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]

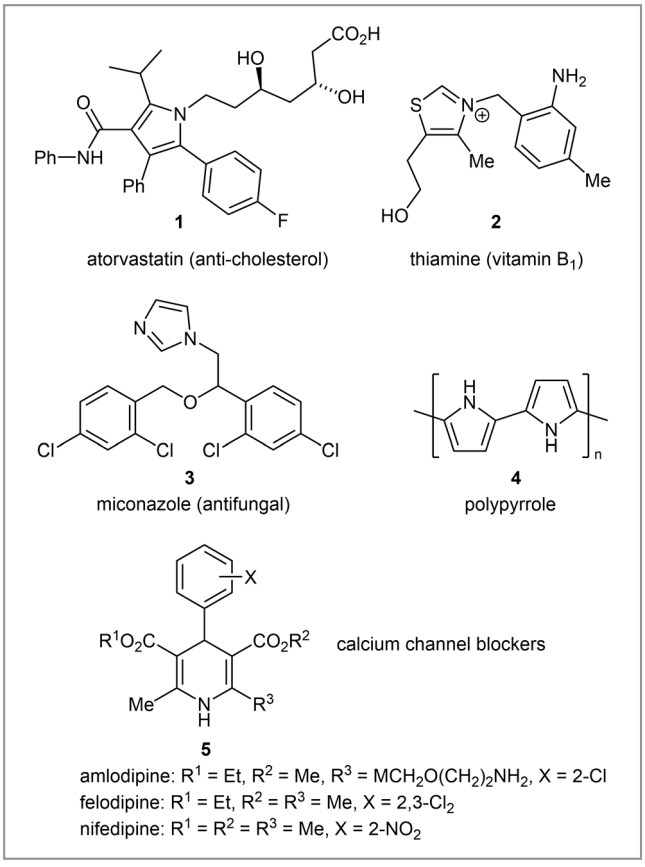
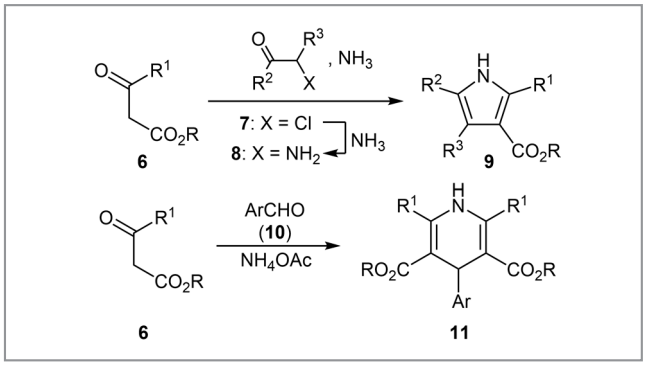


Figure 1 Representative species containing pyrrole or 1,4-dihydropyridine rings

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

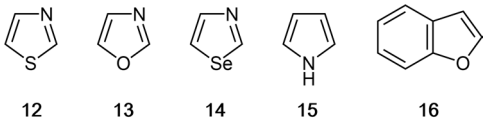
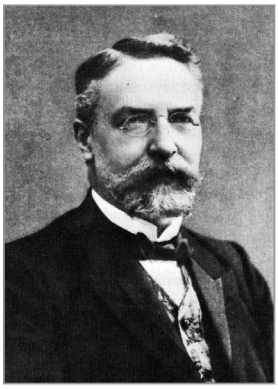


Figure 2 Azoles and their analogues predicted by Hantzsch

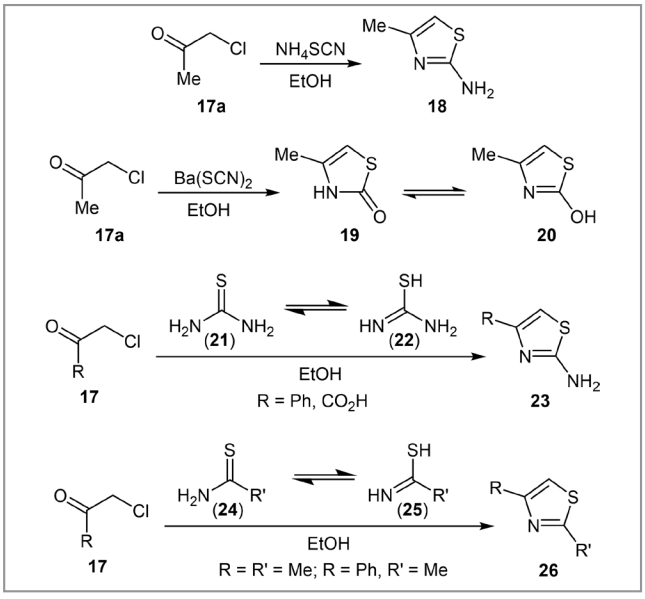


Oskar Widman

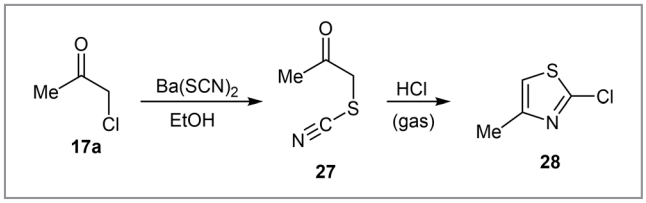
the University of Uppsala and, from 1900–1928, a member of the Royal Swedish Academy's Nobel Committee for Chemistry. When Widman's paper[16] was published, Hantzsch's first paper on azoles had already been published. In his subsequent paper on azole nomenclature,[12] Hantzsch acknowledged Widman's work.

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:

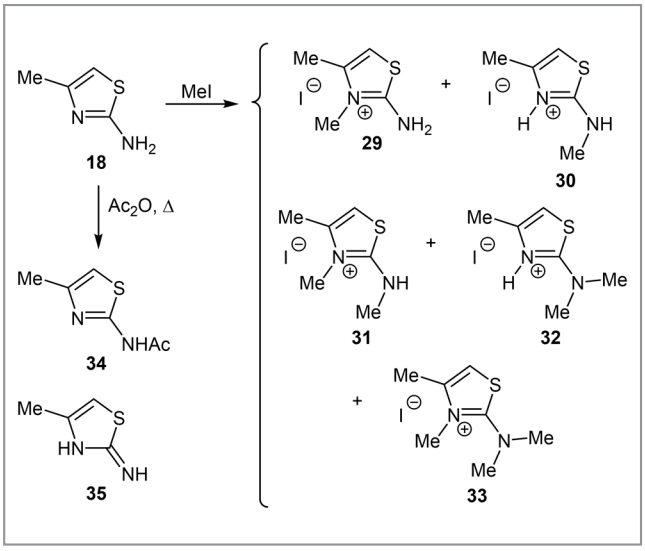
"In a recently published article of the same title, Mr. Tscherniac has criticized some of the work by me and my former students, J. H. Weber and L. Arapides, in such a derogatory way that I have to protest against them, albeit as briefly as possible. Mr. Tscherniac claims that he was the first to isolate 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]

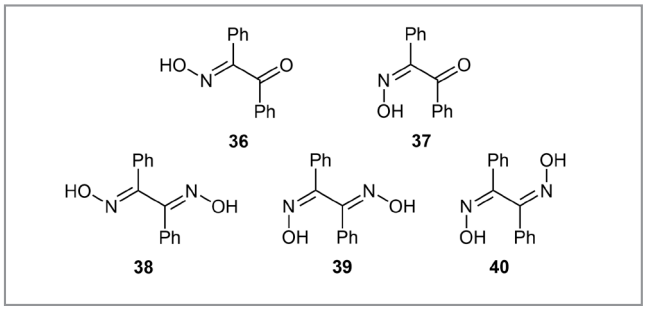


Figure 3 The geometric isomers of benzil mono- and dioxime deduced by Hantzsch and Werner

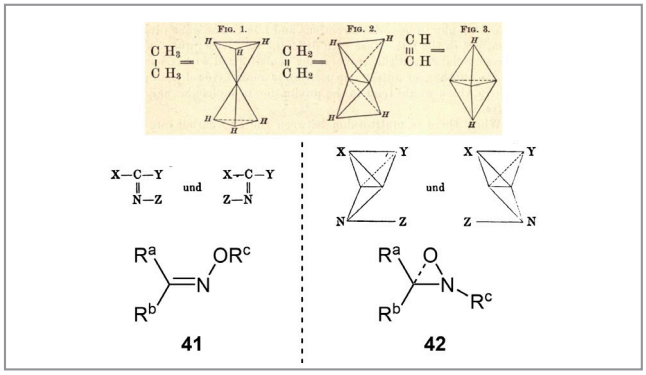
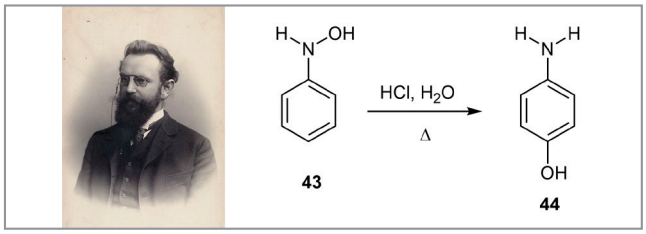


Figure 4 The two oxime isomeric structures considered by Hantzsch and Werner; the Wislicenus–van't Hoff interpretations of single and multiple bonds in hydrocarbons are shown at the top of the figure

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]

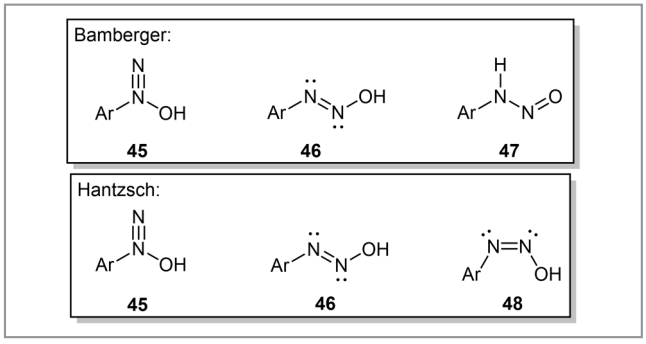


Figure 5 The alternative rationalizations of the structures of aryldiaza compounds by Bamberger and Hantzsch. The pentavalent nitrogen was standard during that era.

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]

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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

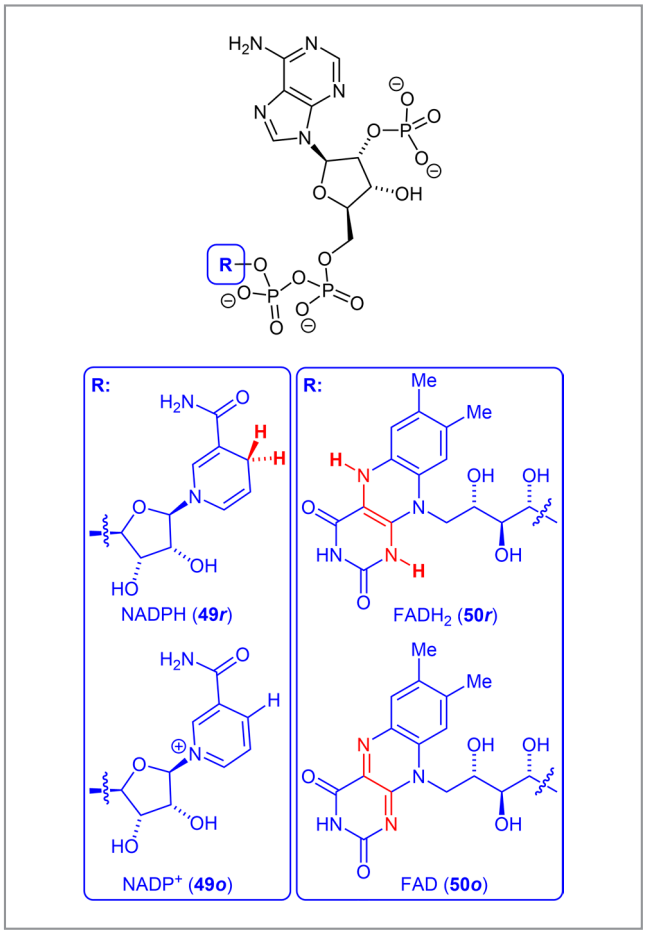
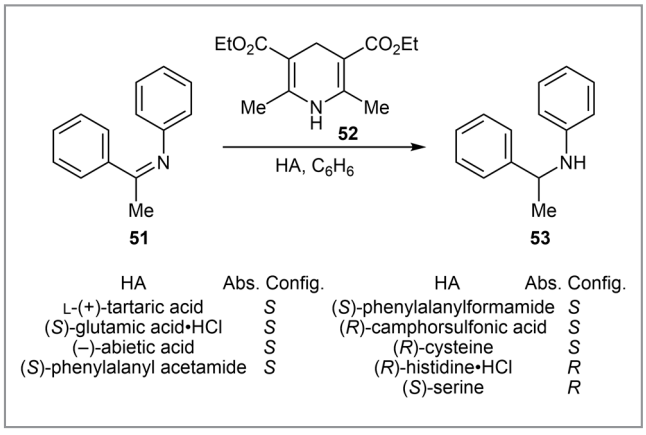


Figure 6 The reduced (***r***) and oxidized (***o***) forms of nicotinamide adenine dinucleotide phosphate (NADPH, **49*r***, and $NADP^+$, **49*o***) and flavin adenine dinucleotide ($FADH_2$, **50*r***, and FAD, **50*o***)



Scheme 6 Early asymmetric transfer hydrogenation of imines

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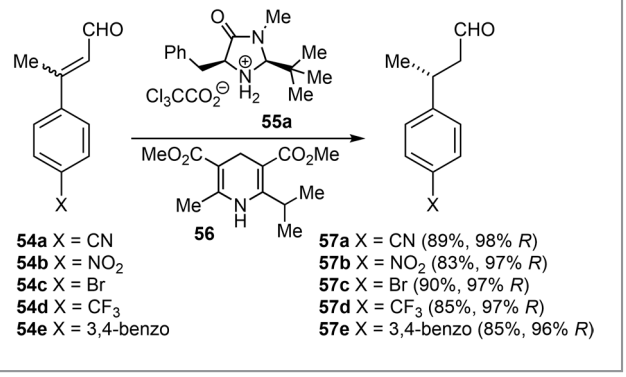
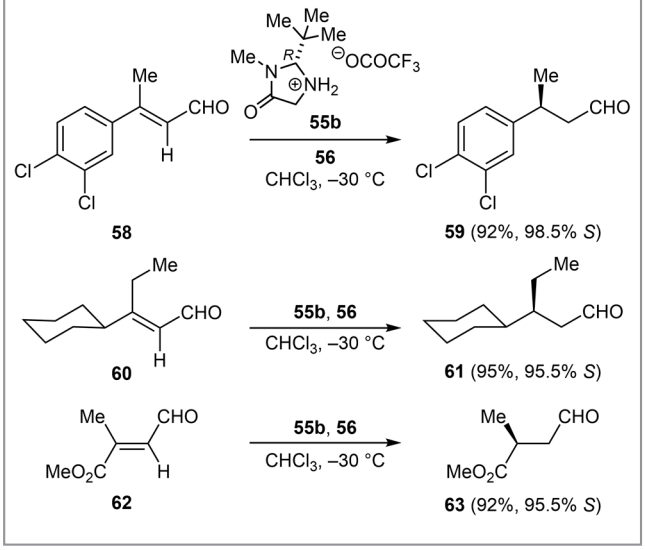


Scheme 7 Enantioselective transfer hydrogenations reported by List

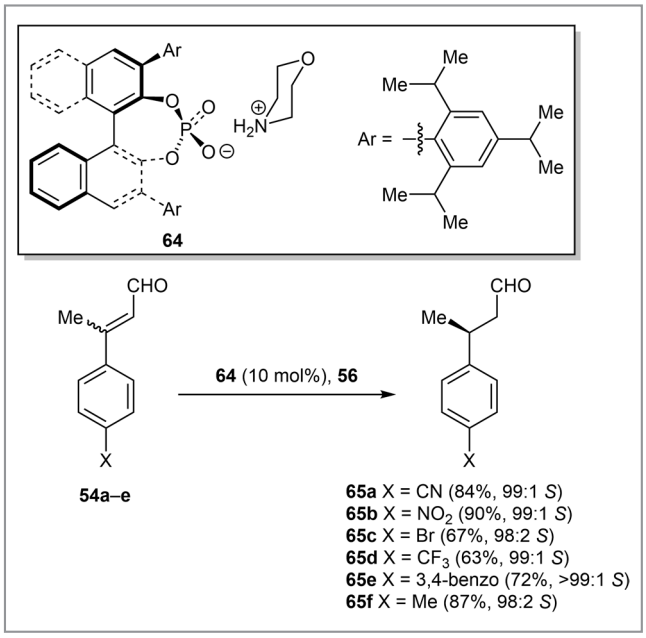


Scheme 8 Enantioselective transfer hydrogenations reported by MacMillan

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

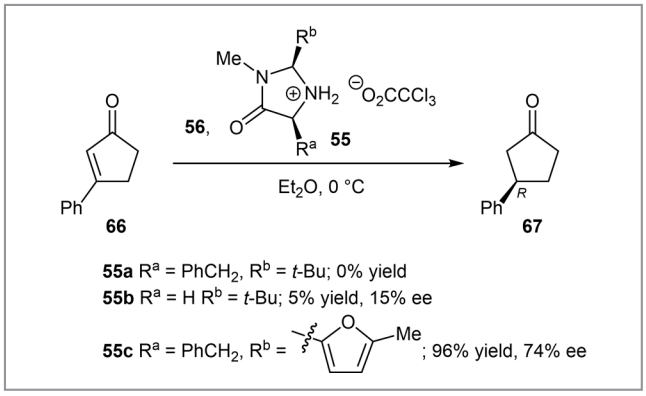
In 2006,[39] Mayer and List showed that counterion of a chiral Lowry–Brønsted acid catalyst can exert high levels of control over the absolute configuration of the transfer hydrogenation of aldehydes (*via* the morpholinium ion). In this case, the *R* enantiomer of the acid catalysts results in high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

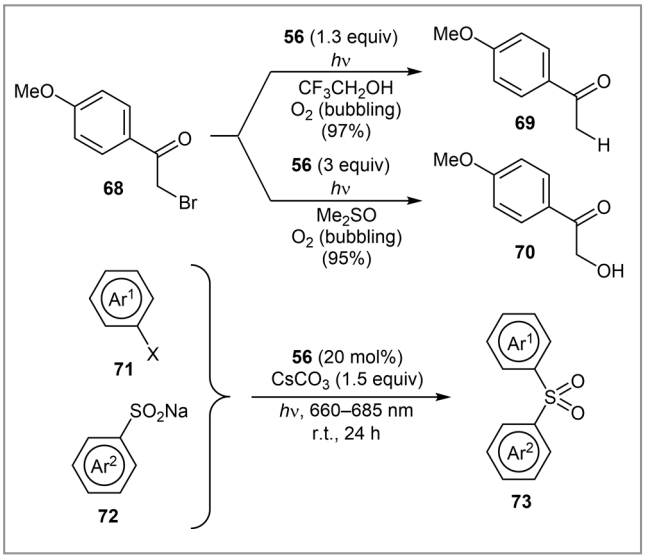
Conjugated ketones are generally more difficult to reduce than similar aldehydes. In 2009, Houk and co-workers published an analysis of the organocatalytic transfer hydrogenation of the cyclic, conjugated enone, 3-phenylcyclopent-2-enone (**66**), to the 3-phenylcyclopentanone **67** with conclusions 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

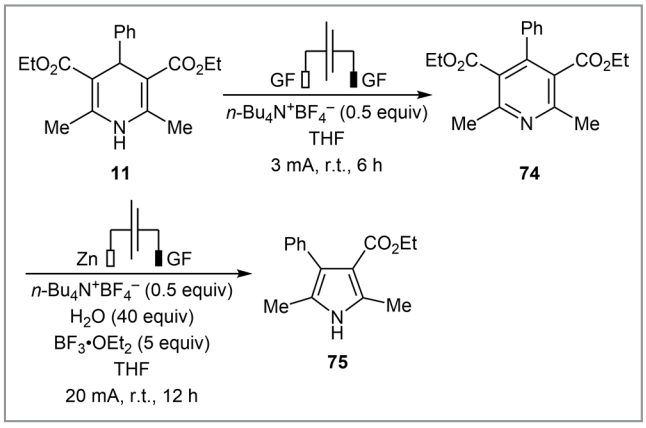
less effective in the reduction of ketones. The exception was the imidazolone **55c**, with the substituted α-furyl substituent (Scheme 10). Even in this case, however, the e.r. is 87:13, compared to the e.r. for aldehydes that are above 98:2.

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

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