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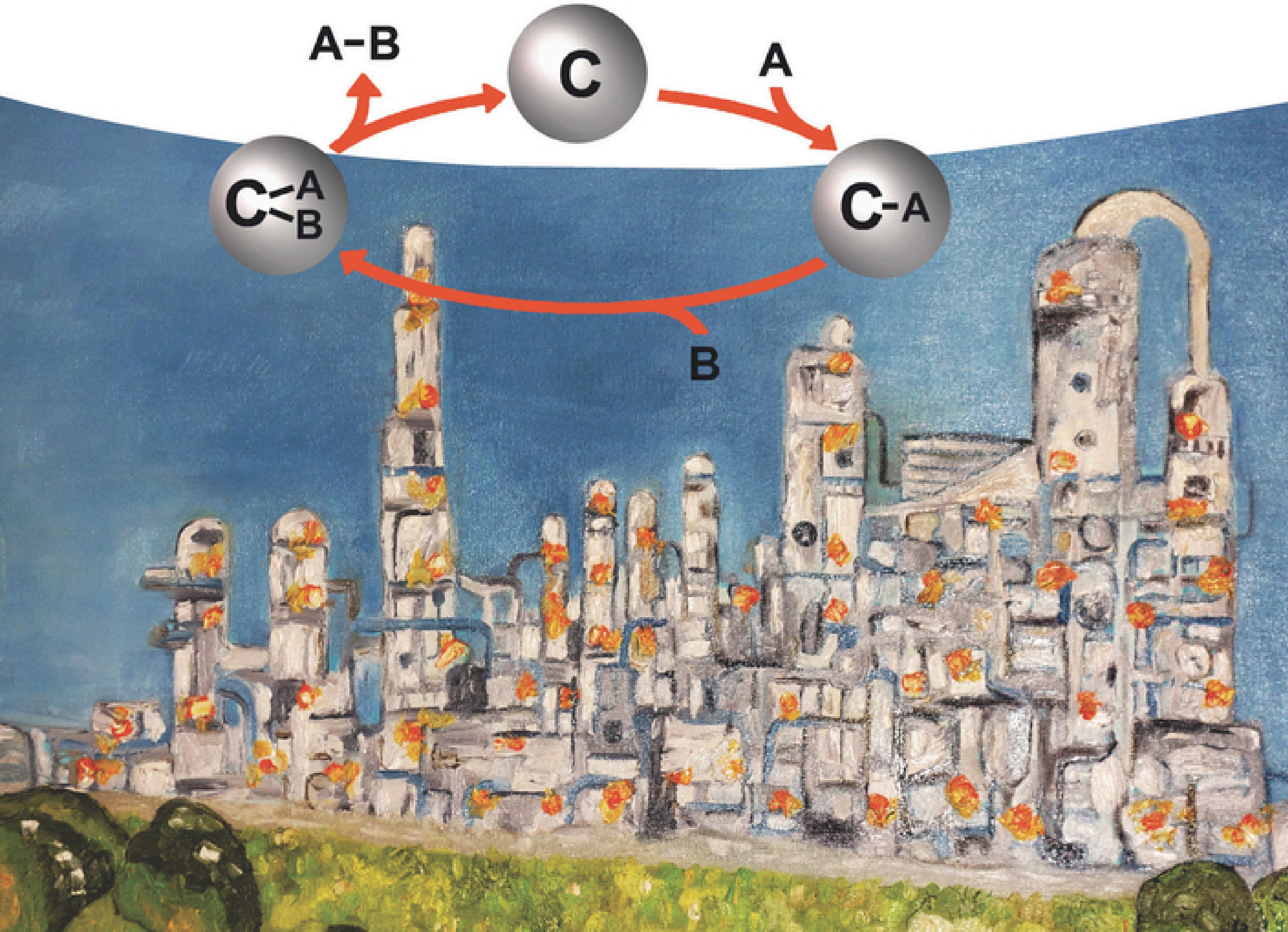
Arno Behr, Thomas Seidensticker, and Dieter Vogt

Applied Homogeneous Catalysis

A Tool for Sustainable Chemistry

Second Edition



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Contents

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Preface of the Authors

This textbook, *Applied Homogeneous Catalysis – A Tool for Sustainable Chemistry*, is written for all those who are interested in homogeneous transition metal catalysis and its applications in the chemical industry. It is an **introductory textbook** that assumes a good basic knowledge of chemistry but no special prior expertise in catalysis. The *Applied Homogeneous Catalysis* (AHC) is not a comprehensive reference book on homogeneous catalysis. It is focused on transition metal catalysis, not dealing with acid/base, heterogeneous or biocatalysis.

The AHC is primarily aimed at **students in chemistry and chemical engineering**; however, also experts in academia and industry may find useful information on certain processes and products, as well as mechanistic details. Students at universities can prepare their lectures or acquire the material in 'handy packages' through self-study. **Practitioners in industry** will quickly find answers to their specific questions and familiarise themselves with their particular areas of work. Through selected references, the reader is enabled to quickly enter also specialised subjects.

This book is a **completely revised new edition** of the book *Applied Homogeneous Catalysis* published in 2012. In this 2nd edition, large parts of the basic information have been taken over from the first version and partly put into the current context. In many sections, however, the content has been completely revised and supplemented with current topics and examples.

This preface is intended to give a brief overview of the revised concept:

- As the subtitle indicates, the book has been given a new focus: Even more than in the 1st edition, it emphasises the potential of applied homogeneous catalysis for **sustainable, green chemistry**. The new introductory chapter answers the important question: 'Adhering to the 12 Principles of Green Chemistry – How does homogeneous catalysis contribute?'
- An extended **team of authors** was devoted to this task: Arno Behr, Thomas Seidensticker and Dieter Vogt are all three experienced researchers and university teachers in the field of homogeneous catalysis and its applications. Their different areas of expertise cover many aspects of homogeneous transition metal catalysis.

From left to right: Arno Behr, Thomas Seidensticker and Dieter Vogt

- Due to the new conception, the book has a slightly different **structure**. It now consists of five parts resulting in a total of 46 chapters:
  - Part I '**Chemical Basics**' presents the fundamental chemical knowledge of transition metal catalysis. This includes chapters on organometallic chemistry, metal catalysts, thermodynamics and kinetics.
  - Part II '**Process Engineering Fundamentals**' presents the concepts for the realisation of homogeneous catalytic processes in industry. This includes the different reactor types and the possibilities to recover the catalyst.
  - In Part III '**Homogeneously Catalysed Reaction Types**', the most important catalytic reactions are described and explained using concise examples. The focus lies on reactions that are already being used in industry, but also reactions are presented that have great potential to be employed in the chemical industry in the future.
  - Part IV '**Associated Catalysis**' presents catalytic conversions that are closely related to classical

  homogeneous transition metal catalysis but use new molecular or technological approaches. These include, for example, nano-, electro-, photo- and organocatalysis.
  - Part V '**New Resources**' deals with homogeneous catalysis using raw materials that will become increasingly important in the future. This includes, for example, the reactions of carbon dioxide and renewable raw materials, but also recycling, e.g., of polymers. Finally, at the end of the book, an outlook is given on the challenges of the future for homogeneous catalysis.
- The new edition still presents reactions and side reactions in detail with respective mechanisms and catalysts. Particular emphasis is given to the performance and scope of the reactions; furthermore the industrial application of the products plays an important role. For updating, on the one hand, the different chapters have been completely revised, and **new sections**, important current examples and new trends have been included. On the other hand, **new chapters** have been added, e.g., hydrofunctionalisation, photocatalysis, organocatalysis, nitrogen activation and polymer recycling.
- What else is 'new'? When browsing through the book, some rather editorial changes are quickly apparent: Each chapter is now preceded by the '**Learning Objectives**', i.e., a brief description of the chapter's content. Moreover, all graphics have been revised. The following **graphical symbols** are still used to mark certain text passages.

  Take-Home Messages
  Technical Information
  Mechanisms
  Exercise Questions
  Literature
  Information on the internet
  Renewables
  Asymmetric catalysis

- In addition to the graphical symbols, figures, equations and tables, **important terms** as well as references to the 'Principles of Green Chemistry (**PGC**)' have now been highlighted in colour (in green!) and some **multi-coloured photos** have been used for a vivid presentation.
- The **references** have now been divided into two parts: The essential textbooks, reviews, and original references are cited straightforwardly in each chapter of the printed book. In addition, a much more comprehensive overview of significant primary literature is available as '**supporting information**' on the Internet (www.wiley.com/go/behr/AHC2). There, the bibliographies are arranged to start with the most recent references so that the reader can quickly obtain the most up-to-date information. Older, important references (backdated to 2000) are not missing.
- A science textbook full of facts might appear a bit dull: that is why we have livened up this book by including so-called **Excursions**. In these textboxes, we, for instance, introduce some important researchers in the field of homogeneous catalysis. In some, we share anecdotes related to the content to amuse you. This is also the purpose of the '**Footballer's quotes**', which complete each chapter. These serve as a reward to readers who answered all 10 **exercise questions** (almost) correctly. By the way: The **answers** to all 450 questions can be found in the book's appendix.

Finally, we thank Nadine Oppenberg for supporting us in the beginning with the graphics. We are particularly thankful to our co-worker Milan D. Kulas, who spent many days (and nights) creating outstanding-quality drawings for the book. We also acknowledge the support of Wiley Publishing. Arno Behr and Dieter Vogt also thank posthumously their teacher, Prof. Dr. Wilhelm Keim, who many years ago introduced them to the interesting and abundantly exciting field of homogeneous transition metal catalysis.

We hope you enjoy reading this new *Applied Homogeneous Catalysis*. If you have any suggestions, please send us an e-mail to the Laboratory of Industrial Chemistry, TU Dortmund University/Germany.

Arno Behr, Thomas Seidensticker, and Dieter Vogt
Dortmund, January 2025

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Introduction

Adhering to the 12 Principles of Green Chemistry: How Does Homogeneous Catalysis Contribute?

Learning Objectives

By the end of this chapter, you will be able to …

- name the 12 principles of green chemistry and describe the role of homogeneous transition metal catalysis in their context.
- explain the environmental and economic benefits of using homogeneous transition metal catalysts in chemical synthesis, and to illustrate this using characteristic examples.

Why does this catalysis book start with a pre-chapter on ‘Green Chemistry’? Did we three authors just come up with this to give the book a green touch and make it sell better? Not only! In particular, this pre-chapter is intended to provide a first impression of how closely ‘Green Chemistry’ and homogeneous catalysis are connected.

We proceed according to the ‘*12 Principles of Green Chemistry*’ (PGC) introduced in the 1990s by *Paul Anastas* and *John C. Warner* (see Excursion: The Godfathers of Green Chemistry). Anastas and Warner compiled all the important methods for designing chemicals that are as environmentally friendly as possible and producing them with a minimum of harmful by-products. These 12 principles are common sense and have been known for a long time to a large extent. However, Anastas and Warner were the first to collect all these principles and write them down concisely. They set the standard for a science of sustainability and chemical production with optimal protection of the environment.

EXCURSION: The Godfathers of Green Chemistry

In 1998, *Paul Anastas* and *John Warner* jointly published the book ‘*Green Chemistry – Theory and Practice*’ with Oxford University Press, in which they describe the 12 principles of environmentally friendly chemistry. Although these principles actually describe the well-known rules of sustainable chemistry, the book became a kind of ‘The Bible of Green Chemistry’.

Paul Anastas (left) received his PhD in Chemistry from Brandeis University and is currently Director of Yale University’s Center for Green Chemistry and Green Engineering. Previously, he held various positions, for example, as Science Advisor at the US Environmental Protection Agency. In addition, he is a devoted fan of his hometown baseball team, the Boston Red Sox.

John Warner (right) received his PhD in chemistry from Princeton and later worked in industry and as a professor in Boston. Since 2020, he has been working with *Zymergen Corporation* to develop new technologies inspired by nature. His motto is: ‘Chemistry is the solution, not the problem!’

Applied Homogeneous Catalysis: A Tool for Sustainable Chemistry, Second Edition. Arno Behr, Thomas Seidensticker, and Dieter Vogt.

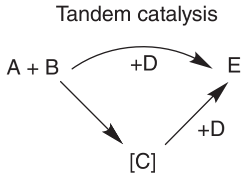
Here Are the 12 Principles:

1. **Prevention**: *It is better to prevent waste than to treat or clean up waste after it has been created*

Let's look together at the classic synthesis of an active pharmaceutical ingredient (API), **ibuprofen**. Since 1969, it has been a widely known drug against rheumatism, headache, inflammation and fever. In the United States, for example, it is known under the trade name Motrin; in the United Kingdom under Brufen and in Germany under Dolormin or Togal. The originally developed synthesis starts from isobutylbenzene and comprises six steps (see Figure 0.1, left side): in a Friedel–Crafts acylation, isobutylbenzene reacts with acetic anhydride to give the ketone (**1**), followed by a reaction with chloroacetic acid ethyl ester to give the epoxide (**2**). Next, hydrolysis and decarboxylation lead to the aldehyde (**3**), which is condensed with hydroxylamine to the oxime (**4**), which in turn is dehydrated to the nitrile (**5**). Finally, this nitrile is hydrolysed to the free carboxylic acid (**6**). Brønsted or Lewis acids are used in three of these steps, which inevitably leads to salts, which must be disposed of or further processed.

An alternative synthetic pathway (Figure 0.1, right side) also starts from isobutylbenzene but involves only three reaction steps: in the first step, isobutylbenzene is acylated using a heterogenised and recyclable HF catalyst. The ketone (**1**) thus formed is hydrogenated with Raney nickel to the alcohol (**7**), which is then carbonylated with carbon monoxide under palladium catalysis to ibuprofen **6**. The catalytic steps of this synthetic pathway, hydrogenation (Chapter 29) and carbonylation (Chapter 23), will be discussed in more detail later in this book. Ibuprofen is synthesised without any significant salt waste in only three (instead of six) steps. Moreover, all the starting materials used (except for the catalyst) are present in the final product. As we will learn from the second principle, such a synthesis is called *atom economic*. This catalytic pathway, the '**Hoechst-Celanese route**,' was awarded the 'Greener Synthetic Pathways Award for Green Chemistry' in 1997.

For the interested reader, we briefly give a second example of how any waste can be avoided by homogeneous transition metal catalysis: **tandem catalysis**, which is discussed in detail in Chapter 34. The basic idea of tandem catalysis is to replace classic multistep reactions ($A + B \rightarrow C$; $C + D \rightarrow E$), by a single process step, in which a series of catalytic reactions is carried out simultaneously in the same reactor ($A + B \rightarrow [C] + \rightarrow E$). In this case, isolation and purification of the intermediate (C) are avoided, which otherwise generates additional waste in the process (Eq. 0.1). Only a single work-up of the reaction mixture is thus required.

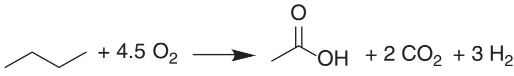


(0.1)

2. **Atom Economy**: *Synthetic methods should be designed to maximise the incorporation of all materials used in the process into the final product*

In order to produce chemicals economically, the substrates have to be selectively converted into the desired products ('**atom efficiency**'). At the same time, the energy consumption should be kept low; therefore, the reaction should be carried out under mild conditions ('**energy efficiency**', see Principle 6). In addition to atom efficiency, the concept of '**atom economy**' is widely used: in a chemical reaction with 100% atom economy, the mass of atoms in reactants equals the mass of atoms in the products. Many homogeneously catalysed reactions are 100% atom economical. We give you an exciting example:

Acetic acid can be produced by *oxidation of alkanes*, for example, of butane. The simplified equation for this reaction is (Eq. 0.2):



(0.2)

The equation is simplified because numerous by-products are formed in parallel (e.g., formic acid, acetone, and butanone), which means that more potential waste is produced in addition to the unwanted co-product carbon dioxide.

Homogeneous catalysis enables a much better solution: in the iridium-catalysed *carbonylation of methanol* with carbon monoxide to acetic acid (Chapter 23), the so-called *Cativa* process, all carbon, oxygen and hydrogen atoms of the starting compounds are found in the final product acetic acid (Eq. 0.3). This reaction is 100% atom efficient.

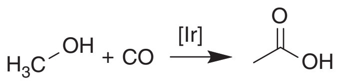


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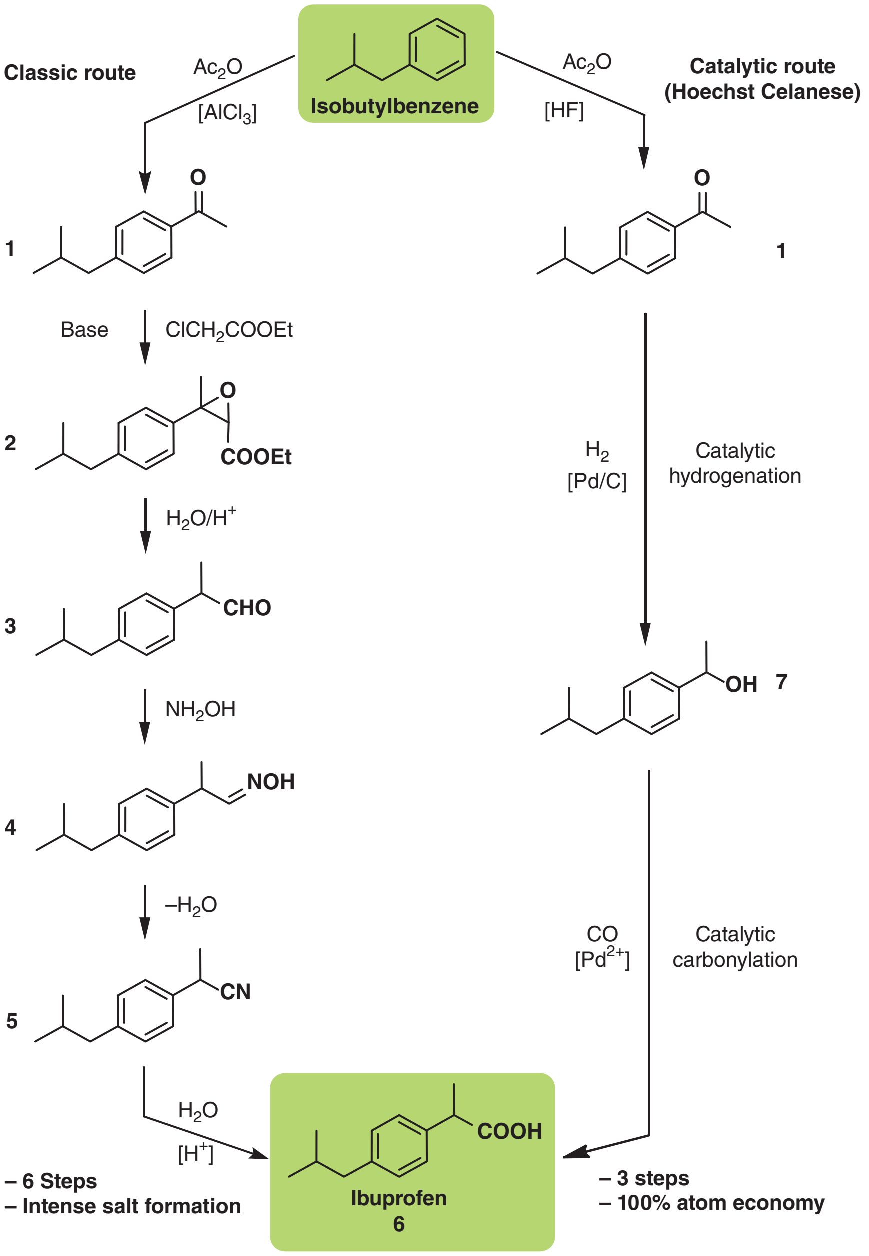
Figure 0.1 Comparison of classic and catalytic routes to ibuprofen.



3. **Less Hazardous Chemical Syntheses**: *Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment*

Polyurethanes are important plastics made from diisocyanates and diols (Figure 0.2). They are not only mainly processed into foams but also used as resins, lacquers, fibres and adhesives. However, the **synthesis of isocyanates** only proceeds with toxic substances, so currently, attempts are made to develop an alternative new catalytic route.

The classic route to isocyanates proceeds in three steps: in the first step, toxic carbon monoxide is reacted with toxic and corrosive chlorine to form toxic phosgene (Eq. 0.4).

$$CO + Cl_2 \longrightarrow COCl_2 \qquad (0.4)$$

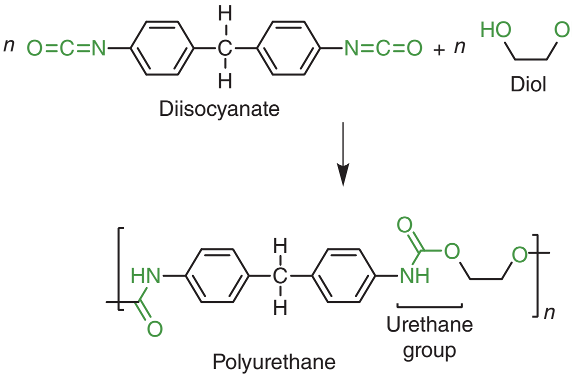
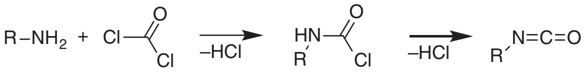


Figure 0.2 Reaction of diisocyanates with diols to polyurethanes (example).

In the second step, an amino compound is produced by hydrogenation of a nitro compound (Eq. 0.5)

$$R{-}NO_2 + 3\,H_2 \longrightarrow R{-}NH_2 + 2\,H_2O \qquad (0.5)$$

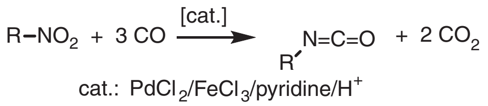
In the last step, the amine is reacted with the toxic phosgene to release two molecules of toxic hydrogen chloride as a co-product (Eq. 0.6)



(0.6)

Currently, chemical research is working on alternative catalytic routes to isocyanates in fewer steps and *without the toxic phosgene*. There are two approaches to this in the following:

- The nitro compound is directly reductively carbonylated with carbon monoxide, releasing non-toxic carbon dioxide. Homogeneous palladium/iron catalysts can be used, and the highly toxic phosgene is avoided (Eq. 0.7).



$$R{-}NO_2 + 3\,CO \xrightarrow{[cat.]} R{-}N{=}C{=}O + 2\,CO_2 \qquad \text{cat.: } PdCl_2/FeCl_3/\text{pyridine}/H^+ \qquad (0.7)$$

- An alternative phosgene-free pathway again directly starts from the nitro compound. With carbon monoxide and an alcohol, a carbamate alkyl ester is formed as an intermediate. This reaction can be carried out with homogeneous palladium-phenanthroline catalysts. In a second step, the alcohol used is rereleased by pyrolysis to form the isocyanate (Eq. 0.8).

$$R{-}NO_2 + R'{-}OH + 3\,CO \xrightarrow{[Pd]} R{-}\overset{H}{N}{-}COOR' + 2\,CO_2 \xrightarrow{\Delta} R{-}N{=}C{=}O + R'{-}OH \qquad (0.8)$$

Both catalytic alternatives are by far less toxic than the classic route.

4. **Designing Safer Chemicals**: *Chemical products should be designed to effect their desired function while minimising their toxicity*

Many organic compounds have a stereogenic centre and therefore occur as a mixture, a racemate. Often, however, only one of the two enantiomers has the desired effect; the other either is ineffective or even has a damaging property. In such a case, producing and using only the desired enantiomer make economic and ecological sense because using the racemate would be a waste of resources.

An important example is **metolachlor**, an herbicide developed in the 1970s by the Swiss company *Ciba-Geigy* and now widely used in agriculture. It is produced by a three-step synthesis:

1. By reacting 6-ethyl-2-toluidine with methoxyacetone, an imine is formed as an intermediate product.
2. The imine is hydrogenated to the secondary amine.
3. Finally, the secondary amine reacts with chloroacetic acid chloride to form metolachlor.

In the original synthesis by *Ciba-Geigy*, a racemic mixture of four isomers was formed (see Figure 0.3).

Metolachlor occurs in two enantiomeric forms, that is, as (*R*)- or (*S*)-metolachlor. Since the bulky substituents on the nitrogen and on the aromatic ring sterically hinder each other, both enantiomers, in turn, occur as two atropisomers so that in total four isomers exist: The two atropisomers of (*S*)-metolachlor (α*R*,1′*S*)- and (α*S*,1′*S*) as well as the two atropisomers of (*R*)-metolachlor (α*R*,1′*R*)- and (α*S*,1′).

In the early 1980s, it was found that only the two *S* isomers have a biological effect, but not the two *R* isomers. However, this means that when one tonne of the racemic mixture is used as an herbicide, 500 kg of a completely worthless substance is released into the environment. This is a contradiction to the fourth principle.

Implementing enantioselective homogeneous transition metal catalysis resulted in a good solution for this problem (Chapter 9): for reaction step 2 of the synthesis, that is, the hydrogenation of the imine to the amine, a homogeneous iridium catalyst with the ligand xyliphos was developed. This catalyst system allows the production of metolachlor with about 90% of the (*S*)-isomer (Figure 0.4).

Since 1996, (*S*)-metolachlor has been produced in a plant with a capacity of >10 000 tonnes per year. In the

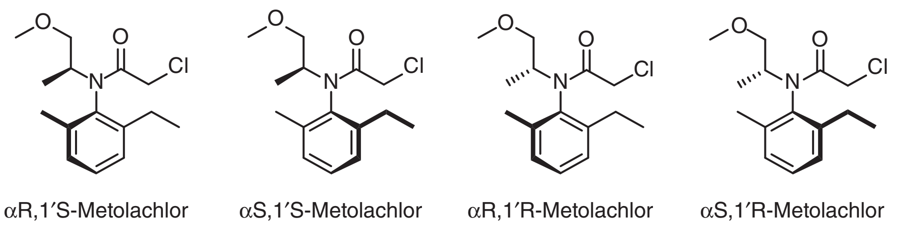


Figure 0.3 The four stereoisomers of metolachlor.

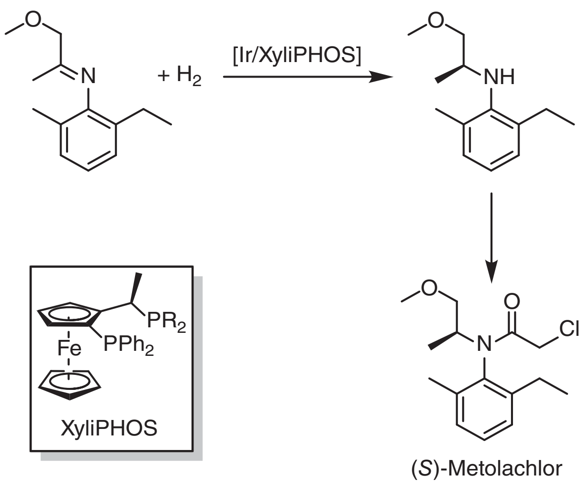
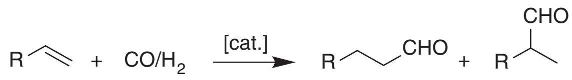


Figure 0.4 The enantioselective hydrogenation in the synthesis of (*S*)-metolachlor.

United States, (*S*)-metolachlor is the most frequently used herbicide, and it is also preferred in the states of the European Community. The racemic mixture of metolachlor, on the other hand, is no longer contained in any authorised plant protection products in Germany, Austria and Switzerland.

5. **Safer Solvents and Auxiliaries**: *The use of auxiliary substances (e.g., solvents and separation agents) should be made unnecessary wherever possible and innocuous when used*

A major industrial reaction is the catalytic **hydroformylation of propene** with synthesis gas to *n*-butanal (Chapter 22), which is used to produce numerous downstream products, for example, plasticisers (Eq. 0.9; $R = CH_3$).



$$R\text{-}CH{=}CH_2 + CO/H_2 \xrightarrow{[cat.]} R\text{-}CH_2CH_2\text{-}CHO + R\text{-}CH(CHO)\text{-}CH_3 \tag{0.9}$$

The hydroformylation of propene leads to a mixture of *n*- and iso-butanal. When homogeneous rhodium-triphenylphosphine catalysts are used, the reaction can be selectively directed to the desired *n*-butanal. However, there is a problem: for economic and ecologic reasons, it is indispensable to separate almost 100% of the extremely expensive precious metal catalyst from the product and to return it into the process completely. Rhodium salts must not be allowed to enter the environment!

One way to carry out hydroformylation on an industrial scale is the '**low-pressure oxo (LPO)**' process of the *Union Carbide Corporation* (today: *DowDuPont)*. After the reaction, the low-boiling butanals are distilled off from the product mixture, and the catalyst is returned to the reactor in a high-boiling thick oil which is used as a solvent. This oil consists of high-molecular-weight condensation products of the aldehydes.

But there is also another way: in 1975, *Emile Kuntz* of *Rhône-Poulenc Industries* (today: *Sanofi-Aventis*) found an alternative solution for the catalyst recycle: triple sulphonation of the triphenylphosphine ligand followed by neutralisation with sodium hydroxide solution produces sodium triphenylphosphine trisulphonate (Na-TPPTS), which shows excellent water solubility. What are the advantages of water?

- Water is a natural resource that is sufficiently available in many industrialised countries.
- It is therefore relatively cheap.
- It is non-toxic and non-flammable.
- Its high heat capacity, high polarity and reasonable solubility of many reaction gases are also often advantageous in chemistry.

But water has another important property: it is immiscible with many organic compounds and thus readily forms two liquid phases. With this property, the problem of rhodium catalyst recycling can easily be solved. After the reaction, a two-phase mixture is formed: an aqueous rhodium catalyst phase and an organic, water-insoluble product phase, which can be separated easily in a simple decanter. The *Ruhrchemie Company* (today: *OQ*) took up this process idea in 1984 and built a large-scale plant with a capacity of 100 000 t a^{-1}, which has since been expanded several times to a total capacity of 500 000 t a^{-1}. Since less than 1 ppb of rhodium is lost during this '**Ruhrchemie/Rhône-Poulenc process**', the procedure is economic as well as ecologic.

However, not all organic reactions can be carried out in water. But there are several other solvent classes in which an environmentally friendly performance of homogeneous catalytic reactions is feasible, for example, in ionic liquids or supercritical liquids (e.g., CO_2). We will learn more about those in Chapter 8.

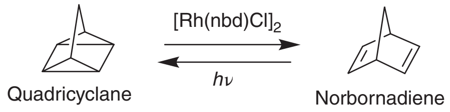
6. *Design for* **Energy Efficiency**: *Energy requirements of chemical processes should be recognised for their environmental and economic impacts and should be minimised. If possible, synthetic methods should be conducted at ambient temperature and pressure*

Many thermal (cracking, steam cracking, pyrolysis, etc.) or heterogeneous catalytic reactions (hydrocracking, reforming, etc.) only take place at high temperatures (400–900 °C), which require significant energy input. In contrast, many homogeneous catalytic reactions already take place at **low temperatures** between 20 and approximately 150 °C. Due to the limited stability of many homogeneous transition metal catalysts, reaction temperatures above 150 °C are rarely used. Important examples of transition metal catalysis are the following:

- Hydroformylation of 1-octene with Rh/biphephos catalysts: 70–90 °C (Chapter 22).
- Cooligomerisation of butadiene with ethene with $RhCl_3$ catalysis: 70 °C (Chapter 24).
- Photocatalytic reactions occur even at room temperature and normal pressure, for example, the cobalt-catalysed cooligomerisation of alkynes and nitriles in the solvent water, yielding pyridines: 20 °C (Chapters 24 and 37).

In addition, there are process engineering options for saving energy. We will discuss these methods in more detail in Chapter 22 on the example of a flow scheme for a hydroformylation process. By clever **heat recirculation** (integration), a lot of energy is saved, thus protecting the environment.

The topic 'energy' also includes another important question for the future: How is it possible to **store energy** – which can be obtained, for example, through solar cells – for a certain period until it is needed? One possibility is shown in Equation (0.10): on sunny days, norbornadiene (nbd) can be photochemically converted into the energy-rich, strained molecule quadricyclane (Chapter 33). If one wants to release this chemically stored energy, the reverse reaction can be catalysed by the homogeneous rhodium catalyst $[Rh(nbd)Cl]_2$. However, side reactions still occur in this reaction, so it is not yet commercially applicable.



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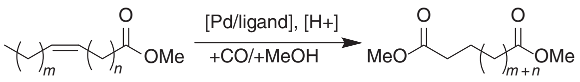
7. **Use of Renewable Feedstocks**: *A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable*

There are already many renewable raw materials (Chapter 44) that can be converted into important valued products using homogeneous catalysis, for example:

- *Fats and oils*, that is, esters of glycerol with unsaturated or saturated fatty acids.
- *Terpenes* or isoprenoids, that is, mostly unsaturated, cyclic or non-cyclic hydrocarbons.
- *Carbohydrates*, for example, sugars, starch or cellulose.

In particular, the unsaturated natural substances, that is, certain fatty acids or their derivatives as well as many terpenes, can be easily converted by homogeneous transition metal catalysis. The reason is that the C=C double bonds of the unsaturated substances can be well-coordinated to transition metal complexes.

An example of a reaction with a fatty substance (Eq 0.11) is the rhodium-catalysed isomerising methoxycarbonylation of **oleic acid methyl ester** to form a long-chain α,ω-diester in a so-called 'tandem reaction' (Chapter 34). This diester can be used to synthesise new types of polyesters that offer a significant advantage for plastic recycling: they can be specifically depolymerised (Chapter 43).



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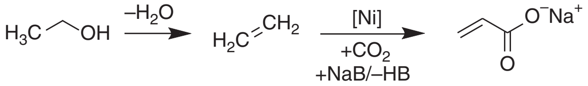
Not only renewable raw materials from nature are of interest for sustainable chemistry but also raw materials that are continuously formed, such as **carbon dioxide** (Chapter 41), which unfortunately is very difficult to activate. Yet, there are already some encouraging catalytic examples, for example, the homogeneously catalysed reaction of ethene with carbon dioxide to acrylates (Eq. 0.12, B = base). This reaction is particularly interesting because ethene can also be obtained by dehydration of bio-ethanol.



(0.12)

8. **Reduce Derivatives**: *Unnecessary derivatisation (use of blocking groups, protection/deprotection, temporary modification of physical/chemical processes) should be minimised or avoided if possible, because such steps require additional reagents and can generate waste*

In organic chemistry, the so-called *protecting groups* are often used in case bifunctional (or multifunctional) starting materials shall be converted selectively at only one position (Figure 0.5). Many classic organic transformations lead to undesired products in an *unselective functionalisation* (A). Protecting groups are thus used for the **protection** (B) of a certain functional group of the starting material before carrying out the actually intended chemical transformation (e.g., *functionalisation*). After the desired reaction, **deprotection** restores the initially protected functional group. Obviously, this strategy has certain disadvantages since two additional steps are required in addition to the desired transformation. At least, the protective groups end up as waste material (commonly even more material, such as solvents, auxiliaries, etc.).

With homogeneous catalysts, **chemoselective functionalisation** is achievable, and thus, unnecessary derivatisation can be avoided (**C**).

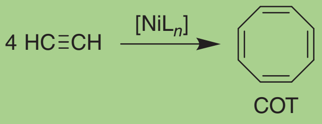
Homogeneous catalysis has already shortened numerous synthesis routes considerably and has thus made them much more sustainable. A very striking historic example is given in the Excursion 'The Quick Way to Cyclooctatetraene (COT)'.

EXCURSION: The Quick Way to Cyclooctatetraene (COT)

Homogeneous transition metal catalysis can contribute significantly to direct and short synthesis routes. Here is an illustrative example:

At the beginning of the 20th century, COT was a very interesting molecule because people wondered whether this molecule would show aromatic character or not. This prompted *Richard Willstätter* (right, Nobel Prize in Chemistry in 1915) to work out its first organic synthesis. The starting material was pseudopelletierine, available from natural sources in only small quantities. In eight synthetic steps – using many detours and protecting groups – Willstätter finally obtained some mg of COT. Unfortunately, his synthesis route was not only laborious but also produced a lot of waste.

In the 1940s, *Walter Reppe* (left) at BASF found an alternative, homogeneous catalytic way to COT: using a nickel catalyst under relatively mild reaction conditions (60 °C, 1,5 MPa), he succeeded in the selective synthesis of COT by tetramerisation of ethyne. This synthesis without significant by-products could also be carried out on an industrial scale, thus producing many kg of COT in a short time (Eq. 0.13).



(0.13)

Comparing these two synthesis routes clearly shows the superiority of the catalytic alternative over the classic synthesis processes.

9. **Catalysis**: *Catalytic reagents (as selective as possible) are superior to stoichiometric reagents*

As early as 1894, the American chemist *Francis Clifford Phillips* discovered that ethene can coordinate to palladium chlorine complexes and that acetaldehyde is set free by adding water to these complexes (Eq. 0.14). However, this reaction proceeds exclusively **stoichiometrically**, that is, only one mole of acetaldehyde is produced per mole of

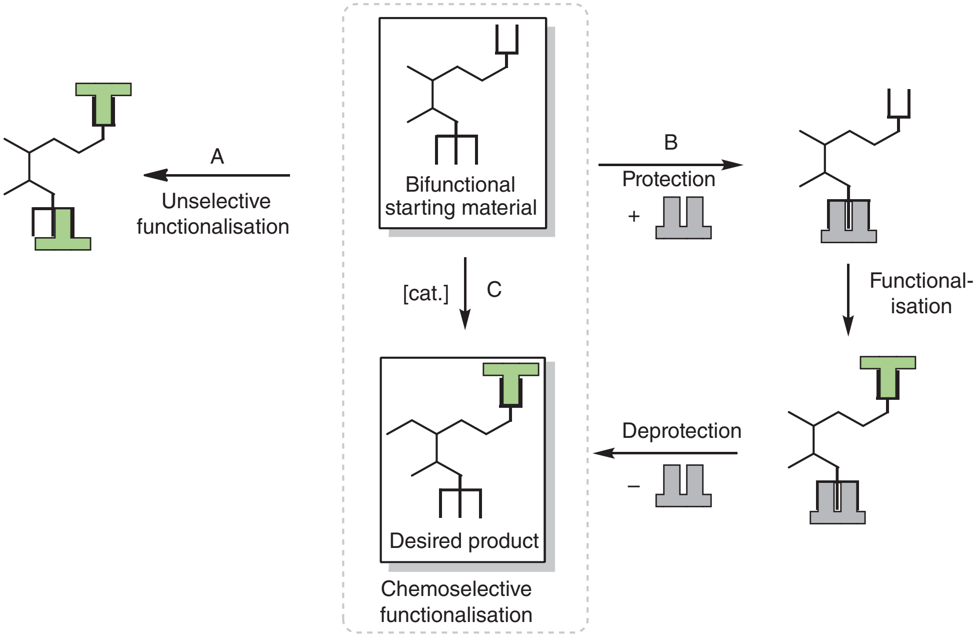


Figure 0.5 Homogeneously catalysed chemoselective functionalisation of a bifunctional starting molecule.

palladium. After the reaction, metallic palladium Pd(0) precipitates from the mixture and is no longer active in catalysis.

This example from large-scale chemistry clearly demonstrates the economic and ecologic advantages of catalysis over stoichiometric reaction sequences.

$$H_2C{=}CH_2 + PdCl_2 + H_2O \longrightarrow H_3C{-}CHO + Pd(0) + 2\,HCl \qquad (0.14)$$

Therefore, this stoichiometric reaction could not be used for the industrial synthesis of acetaldehyde. It was only a further development by the '*Consortium of Electrochemical Industry*, (later '*Wacker-Chemie*') in Munich/Germany that succeeded in converting the stoichiometric reaction into a **catalytic synthesis** of acetaldehyde (Chapter 30):

- Pd(0) was oxidised back into Pd(II) by Cu(II) chloride (Eq. 0.15).
- and Cu(I) chloride formed in the process was converted back into Cu(II) chloride by reaction with atmospheric oxygen in acidic solution (Eq. 0.16).

In a chemical plant in which all these processes run in parallel, it was thus possible to produce acetaldehyde on a large scale (Eq. 0.17). Today, this is known as the '**Wacker-Hoechst process**'.

$$Pd(0) + 2\,CuCl_2 \longrightarrow PdCl_2 + 2\,CuCl \qquad (0.15)$$

$$2\,CuCl + 2\,HCl + 0.5\,O_2 \longrightarrow 2\,CuCl_2 + H_2O \qquad (0.16)$$

$$H_2C{=}CH_2 + 0.5\,O_2 \longrightarrow H_3C{-}CHO \qquad (0.17)$$

10. Design for Degradation: *Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment*

Numerous mass plastics in modern times (polyethylene, polypropylene, polystyrene, PVC, etc.) only degrade very slowly. The result is a dramatic accumulation of plastic waste in the environment, especially in the oceans. Therefore, the world needs easy access to degradable plastics, preferably based on renewable raw materials (see Principle 7).

Homogeneous transition metal catalysis also provides a solution to this issue: in the palladium/acid-catalysed isomerising methoxycarbonylation of oleic acid methyl ester (Chapter 44), a linear C19 diester, the dimethyl ester of 1,19-nonadecanedioic acid, is formed under mild reaction conditions (T = 80 °C and 3 MPa). This reaction was already presented in Eq. (0.11).

Hydrogenation of this diester gives the corresponding diol, 1,19-nonadecanediol. Polycondensation of the diester with this diol produces the **new polyester-19,19**. This consists – comparable to polyolefins – of long alkyl

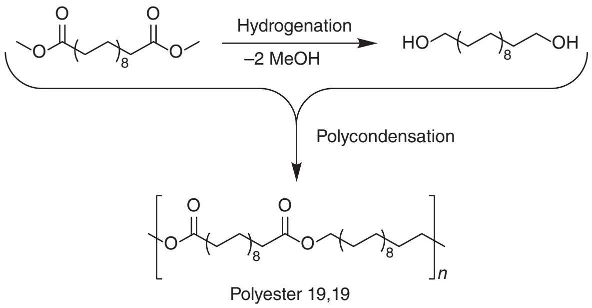


Figure 0.6 Polycondensation yielding the polyester-19,19.

chains, which, unlike polyolefins, are interrupted at regular intervals by an ester group (Figure 0.6). While biological degradation of the alkyl chain is extremely slow, the cleavage of the ester groups can be easily used for the targeted depolymerisation of the polyester. This leads to a plastic that differs only slightly from polyethylene in its application properties but that can be specifically split into its monomers, which can then be reused.

11. Real-Time Analysis *for Pollution Prevention: Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances*

Suppose there are malfunctions during operation of a chemical plant. In that case, the reaction conditions are not optimal, product yield and selectivity can decrease and the amount of undesired by-products can increase. In many cases, it takes a lot of time before a subsequent product analysis indicates that something has gone wrong.

For this reason, Green Principle No. 11 calls for monitoring what is happening in the reactor during the production process, that is, online. This is often not possible with heterogeneously catalysed reactions because the efficiency and activity of the solid catalyst are not easy to analyse in the running reactor. Homogeneous catalysis, however, is different: here, we are exclusively dealing with fluid phases in which the catalyst is dissolved. Thus, in principle, it is much easier to investigate the various material flows, while the plant is in operation.

Homogeneous catalysis has the additional advantage that its course can be investigated by analysing the fluid phases using various **spectroscopic methods** under actual process conditions. More detailed information on the use of UV/VIS, IR, MS or NMR spectroscopy can be found in Chapter 12. Using the proper spectroscopic methods, you can promptly intervene in the reaction process and avoid waste.

12. Inherently Safer Chemistry *for Accident Prevention: Substances and the form of a substance used in a chemical process should be chosen to minimise the potential for chemical accidents, including releases, explosions and fires*

Even in homogeneous catalysis, classes of substances are used that can be hazardous: alkenes and aromatics, for example, are flammable, and ethyne is explosive. Hydrocyanic acid used in hydrocyanations is very toxic; the same applies to carbon monoxide used in hydroformylations or carbonylations. To achieve a particular target product, one must therefore look for the least hazardous way possible. The advantage of homogeneous catalysis is that it offers numerous variants for producing the desired molecule. So you can choose the most harmless path for your product.

In chemical plants, a hazard can arise from processes that run at high reaction pressure. Here, too, homogeneous catalysis offers great advantages: Almost all homogeneous catalytic processes run at low pressures and temperatures (see Principle 6). Two examples of the possibilities to control the process with the help of homogeneous transition metal catalysis are given here.

Example 1: Variants of Hydroformylation

- Hydroformylation with cobalt catalysts requires high pressures of up to 30 MPa and temperatures of up to 180 °C. From an engineering point of view, these reaction conditions are challenging to handle; complex measures must be taken to ensure plant safety.
- Hydroformylation with rhodium catalysts, however, is inherently safer: in the so-called low-pressure Oxo process (Chapter 22), pressures of up to a maximum of 1,8 MPa and temperatures of up to 95 °C are applied.

Example 2: Variants of Polyethylene Syntheses

- The classic polyethylene, low-density polyethylene (LDPE), is produced by radical polymerisation at high pressures of up to 300 MPa and high temperatures of up to 300 °C (Chapter 26).
- The high-density polyethylene (HDPE) produced by homogeneous catalysis uses Ziegler–Natta catalysts based on the transition metals titanium or zirconium. This polymerisation can even be carried out in simple glass apparatus under more or less ambient conditions.

Both examples clearly show that the application of homogeneous catalysis brings several advantages at the same time:

- Low pressures require less energy input (see Principle 6) and thus lower operating costs.
- The apparatus can be constructed more simply; this reduces investment costs.
- Low-pressure processes can be handled much better; this significantly increases safety.

Take-Home Messages

Applied Homogeneous Catalysis (AHC) and the 12 Principles of Green Chemistry (PGC) – established by Anastas and Warner – are closely interlinked:

1. AHC helps to **prevent waste** (which is better than cleaning up the waste after it has been created).
2. AHC is often **atom economic,** that is, all materials used in the process are incorporated in the final product.
3. AHC can enable **less hazardous syntheses.**
4. AHC enables the synthesis of **safe chemicals** and the targeted production of enantiomerically pure active substances.
5. AHC uses **few auxiliary substances** and can also run in non-hazardous solvents, for example, in water.
6. AHC can be conducted at low temperatures and is therefore very **energy efficient.**
7. AHC uses a great number of **renewable feedstocks** as well as cheap raw materials, which are hardly used so far (such as carbon dioxide or alkanes).
8. AHC does not use protecting group chemistry and **avoids unnecessary derivatisation**.
9. AHC proceeds **catalytically**, not stoichiometrically.
10. AHC enables the synthesis of readily **degradable products**, such as decomposable polymers.
11. AHC occurs in fluid phases. Hence, easy spectroscopic **real-time online analysis** is possible, which allows process control before forming hazardous substances.
12. AHC provides various synthesis options, allowing the selection of an **inherently safe** reaction. Because of low pressures, the potential for chemical accidents is minimised.

Exercise Questions

0.1 When were the 12 principles of green chemistry first formulated and by whom?

0.2 What is the disadvantage of many classic organic syntheses? How can these drawbacks often be circumvented?

0.3 What is tandem catalysis?

0.4 Compare the two acetic acid syntheses starting on the one hand from butane and on the other from methanol. Which method is more advantageous? Discuss the reasons!

0.5 Why is it economically and ecologically more reasonable to employ only the (*S*)-enantiomer of metolachlor as a herbicide? In which step of the metolachlor synthesis can the enantioselectivity be catalytically controlled?

0.6 What are the advantages of water as a solvent? Give an example where it is usefully employed in homogeneous catalysis. Describe this process in some more detail!

0.7 In which temperature range do most homogeneous catalyses take place? Compare this with heterogeneous catalysis!

0.8 Name some classes of renewable raw materials that can be used in homogeneous catalysis. Why?

0.9 Discuss the steps in the Wacker–Hoechst process for synthesising acetaldehyde from ethene. Which stoichiometric step was already known for a long time, and how was it possible to develop a large-scale catalytic acetaldehyde synthesis