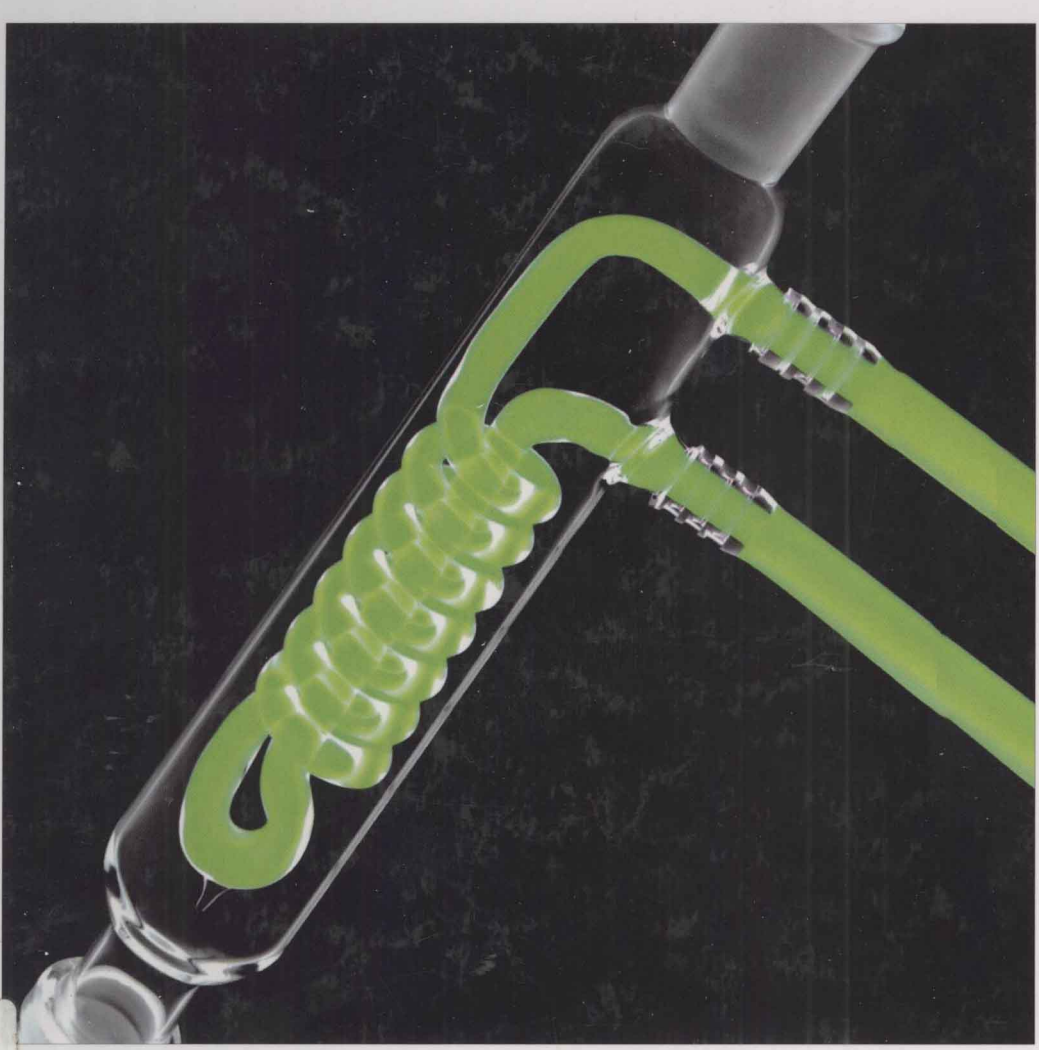
RSC Green Chemistry Series

Edited by Roberto Ballini

Eco-Friendly Synthesis of Fine Chemicals



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Eco-Friendly Synthesis of Fine Chemicals

RSC Green Chemistry Book Series

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Green Chemistry is one of the most important and rapidly growing concepts in modern chemistry. Through national awards and funding programmes, national and international courses, networks and conferences, and a dedicated journal, Green Chemistry is now widely recognised as being important in all of the chemical sciences and technologies, and in industry as well as in education and research. The RSC Green Chemistry book series is a timely and unique venture aimed at providing high level research books at the cutting edge of Green Chemistry.

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Preface

The late 20th and early 21st centuries have seen a phenomenal growth of the global economy and a continuous improvement of the standard of living in industrialized countries. Sustainable development has consequently become an ideal goal in recent years. In the early 1990s the concept of "green chemistry" was launched in the USA as a new paradigm, and since 1993 it has been promoted by the National Science Foundation (NSF) and the Environmental Protection Agency (EPA).

The success of the pharmaceutical industry is, in large part, due to the towering achievement of organic chemistry – a mature science that emerged as a distinct discipline well over 150 years ago. This history is both a blessing and a curse. Many of our most reliable strategies for assembling target molecules employ reactions that are 50 to 100 years old and that are often named in honour of their discoverers. During these early years, the chronic toxicological properties of chemicals were often completely unknown and many, unwittingly, became indispensable tools of the trade.

Early pioneers in green chemistry included Trost (who developed the atom economy principle) and Sheldon (who developed the E-Factor). These measures were introduced to encourage the use of more sustainable chemistry and to provide some benchmarking data to encourage scientists to aspire to more benign synthesis.

The present book is intended to provide an important overview of various processes and procedures devoted to the eco-sustainable syntheses of fine chemicals.

The contributions of catalyses as well as of photochemistry, high pressure and microwave irradiation are thoroughly examined. Nevertheless, the key role of solvents has also been considered. In addition, a chapter has been dedicated to the application of a simple reaction to the synthesis of complex molecules.

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Thus, I believe that this book represents an important contribution to eco-sustainable chemistry and should be of interest for both young and senior researchers involved in this field.

I would like to thank all the distinguished scientists and their co-authors for their rewarding, timely and well-referenced contributions. Grateful acknowledgements are also offered to the RCS editorial staff.

Roberto Ballini

Contents

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CHAPTER 1

Catalysis in Non-conventional Reaction Media

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1.1 Introduction

1.1.1 The Context

The concept of green or sustainable chemistry was born around 1990 thanks to a small group of chemists who, ahead of the times, clearly saw that the need for more environmentally acceptable processes in chemical industry had to become a top priority in R&D activities. In 1990, the Pollution Prevention Act was the spark that ignited awareness of the need for innovative chemical technologies that accomplished pollution prevention in a scientifically sound manner. In 1991 Paul Anastas coined the term and defined the field of "Green Chemistry". In the same year the first "Green Chemistry" program, the "Alternative Synthetic Pathways" research program, was launched. From a theoretical viewpoint, concepts like "atom economy" proposed by Trost[1] and the "E factor" introduced by Sheldon,[2] gave impetus to the creation of a new way of thinking about chemistry and to the development of a green metric able to provide quantitative support to compare the "greenness" of alternative products and processes.[3] From a functional point of view, several endeavours aimed to promote green chemistry activities got under way. In 1995 the Presidential Green Chemistry Challenge Award, proposed by Anastas to the White House,

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was approved. Since then, every year the Presidential Green Chemistry Challenge Awards highlight successes in research, development and industrial implementation of technologies that prevent pollution at source while contributing to the competitiveness of the innovators.[4] In 1997Anastas co-founded the Green Chemistry Institute, which worked closely with industries and universities on environmental issues, and expanded its international network to consortia in 27 nations. Other initiatives in the green chemistry field rapidly spread throughout the world, *e.g.* in Italy, Canada, UK, Australia and Japan. The *Green Chemistry* journal was launched in 1999 by the Royal Society of Chemistry, and it was accompanied in 2008 by *ChemSusChem* published by Wiley-VCH. Less than two decades after its beginnings, green chemistry issues are providing an enormous number of challenges and are the central concern of those who practice chemistry in industry, education and research. In Europe the SusChem Technology Platform[5] and in the US the Technology Vision 2020 of the Chemical Industry[6] are turning their chemistry research agenda into new goals, jobs and business through innovation directed towards sustainability and environmental stewardship.

1.1.2 The 12 Principles of Green Chemistry

In 1998, Anastas and Warner teamed up to write the best selling and most cited book in the field of Green Chemistry, *Green Chemistry: Theory and Practice*, which explicated the 12 principles of Green Chemistry.[7] The principles, intended as guidelines for practical chemistry, provided a road map for chemists both of academia and industry to promote pollution prevention through environmentally conscious design of chemical products and processes. The 12 principles are:

1. It is better to prevent waste than to treat or clean up waste after it is formed.
2. Synthetic methods should be designed to maximise the incorporation of all materials used in the process into the final product.
3. Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4. Chemical products should be designed to preserve efficacy of function while reducing toxicity.
5. The use of auxiliary substances, *e.g.* solvents, separation agents, should be made unnecessary wherever possible and innocuous when used.
6. Energy requirements should be recognised for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperatures and pressure.
7. A raw material feedstock should be renewable rather than depleting, whenever technically and economically practical.
8. Unnecessary derivatization (blocking group, protection/deprotection, temporary modification of physical/chemical processes) should be avoided wherever possible.

9. Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
10. Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products.
11. Analytical methodologies need to be further developed to allow for real-time in-process monitoring and control prior to the formation of hazardous substances.
12. Substances and the form of a substance used in a chemical process should be chosen so as to minimize the potential for chemical accidents, including releases, explosions and fires.

The 12 guidelines essentially fall into four groups: efficient use of energy, hazard reduction, waste minimization and the use of renewable resources. Although each heading clearly indicates a proficient solution toward sustainability, the more guidelines or green technologies a master plan meets the greater is its intrinsic value. An example could be offered by a process involving the addition reaction (100% atom economy) of two starting materials derived from renewable feedstocks (rule no. 7) taking place in a perfect stereoselective way (waste minimization) at room temperature (energy efficient) in water (a prototypical green solvent) under the action of a low amount of a recyclable catalyst (rule no. 9).

The present chapter presents a few snapshots from the recent literature on the integration of the theme of catalysis with the topic of green solvents. The examples discussed witness how molecular design makes its own contribution to the breakthrough approach to innovative problem-solving, providing sustainable solutions to the chemical industry. Part of these cutting-edge results, suitably integrated by the state of the art process engineering, have the chance to evolve into low cost, robust, efficient and easy to operate sustainable technologies.

1.1.3 Catalysis

Adopting a K. B. Sharpless statement,[8] catalysis is the engine that drives the development of chemistry. Everybody can easily recognize that top achievements in applied chemistry are focused on industrial applications of catalysis, rational design, serendipitous discovery or combinatorial identification of new ligands, catalysts, new solid supports (organic, inorganic, amorphous or mesoporous silica phases, metal organic frameworks, *etc*).

An ideal catalyst should approach 100% selectivity while reaching high levels of productivity. Selectivity refers first of all to (i) chemoselectivity, which means the catalyst must be able to select preferred reactants from complex mixtures, (ii) regioselectivity, which means selection of preferred sites of the reacting substrate and (iii) stereoselectivity, which means preferred formation of a single stereoisomer.

At the beginning of this decade Gladysz defined what should be an ideal catalyst.[9] He proposed the following features: the rapid production (turnover

frequency, TOF) of an infinite amount of product (turnover number, TON), preferentially at room temperature and under atmospheric pressure, which implies no deactivation and poisoning under the reaction conditions. This "ideal" catalyst does not require an inert atmosphere to operate, is insensitive to reactant impurities and affords product yields of 100%. Gladysz clearly noted that these unattainable limits can never be realized but help to focus attention on what we should strive for. The "infinite TON" limit, for example, would make catalyst recovery efforts unnecessary, a quest that is unrealistic. The design of recoverable catalysts has become, indeed, a central field of catalysis research.[10] In fact, catalyst decomposition associated with leaching of the active species and decomposition itself have to be taken into account. In practice, design efforts for effective recoverable catalysts must address the removal of these catalyst impurities from solution.

Catalysis is generally hypothesis driven: the chemist uses experience to envisage candidate catalysts, which are then tested, investigated and optimized, including the use of high throughput and library technologies. There is an increased need for new paradigms of how catalysis research and rational design has to be done. But there is an even more urgent need: that of addressing in R&D activities both classic economy-linked problems (cost, yield, selectivity, time, resistance to poisoning and deactivation, minimization of product contamination by catalyst residues),[11] and sustainability concerns. They focus on minimizing waste production, energy consumption and use of toxic and ecotoxic chemicals. An impressive example from the golden era of petrochemistry is the SOHIO ammoxidation of propane with ammonia, which replaced the IG FARBEN process based on acetylene and hydrogen cyanide.[12] Particularly in the case of costly and highly specialized catalysts the optimization of catalyst recovery and reuse is a fundamental demand, too, for economic and environmental reasons. Moreover, from a practical viewpoint, an optimum catalytic process should be wide in scope, easy to perform and insensitive to oxygen and water, which could become the solvent of choice. This is what characterizes, for example, the Cu-catalysed azide-alkyne cycloaddition, a reliable and practical reaction, which proved very useful, for example, for accelerating the drug discovery process.[13] The reaction, work-up and purification should use benign solvents, avoiding chromatography or time-consuming distillation or crystallization unit operations.

Catalysis is traditionally divided into heterogeneous and homogeneous catalysis. In classic solid/liquid or solid/gas heterogeneous catalysis, the catalyst provides a surface on which the reactants are temporarily adsorbed. Bonds in the substrate are weakened sufficiently by adsorption or chemisorption for new bonds to be created. Syngas conversion, hydrogenation and oxidation processes are by far the most important industrial applications. Catalyst synthesis technology is applied to the manufacture of high surface area metal species, including nanoparticles, and metal oxides, usually supported in another metal oxide such as alumina, silica and zeolites. The chemical industry often favours heterogeneous catalysis for the easy recovery and good stability of the catalyst, the practical downstream separation processes involved, and the easier