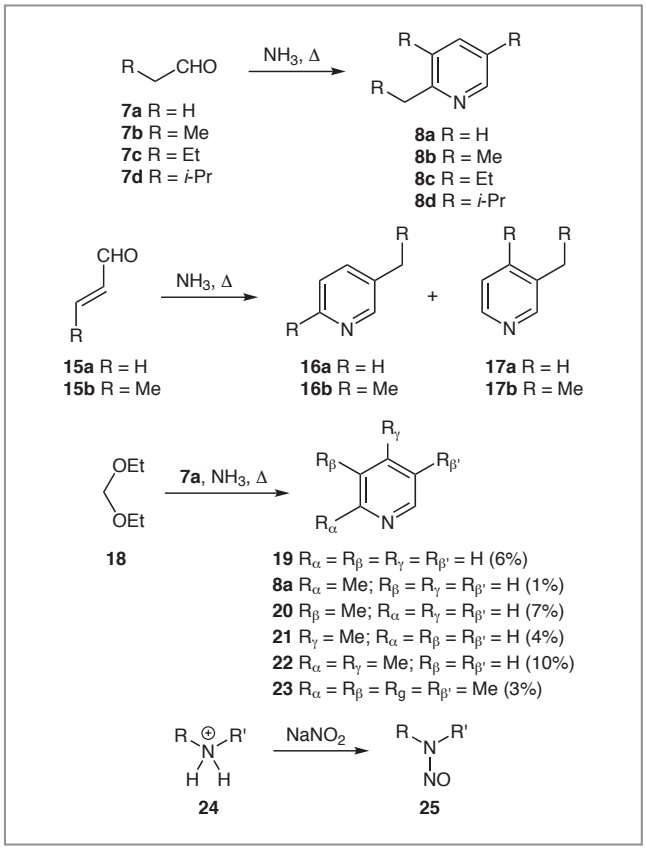


Figure 3 (left) Chichibabin's thermolysis of pyridinium salts and (right) his *M. Khim.* dissertation

In 1905, Chichibabin published his first report of the synthesis of pyridines from aldehydes and ammonia;[3] that same paper carried a footnote[16] that some of the experimental details had been published earlier. It was not until over a decade and a half later before he again entered the field, with five papers in Russian in 1921,[17] and six papers in German in 1924.[18] As part of this project, Chichibabin and his students developed aluminum oxides and hydroxides as catalysts for the reaction.

In the later series of papers, Chichibabin and his students were able to expand the scope of the reaction for the preparation of diverse pyridine derivatives (Scheme 3). Thus, using single monosubstituted acetaldehyde derivatives **7a–d** gave the 2-(alkylmethyl)-3,5-dialkylpyridines **8a–d**. The use of a monosubstituted acrolein derivative (**15**) led to the production of 2,5-disubstituted and 3,4-disubstituted pyridine derivatives **16** and **17**. Using acetaldehyde with a formaldehyde equivalent (e.g., the diethylacetal **18**) led to the production of pyridines carrying anywhere from zero to four alkyl groups, as illustrated in Scheme 3. In this reaction, the major product, 3,5-lutidine (**22**) was formed from two equivalents of acetaldehyde and one equivalent of the acetal. The overall yield of pyridines in this reaction was 31%. The reaction also produced secondary amine by-products, and these were removed from the basic pyridines by treating the hydrochloric acid solution of the bases with sodium nitrite, thus converting the secondary amine hydrochlorides **24** into non-basic *N*-nitrosamines **25**. Chichibabin and Oparina[18f] separated the mixture of alkylated pyridines by fractional distillation and then fractional crystallization of their picrates.

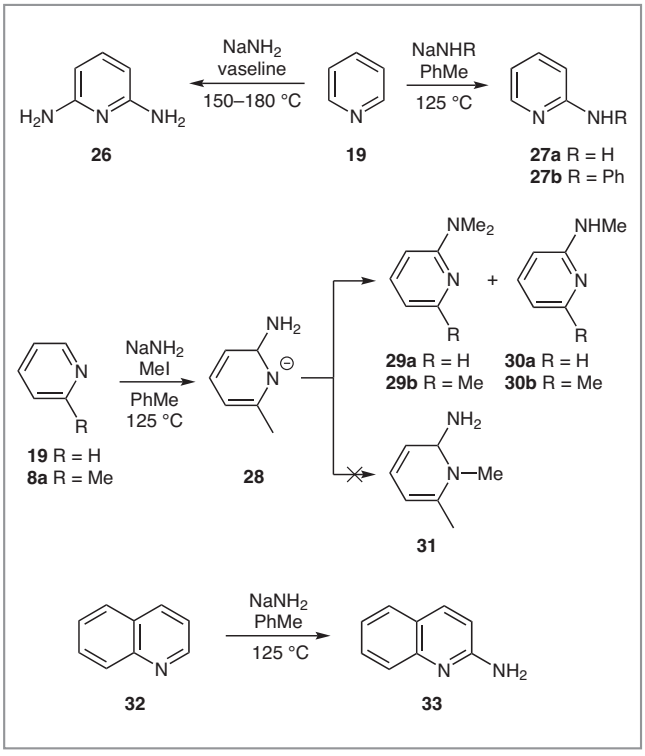


Scheme 3 The variations of the Chichibabin pyridine synthesis reported by Chichibabin and his students

Chichibabin Amination

The best-known reaction carrying Chichibabin's name is the amination of pyridines and quinolines with sodium amide in a hydrocarbon solvent.[2] In their initial paper, Chichibabin and Zeide showed that in refluxing toluene around 125 °C, pyridine (**19**) was converted into 2-aminopyridine (**27**),

and that in a paraffin solvent at 150–180 °C, a second amino group was inserted, giving 2,6-diaminopyridine (**26**). The mechanism of the reaction begins with the addition of amide anion to the heterocyclic ring to give the conjugate base of a 2-amino-1,2-dihydropyridine (**28**), which the authors sought to trap by means of methylation. The expected product, **31**, was not obtained, but the mono- (**30**) and dimethylaminopyridines (**29**) instead, which showed that the rearomatization by elimination of hydride is faster than alkylation of the anion. The authors also reported the amination of quinoline to give 2-aminoquinoline (**33**). The reactions reported in the initial publication are gathered in Scheme 4.

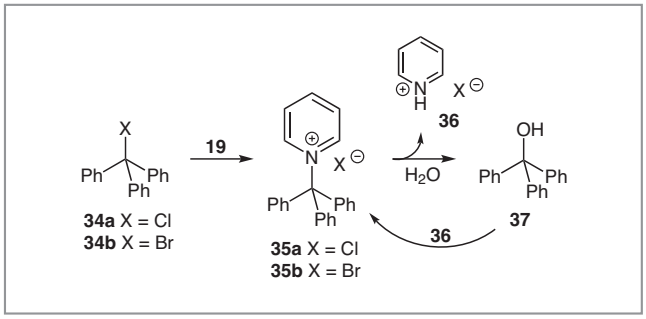


Scheme 4 Representative Chichibabin amination reactions

Chichibabin saw the potential for both pharmaceuticals and dyes based on the pyridine ring system. Consequently, he and his students at Shanyavskii Moscow State University carried out an extensive research program on the exploitation of the reactions of aminopyridines. In 1918, he and his students published twelve papers in this area encompassing 74 pages in the *Zhurnal*.[19]

Triarylmethyl Compounds

In 1900, Russian émigré Moses Gomberg reported the discovery of the triphenylmethyl radical,[20] the first stable free radical. This discovery quickly attracted the interest of Chichibabin, who began a long-term research program into the chemistry of trivalent carbon compounds. His first works involved the synthesis of pyridine derivatives of triphenylmethane. The alkylation of pyridine with a triphenylmethyl halide **34** gave the corresponding salt **35**, but on work-up with water, the pyridinium halide **36** and triphenylmethanol (**37**), presumably by an S_N1 mechanism; treatment of **37** with **36** gave the same salt (Scheme 5).[21] This work was expanded into the study of the structure of 'hexaphenylethane'.[22] In 1912, this work formed the basis of Chichibabin's *Dr. Khim.* dissertation.[23]



Scheme 5 Reactions of triphenylmethyl halides with pyridine

Early on, Chichibabin had come to the conclusion that the correct structure of hexaphenylethane was actually the quinoid dimer **38**. In 1907, he published the synthesis of a violet solid, **39**, that is known today as Chichibabin's hydrocarbon (Figure 4).[24] Among other things, this fascinating compound has C_i symmetry.[25]

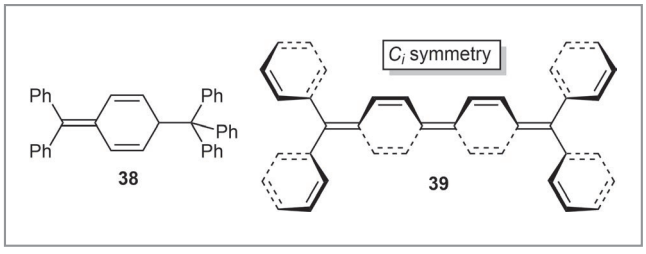
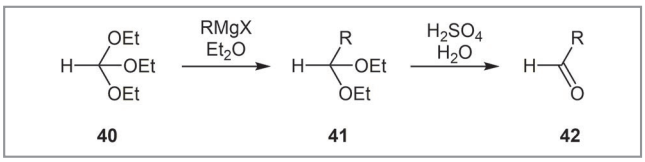


Figure 4 Chichibabin's hydrocarbon

Bodroux–Chichibabin Aldehyde Synthesis

In 1904, Chichibabin and French chemist F. Bodroux published three papers describing the synthesis of aldehydes through

the preparation of acetals by the reaction between Grignard reagents and ethyl orthoacetate (Scheme 6).[26]



Scheme 6 The Bodroux–Chichibabin aldehyde synthesis

David Lewis

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