METHODS AND REAGENTS FOR GREEN CHEMISTRY

An Introduction

Edited by

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To my family, who support me every day and make my work easier.
P.T.

The three editors would like to thank Dr. Lara Clemenza, who acted as co-editor of the collection of lectures from the Summer School on Green Chemistry from which this volume is derived.
We are sure that the publication of this book would not have been possible without her precious and much appreciated contribution.

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FOREWORD

The Summer School on Green Chemistry was founded in 1998, in the wake of the growing interest in green chemistry among the chemical community. For the first time it was being recognized by chemists that there could be—and had to be—mutual understanding and collaboration between (A) the players involved in chemical production, and (B) representatives from all the social categories concerned with safeguarding the environment and human health. It appeared clear that the existing gap could be bridged best by young chemists able to redesign chemical production so it was safe, environmentally friendly, socially acceptable, and profitable. In short: green. The Summer School on Green Chemistry was devised by the Italian Interuniversity Consortium "Chemistry for the Environment" (INCA, www.unive.it/inca) as a high-level training school for young chemists to meet this goal.

The school became reality in 1998 with a grant from the European Commission's IV Framework Programme (FP) Training and Mobility of Researchers (TMR) program, and continued within the V FP as part of the improving program, as well as through funding from INCA, the Italian Ministry for Foreign Affairs, NATO, and INTAS. At the time the present volume goes to press (2007) the school has continued as a NATO Advanced Study Institute.

The innovative approach to the design of clean chemical reactions and processes has proved very successful, as shown by the increase in the number of applicants to the school year after year. From 1998 to 2005 nearly 500 chemistry researchers, between the ages of 25 and 35, from both academic and industrial backgrounds, have attended the school.

The success of the school can be judged by the large amount of positive feedback we as organizers have received over time. Many of the participants, after

returning home, either continued research in green chemistry with a broader understanding of the issues, or started applying the green chemistry principles to their research.

Many students have benefited from meeting some of the teachers at the school, by visiting them in their laboratories, and by establishing collaborations among themselves and with the research groups represented at the school. Numerous friendships also have been established. All these links make up a wide web of people with a common interest in green chemistry, a network that has spread over through most of Europe, and beyond.

The school was established in Venice, Italy. For most of the young participants it was the first time they visited the city, which provided the perfect setting for informal and pleasant contact among all participants.

After the first three sessions of the Summer School on Green Chemistry it became apparent that a textbook was needed, since the lecture notes handed out to the participants represented the only comprehensive printed material existing on the subject. Thanks to the editorial effort by the teachers, with the support of INCA, the first edition of the volume, "*GREEN CHEMISTRY—A Collection of Lectures from the Summer Schools on Green Chemistry*," was produced in 2001. This book was based on the lecture notes, plus some explanatory text. The volume was made available on the Internet and handed out to the students attending the school that year. It was updated and enlarged twice, in 2002 and 2004, by incorporating new and revised chapters.

The Summer School on Green Chemistry has proved to be a stepping stone in the careers of many young researchers who wished to combine state-of-the-art research in chemistry with environmental awareness. It has also been central to a spontaneous network of scientists who practice green chemistry, and who found common ground for research, collaborations, and the teaching of green chemistry.

The present volume is the consolidation of eight years of work, during which new developments and a deeper understanding of green chemistry have developed. Hopefully, it will provide food-for-thought for the reader.

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PREFACE

In 2005, Yves Chauvin (Institut Français du Pétrole), Robert Grubbs (California Institute of Technology), and Richard Schrock (Massachusetts Institute of Technology) were the recipients of the Nobel Prize in Chemistry, "For the development of the metathesis method in organic synthesis." Motivation explicitly states: "This represents a great step forward for 'green chemistry,' reducing potentially hazardous waste through smarter production. Metathesis is an example of how important basic science has been applied for the benefit of man, society and the environment."

To my knowledge, this was the first time the Royal Swedish Academy of Science, with the preceding statement, extended the existence of a tight connection between Science and Ethics. For the sake of correctness, however, the 2001 Nobel laureates in chemistry (Knowles, Noyori, and Sharpless) came from the area of green chemistry. Their awards were for the new chiral syntheses in green manufacture and the discovery of improved "clean" ways to produce pharmaceuticals, an industry that is still one of the highest polluters.

Actually, chemists have always had the benefits of chemistry for society in mind. This was clearly illustrated by Giacomo Ciamician (Trieste, 1857; Bologna, 1922) in the following futuristic sentence published almost one hundred years ago (*Science*, ***36***, 385 (1912)):

> On arid lands there will spring up industrial colonies without smoke and without smokestacks; forests of glass tubes will extend over the plains and glass buildings will rise everywhere; inside of these will take place the photochemical processes that hitherto have been the guarded secret of the plants, but that will have been mastered by human industry which will know how to make them bear even more abundant fruit than nature, for nature is not in a hurry but mankind is.

Because of this assertion, Ciamician can be considered the father of green chemistry, sharing with today's conception of this discipline the same disapproval of pollution, the same care for mankind, and the same intent to use natural resources. And the dream can today come true, thanks to modern technologies and to wider societal awareness and recognition.

Green chemistry is currently being acknowledged at scientist conventions, such as the recent European Science Open Forum (ESOF 2006), held in Munich, on July 15–18, 2006. ESOF 2006 was the second pan-European General Science Meeting. Its purpose was to promote interaction and dialogue between science and the general public. Green chemistry achieved the same recognition level as other more popular scientific disciplines, such as astronomy, natural disaster prevention, biodiversity, genomics, evolution, and medical science. It was acknowledged to be one of the main options for safeguarding the environmental, as evidenced by the basic enquiry: "Is green chemistry a real option?" This question clearly shows what the media and society want to know from chemists. And a positive answer to this question was given by the session entitled: Green Chemistry: A Tool for Socio-Economic Development and Environmental Protection.

At the same time, a few scientific networks have been established to foster the development of research through high-level capacity building in science, the improvement of regulatory frameworks and public policy design, the enhancement of public outreach and education, and other interventions. Two such organization have recently been created: the International Green Network (IGN) and the Mediterranean Green Network (MEGREC). A brief description of these organizations may clarify the purposes and benefits of this discipline.

The IGN mission includes research, coordination, and sponsorship of scientific collaborations, targeted training for a new generation of scientists, and the support of sustainable development. IGN consists of eight research centers, one in each of the G8 countries, and it will accelerate movement toward a sustainable-energy and materials economy, by bringing together scientists, engineers, research institutions, firms, analysts, and government regulators. IGN will provide know-how, coordination, and sponsorship for scientific collaborations, proper training for the new generation of chemists, and support for sustainable use of chemistry in developing nations. In addition, it will assist industrial production in G8 nations, foster the development of novel competitive technologies, and address such issues as climate change and energy, as well as other environmental concerns, from a chemical standpoint.

MEGREC constitutes a platform for the development of research and training in green chemistry in the countries of the Mediterranean basin, with focus on water management, the exploitation of local natural resources, the production and use of fertilizers, and monitoring and reducing the presence of toxic compounds in the food chain. With a clear focus on priorities for local areas, but with the extended know-how of all the partners.

Such recent developments show how science can also positively relate to ethics, thanks to green chemistry. Green chemistry represents a strategic challenge for the present and the future of the chemical industry, its development being

mostly linked to the interrelated needs of and benefits for environment, economy, and society that must be initially approached through new ideas in fundamental research.

The scientific content of green chemistry can be easily taken for the aims of IGN, whose main research topics are: energy, green manufacture, life-cycle analysis, pollution prevention, food security, and chemical resources management.

In order to produce the expected and desired results, programs and strategies must be devised for the development and application of chemistry, and must involve explicit support from national governments to networked organizations that are involved in research, educational/academic, and industrial systems. This interaction is fundamental to the production of long-term and durable benefits.

By considering the opinions of the civil society and tackling the questions concerning chemical production it raises, the governments can achieve a relevant positive result: the merging of the consensus of the academic world and industry with that of youth and public opinion, which are increasingly focusing their attention on the environment and human health protection.

This book covers three leading topics of green chemistry: green reagents, alternative reaction conditions, and green catalysis. It is the culmination of more than 10 years of research in this field. I therefore thank the many authors who contributed to this volume, who year after year were constantly present as expert lecturers at the yearly Summer School on Green Chemistry (Venice), promoted and organized by the Consorzio Interuniversitario "Chimica per l'Ambiente" (Chemistry for the Environment), INCA, and enthusiastically exchanged their expertise with colleagues and students throughout the world.

Finally, if you wonder why the word "Introduction" is included in the title of this book, it is because research in this field is far from completed, and chemists have a long way to go before they meet and satisfy the needs of the environment, economy, and society.

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PART 1

GREEN REAGENTS

1

THE FOUR-COMPONENT REACTION AND OTHER MULTICOMPONENT REACTIONS OF THE ISOCYANIDES

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INTRODUCTION

The usual syntheses of products from three or more educts require several preparative processes, and its intermediate or final product must be isolated and purified after each reaction. As the number of steps increase, the amounts of solvents and the preparative work grows, while the yields of products decrease and more and more solvents and by-products must be removed. In such reactions, scarcely all optimal aspects of green chemistry can be accomplished simultaneously.

Practically irreversible multicomponent reactions (MCRs), like the Ugi 4-component reaction (U-4CR), can usually fulfill all essential aspects of green chemistry. Their products can be formed directly, requiring minimal work by just mixing three to nine educts. Often minimal amounts of solvents are needed, and almost quantitative yields of pure products are frequently formed.

The chemistry of the isocyanide U-4CR was introduced in the late 1950s, but this reaction was relatively little used for more than three decades, only around 1995 almost suddenly it was recovered by the chemical industry.[1]

In the last few years the variability of educts and products of the U-4CR has essentially increased, so that by now the majority of new products have been prepared. The U-4CR allows the preparation of more different types of products than

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any other reaction. If such a product with desirable properties—a lead structure—is found, large amounts of related compounds can be prepared easily by the U-4CR and similar reactions.

It is barely possible to still find novel reactions of one or two components, whereas the chemistry of the MCRs is not yet exhausted. Still, many new combination of up to nine different types of MCR educts can form new types of products that can totally differ from the already known chemistry.[1]

1.1 THE CLASSICAL MCRs

Chemical reactions are in principle equilibria between one or two educts and products. In practice, the preferred preparative reactions proceed irreversibly. Syntheses of products from three or more educts are usually sequences of preparative steps, where after each reaction step its intermediate or final product must be isolated and purified while the yield decreases. Exceptions can be the reactions of three components on solid surfaces and also some MCRs with α-additions of intermediate cations and anions onto the isocyanides.[1,2]

Besides the usual chemistry, an increasing number of chemical compounds can be prepared by MCRs just by mixing more than two educts.[3–5] Such processes do not proceed simultaneously, but they correspond to collections of subreactions, whose final steps form the products. Any product that can be prepared by an MCR whose last step is practically irreversible requires considerably less work and is obtained in a much higher yield than by any conventional multistep synthesis.

Three basic types of MCRs are now known.[5] The MCRs of type I are collections of equilibrating subreactions. In type II the educts and intermediate products equilibrate, but their final products are irreversibly formed. The MCRs of type III correspond to sequences of practically irreversible reactions that proceed from the educts to the product.[6]

In 1960 Hellmann and Opitz[7] introduced their α-*Aminoalkylierung* book, wherein they mentioned that the majority of the "name reactions" by MCRs belong together since they have in common their essential features. This collection of 3CRs can be considered as Hellmann–Opitz 3-component reactions, (HO-3CRs). They are either α-aminoalkylations of nucleophiles of MCR type I, or they form intermediate products that react with further bifunctional educts into heterocycles by 4CRs of type II. Their last step is always a ring closure that proceeds irreversibly.

This MCR chemistry began in 1850 when the Strecker reaction S-3CR[8] of ammonia, aldehydes, and hydrogen cyanide was introduced. Since 1912 the Mannich reaction M-3CR[9] of secondary amines, formaldehyde, and β-protonated ketones is used.

The MCRs of type II forming heterocycles begin with α-aminoalkylations of nucleophilic compounds, and subsequently these products react further with bifunctional educts whose last step is always an irreversible ring formation. Such

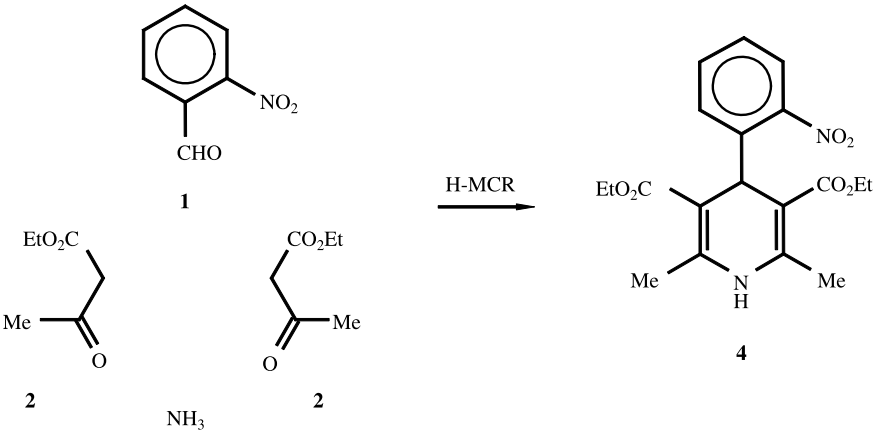
reactions were introduced in 1882 by Hantzsch[10] and by Radziszewski.[11] Shortly after this Biginelli[12] also entered a similar type of forming heterocycle by MCRs. In the 1920s Bucherer and Bergs[13] began to produce hydantoin derivatives by BB-4CRs. This reaction begins with an S-3CR whose product then reacts with CO_2 and forms irreversibly the hydantoin. The products of the S-3CR and of the BB-4CR can both be hydrolized into α-aminoacids, but the synthesis via the BB-4CR is used preferentially, since this leads to products of higher purity and with higher yields.

In the early Gatterman's preparative chemistry book,[14] the one-pot synthesis of dihydropyridine derivatives like those formed by the Hantzsch reaction was one of practical laboratory exercises.

Schildberg and Fleckenstein observed that calciumantagonists can advantageously influence the peripheric vessels and those of the heart.[15] With the 4-aryldihydropyridine-3,5-dicarboxylic esters **4** (Scheme 1.1) that have such effects, the first pharmaceutical products synthesized by Hantzsch reactions were independently introduced by the Bayer AG[16] and Smith Cline & French.[17]

As the last classical MCR in the 1950s, Asinger[18] introduced the 3CRs and 4CRs to form thiazole derivatives. It seems that these A-MCRs can belong to type I or to type II.

In preparative chemistry only a few MCRs of type III are known;[6] however, in living cells, the collections of the biochemical compounds are formed by MCRs of type III. In that case the formation of the individual products proceeds by subreactions that are accelerated by the enzymes present in the suitable areas within the living cells. The resulting collections of products can be considered to be their libraries.



Scheme 1.1 Hantzsch synthesis of 4-aryldihydropyridine-3,5-dicarboxylic esters.

1.2 THE FIRST CENTURY OF THE ISOCYANIDES

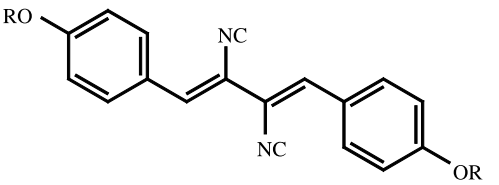
The chemistry of the isocyanides[3] began when, in 1859 Lieke[19] formed allyl isocyanide from allyl iodide and silver cyanide, and when, in 1866 Meyer[20] produced in the same way 1-isocyano-1-desoxy-glucose. In 1867, Gautier[21a] used this procedure to prepare alkylisocyanides, and Hofmann[22] introduced the formation of isocyanides from primary amines, chloroform, and potassium hydroxyde. Gautier[3,21b] also tried to prepare an isocyanide by dehydrating an amine formiate via its formylamine using phosphorus pentoxide, but this process produced no isocyanide. Gautier had not yet realized that acidic media destroyed the isocyanides.

However, for a whole century the chemistry of the isocyanides remained as a rather empty part of organic chemistry, since they were not yet easily available, and furthermore they had a very unpleasant smell. At that time, only 12 isocyanides had been prepared and only a few of their reactions had been investigated.[3]

In the 1890s, Nef[23] mentioned that the functional group —NC of the isocyanides contains a divalent carbon atom C^{II}, and therefore there is a large difference between their chemistry and that of the other chemical compounds that contain only tetravalent carbon atoms C^{IV}. Any synthesis of isocyanides corresponds to a conversion of C^{IV} into C^{II}, and all chemical reactions of isocyanides correspond to transitions of the carbon atoms C^{II} into C^{IV}.

In this period, the most important reactions of the isocyanides were the formations of tetrazole derivatives from isocyanides and hydrazoic acid, a process introduced in 1910 by Oliveri-Mandala and Alagna,[24] and then in 1921 Passerini introduced the reaction (P-3CR),[25] which was the first 3-component reaction of the isocyanides. In the 1940s Baker,[26] and later Dewar,[27] proposed mechanisms of the P-3CR. The important role of the intermediate hydrogen bond between the carboxylic acid and the carbonyl compound in suitable solvents was mentioned.[4]

In 1948, Rothe[4,28] discovered the first naturally occurring isocyanide in the *Penicillum notatum Westling* and in the *Penicillum chrysogenum*. This compound was soon used as the antibiotic *xanthocillin* **5a**. Later Hagedorn and Tönjes[29] prepared its *O*,*O*′-dimethylether of *xanthocillin* **5b** by dehydrating its N,N′-diformylamine with phenylsulfonylchloride in pyridine (Scheme 1.2). Since



5a: R = H
5b: R = Me

Scheme 1.2 Xanthocillin.

1973 an increasing number of naturally occurring isocyanides has been found in plants and living cells.[30]

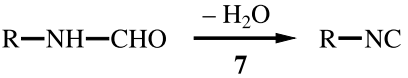
1.3 THE MODERN CHEMISTRY OF THE ISOCYANIDES

A new era of the isocyanide chemistry began in 1958 when the isocyanides became generally available by dehydrating the corresponding formylamines in the presence of suitable bases (Scheme 1.3).[4] A systematic search for the most suitable dehydrating reagent revealed early on that phosgene[31] is excellent for this purpose. Later, when phosgene transportation was not allowed anymore, it was locally produced from triphosgene.[32] Also diphosgene[33] and phosphorus oxychloride,[4] can be used, particularly in the presence of di-isopropylamine.[34] Baldwin et al.[35] prepared naturally occurring epoxy-isocyanides from the corresponding formylamines by dehydrating the latter with trifluoromethyl sulfonic acid anhydride in the presence of di-isopropylamine.

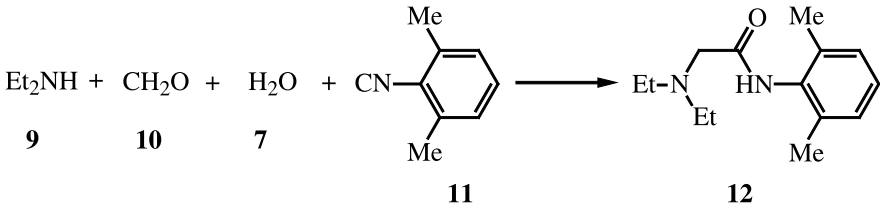
In the 1971 book *Isonitrile Chemistry*[3] 325 isocyanides were mentioned, and almost all of them had been prepared by dehydration of formylamines.

After some model reactions, Ugi et al.[3a–d] accomplished a new way of preparing Xylocaine® by one of the first U-4CRs. In 1944 Xylocaine **12**[36] (Scheme 1.4) was introduced by the A. B. Astra company in Sweden, and since then Xylocaine has been one of the most often used local anasthetics, particularly by dentists. In its early period, A. B. Astra patented 26 chemical methods of preparing **12**.

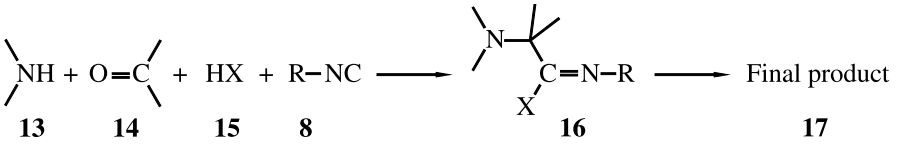
In January 1959, Ugi and co-workers decided to prepare **12** from diethylamine **9**, formaldehyde **10**, and 2,6-xylylisoxcyanide **11**. Initially they considered this as a variation of the Mannich reaction.[10] In their first experiment they noticed that this reaction is so exothermic that an immediate mixing of the educts can initiate an explosion,[3,37] and it was realized that this reaction was in reality a 4-component reaction in which water **7** also participates.



Scheme 1.3 General formation of isocyanides.



Scheme 1.4 Four-component reaction of Xylocaine®.



Scheme 1.5 The Ugi reaction.

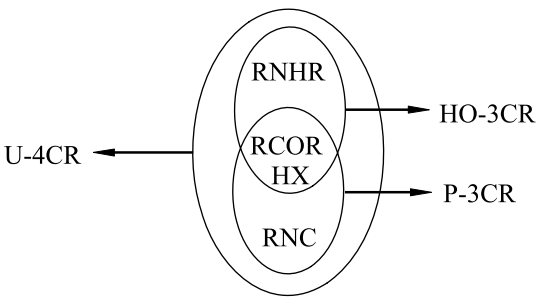
During the first month of this experiment, it was realized that this reaction is extremely variable. Thus, diverse amines (ammonia, primary and secondary amines, hydrazine derivatives, hydroxylamines) **13**, carbonyl compounds (aldehydes, ketones) **14**, acid components **15** or their anions (H_2O, $Na_2S_2O_3$, H_2Se, R_2NH, RHN-CN, HN_3, HNCO, HNCS, RCO_2H, RCOSH, $ROCO_2H$, etc.), and the isocyanides **8**[3,4,38] could form the α-adducts **16** that rearrange into their products **17** (Scheme 1.5).

Since 1962, this reaction has been called the Ugi reaction,[4a] or it is abbreviated as the U-CC,[38a] or as the U-4CR.[38b] The U-4CR can formally be considered to be a union,[39] 4CR = HO-3CR ∪ P-3CR **18** (Scheme 1.6), of the HO-3CR and the P-3CR that have in common the carbonyl compounds and acids, while the HO-3CR also needs an amine and the P-3CR an isocyanide.

In each type of chemical reaction, the skeleton of the product is characteristic, and only its substituents can be different, whereas in the U-4CR and related reactions of the isocyanides the skeleton of the products can also include different types of amines and acid components. This is illustrated by the eight skeletally different products in Scheme 1.7. Besides these compounds, many other types of compounds also can be prepared by the U-4CR.

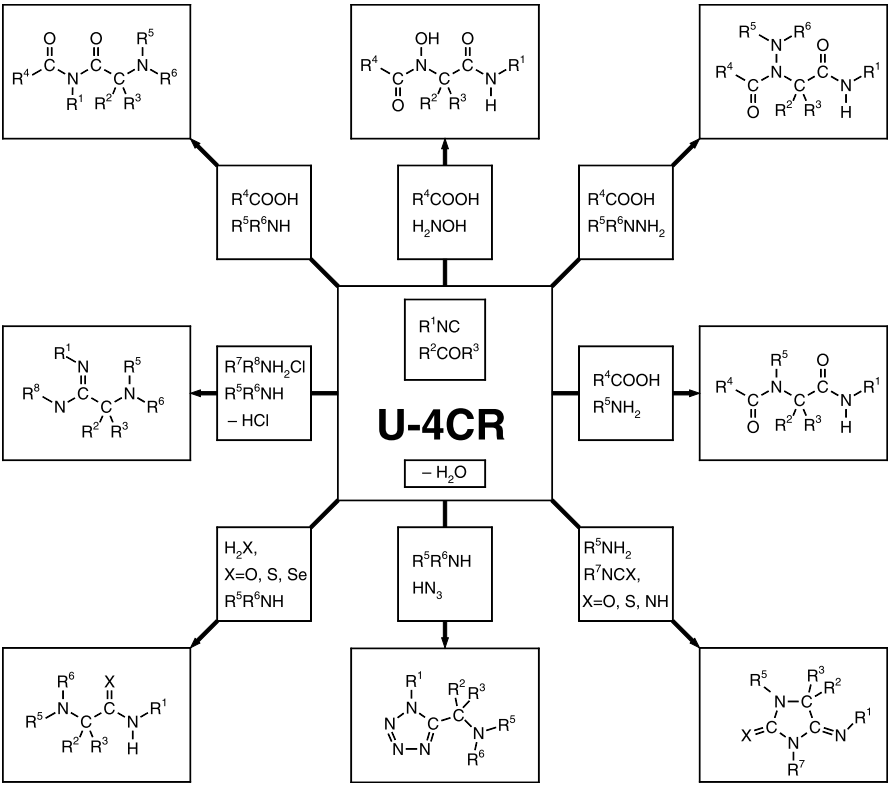
Ordinary chemical reactions have their "scopes and limitations" for various reasons. Many sterically crowded products cannot be formed by conventional syntheses, but they can still be prepared by the U-4CR. Thus, the product **22**[40] can be formed only by the U-4CR, (Scheme 1.8).

The U-4CR forms its products by less work and in higher yields than other syntheses. The U-4CR is nowadays one of the most often used chemical reaction



18

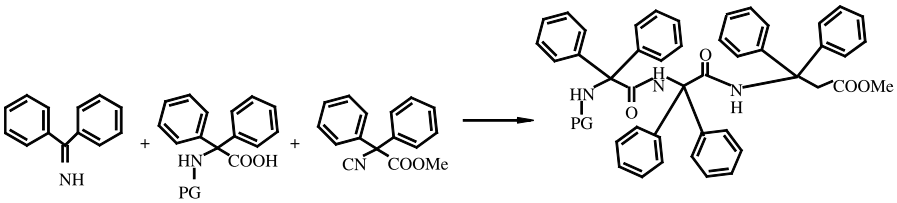
Scheme 1.6 The U-4CR as a union of the HO-3CR and the P-3CR.



Scheme 1.7 The wide variability of the U-4CR.

for the formation of chemical libraries. These libraries had already been proposed in 1961 (Ref. 3, p.149; Ref. 41), but only in the 1980s the chemical industry has recognized the advantages of the libraries.[5,42,43]

In ordinary reactions where two educts participate, 10 different components of each educt type can form 100 constitutionally different products. The U-4CR can form 10,000 different products when 10 different starting materials of each type of educt[44] are involved. In this way, libraries of an extremely high number



19 **20** **21** **22**

Scheme 1.8 Synthesis of a sterically extremely hindered product by the U-4CR.

of products can be formed via the U-4CR. Combined with other combinatorial methods, the search for new desirable products can thus be accomplished particularly well.

A product of the U-4CR is only formed in a good yield and purity if the optimal reaction conditions are used. The U-4CR proceeds faster and in a higher yield, when the amine component and the carbonyl compound are precondensed, and the acid component and the isocyanide are added later.[44] Very often methanol or trifluoroethanol are suitable solvents, but sometimes a variety of other solvents can be used as well. Furthermore, the sequence of the educts and their concentrations must be optimal and a suitable temperature of the reaction must be used. In many cases, the U-4CR can be improved by a catalyst.[1,45]

In a special case, the reaction mechanism of the U-4CR was investigated.[3,44,46] The aldehyde and chiral amine were precondensed into the Schiff-base isobutyraldehyde-(*S*)-α-phenylethylamine that was reacted with benzoic acid and *tert*-butylisocyanide in methanol at O°C. In one series of experiments, the dependence of the electrical conductivity of this Schiff-base and the carboxylic acid was determined, and in a second series of experiment, the relation between the educt concentrations and the ratio of diastereoisomeric products caused by competing different stereoselective U-4CRs was investigated. The ratio of the diastereomeric products was determined by their optical rotations.[44] The large collection of numerical values of these experimental data were evaluated by a mathematically based computer program. It was found that four pairs of stereoselective processes compete and, depending on the concentrations of the educts, one or the other diastereomeric product is preferentially formed. This knowledge made it generally possible to find the optimal conditions of the U-4CR by fewer experiments than usual.

Rather early it was recognized how much easier natural products and related compounds can be prepared by the U-4CR,[1,4] but the advantages of searching for new desirable pharmaceutical and plant-protecting compounds became evident only during the last few years, when industry began to produce the U-4CR products.[1,42]

For a whole decade a research group at Hofmann-LaRoche AG tried, without success, to find suitable thrombine inhibitors by the coventional methods. But only in 1995 Weber et al.[47] discovered two such desired products, **23a** and **23b** (Scheme 1.9), when they used libraries of 4-CR products for their systematically planned search, which also included mathematically oriented methods.

Recently, the Merck Research Laboratory demonstrated an important example.[48] Initially the HIV protease inhibitor Crixivan™ (MK 639) **29** (Scheme 1.10) could not be prepared very well by a complicated conventional multistep synthesis, but **29** became available when it was prepared by an easier synthesis, whose essential step was accomplished by a U-4CR.

Park et al.[49] used U-4CR libraries to prepare Ras-Raf protein-binding compounds like **30** that are active against HIV. The patented product **31** has been formed by Lockhoff[50] at the Bayer AG using a U-4CR of four different protected glucose derivatives that were later deprotected. The product **32** of