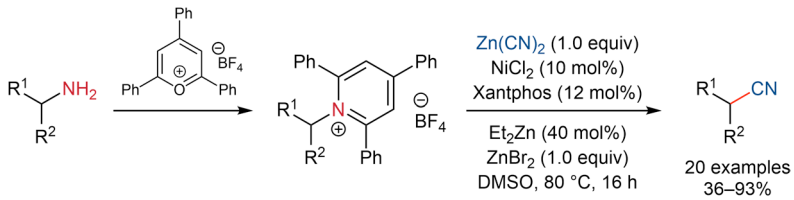
Synform

People, Trends and Views in Chemical Synthesis

2021/12

Nickel-Catalyzed Deaminative Cyanation: Nitriles and One-Carbon Homologation from Alkyl Amines

Highlighted article by J. Xu, J. C. Twitty, M. P. Watson



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Thieme

Dear Readers,

The 2021 Nobel Prize in Chemistry was awarded to Benjamin List and David MacMillan for developing organocatalysis. This – besides being fantastic news for the entire organic chemistry community – is incredibly exciting for the whole Thieme Chemistry family, as Ben has been the Editor-in-Chief of Synlett since 2015, when he took over from Peter Vollhardt. It makes me incredibly proud to work with Ben – who is an endless source of ideas and enthusiasm – on Thieme Chemistry editorial projects. I have to admit that this is the first time it has occurred to me that I know a Chemistry Nobel Awardee so well, although many years ago I was lucky enough to be co-author of a paper with another Nobel Prize winner (Robert Huber, 1988); however, I never met him personally. When the 2021 Chemistry Awards were announced on Oct 6th I was working from home, and that morning I had the TV on in the background. At around 12 noon my eye was caught by the TV screen where I seemed to recognize a familiar face during the Italian News programme. I thought: what the hell... It took me a few seconds to connect the dots and realise that the familiar face was Ben's!!! I jumped from the chair and – after a few Italian swearwords that I will not translate here – I turned the volume on, then my heart rate went crazy: that really was Ben, who just got the Nobel Prize!!! Then a flood of emails from the Thieme Chemistry friends started to kick in and it really looked like an online family party had been thrown. But let's not forget who shared the Prize with Ben: David MacMillan. I met David – a proud Scotsman, by his own words – once during the 22nd International Symposium on Fluorine Chemistry in Oxford (UK), when he gave the opening plenary lecture (that really was a great talk...). It must have been the 22nd of July 2018; at that time I was still working at the University of Aberdeen in Scotland. After the session, our common friend David O'Hagan asked me whether I would join them – with a handful of other people – for dinner at a nearby pub. David MacMillan was sitting in front of me, and I vividly remember that after a few pints I felt brave enough to tell him: I think your work is incredible and I really believe you are going to win the Nobel Prize. MacMillan did not answer, he just smiled back at me, but I think deep down he knew he was going to win it and now I am really glad to have been a good oracle on that occasion. Who knows whether among the SYNFORM articles we are publishing this year there is more Nobel Prize material? Time will tell... Meanwhile, this closing issue of 2021 is opened by a YCF interview with a Thieme Chemistry Journals Awardee: Erin Stache (USA) who takes us through her very timely research interests in sustainable polymer chemistry (by the way, COP26 is taking place in Glasgow while I am writing this editorial) and beyond. The second article covers a recent ground-breaking mechanochemistry paper by Felipe García & Mihaiela Stuparu (Singapore), who describe a novel entry to curved fused-ring systems. The third article is another fantastic "Name Reaction Biography" – by David Lewis – on Arthur Rudolph Hantzsch, who pioneered the synthesis of heterocycles in the late 19th and early 20th centuries. Finally, the last article of the year is a Literature Coverage report on the exciting nickel-catalyzed deaminative cyanation developed by Mary Watson (USA). And with this, two important things remain to be done: first, my enthusiastic congratulations to Benjamin List and David MacMillan for their fantastic Nobel Prize; second, my warmest greetings to all of you – dear Readers – for a Merry Christmas and a Happy New Year!!!

Enjoy your reading!

In this issue

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Young Career Focus: Professor Erin Stache (Cornell University, USA)

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 Professor Erin Stache (Cornell University, USA).

Biographical Sketch

Professor E. Stache

Erin Stache received her B.S. in chemistry in 2008 from the University of Wisconsin-Green Bay (USA) and her M.S. in chemistry in 2011 from Colorado State University (USA). After working in industry for several years, she received her Ph.D. in chemistry in 2018 from Colorado State University, advised by Prof. Tomislav Rovis and Prof. Abigail G. Doyle. During her Ph.D., she developed new methods for C–O bond activation using photoredox catalysis. Erin began her postdoctoral studies at Cornell University (USA), working with Prof. Brett P. Fors as a Cornell Presidential Postdoctoral Fellow. Following this appointment, Erin started her independent research career at Cornell University as an assistant professor in the Department of Chemistry and Chemical Biology. Her research focuses on sustainable polymer chemistry, including developing new polymerization methods for biodegradable polymers and identifying novel depolymerization strategies. Erin received the President's Council of Cornell Women 2020–2021 Affinito-Stewart Grant and the Thieme Chemistry Journals Award in 2021.

INTERVIEW

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

Prof. E. Stache My research lab focuses on sustainable polymer chemistry from several different perspectives. Our research is quite interdisciplinary, incorporating elements from organic, physical, and inorganic chemistry. Having completed a Ph.D. in synthetic methodology and a postdoc in polymer synthesis, I hope to combine modern synthetic methods with polymer and materials synthesis. Utilizing elements of photoredox catalysis, transition-metal catalysis, and biocatalysis, we will develop novel polymerizations of biodegradable materials, identify novel biorenewable monomers, and advance depolymerization strategies for commodity polymers.

SYNFORM *When did you get interested in synthesis?*

Prof. E. Stache I remember very specifically when I became interested in organic synthesis – drawing my first arrow-pushing mechanism. I initially intended to pursue medical school to become a doctor, but the first semester of organic chemistry completely changed my trajectory. The mechanism was probably hydration or hydrobromination of an alkene, and drawing the flow of electrons through arrows just made sense. I decided to pursue an REU program at Georgia Tech (USA) with Prof. Seth Marder, followed by graduate studies at Colorado State University (USA) with Prof. Eric Ferreira. I developed C–H functionalization reactions using a transient directing group strategy.[1] A Ph.D. is full of ups and downs, and there was a period where I left the program to explore other career options. I worked as a veterinary assistant, a quality control chemist at Tolmar, Inc., a summer instructor for organic chemistry, and finally, as a development engineer at HRL Laboratories in Malibu, CA, USA. At HRL, I developed methods in materials engineering, which propelled me to finish my Ph.D. so I could pursue a career in academia. I resumed my Ph.D. at CSU with Prof. Tom Rovis but conducted my research

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at Princeton (USA) in collaboration with Prof. Abby Doyle. At Princeton, we exploited photoredox catalysis for asymmetric transformations, as well as new bond activations.[2,3] Wanting to continue in polymer chemistry and polymer synthesis, I joined the lab of Prof. Brett Fors as a Cornell Presidential Postdoctoral Fellow. At Cornell, relying on my synthetic roots, we developed a hydrogen-atom transfer RAFT polymerization to graft polymers controllably from C–H bonds.[4] I was fortunate enough to obtain a tenure-track faculty position at Cornell, where I started my independent research lab in July 2020.

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

Prof. E. Stache Organic synthesis has transformed our society in countless ways, from drug discovery to the development of plastics. With time, synthesis has become much more sophisticated, but the challenges we still face are increasingly complicated. For example, we've spent more than 50 years perfecting the synthesis of plastics essential to our everyday lives. Still, we've come to realize that the invention of commercial plastics is now one of the most significant challenges we face.[5] In addition to developing synthetic strategies to upcycle these recalcitrant materials, we must develop new materials from biorenewable sources and those that can be recycled while not losing physical properties. This means creating more efficient strategies for monomer synthesis and the development of new polymerization techniques. All these challenges, and with them, opportunities, rely on the continued development and sophistication of organic synthesis.

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

Prof. E. Stache As one might deduce from my thoughts on the future role of synthesis, my research lab heavily focuses on sustainable polymer chemistry. When we design research projects and goals, we think about reimagining the life cycle of a polymeric material (Figure 1). Monomers frequently come from petroleum feedstocks, particularly those we use daily, like ethylene, propylene, and styrene. We see this as an opportunity to develop syntheses of new monomers or develop new polymerization strategies to repurpose biorenewable monomers to synthesize these high-performance plastics. The other focus of our group is to develop strategies to deal with existing plastic waste. The economic viability of mass-producing non-recyclable polymers is a formidable foe, so it's essential to address the plastic waste crisis from degrading commercial polymers as well. We are developing synthetic strategies to degrade, upcycle, and chemically recycle commercial polymers, relying on modern synthetic methods and catalysis.

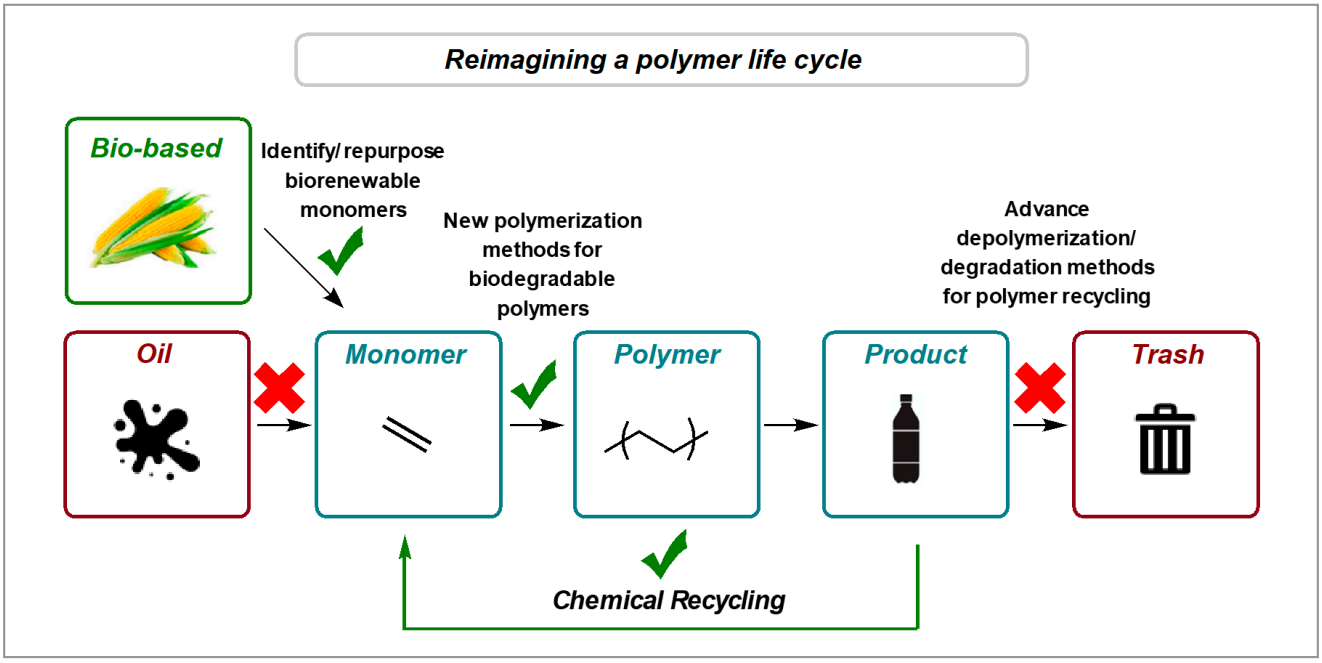

Figure 1 Proposed life cycle of a polymeric material

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

Prof. E. Stache My most important scientific achievement is believing enough in my abilities to return to graduate school and finish my Ph.D. I certainly didn't do it alone – I had incredible mentors both in industry and academia who supported and encouraged me the entire way. Without it, I wouldn't have the opportunities I have now to start a research program with some fantastic graduate students, giving them a chance to learn, grow, and make their impact on the scientific community and the world. I also hope that my non-traditional trajectory towards academia shows there is no single or "correct" path to a career. Even if a career path gets interrupted or off-track, success is achievable in the end with hard work and perseverance.

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Mechanochemical Transformation of Planar Polyarenes to Curved Fused-Ring Systems

Nat. Commun. **2021**, *12*, 5187; DOI: 10.1038/s41467-021-25495-6

Electronic and redox-active materials are revolutionizing key areas such as energy storage – e.g. in the form of rechargeable batteries and supercapacitors – or CO_2 utilization and transformation. Among these functional materials, polyarenes and various forms of carbon polymers are of particular interest. The group of Professor Mihaiela Stuparu, from the Nanyang Technological University (Singapore), has been developing the chemistry and the applications of curved nanocarbons over the last decade (*Acc. Chem. Res.* **2021**, *54*, 2858–2870). "Corannulene is a fascinating bowl-shaped polycyclic aromatic hydrocarbon structure. It can be imagined as the smallest curved fragment of fullerene C_{60}," said Professor Stuparu. "It must be noted, however, that Barth and Lawton synthesized this molecule nearly two decades prior to the discovery of fullerene C_{60} (*J. Am. Chem. Soc.* **1966**, *88*, 380–381). Their solution-phase synthesis involved 17 steps and provided corannulene in <1% yield. After a period of dormancy, Scott's new synthesis of corannulene revived interest in this molecule and its multifaceted properties (*J. Am. Chem. Soc.* **1991**, *113*, 7082–7084). Scott's synthesis was based on a gas-phase technique. This technique is known as flash-vacuum pyrolysis (FVP) in which molecules are subjected to high temperatures (>1000 °C) under an inert atmosphere. Such high-energy conditions allow the planar precursor molecules to adopt unnatural conformations that can be trapped to access curved polyaromatic nuclei."

Professor Stuparu went on by explaining that since mechanochemistry also creates extraordinary reaction conditions through impact and shear forces, they reasoned that similar to FVP it may also prove to be a useful synthetic tool in accessing curved aromatic structures. Professor Stuparu further added: "The attraction of mechanochemistry lies in its simple operation, i.e., milling and grinding of solid reactants is expected to yield products in a fast and scalable manner. Our first efforts in this regard were focused on a corannulene–phenanthrene hybrid structure (*Angew. Chem. Int. Ed.* **2020**, *59*, 21620–21626) (Figure 1a). We noticed that mechanochemistry indeed led to faster reaction times and higher yields as compared to the solution-phase synthesis. Encouraged by these results, we planned to synthesize corannulene itself." Professor Stuparu explained that the idea was that under mechanochemical forces, the bay regions of a precursor molecule such as tetrabromomethylfluoranthene would come in close proximity to each other to react and generate two new six-membered rings (Figure 1b). The researchers found that although corannulene could be produced in this way, the yields remained low (<5%). Professor Stuparu added: "During the optimization efforts, we added tetrabutylammonium chloride (TBACl) merely as a salt to facilitate mixing between the reactants. This led to a marked enhancement in the yield to >65%. It is only upon scrutinizing the trace amounts of other molecules generated in the reaction that we realized that TBACl is likely to have participated in the reaction and resulted in a halide-exchange reaction before the formation of the new aromatic rings (Figure 1c)." This hypothesis was confirmed by the Stuparu group through mechanochemical preparation of tetrachloromethylfluoranthene and its efficient conversion into corannulene (Figure 1d).

Prof. Stuparu concluded: "To discover the halide-exchange reaction and formation of the phenanthrene nucleus from benzyl halide precursors was exciting, furthermore it has numerous potential applications for instance in the mechanochemical generation of helicenes. On the other hand, successful transformation of planar polyarenes into a curved geometry by creating new C–C bonds along the rim of the molecular structure opens up new possibilities of creating highly strained π-surfaces."

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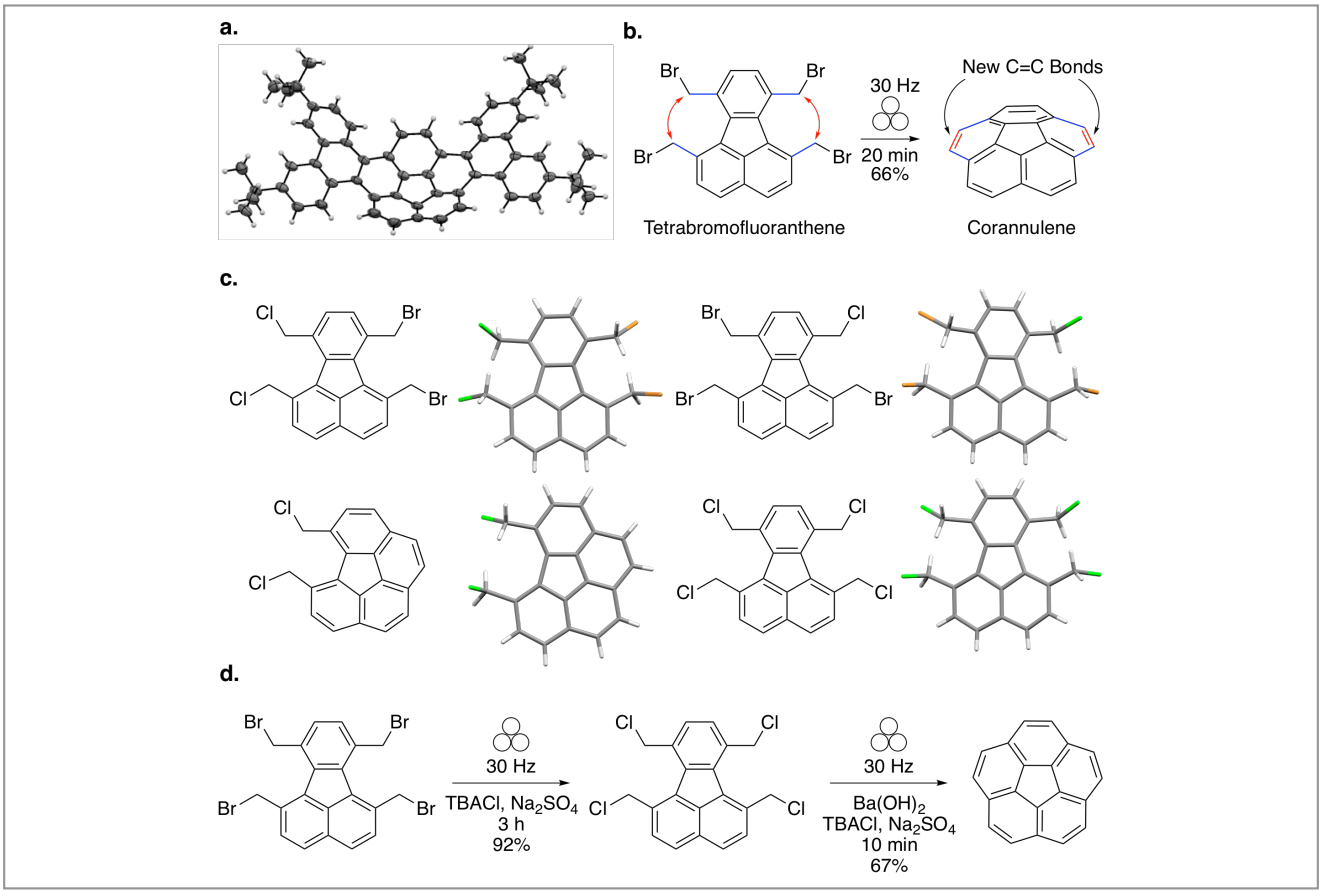
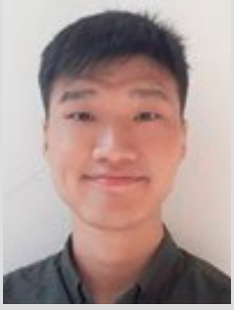


Figure 1 Mechanochemical synthesis of curved arenes. (a) X-ray crystal structure of the corannulene–phenanthrene hybrid structure. (b) Synthesis of corannulene from tetrabromomethylfluoranthene precursor. (c) Chemical and X-ray crystal structures of chlorinated compounds isolated from the corannulene synthesis. (d) The mechanochemical halide-exchange reaction and subsequent formation of corannulene from the tetrachloromethylfluoranthene precursor.

About the authors



T. Yong

Teoh Yong joined the research group of Prof. Mihaiela Stuparu as an undergraduate student at the Nanyang Technological University (Singapore), initially as a URECA student and then as a Final Year Project Student. It is during this time that he "discovered" corannulene. He continued working in the Stuparu group after finishing his bachelor's studies during which time he developed the mechanochemical synthesis of corannulene. He is currently a doctoral student in the research group of Professor Tomislav Friščić at McGill University (Canada).

Prof. F. García

Dr. Gábor Báti was born in 1989 in Budapest, Hungary. He received both B.Sc. (2012) and M.Sc. (2014) degrees in chemistry from Eötvös Loránd University (ELTE), Hungary, then pursued PhD studies in Nanyang Technological University (NTU), Singapore. Currently he is a Research Fellow at NTU in Professor Mihaiela Stuparu's lab, mainly focusing on the synthesis of curved polyaromatic systems.

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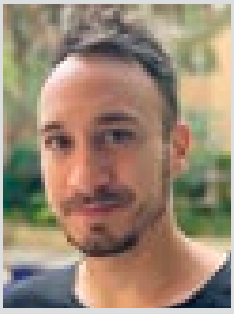

Dr. G. Báti

Prof. Felipe García's research group at the Nanyang Technological University (Singapore) is involved with developing complex and robust main group systems for technological and biological applications and mechanochemistry for the sustainable synthesis of compounds and materials.

Prof. M. Stuparu

Prof. Mihaiela Stuparu's research group is interested in developing new synthetic methodologies to curved polyarenes and studying their properties and potential applications. In this regard, the group has developed photochemical and mechanochemical methods for accessing non-planar nano-graphenes based on the corannulene motif.

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Arthur Rudolph Hantzsch (1857–1935) and the Synthesis of Nitrogen Heterocycles

Heterocyclic compounds containing nitrogen in the ring often exhibit useful biological properties (Figure 1), as in the anti-cholesterol drug, atorvastatin, and the dihydropyridine calcium channel blockers[1] (**1**) such as amlodipine, felodipine and nifedipine. Polypyrroles[2] are intrinsically conducting polymers, which makes them suitable for applications in electronics, as well as molecular biology and medicine.

The subject of this Name Reaction Biography is Arthur Rudolph Hantzsch (1857–1935),[3] who discovered methods for the synthesis of highly substituted pyrroles[4] and dihydropyridines,[5] as well as azoles containing two heteroatoms. A recent review has reported the revival of the Hantzsch pyrrole synthesis under 'unconventional' conditions, including microwave irradiation and mechanochemistry.[6]

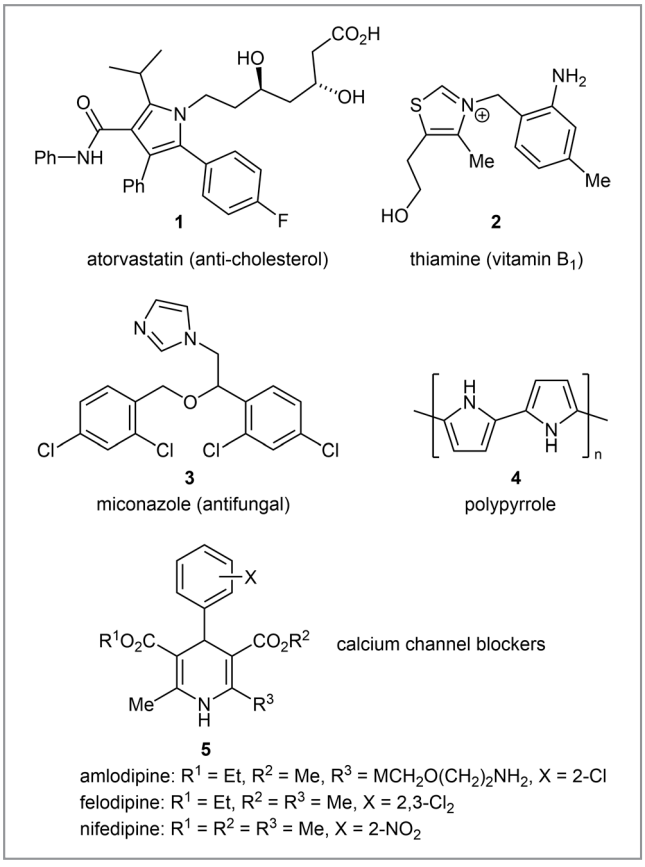
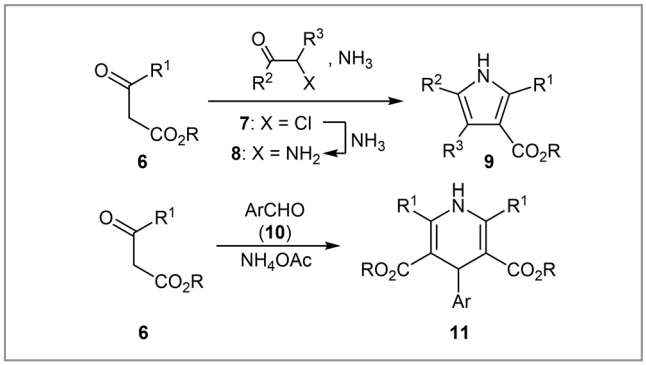


Figure 1 Representative species containing pyrrole or 1,4-dihydropyridine rings

The Hantzsch methods for the syntheses of nitrogen heterocycles with one heteroatom (pyridines and pyrroles) are summarized in Scheme 1. In these reactions, a β-keto ester **6** reacts with an α-chloro ketone **7** and ammonia (which react to form an α-amino ketone, **8**) to give a densely substituted pyrrole **9**,[4] or with ammonia and an aldehyde (usually an aromatic aldehyde, **10**) to give a Hantzsch ester, **11**, that contains a densely substituted 1,4-dihydropyridine ring.[5]



Scheme 1 The Hantzsch pyrrole and dihydropyridine syntheses

Hantzsch in Würzburg, 1879

Hantzsch was born in Dresden, into a family of wine merchants: his father, Georg Rudolf (1829–1889), was a wine wholesaler, and his grandfather, August Traugott (1796–1869), owned a vineyard and was a wine merchant in the city. After his 1875 graduation from the Kreuz-gymnasium, which was a secular institution despite its name, Hantzsch began his university education at the Dresden Polytechnic Institute. He was a student at the Polytechnic from 1875–1879. He completed his Ph.D. research there under Rudolf Schmitt (1830–1898), a student of Kolbe and discoverer of the Kolbe–Schmitt reaction,[7] but before 1900, Polytechnics in general were not entitled to confer doctoral degrees, and Dresden was no exception. Consequently, Hantzsch transferred to Würzburg for one semester, graduating with his Ph.D.

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in 1880[8] under the formal supervision of Johannes Wislicenus (1835–1902).

Interestingly, Wislicenus himself had faced a similar hurdle: his radical religious views had led him and his father to flee to the USA just ahead of arrest. It also meant that even after his return to Germany, he could not graduate from Halle without abrogating his religious views. So, despite having done all the work for his Ph.D. there under Wilhelm Heinrich Heintz (1811–1880), he had to submit his dissertation elsewhere: he chose Zürich with Georg Andreas Karl Städeler (1821–1871), whom he had known less than two weeks at the time, as his formal supervisor.

Schmitt (left) and Wislicenus (right)

For the next five years, Hantzsch served as Assistant in the Physical-Chemical Laboratory of the University of Leipzig, where he completed his *habilitation* on the synthesis of dihydropyridines in 1883.[9] The same year, he married Katharina Susanna Schilling (d. 1904), the sister of the architect, Georg Rudolf Schilling (1859–1933). Schilling had been involved in the formation of the Dresden Villa Building Society (Neubert & Co.) that had been founded in equal parts by Schilling and Graebner, and by Friedrich Moritz Alexander Neubert in October 1905. When Neubert left the company in 1908, Schilling and Graebner converted it from an open trading company into a limited partnership. Hantzsch became a limited partner.

In 1885, Hantzsch moved as Professor to the Zürich Polytechnic (now ETH Zürich), where he began his work on thiazoles. In 1893 he moved to Würzburg as successor to Emil Fischer. There, as Head of the Chemisches Institut, which had been designed by Fischer, he occupied rooms in the building. It was dedicated in 1896 and used until 1912.

In 1903, he moved to Leipzig as Ordinary Professor and successor to Wislicenus in the Chair of Chemistry in the Philosophical Faculty. He remained there until his retirement in 1928. From 1920–1921, he served as Dean of the Faculty.

The former Chemisches Institut building in Würzburg

His distinguished career led to his election as a member of The German Academy of Natural Sciences (Leopoldina), The Austrian Academy of Sciences (Vienna), the Mathematics-Physics Class of the Royal Saxon Society of Sciences (Leipzig) from 1904–1919, and its successor, the Saxon Academy of Sciences (Leipzig), from 1919 to his death, and a Foreign Member of the Göttingen Academy of Sciences.

Hantzsch began his research with synthetic organic chemistry. In 1883, Victor Meyer had pointed out the similarities in chemical and physical properties of five-membered thiophene and six-membered benzene.[10] By analogy, Hantzsch proposed a similar relationship between five-membered thiazole and six-membered pyridine. He synthesized thiazole in 1887,[11] and suggested that other azoles should exist (Figure 2).[12] In rapid succession, he and his students published a large number of papers describing the synthesis and reactions of, among others, derivatives of thiazole (**12**), oxazole (**13**), selenazole (**14**),[13] as well as pyrrole (**15**).[14] Earlier, he had prepared benzofuran (**16**).[15]

Hantzsch's work in heterocyclic chemistry led to the Hantzsch–Widman nomenclature system,[11,12,16] proposed independently by Hantzsch and Swedish chemist Oskar Widman[17] (1852–1930), who was Professor of Analytical Chemistry at

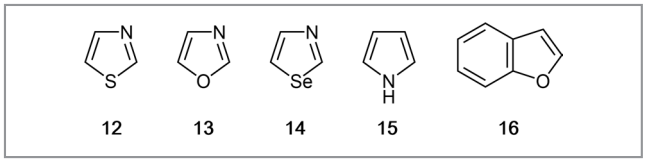
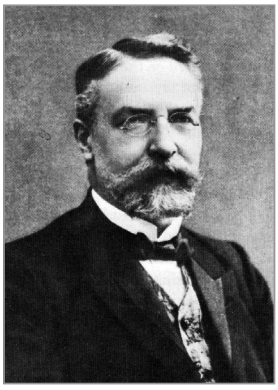


Figure 2 Azoles and their analogues predicted by Hantzsch

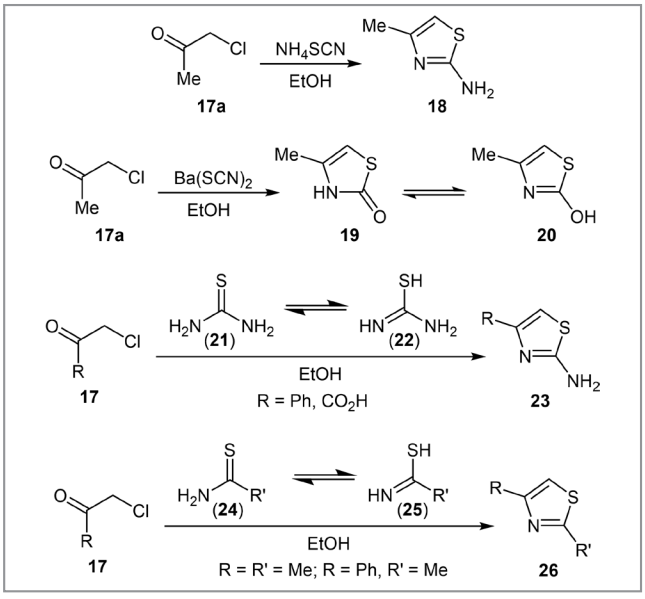


Oskar Widman

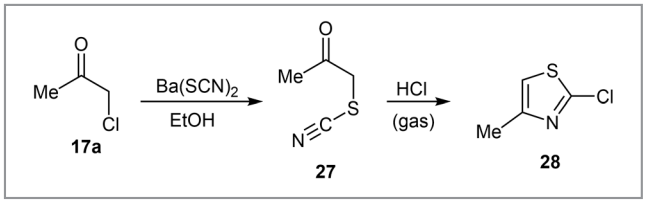
the University of Uppsala and, from 1900–1928, a member of the Royal Swedish Academy's Nobel Committee for Chemistry. When Widman's paper[16] was published, Hantzsch's first paper on azoles had already been published. In his subsequent paper on azole nomenclature,[12] Hantzsch acknowledged Widman's work.

The general methods developed by Hantzsch and his students for the synthesis of thiazole derivatives are summarized in Scheme 2. They all consist of the reactions between an α-halo ketone **17** and a sulfur nucleophile: 1) When the nucleophile is *ammonium* thiocyanate, a 2-aminothiazole (e.g., **18**) is obtained. 2) Using *barium* thiocyanate gives the thiazol-2-one **19** and its enol tautomer **20**. 3) Thiourea (**21**), which Hantzsch proposed reacts through the labile thiol tautomer **22**, reacts to give 5-alkyl-2-aminothiazoles **23**; and 4) a primary thioamide **24**, which Hantzsch also proposed reacts through its thiol tautomer **25**, reacts to give a 2,5-dialkylthiazole **26**.

Hantzsch's first publications on thiazole derivatives, and especially those with and by his student, Leonidas A. Aripides, involved him in a long-term polemic with Russian-born British industrial chemist Joseph Tcherniac (1851–1928),[18] who reported that the reaction (Scheme 3) between chloroacetone (**17a**) and thiocyanate anion gave thiocyanoacetone (**27**), which reacted with hydrogen chloride gas to give a compound that they assigned as 2-chloro-5-methylthiazole (**28**).[19]



Scheme 2 Syntheses of thiazole derivatives



Scheme 3 Tcherniak's interpretation of the reaction between chloroacetone and barium thiocyanate

In his paper, "Zur Geschichte des Rhodanacetons," Tcherniac suggested that the work of Hantzsch and Aripides was in error, as well as accusing them of ignoring his earlier work;[20a] footnote 2 (p. 3649) of the subsequent paper, „Methyloxythiazol, Darsetellung und Eigenschaften,"[20b] states:*

"In his last comment, Mr. Hantzsch speaks 'of a reaction discovered by him, overlooked by Tcherniac.' If Mr. Hantzsch means by that the soda reaction that I discovered and overlooked, he is utterly mistaken. I discovered the reaction, not him; the only thing that belongs to Mr. Hantzsch is the salting out."

In the first paragraph of his response, with the same title,[20c] Hantzsch makes the following equally inflammatory statement:

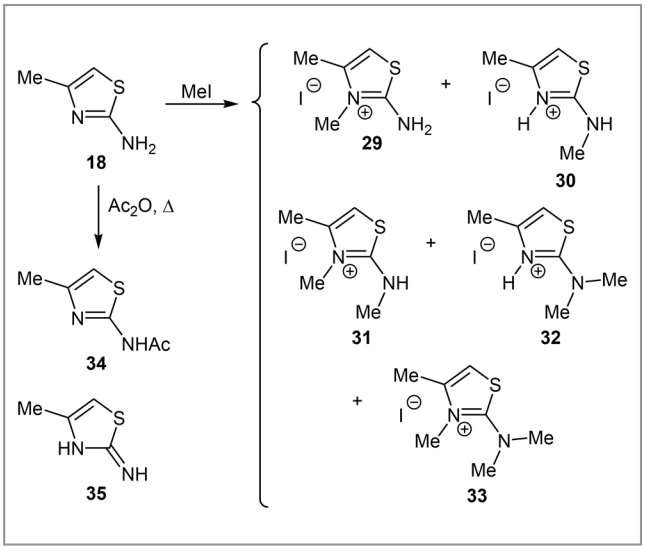
"In a recently published article of the same title, Mr. Tscherniac has criticized some of the work by me and my former students, J. H. Weber and L. Arapides, in such a derogatory way that I have to protest against them, albeit as briefly as possible. Mr. Tscherniac claims that he was the first to isolate pure rhodanacetone, that we initially denied its existence at all, but later should have recognized it, and that our statements and experiments about rhodanacetone and especially about its conversion to the isomeric oxythiazole discovered by us are all incorrect."

Tcherniac was still rebutting Hantzsch's arguments 27 years later.[20d]

In keeping with the best practices of his era, Hantzsch converted his 2-amino-4-methythiazole into the corresponding methiodides. These quaternary salts were normally crystalline solids. In the 2-aminothiazole system, this was not straightforward, and he characterized three methiodides, which most probably correspond to the iodides of the *N*-methylthiazolium ions **29**, **31** and **33** (Scheme 4).

The presence of the 2-amino group was established by acetylation, which gave a product, **34**, that was acidic enough

to react with sodium to give hydrogen gas. On this basis, Hantzsch assigned the structure as the 2-amidothiazole (**18**) rather than its imine tautomer, **35**.



Scheme 4 Derivatization of 2-amino-4-methylthiazole

Among Hantzsch's first graduate students was Alfred Werner, the 1913 Nobel Laureate in Chemistry. In 1890, Hantzsch and Werner began their stereochemical studies of imine derivatives with work on the stereochemistry of oximes.[21] They deduced that there should be two isomeric benzilmonoximes (**36**, **37**), which they named the *syn* and *anti* forms, and three isomeric dioximes (**38**, **39**, **40**) (Figure 3).

Alfred Werner

Hantzsch continued his work by examining the stereochemistry of other compounds with double bonds involving nitrogen.[22] In one year of work, he provided overwhelming evidence for the planar stereochemistry of nitrogen. He extended his theory to nitrogen–nitrogen double bonds in 1894 with his first paper on diazo compounds.[23]

In that work, they raised the possibility that the stereoisomerism of oximes might come from a constitutional isomer (**42**) containing pyramidal, rather than planar, carbon and nitrogen atoms based on the Wislicenus interpretation of geometric isomerism in alkenes (Figure 4).[24]

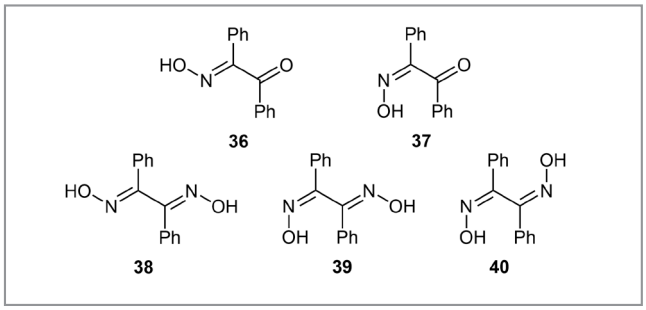


Figure 3 The geometric isomers of benzil mono- and dioxime deduced by Hantzsch and Werner

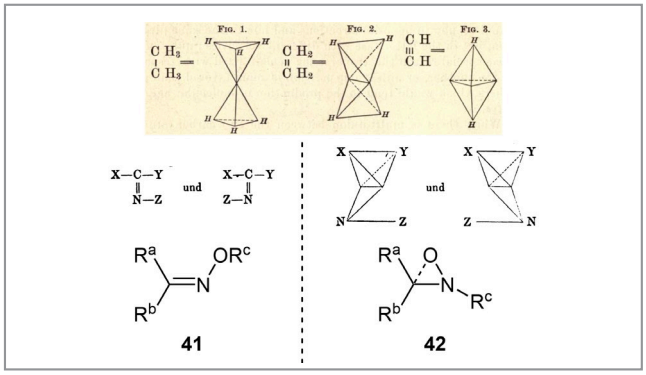
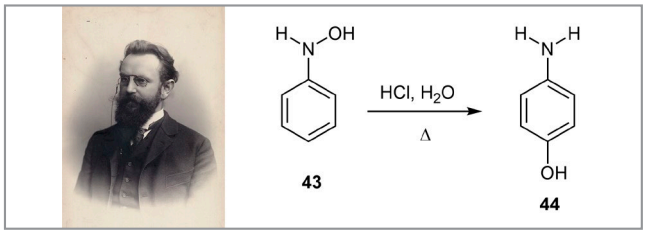


Figure 4 The two oxime isomeric structures considered by Hantzsch and Werner; the Wislicenus–van't Hoff interpretations of single and multiple bonds in hydrocarbons are shown at the top of the figure

This paper began Hantzsch's lengthy and acrimonious controversy with Eugen Bamberger (1857–1932),[24a,25,26] the discoverer of his own eponymous rearrangement of arylhydroxylamines **43** into *p*-hydroxyanilines **44** (Scheme 5).[27]



Scheme 5 Eugen Bamberger and his rearrangement

Some idea of the tone of the arguments may be gleaned from Bamberger's "Schlusserklärung (Final Declaration)"[28a] published in 1896, which contains the following numbered list of objections:

"1. A large part of his earlier assertions are now attributed by Mr. Hantzsch himself to observation errors and are no longer upheld; These things, seeming theoretically important in the light of the way of presentation at the time, sink – now they are admitted as erroneously – down to insignificant secondary matters.

"2. The self-evident fact is doubted, for no apparent reason, that I 'operated continuously, at 0° and generally with the exclusion of air'!

"3. Mr. Hantzsch is now carrying out various attempts under conditions considerably different from those mentioned earlier, and therefore, also, under different conditions than those used in my control. These attempts therefore did not affect my criticism at all. In other cases, things are now being held against me that have never been mentioned and that I have never admitted.

"4. Still other attempts have been carried out by Mr. Hantzsch – as his own words prove – now just as incorrectly as before.

"5. He fails to bring up a series of experimental errors accused of him; I can assume that he tacitly admits it.

"6. With regard to the "almost absolute purity" of the disodium diazosulfonate, a third party must decide who repeats the representation of this salt.

This list is followed by the following (italics original):

"I stand by the correctness of my observations and uphold the results of my experimental criticism word for word.

"Furthermore, remarks directed against me by Mr. Hantzsch – whatever their nature – I will leave unanswered.

"I hereby, for my part, end the controversy by repeating (see these Berichte 29, 446) that nothing at all is possible about the formula relationships of the 'isomeric' diazometallic salts (whose similar composition in the sense of Alph.N_2.OMe has not even been unequivocally established so far). I know that of all possible explanations the stereochemical one seems to me the most hopeless."

Hantzsch's "Ueber intramolekulare Umlagerungen von Diazoniumrhodaniden," published the same year,[28b] contains the following rebuttal:

"These *Berichte*, *29*, 456. On the occasion of this and similar occurrences, Mr. Bamberger says: "These phenomena are certainly not reminiscent of potassium salts". Of course, I never wanted to understand my proven assertions that diazonium is a composite alkali metal as if the diazonium salts, let alone the halogen-substituted ones, measured the potassium salts in all their properties. To accept this would be absolutely absurd."

Here and above, Hantzsch and Bamberger are referring to the same paper.[29]

At that time, it was known that three distinct diazo families existed, known as diazonium salts (**45**), normal diazotates (**46**), and isodiazotates. Bamberger argued that the isodiazo compounds were actually nitrosamines (**47**) and the isomeric normal diazotates (**46**) were true diazo compounds. Hantzsch showed that they were, instead, merely the *syn* (**48**) and *anti* (**46**) forms of the diazotate (Figure 5).[30]

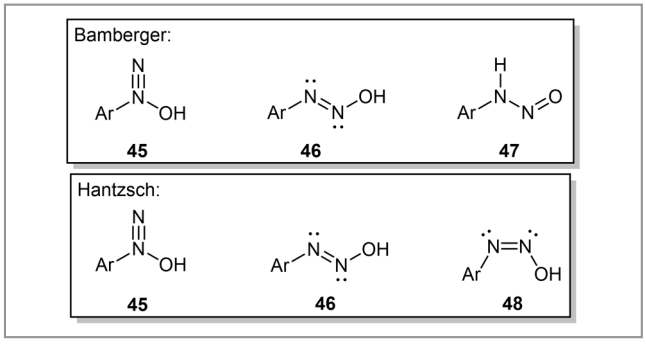


Figure 5 The alternative rationalizations of the structures of aryldiaza compounds by Bamberger and Hantzsch. The pentavalent nitrogen was standard during that era.

The long-running polemic with Bamberger, in which they exchanged many papers, covered many topics, and was decisive in the development of organic chemistry. Hantzsch used physicochemical data from cryoscopic, conductivity, and absorption spectroscopy studies. Bamberger used only reactions and syntheses for evidence of structure. He distrusted the physicochemical methods and arguments of Hantzsch, boasting that he used only pure *organic chemical* methods. Hantzsch's methodology permitted him to clarify the complex interrelations of unstable compounds that underwent rapid tautomerization in solution, something Bamberger could not do.

Hantzsch first summarized his views on stereochemistry in his monograph, *Grundriss der Stereochemie*, published in 1893,[31a] with an expanded and improved second edition a decade later.[31b] Hantzsch's work in stereochemistry largely ended with the turn of the twentieth century, when he turned his attention to the study of acids, bases and indicators. He summarized his work with diazo compounds in his monograph, *Die Diazoverbindungen*, initially published in 1902, in Stuttgart,[32a] and then in Berlin, in 1921.[32b] He discovered that the deprotonation of phenylnitromethane yielded not a carbanion base, but the conjugate base of a tautomeric species (which he trapped by protonation of the salt), which he called the aci form of the compound.[33]

Hantzsch Esters: A Resurrection of Sorts

NADPH, reduced nicotinamide adenine dinucleotide phosphate, **49*r*** (Figure 6), is an essential electron donor in all organisms.[34] It most frequently participates in the reduction of polar groups such as carbonyl groups and iminium ions. The oxidized form of the compound, $NADP^+$ (**49*o***) performs the reverse reaction, oxidizing alcohols to ketones, and amines to iminium ions.

The complementary biological reducing agent, reduced flavin adenine dinucleotide, $FADH_2$, **50*r*** (Figure 6), participates in hydrogenation reactions to saturate a carbon–carbon π bond. The reverse reaction, which uses the oxidized form of the cofactor, FAD (**50*o***), carries out biological dehydrogenations to introduce alkene π bonds into saturated alkyl chains.

The Hantzsch dihydropyridines have become important reagents in the transfer hydrogenation of π-bonded systems, including C=C, C=N and C=O π bonds in the presence of an acid.[35] One of the early applications of the reaction in asymmetric synthesis revealed that salts of α-amino acids carrying a group capable of hydrogen bonding were most successful in giving modest levels of asymmetric induction (Scheme 6).[36] With the exception of L-serine, the use of the conjugate acids of L-amino acids as the acid catalyst in the reduction of acetophenone anil (**51**) all gave the (*S*)-1-phenylamino-1-phenylethane (**53**) as the major product of the reaction.

This early work led to the research that earned Benjamin List and David MacMillan the Nobel Prize for Chemistry in 2021. The breakthrough in biomimetic reductions was reported by List and co-workers in 2004.[37] In these papers, List noted that stoichiometric amounts of secondary ammonium salts exercised a strong catalytic effect on the hydrogen-transfer reduction of carbonyl compounds using the Hantzsch ester **48 56** as the sacrificial hydrogen atom donor. In the same papers, the reaction was expanded to explore the use of chiral ammonium salts (e.g., **55a**) in sub-stoichiometric amounts (Scheme 7).[38]

By using the chiral ammonium salt (2*S*,5*S*)-**55a** as the catalyst and the dihydropyridine **56** as the sacrificial reductant, high levels of enantioselectivity for the *R* enantiomer of the 3-arylbutanal **57** were achieved.[38]

The secondary amines whose salts are most widely used as catalysts in these transfer hydrogenations are chiral imidazolines such as (*R*)-**55a**, developed by MacMillan. Scheme 8 shows representative results obtained by MacMillan with this organocatalyst and the Hantzsch ester **56**, where the *R* imidazolone gives predominantly the *S* enantiomer of the product. This shows that these organocatalysts generate the product

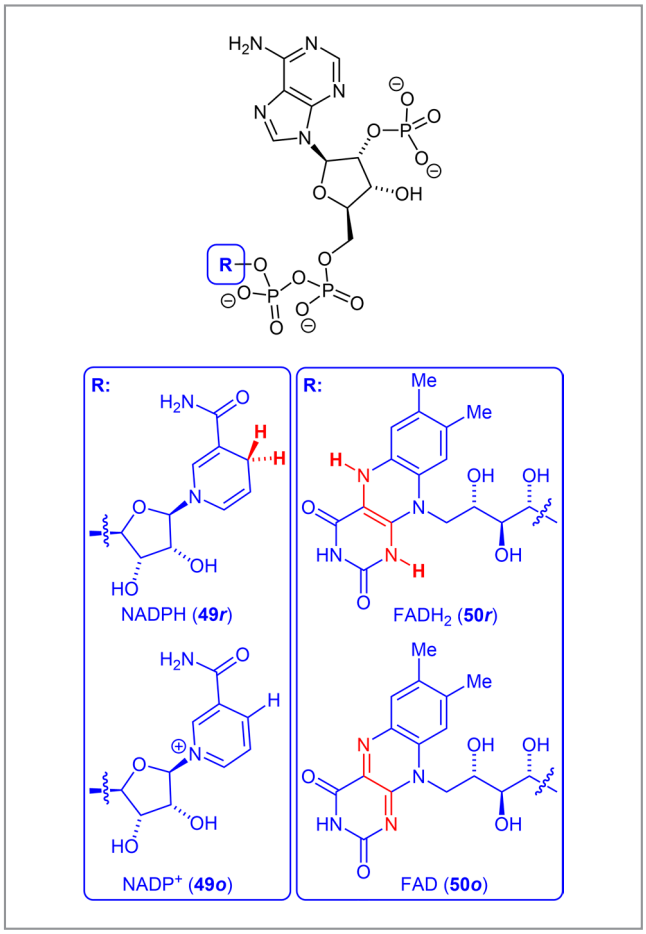
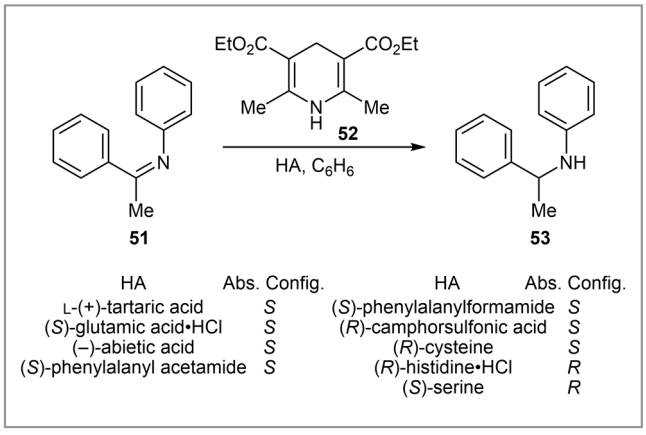
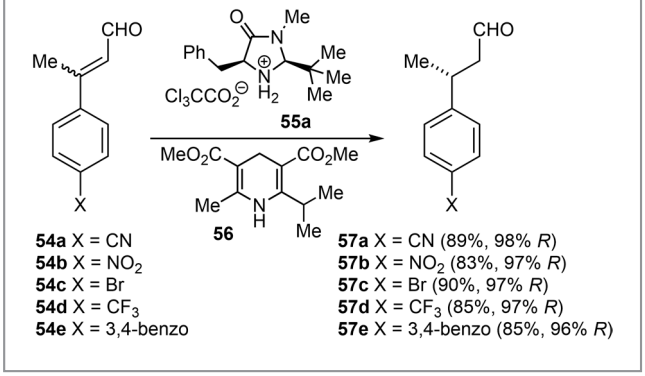


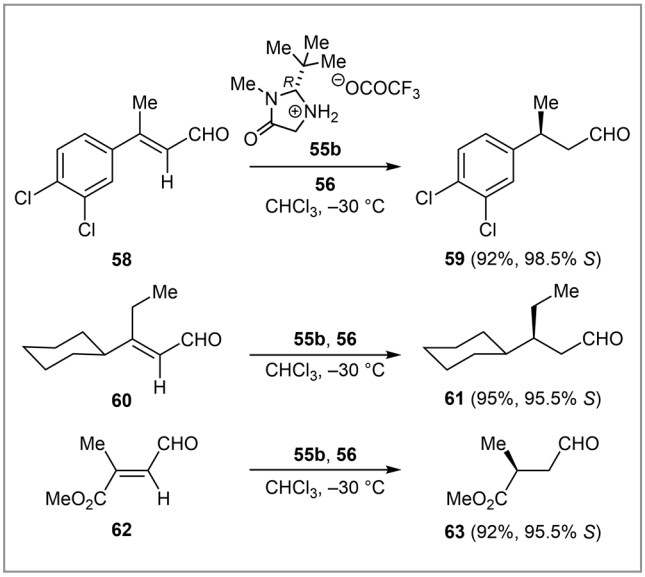
Figure 6 The reduced (***r***) and oxidized (***o***) forms of nicotinamide adenine dinucleotide phosphate (NADPH, **49*r***, and $NADP^+$, **49*o***) and flavin adenine dinucleotide ($FADH_2$, **50*r***, and FAD, **50*o***)



Scheme 6 Early asymmetric transfer hydrogenation of imines



Scheme 7 Enantioselective transfer hydrogenations reported by List

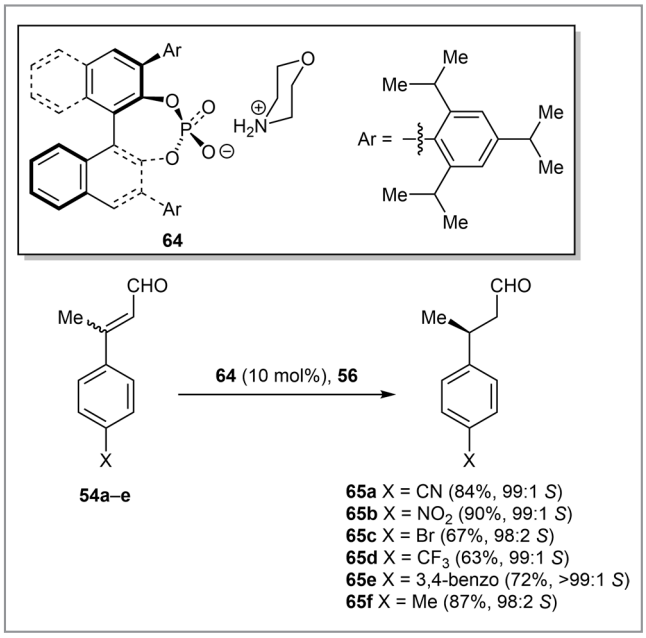


Scheme 8 Enantioselective transfer hydrogenations reported by MacMillan

with the absolute configuration opposite to the configuration at C-2 of the organocatalyst.

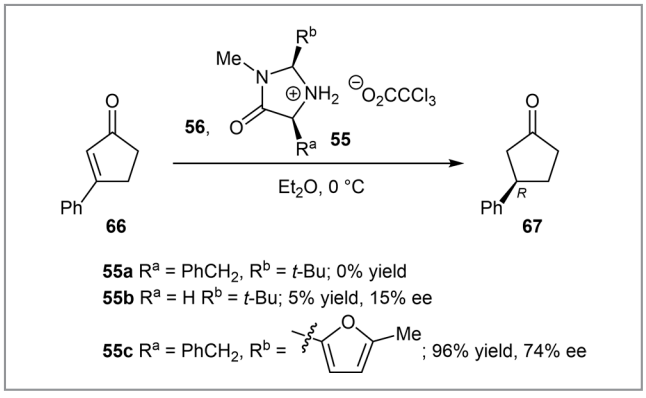
In 2006,[39] Mayer and List showed that counterion of a chiral Lowry–Brønsted acid catalyst can exert high levels of control over the absolute configuration of the transfer hydrogenation of aldehydes (*via* the morpholinium ion). In this case, the *R* enantiomer of the acid catalysts results in high levels of *S* selectivity (Scheme 9).

The same year, Menche and co-workers showed that thiourea is a good catalyst for the reductive amination of ketones by hydrogen bond activation of the imine and transfer hydrogenation from a Hantzsch ester.[40]



Scheme 9 A chiral Lowry–Brønsted acid catalyst for transfer hydrogenation using Hantzsch ester 56 as the sacrificial reductant

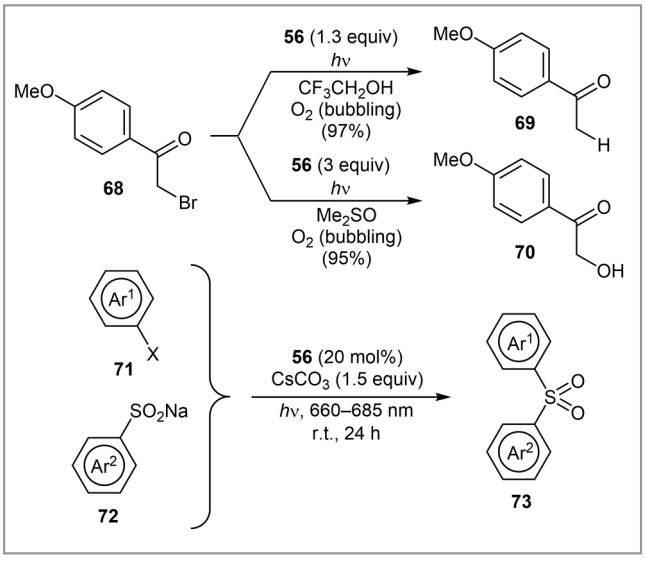
Conjugated ketones are generally more difficult to reduce than similar aldehydes. In 2009, Houk and co-workers published an analysis of the organocatalytic transfer hydrogenation of the cyclic, conjugated enone, 3-phenylcyclopent-2-enone (**66**), to the 3-phenylcyclopentanone **67** with conclusions about the origins of the stereoselectivity of the reaction in such enones.[41] Experimentally, they found that imidazolones that had been excellent catalysts for the reduction of conjugated aldehydes (e.g., **55a** and **55b**) were generally much



Scheme 10 Asymmetric transfer hydrogenations of a cyclic, conjugated enone

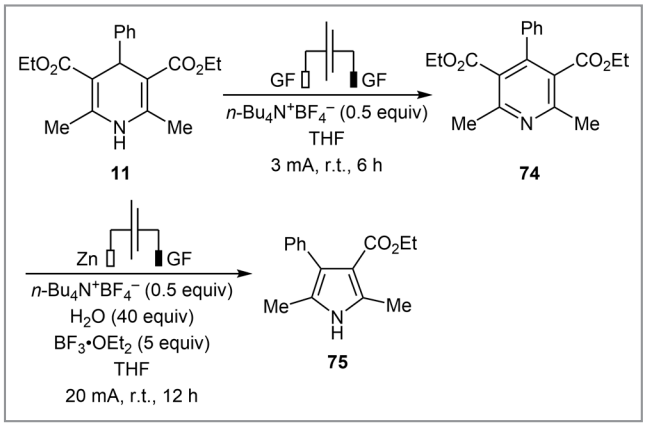
less effective in the reduction of ketones. The exception was the imidazolone **55c**, with the substituted α-furyl substituent (Scheme 10). Even in this case, however, the e.r. is 87:13, compared to the e.r. for aldehydes that are above 98:2.

In recent years, the Hantzsch esters have found application in photocatalytic reactions in either the presence or the absence of transition-metal catalysts (Scheme 11).



Scheme 11 Hantzsch esters as single-electron-transfer photoreducing agents

Their usefulness arises from the facile photoelectron transfer from the excited state of the Hantzsch ester to a reducible compound: E_{ox} (**56***) = –2.28 *vs.* SCE.[42] This means the excited state is a reductant strong enough to both produce free radicals from organic bromides, and to reduce Ru(II) to Ru(I). The reaction is also applicable to cross-coupling reactions such as the coupling of the aryl halide **71** and the arenesulfinate salt **72** to give the sulfone **73** (Scheme 12).[43] A fascinating—to this author, at least—recent paper describes an electrochemical contraction of Hantzsch pyridine **74** to give Hantzsch pyrrole **75**.[43] The same reaction can be applied to the Hantzsch dihydropyridine **11** in a two-step process where the dihydropyridine is oxidized electrochemically to the pyridine **74**, which then undergoes a four-electron electrooxidation to give the pyrrole **75** by extrusion of ethyl acetate.



Scheme 12 The electrochemical ring contraction of Hantzsch dihydropyridine esters to Hantzsch pyrroles

David Lewis

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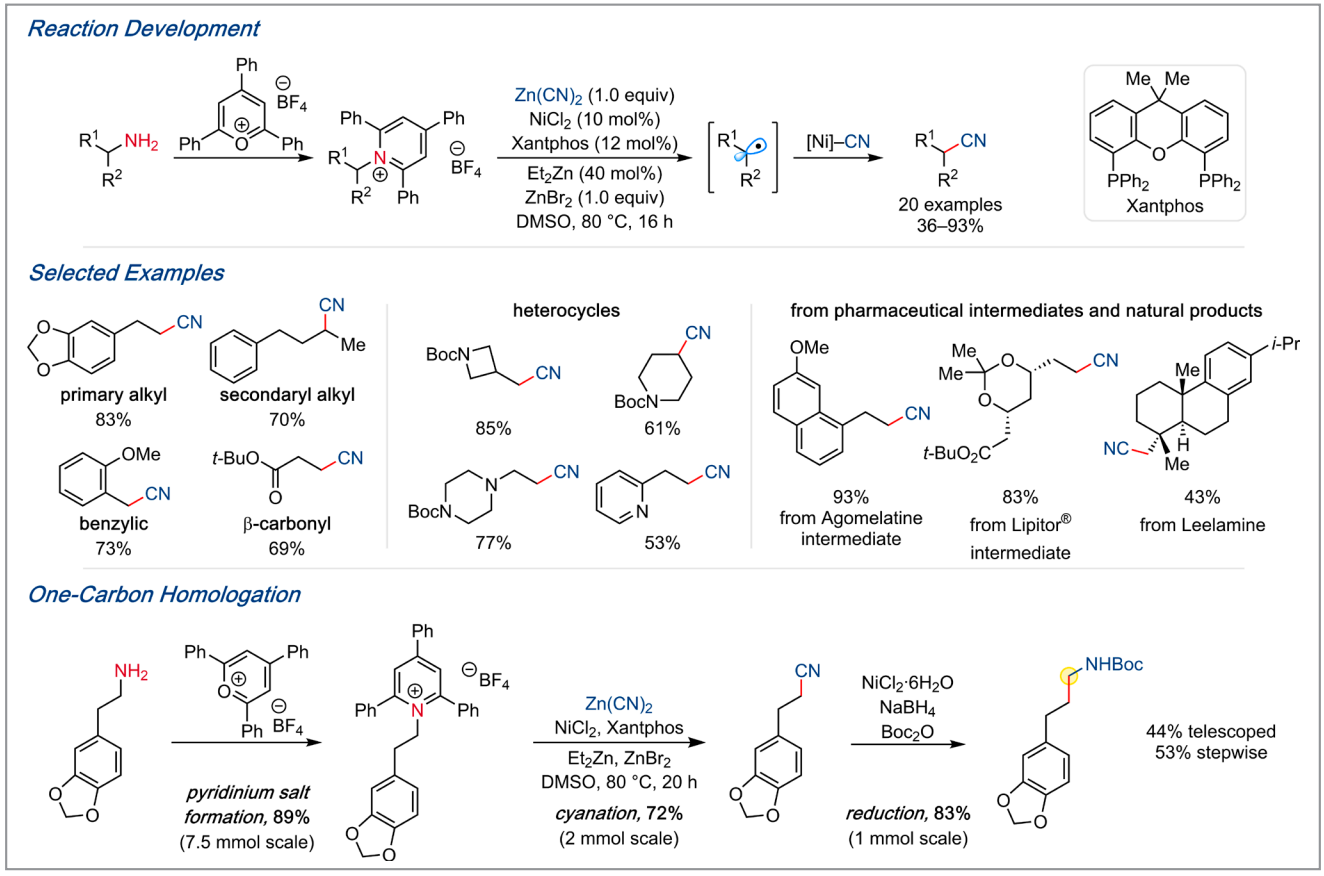
Nickel-Catalyzed Deaminative Cyanation: Nitriles and One-Carbon Homologation from Alkyl Amines

Org. Lett. **2021**, *23*, 6242–6245

A wide range of methods for achieving the cyanation of alkyl halides – which delivers useful alkyl nitrile products – are well established, including several metal-catalyzed cross-coupling reactions.[1–3] However, the use of low-toxicity sources of cyanide as well as the expansion of the pool of viable substrates to compounds other than alkyl halides (and related molecules) are among the issues that still need to be solved in this fundamental reaction. In particular, nickel-catalyzed cross-couplings of alkyl halides with less toxic cyanide sources formed much of the inspiration for the methodology developed in this paper from Professor Mary Watson at the University of Delaware (Newark, USA).[4] Professor Watson explained: "This new method offers an alternative class of starting materials, alkyl amines, to access highly valuable nitrile products. The ability to use an amine precursor can be advantageous when the alkyl amine is commercial or less expensive than an alkyl halide, or when the amine is more easily synthesized than an alkyl halide. The use of alkyl amines also offers opportunities for late-stage functionalization, because a protected amine can be carried through multiple synthetic steps, revealed, and converted into the pyridinium salt at the appropriate point in the synthetic sequence. The use of pharmaceuticals, pharmaceutical intermediates, and natural products containing alkyl amines offers another opportunity for late-stage deaminative reactions."



Scheme 1 The new Ni-catalyzed deaminative cyanation: scope and applications

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According to Professor Watson, in addition to offering another substrate class for nickel-catalyzed cyanations, a key innovation presented by this method is the one-carbon homologation of alkyl amines. "There were no previous methods that allow one-carbon homologations of these important molecules. Typically, adding a carbon to a lead structure would require a complete re-synthesis. This method allows scientists to study the optimal position of the amino group without going back to square one synthetically," remarked Professor Watson.

"With respect to other cross-couplings of alkylpyridinium salts, most deaminative cross-couplings of alkylpyridinium salts will deliver final products equipped with aryl, vinyl, or alkyl groups," explained Professor Watson, who added: "This method is one of the few that transforms the amino group into another functional group (the nitrile) with as many or even more possibilities for derivatization as the original amine."

Professor Watson continued: "There are still several open mechanistic questions though. In particular, the conditions that were empirically identified include multiple zinc reagents, opening the possibility for the involvement of several different zinc species in the process. At present, it is especially unclear how $ZnBr_2$ assists in this reaction. The use of Xantphos as ligand is also somewhat unique in nickel-catalyzed deaminative reactions. Understanding how this ligand enables the desired reaction may offer opportunities to develop other, challenging deaminative or cyanation reactions."

One of the major applications of this nickel-catalyzed deaminative cyanation is the one-carbon homologation of alkyl amines. Co-author Cameron Twitty extensively optimized a telescoped procedure for this one-carbon homologation sequence. "Although solvent-switching was necessary, column chromatography could be avoided until the last step, and the product can be isolated in comparable yield to the sequence with careful purification after each step," commented Professor Watson.

Dr. Jianyu Xu, the first author, also demonstrated that the cyanation works well on pharmaceutical intermediates and natural products. The group anticipates this method may be particularly useful to discovery efforts in medicinal chemistry.

Professor Watson remarked: "When I first started giving talks about our deaminative cross-couplings of alkylpyridinium salts, many academics thought it was nuts. "Why would you take out the amine that is driving the bioactivity?" they would ask. I believe that the adoption of deaminative methods by the pharmaceutical industry has changed most people's minds, but this idea stuck with us: Why delete a nitrogen? Perhaps we could just move its position. Dr. Jianyu Xu decided to invent a method to allow such a one-carbon homologation, and that's how this method came to be." She concluded: "It's exciting that this cyanation method not only provides a one-carbon homologation approach, but also delivers nitrile intermediates, which are highly useful in their own right."

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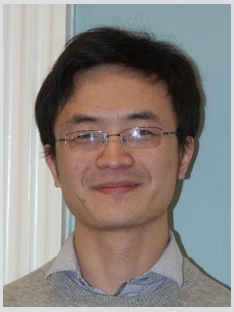
About the authors



Dr. J. Xu

Dr. Jianyu Xu is from Zhejiang, P. R. of China. He earned his B.E. in Pharmaceutical Engineering from East China University of Science and Technology (P. R. of China) in 2014, where he performed research with Profs. Feng Ren and Jin Zhu. He then pursued PhD studies at the University of Delaware (USA), where he worked with Prof. Mary Watson. His graduate work includes a range of nickel-catalyzed reactions spanning deaminative cross-couplings of alkylpyridinium salts to stereospecific cross-couplings of benzylic carboxylates to set all-carbon quaternary stereocenters. He completed his PhD in 2020, and is currently a Senior Scientist at Insilico Medicine in Shanghai, P. R. of China.

J. C. Twitty

J. Cameron Twitty is from Gilbert, South Carolina, USA. He earned his B.S. from the College of Charleston (USA) in 2017, where he performed research with Prof. Tim Barker. He began his PhD studies at the University of Delaware (USA) in 2018, where he is developing new deaminative reactions of alkylpyridinium salts under the mentorship of Prof. Mary Watson.

Prof. M. P. Watson

Professor Mary P. Watson is a Professor of Chemistry at the University of Delaware (USA). She grew up in Tampa, Florida, USA, and then earned her A.B. from Harvard University (USA) in 2000. As an undergraduate, she performed research with Prof. David Evans, as well as Prof. Kenneth Wagener at the University of Florida (USA). She earned her PhD in 2006 from the University of California, Irvine (USA), where she pursued methodology and mechanistic studies of the palladium-catalyzed allylic imidate rearrangement under the mentorship of Prof. Larry Overman and in collaboration with Prof. Robert Bergman. She then worked with Prof. Eric Jacobsen at Harvard University as an NIH NRSA postdoctoral fellow (2006–2009), where she developed nickel-catalyzed arylcyanation reactions. In 2009, she began her independent career at the University of Delaware, where she leads a talented team in the development of new methods for organic synthesis, enjoys helping to organize the annual Empowering Women in Organic Chemistry conference, and is the proud mom of twin daughters.

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