Scientific Background on the Nobel Prize in Chemistry 2021

ENAMINE AND IMINIUM ION–MEDIATED ORGANOCATALYSIS

The Nobel Committee for Chemistry
Enamine and iminium ion–mediated organocatalysis

The Royal Swedish Academy of Sciences has decided to award Benjamin List and David W. C. MacMillan the Nobel Prize in Chemistry 2021, for the development of asymmetric organocatalysis.

The Laureates’ seminal work in 2000 conceptualized the area of organocatalysis and stimulated its development. Today, organocatalysis constitutes the third pillar of catalysis, complementing biocatalysis and transition metal catalysis.

Introduction

We all have an intimate relationship with molecules. They may be tailor-made molecules that can be delivered to cure patients, to store and relay information, to fertilize crops or to make our running shoes faster. Such molecules, with designed properties, are made by chemical synthesis, i.e. a series of reactions, and the knowledge of how to make molecules in an efficient and sustainable manner is closely linked to the progress of our society.

Complex molecules, be they human-made in a lab or assembled by other organisms biologically (biochemicals), are assembled in a series of reaction steps from simple starting materials. Some or all steps in such a reaction sequence can be subjected to catalysis.

Catalysis is a fundamental aspect of chemistry: the rate of a chemical reaction is increased by the addition of a catalyst, which itself is not consumed in the process. The concept was introduced in 1835 by the Swedish chemist J.J. Berzelius. It is not surprising that catalysis is used routinely in academia and industry, and is involved in much of the industrial conversion of chemical feedstocks into valuable products such as pharmaceuticals and agrochemicals; it has been estimated that catalysis contributes to more than 35% of the world’s GDP. Advances in chemical synthesis and catalysis are also strongly connected to sustainable technological developments, as has been pointed out by R. Noyori (Nobel Laureate, Chemistry 2001).

Catalysis in biological systems, which is mediated by enzymes, is also a prerequisite for life as we know it. Notably, a catalyst can provide an alternative reaction pathway compared with an uncatalysed one.

The use of low-molecular-weight organic molecules as catalysts for chemical transformations is not a new phenomenon. The first documented example was described in 1860, when Liebig reported that acetaldehyde catalyses the hydrolysis of cyanogen into oxamide. Without the catalyst, a complex mixture was obtained, while in the presence of acetaldehyde, acting as a Lewis acid catalyst, an almost quantitative yield of oxamide was obtained. However, the term organocatalysis refers to the use of small organic molecules, containing mainly carbon, hydrogen, nitrogen, sulphur and phosphorus but no metals, as promoters in catalysis.
Today a large number of different organocatalysts have been developed, as well as reactions which they promote. They can be classified according to the mechanistic role of the catalyst (Lewis acid or base, Brønsted acid or base), highlighting the catalysts’ function of removing or donating electrons or protons from or to the substrate or transition states. An alternative classification is the distinction between covalent catalysis, in which the catalyst forms a covalent bond to the substrate, and non-covalent catalysis, in which instead the catalytic cycle depends on non-covalent interactions such as hydrogen bonding.


**Background**

The following discussion focuses on organocatalysis. Reactions catalysed by non-chiral organic molecules will not be covered unless necessary for the general understanding of the development of the field.

Before 2000, several observations of organocatalysis were reported, although most appeared as unique isolated examples rather than part of development of a comprehensive methodology. The first example of the application of small chiral organic molecules as catalysts is attributed to Bredig and Fiske, who, in 1912, showed that the addition of hydrogen cyanide (HCN) to benzaldehyde to form the corresponding cyanohydrins is catalysed by the chiral bases quinine (1) and quinidine (2) (Figure 1). The cyanohydrin obtained when using catalyst 1 is enantiomeric compared to the one obtained when using catalyst 2; unfortunately, the cyanohydrins were obtained in low enantiomeric ratios (er). Although catalysts 1 and 2 are diastereomers, they produce enantiomeric products, a characteristic that has been used with much success in asymmetric catalysis. Half a century later, Pracejus showed that the quinine-derived catalyst 3 promotes the asymmetric addition of methanol to methylphenylketene, affording the corresponding methyl ester in er 87:13. Quinine (1) has also been used by Wynberg as a catalyst in the Michael reaction between nitroalkanes or β-keto esters and unsaturated ketones, affording the adduct in a modest er.
Along the way, several noteworthy observations were made. As early as 1928, the connection between the catalytic activity of small organic molecules and enzymes was discussed by Langenbeck, who also coined the term organic catalysts (organische Katalysatoren). Several years later, Fischer and Marschall (1931) showed that amino acids are excellent catalysts for the aldol reaction, and Langenbeck and Borth (1942) later showed that chiral amino acids also can be used for this purpose. The general mechanism for class I aldolases was uncovered in the 1960s and 1970s, and was shown to proceed through an enamine formation between a lysine residue in the enzyme and a carbonyl group in the substrate. By the 1970s, much information was already available about how organic molecules act as catalysts, but the time was not yet ripe to develop a comprehensive understanding of the area.

The last example in this section relates to hydrogen-bonding catalysis. In 1998, Jacobsen and co-workers showed that thiourea, identified using a library screening, is an efficient catalyst for the Strecker reaction between N-allylbenzaldimine and HCN to yield the corresponding adduct in high yield and er (eq. 1, The bond that is formed in the reaction is highlighted with red color and the new stereocenter is indicated with an asterisk *). Both thioureas and ureas are excellent catalysts for a number of asymmetric transformations and have been developed as bifunctional catalysts, by which both a nucleophile and electrophile can be simultaneously activated.

\[
\text{Ph} + \text{HCN} \xrightarrow{1. \text{catalyst 4 (2 mol\%)}} \text{PhCN} \xrightarrow{2. \text{TFAA}} \text{PhCN} \\
\text{PhNHCH=N} + \text{HCN} \xrightarrow{1. \text{catalyst 4 (2 mol\%)}} \text{PhCN} \xrightarrow{2. \text{TFAA}} \text{PhCN}
\]
The year 2000: Enamine and iminium ion catalysis

In 2000, two publications defined the starting point for the impressive development of the area of organocatalysis. In the first publication, List and co-workers outlined an L-proline catalysed intermolecular aldol reaction (enamine catalysis/Lewis base catalysis). Later the same year, MacMillan and co-workers discussed a Diels-Alder reaction between α,β-unsaturated aldehydes and cyclopentadiene catalysed by a chiral imidazolidinone (iminium ion catalysis/Lewis acid catalysis). In the following discussion, enamine and iminium ion catalysis will be discussed separately.

Enamine catalysis: In 2000, List, Lerner and Barbas III showed that the naturally occurring amino acid L-proline catalyses an intermolecular aldol reaction, which is a carbon-carbon bond-forming reaction, between acetone and a series of aromatic aldehydes (including isobutyraldehyde, eq. 2). They proposed that the reaction proceeds via an enamine intermediate, resulting in a Highest Occupied Molecular Orbital (HOMO) raising and increased nucleophilicity compared to the corresponding enol ether, and that the carboxylic acid functionality in the catalyst helps to stabilise the metal-free Zimmerman-Traxler transition state through hydrogen bonding. The catalyst is thus covalently attached to the substrate and controls the stereochemical pathway of the intermolecular aldol reaction. Subsequent computational studies of the reaction have refined this picture and highlight the role of the carboxylic acid proton as an intramolecular acid catalyst that provides charge stabilisation to the forming alkoxy anion. The researchers also suggested that the L-proline catalyst functions as a ‘micro-aldolase’, i.e. as an enzyme mimic, and that other organic reactions might be susceptible to a similar proline-mediated enamine catalysis.

Some important findings preceded this work. In the early 1970s, the groups of Hajos and Parrish (1971, 1974) and Eder, Sauer and Wiechert (1971) independently reported pioneering contributions to the field of asymmetric catalysis. They showed that L-proline catalyses the cyclisation of the achiral triketone 5 to furnish the Wieland-Miescher ketone (6, the Hajos-Parrish-Eder-Sauer-Wiechert, or HPESW, reaction), which is an important intermediate in the synthesis of several natural products (Scheme 1). For example, the HPESW reaction has been used for the synthesis of steroids. The reaction proceeds in high yields and produces compound 6 in high enantiomeric excess.
The paper by Wiechert and colleagues is rather laconic and provides no information about the scope and mechanism of the reaction. In contrast, Hajos and Parrish put forward a mechanism involving a carbinolamine that is now obsolete, since it is appreciated that the reaction proceeds through enamine catalysis, but, perhaps more importantly, the authors recognized that the proline catalyst plays the same role as an enzyme. However, these studies were not followed up by the authors, nor did they result in a general concept of using chiral amines in asymmetric enamine catalysis. Indeed, later studies by Agami and colleagues using L-proline to catalyse intramolecular aldol reactions afforded the products in moderate to low $er$.\(^{31}\)

![Scheme 1. Synthesis of the Wieland-Miescher ketone (6) by Hajos and Wiechert.](image)

In the 1990s, the group of Lerner and Barbas III successfully generated antibodies that catalyse the intramolecular aldol reaction.\(^{32}\) The catalytic antibodies were generated so as to mimic class I aldolase enzymes. These enzymes and catalytic antibodies use the amine moiety of a lysine residue in the active site of the protein to form an enamine with the substrate, which then adds to an aldehyde to complete the aldol reaction. In particular, the catalytic antibody 38C2 showed a broad substrate scope and afforded products in high $er$ (eq. 3).\(^{33}\) This antibody was also elegantly applied in a key step in the synthesis of several brevicomins, which are pheromones of several bark beetles (Scheme 2).\(^{34}\)
Scheme 2. Synthesis of brevicomins 7 and 8 using the catalytic antibody Ab38C2 in the aldol reaction.

**Iminium ion catalysis:** In 2000, Ahrendt, Borths and MacMillan showed that the chiral imidazolidinone 9 can catalyse the Diels-Alder reaction between $\alpha,\beta$-unsaturated aldehydes and dienes (eq. 4). The organocatalyst 9, which is prepared in three steps from the methyl ester of the naturally occurring amino acid L-phenylalanine, condenses with the unsaturated aldehyde to form the corresponding iminium ion, in which the energy of the Lowest Unoccupied Molecular Orbital (LUMO) is lowered compared to that of the aldehyde. This lowering of the energy of the LUMO results in an increased reactivity towards the diene, and a higher reaction rate of the ensuing Diels-Alder reaction compared to the uncatalysed reaction. Similar LUMO lowering activation can be attained by using metal-based Lewis acids, a technique that has been much studied.
In the case presented by MacMillan and colleagues, the catalyst is covalently attached to the substrate, which provides good possibilities for transferring the chiral information from the organocatalyst to the product, and the researchers discussed a model rationalizing the observed stereoinduction. In order to allow for efficient catalysis, the iminium ion of the initially formed cycloadduct (not shown in eq. 4) must be sufficiently kinetically labile to allow for its hydrolysis under the reaction conditions and regeneration of catalyst 9. The key insight in the work by MacMillan and co-workers is the concept that the LUMO lowering through catalytically generated iminium ion intermediates provides a general platform on which other asymmetric reactions can be designed and developed.

This case also was preceded by important findings in the literature. Baum and Viehe (1976) showed that the unsaturated iminium ion 11, derived from the corresponding acetylenic amide, reacts with cyclopentadiene in a Diels-Alder reaction to furnish compound 12 (eq. 5). In this study, the researchers concluded that the iminium ion moiety in 11 provides a substantial activation of the triple bond, i.e. LUMO lowering, compared to the situation in amide 10, which is the reason for the smooth conversion into adduct 12. This notion was further elaborated by Jung and co-workers (1989), who showed that the chiral iminium ion 13 underwent a smooth Diels-Alder reaction with cyclopentadiene to give adduct 14, which was hydrolysed to furnish amide 15 with high yields and excellent diastereomeric excess (eq. 6). In both these cases, the iminium ions moieties in compounds 12 and 15 are not sufficiently kinetically labile to allow for a facile hydrolysis of these functionalities under the reaction condition, which precludes an organocatalytic reaction manifold.

Another important impetus was provided by Yamaguchi and co-workers in 1993. These researchers showed that the rubidium salt of L-proline (17) is an efficient catalyst in the Michael addition of diisopropyl malonate to a series of \( \alpha,\beta \)-unsaturated aldehydes and ketones 16, to yield the corresponding addition products 19 (eq. 7). It was noted that the secondary amine moiety and carboxylate functionality in catalyst 17 are essential for the catalyst activity, and it was proposed that the reaction proceeds through the reversible formation of iminium ion 18.
Thus, once the Michael addition to intermediate 18 has proceeded, hydrolysis of the iminium ion moiety will ensue to generate 19 and the catalyst. The following year, Kawara and Taguchi (1994) described a similar Michael reaction using catalyst 20 to promote the reaction (eq. 8).39

\[
\text{R}^1\text{CH}_2\text{CH} = \text{CH}\text{R}^2 + \text{CH}_2\text{(CO}_2\text{Pr)}_2 \xrightarrow{\text{17 (5 mol\%)} \text{CHCl}_3, \text{rt}} \text{R}^1\text{CH} = \text{CH}\text{R}^2\text{NH}_2 \xrightarrow{\text{18}} \text{R}^1\text{CH} = \text{CH}\text{R}^2\text{(CO}_2\text{Pr)}_2
\]

(7)

\[
\text{R}^1\text{CH}_2\text{CH} = \text{CH}\text{R}^2 + \text{CH}_2\text{(CO}_2\text{R}^3)_2 \xrightarrow{\text{20 (5 mol\%, n = 1, 2)} \text{HFIP} \text{toluene, rt, 1 week}} \text{R}^1\text{CH} = \text{CH}\text{R}^2\text{(CO}_2\text{R}^3)_2
\]

(8)

Significance: The most significant advances in organic synthesis are those that clarify new principles for inducing reactivity and controlling reaction pathways; the development of the concept of organocatalysis and the fundamental design principles for developing such catalysis is clearly a significant advancement of the field. New opportunities to perform chemical reactions, such as organocatalysis, expand the toolbox that is available to chemists and allow for designing new reaction pathways for organic molecules. Such improvements and discoveries result in more efficient reaction pathways, which, as a consequence, will have a reduced environmental impact.

The use of small organic molecules as catalysts for organic reactions is not unprecedented in organic chemistry. However, the work by List and MacMillan resulted in a turning point; there is a clear before and after. Their work conceptualized the area of organocatalysis, focusing on asymmetric catalysis, and indicated principles for designing new organocatalytic reactions based on modern concepts such as LUMO lowering and HOMO raising.

In the years that followed these Laureates’ first publications in 2000, this research area has flourished: an impressive number of new reactions, catalysts and applications were described in the literature—this period has been referred to as the ‘organocatalysis gold rush’.40 Today, the area is well established in organic chemistry and has branched into several new and exciting applications. Also, organocatalysis is now recognized as the third pillar of asymmetric catalysis, together with biocatalysis and transition metal catalysis.
Post-2000 developments

Since the papers by List and MacMillan in 2000, impressive developments have followed in the area of organocatalysis, and new catalysts and reactions have been developed for all classes of organocatalysts (Lewis acid or base, Brønsted acid or base). This summary focuses on advances pertaining to enamine (Lewis base) and iminium ion (Lewis acid) catalysis; for a more detailed discussion covering all aspects of organocatalysis, several excellent reviews are available.41

Both List and MacMillan have continued their activities in the field, developing several new organocatalytic reactions using L-proline and chiral imidazolidinones as catalysts, respectively. Besides the intramolecular aldol reaction discussed above, List’s group used L-proline as a catalyst for the development of efficient asymmetric Mannich reactions,42-43 double Mannich reactions (eq. 9),44 α-amination of aldehydes,45 and conjugate reductions,46 among other processes.47 Similarly, MacMillan’s group pioneered the use of chiral imidazolidinones as organocatalysts in 1,3-dipolar cycloadditions,48 Friedel–Crafts reactions,49 Michael additions (eq. 10),50 and domino reactions,51 including other transformations.52

The Jørgensen-Hayashi catalyst: In 2005, Jørgensen and co-workers described the α-sulfonylation of aldehydes using a diarylprolinol silyl ether as a catalyst (eq. 11)53, and later the same year, Hayashi showed that this type of catalyst is also competent in the Michael addition of propanal to nitrostyrene (eq. 12)54; both reactions proceed by an enamine mechanism. Soon afterwards it was also shown that catalyst 21 was competent in the epoxidation of α,β-unsaturated aldehydes, e.g. cinnamaldehyde, into the corresponding epoxide 22 (Scheme 4a).55

These reactions highlight some important aspects of this chemistry. They demonstrate that a diarylprolinol silyl ether is competent to promote reactions involving both enamine catalysis (eqs. 11 and 12) and iminium ion catalysis (Scheme 3). Since their introduction, diarylprolinol
Silyl ethers have proven to be a powerful catalyst for this chemistry with a wide scope of applications, due to increased steric hindrance and higher stereoselectivity compared to L-proline and imidazolidinone catalysts. The reaction in Scheme 3 also shows that iminium ion catalysis can be coupled to enamine catalysis. The iminium ion that is generated in step 1 is an electrophile and is consumed in step 2 to form enamine (Scheme 4b). Enamines are nucleophiles and have a different reactivity compared to iminium ions, and this is made use of in the conversion of intermediate into compound. The possibility of coupling the reactivity of iminium ion and enamine catalysis has been cleverly exploited for the synthesis of complex organic molecules and is briefly discussed at the end of this section.

Scheme 3. (a) Organocatalytic epoxidation of cinnamaldehyde using hydrogen peroxide (H₂O₂) and diarylprolinol catalyst 21. (b) The reaction proceeds by initial formation of iminium ion, which is attacked by hydrogen peroxide to form enamine (iminium ion catalysis). Intramolecular expulsion of hydroxide ion, or its equivalent, from this species generates iminium ion (enamine catalysis) which is hydrolysed to furnish epoxide and regenerate catalyst 21.
**SOMO activation using organocatalysis:** Enamines are nucleophiles that are characterized by having a relatively high energy HOMO and that react with electrophiles. MacMillan and co-workers hypothesized that a one-electron oxidation of an enamine should generate the corresponding radical cation with a singly occupied molecular orbital (SOMO) that is activated toward enantioselective coupling with π-rich nucleophiles (Scheme 4). For such a strategy to be successful, the enamine must undergo selective oxidation (step 2) in the presence of a secondary amine and an aldehyde, and the catalyst must induce high enantiomeric selectivity in the coupling step (step 3).

This has indeed proven to be possible and this chemistry has been applied for the α-allylation, α-arylation and intramolecular cyclisation of aldehydes, furnishing the products in high yield and ee. As an example, this chemistry has been applied in an efficient synthesis of the naturally occurring indolizidine alkaloid (−)-tashiromine (Scheme 5). In this synthesis, the organocatalytic SOMO activation is used to construct the fused bicyclic ring system in compound 33 by allowing the cation radical, which is formed by oxidizing the enamine that is obtained from the aldehyde and catalyst 32 to add to the pyrrole moiety, and simultaneously install one new stereocentre in high ee.

![Scheme 4. Catalytic cycle for the allylation of aldehydes using SOMO catalysis. Aldehyde 26 condenses with the organocatalyst to form enamine 27 (step 1, 27 is in equilibrium with the corresponding iminium ion, which is not shown). A one-electron oxidation of 27 furnishes cation radical 28 (step 2), which can couple with π-rich nucleophiles (step 3) such as allyltrimethyl silane (28) to furnish intermediate 29. Fragmentation of this species will give iminium ion 30 (step 4), which is hydrolysed to the allylated aldehyde 31 and regenerates the organocatalyst (step 5).]
Merging organocatalysis with photoredox catalysis: The possibility to convert solar energy into chemical energy is of great importance for developing a sustainable society. The inspiration for this research stems from photosynthesis, where plants use solar energy to convert a simple feedstock into chemical energy in the form of carbohydrates. One possible way to mimic this chemistry is to use transition metal catalysts (photoredox catalysts, P) to harvest light, which can then activate stable organic molecules by single-electron oxidation or reduction. This furnishes open-shell intermediates that are not readily accessible and opens the possibility to trigger otherwise difficult two-electron reaction pathways by using two one-electron transfer steps mediated by the photocatalyst.

In 2008, Nicewicz and MacMillan merged this chemistry with organocatalysis, resulting in an efficient α-alkylation of aldehydes (eq. 13). The role of the photocatalyst P in this reaction is to reduce the alkyl halide to an alkyl radical and a halide ion (Scheme 6, step 2). The alkyl radical then adds to an enamine, forming a carbon-carbon bond and a new alkyl radical (step 3). This species is then oxidized by the photocatalyst to yield an iminium ion (step 4), which is hydrolysed to the product and returns the organocatalyst (step 5). Two catalytic cycles are involved, one with the organocatalyst and another with the photoredox catalyst, with two points of contact.

Nicewicz and MacMillan’s investigation, together with those led by Yoon and Stephenson, spurred considerable interest in the chemistry community, and much effort has been invested in developing photoredox-catalysed reactions. The power of this chemistry is that by using sustainable reaction conditions, it allows access to intermediates not attainable by traditional thermal activation. New chemistry has been developed, and photoredox catalysis has now been applied in most areas of organic chemistry, both in academia and industry.
Scheme 6. Mechanism of the organocatalytic photoredox–mediated reaction in eq. 14. The photocatalyst \( P [Ru(bpy)_3Cl_2] \) absorbs visible light (marked in yellow) to form the excited state \( P^* \) (step 6). \( P^* \) is a powerful oxidant that can remove an electron from a sacrificial enamine to generate \( P^- \) (not shown in Scheme 6). \( P^- \), in turn, is a reductant that reduces the alkyl halide to the corresponding alkyl radical and bromide ion, as well as regenerating photoredox catalyst \( P \) (step 2). The alkyl radical then enters the organocatalytic cycle and combines with enamine 37 to furnish a new open-shell species, radical 38 (step 3); note that in this step a new carbon-carbon bond is formed as well as a new stereocentre. Intermediate 38 is oxidized by the excited photoredox catalyst \( P^* \), affording enamine 39 and \( P^- \) (step 4). The product 36 is then obtained by hydrolysis of 39, which also regenerates the organocatalyst. Note that the photoredox catalytic cycle is closed by \( P \) absorbing visible light to reach the excited state \( P^* \) (step 6). The two catalytic cycles are connected but have different functions: the photoredox catalytic cycle generates and removes reactive open-shell intermediates from the reaction mixture, while the organocatalytic cycle provides a vehicle for the carbon-carbon bond–forming reaction and asymmetric induction.

Applications to the synthesis of complex organic molecules: The objective of organic synthesis is the production of organic molecules, be it for pharmaceutical, agricultural or natural products or other applications. Organocatalysis has found widespread application in this area. The efficiency of long multistep synthetic sequences is often problematic and usually affords the desired compound in only minute quantities. One strategy to alleviate this inherent drawback is inspired by the biosynthesis of organic molecules, where cascades of enzymes are used to...
convert simple starting materials into complex molecules in a highly regulated process. In organic synthesis, this is mimicked by using cascade reactions in which the product of the first reaction step is the starting material for the subsequent one, thus avoiding unnecessary purification operations between each reaction step.\textsuperscript{65-67}

An elegant example of this chemistry is the total synthesis of $\alpha$-tocopherol (vitamin E), which is a powerful antioxidant, by the Woggon group (eq. 14).\textsuperscript{68} In this cascade reaction, comprising an aldol reaction followed by an oxa-Michael reaction, two new bonds and one new stereocentre are installed in a single operation, thus forming the pyran moiety of $\alpha$-tocopherol (Scheme 7).

Scheme 7. Mechanism of the cascade reaction for the formation of compound 43. In this cascade reaction, aldehyde 42 condenses with catalyst 40 to form the corresponding dienamine 44, which then reacts with aldehyde 41 in an intramolecular aldol reaction to form iminium ion 45. Iminium ion 45 then participates in an intramolecular oxa-Michael reaction to form compound 46. Hydrolysis of 46 regenerates catalyst 40 and, after acetalization, furnishes tricycle 43.
Organic synthesis has an important role in preclinical pharmaceutical research, where there is a great demand for new organic molecules to be tested in different disease models. The goal of this activity is to develop new pharmaceuticals to treat diseases, and it is not surprising that organocatalytic methods have been applied in this area.\textsuperscript{56, 69}

One example is treatment of hypertension (high blood pressure). Renin, a protease protein secreted by the kidneys, hydrolyses the protein angiotensinogen in the blood stream into the peptide angiotensin I. Further hydrolysis of angiotensin I results in the formation of angiotensin II, which is a vasoactive peptide involved in hypertension. One possibility to treat hypertension is then to inhibit renin and prevent the formation of angiotensin II. Researchers at Novartis proved that this is indeed possible, and in 2007, their novel renin inhibitor aliskiren (Rasilez) was approved by the US Food and Drug Administration. An organocatalytic approach to aliskiren described by these researchers is outlined in Scheme 8.\textsuperscript{70} A Michael addition between the enamine generated from isovaleraldehyde and the Jørgensen-Hayashi type organocatalyst 47 and nitroethene (generated \emph{in situ} from compound 48) followed by reduction furnishes compound 49. This material is then converted into aldehyde 50, which is subjected to a nitro-aldol reaction with compound 49 to afford 51. It should be noted that compound 49 is cleverly used two times in this synthesis for the preparation of 51! Compound 51 is transformed into 52, which is a key intermediate in the synthesis of aliskiren.

\begin{figure}
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\includegraphics[width=\textwidth]{scheme8.png}
\caption{Organocatalytic approach to the anti-hypertensive drug aliskiren.}
\end{figure}

\textbf{Consequences and applications}

Developments in organic synthesis that clarify new principles for inducing reactivity and controlling reaction pathways are central to the advancement of the discipline. This year’s Laureates have made a pioneering contribution to this area. Their conceptually novel work from
2000 attracted much attention from the research community and marks the start of modern research in organocatalysis, sparking an evolution that is still ongoing. The research area is vast, not only comprising enamine and iminium ion catalysis, and today organocatalysis has matured into a tool that is routinely used in synthesis planning and execution, both in industry and academia.

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References

9. For more information, see: https://www.nobelprize.org/prizes/list/all-nobel-prizes-in-chemistry/
11. E.g. the (DHQ)2-PHAL and (DHQD)2-PHAL ligands used in the asymmetric dihydroxylation reaction developed by K.B. Sharpless and for which he received the Nobel Prize in Chemistry in 2001.
16. Fischer, F. G.; Marschall, A., Ber. 1931, 64, 2825-2827.
26. The terms ’enamine catalysis' and 'iminium ion catalysis' will for convenience be used in this presentation, although such species are perhaps better characterized as intermediates rather than catalysts.


**Further reading**