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MCR XVII. Three Types of MCRs and the Libraries – Their Chemistry of Natural Events and Preparative Chemistry[#]

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The one-pot Multicomponent Reactions (MCRs)[1] convert more than two different components into their products with at least two new chemical bonds, and the products contain all educts or at least some parts of them. Many chemical reactions have several, but not all, aspects of the MCRs. Three different basic types (I–III) and two subclasses (A and B) of MCRs can take place. Chemistry had started in the nature of our world roughly 4.6 billion years ago, including MCRs of the types I and II, forming libraries of many different products. A little later, the living cells came into existence, and their biochemical MCRs of all three types started. In their various local parts their biochemical products are selectively formed by their enzyme-assisted procedures, but many of their MCRs belong to type III.

The preparative chemistry of MCRs started in the middle of the last century, when the first equilibrating but isolateable 3CR products of type IB were formed. The pre-final reactions of type I form compounds, which react further and form their final products irreversibly by MCRs of type II. The type IIA products are usually heterocycles, whereas those of type IIB are generally products of isocyanides. The U-4CR of type IIB was introduced and this led to a

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[#] This paper is dedicated to the 70th birthday of Prof. George Olah.

new preparative MCR chemistry. Their educts and intermediate products equilibrate (type IA) and undergo irreversible $C^{II} \rightarrow C^{IV}$ α-additions of the isocyanides, followed by a variety of rearrangements into their final products (type IIB). In recent years, unions of higher numbers of components were introduced, forming even more diverse types of products. The MCR libraries were proposed in 1961, and since 1995 this chemistry has become an essential part of the chemical research in industrial search for new desirable products. This methodology requires much less work than all previous methods and proceeds many orders of magnitude faster.

INTRODUCTION

Many different chemical processes are one-pot reactions if they convert their educts directly into their products. However, the term 'one-pot MCR' is usually only meaningful if their products contain at least two new chemical bonds. Thus, the MCRs are just one part of the one-pot chemistry.

In principle, all chemical reactions are equilibrating exchanges between one or two educts and products. However, the preferred preparative reactions are practically irreversible procedures. If a chemical product is formed from many educts, its preparation is usually accomplished by a sequence of different chemical procedures,

The conventional multistep synthesis requires increasing amounts of work and decreasing final yields of the product, since these have to correspond to sequences of isolations and purifications of many intermediates and their final products. Nowadays, however, more and more collections of different educts are directly converted by one-pot MCRs, an increasing number in recent years, whereas the MCRs with irreversible final steps need almost no preparative work, and quantitative yields of pure products result. If no appropriate reactions are used, then some by-products are formed by competive reactions. Whenever a product can be formed by an MCR, this is advantageous in preparative chemistry.

The MCRs do not convert their collection of components simultaneously in a single step, but undergo many sub-reactions of two components, so that some of their sequences lead to products and by-products. These various steps of MCRs can equilibrate, including formations of their products, or the products can result irreversibly, and their previous steps can react reversibly or as sequences of practically irreversible sub-reactions.

This definition covers many totally different types of one-pot reactions, which have many but not all aspects in common with the MCRs. So, for in-

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Abbreviations: MCR: **M**ulti**C**omponent **R**eaction; 3, 4 ...: number of reacting components; capital letters: abbreviations of name reactions, for example the S-3CR = **S**trecker's **3 C**omponent **R**eaction; Me = Methyl; Et = Ethyl; Fc = Ferrocenyl; *i*Pr = Isopropyl; *t*Bu = *tert.*-Butyl; *c*Hex = Cyclohexyl; Ph = Phenyl.

stance, the direct synthesis of five moles of hydrogen cyanide into adenine by converting[2] is an example of a one-pot reaction, and the completely different ždomino' reaction of the multi-cycloaddtion that converts educts of many multiple bonds into polycyclic products of five- and sixmembered rings[3] can also be a one-pot reaction, and a large collection of the MCR components form a constitutional variety of products, so that each educt contains a different functional group.[4–10] The latter reactions are related to the MCRs, but they do not satisfy all aspects of the definiton.

THE EARLY MCR CHEMISTRY OF OUR WORLD, INCLUDING THE LIVING CELLS

The formation of organo-chemical products and their libraries began 4.6 billion of years ago. In the natural atmosphere many chemical compounds were formed and they participate still now not only with the conventional chemical reactions of two components but also with a variety of MCRs. Thus, not only a single product was formed but also collections of many different chemicals as their libraries. Then probably not only the usual chemical reactions of the participating components took place in nature, which is indicated by Miller's famous experiment, which produces educts that react to natural building blocks,[11] the amino-acids *via* the S-3CR.[12] Since sufficient concentrations of their educts were probably too low for most of such reactions, their formations can have taken place on mineral surfaces,[11a] but also the MCRs and their libraries participated.

Soon also living cells began to exist. These contain libraries of many different chemical products which are normally formed by MCRs of sequences of subreactions. All of their temporarily produced educts and their products are formed enzymatically so that their competing by-products forming reactions participate to a lesser extent. The living cells continously generate large collections of chemical compounds that correspond to libraries. Most of their enzymatically formed products are žpurified' by enzymatic removal of the simultaneously formed impurities.[13]

THE START AND GROWTH OF THE MCRS PREPARATIVE CHEMISTS

The first product of an MCR was introduced in 1838 by Laurent and Gerhardt,[14] who converted bitter almond oil and ammonia into a crystalline product **10** of an MCR of the twice reacting benzaldehyde **1** (R^1=H, R^2=Ph), ammonia **2a**, and hydrogen cyanide **3a** (Figure 1).[4]

Officially, the preparative chemistry of MCRs began 12 years later, when the S-3CR of **1**, **2a** and **3a** (Figure 2)[5,6,12] was introduced. The starting

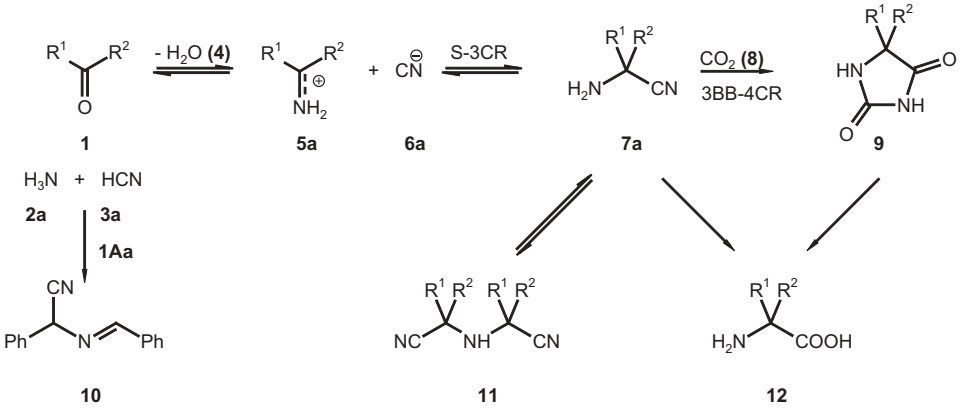


Figure 1

materials of the S-3CR equilibrated with the product **7a** and by-product **11** and in most cases a low yield of products resulted. In 1929, Bergs and Bucherer introduced their reaction, BB-4CR,[4,7,8i] by combining educts **1**, **2a** and **3a** of the S-3CR with CO_2 **8**, forming the hydantoin derivatives **9** in very high yields. This is due to the irreversible final formation of **9**, whose hydrolysis is nowadays the preferred method of preparing the α-aminoacids **12** (Figure 1; see also Figure 2). Since these are obtained *via* BB-4CR much better than by the S-3CR, the latter is not used any more.

The last irreversible step of converting product **7a** of the reversible S-3CR (MCR of type IB) into that of BB-4CR (MCR of type IIA) illustrates particularly well the difference between these two different types of MCRs.[8i]

The era of finding old or new α-aminoalkylating 3MCRs ended,[5,6] when Hellmann and Opitz published their book α-*Aminoalkylierung* in 1960.[4] They had realized that most of the then known MCRs were either 3MCRs of the α-aminoalkylations of nucleophiles, which form α-aminoalkyl compounds (**1–3** → **7**; Figure 2), or in some cases they proceeded further with by-functional reagents into heterocycles by 4MCRs, and some other heterocycles forming MCRs are closely related.[4] Many of these 'name reactions' are MCRs or similar to MCRs. This collection of reactions is now also referred to as the Hellmann-Opitz reaction, the HO-3CR.

The Early and Later Chemistry of Isocyanides

The first isocyanide was prepared in 1859,[8a] but they were not available for a whole century, since all the now known methods of preparing isocyanides did not exist. Therefore, and due to the intense bad smell of the isocyanides, their chemistry remained a rather neglected part of organic chemis-

try. One of the few exceptions was the intensely investigated Passerini reaction in the period between 1921 and 1932 (Figure 2; **1**+**3A**+**13** → **16**),[8b–10] the P-3MCRs, which was the first MCR of the isocyanides (MCR of type IIB). This chemistry was later extended to a few other acid components.[10]

The isocyanides are the only stable organic chemical compounds whose functional groups contain a divalent carbon atom C^{II}, and all of their chemical reactions correspond to exothermic irreversible transitions of C^{II} into C^{IV}. The preparative advantages of the isocyanide chemistry, and particularly their MCRs, were realized gradually, but it was only since the 1990s that they have become a widely used methodology, particularly in the chemical industry.[5,6,8]

In 1958, the isocyanides became available by dehydrating the *N*-formylamines[8a,15] and since then this chemistry has been increasingly active. One year later the four component reaction of the isocyanides was introduced,[16] and from 1962 on this is reffered to as the Ugi reaction,[10a] or the U-4CR.[7] The U-4CR and its unions with further reactions is nowadays a very active part of organic chemistry.[5]

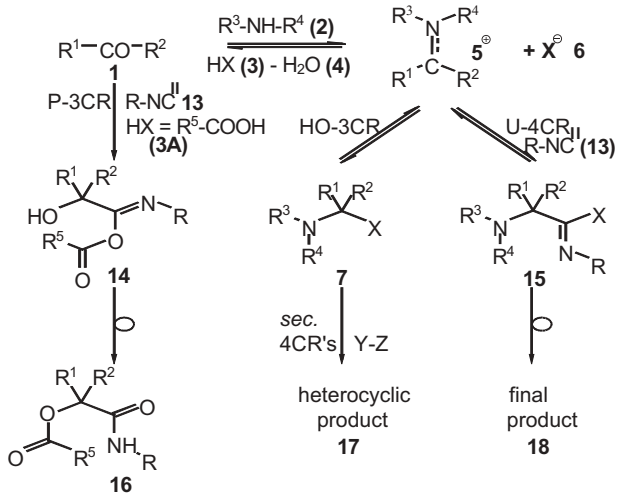


Figure 2

The first steps of the U-4CR correspond to equilibrating HO-3MCRs of **1–3**, **4–6** and **7** (3CR of type IA) (Figure 2). The intermediates **5** and **6** undergo irreversible α-additions onto isocyanides **13**, forming their α-adducts **15** that rearrange irreversibly into the final products **18**. Their great structural variety is due to the different mechanistic types of rearrangements, which are essentially determined by the types of acid components **3**, and

they depend also on the presence of primary (R^3=H, R^4=Alkyl/Aryl) or secondary amines **2**.[8d]

When the U-4CR was introduced, it was also realized that their yields of products are low if no well-selected reaction conditions are used and in this case a variety of by-products can be formed. In 1963, McFarland[17] found out that, besides the expected products, a great variety of by-products can be formed, whose structures were identified. Later on many further by-products were formed,[18] and it was found that certain rather slow reactions of the U-4CR can be autoxidized.[19] Therefore, if the carbonyl and amino components **1** and **2** of the U-4MCRs are precondensed and react under good conditions, then pure products can be formed very quickly in up to quantitative yields[5,6,8c,10,18] and no by-products are formed.

It was realized that the U-4MCRs of chiral primary amine components proceed stereoselectively,[8c] and their courses of reactions depend very much on their reaction conditions. Even the concentrations of their educts can strongly interfere with the course of U-4MCRs.[8g] It was therefore assumed that different reaction conditions of the U-4MCRs can lead to quite different types of reaction mechanisms. A model reaction of the U-4CR of a chiral amine was investigated.

P-3CR components have usually a very low stereoselectivity. However, there is an unusal example of a highly stereoselectively proceeding P-3CR: If P-3MCRs of the 1(*S*)-camphor-2-*cis*-methylene-isocyanide are carried out, usually high stereoselectivities take place,[20] whereas when this isocyanide is used, no chiral products are formed by the U-4MCRs.

As a stereoselective model reaction, the isobutyraldehyde-(*S*)-α-phenylethyleneimine was reacted with benzoic acid **3A** (R^5 = Ph) and *t*-butyl isocyanide **13** (R=*t*Bu) in methanol at 0 °C.[8c,22,23]

Two series of experiments were performed: in the first series of experiments, the equilibria of the starting materials A, B and C and the participating intermediates X_1–X_5 were determined by measuring their electrical conductivities of various concentrations of **15** and **3Aa**, and a second series of experiments was carried out, where many different concentrations of educts were converted into their diastereomeric products Y,[8f] whose ratios were then determined.[22]

The resulting experimental data were evaluated by solving their rather complicated mathematical problems using a computer-assisted product. Thus, its reaction mechanism could be determined as one of the first solutions of a complicated scientific problem, where a combination of chemistry, physical data, mathematics and computer methodology was used. It was also realized that such unions of different fields can very successfully lead to a completely different logical reasoning, understanding and planning in chemistry and its designing computer programs.[23]

Simple Types of MCRs

The knowledge of the book α-*Aminoalkylierung*[43] and the stereoselective reaction mechanism of the U-4CR made it clear which basic reversible and partly irreversible types of MCRs play an important role. This gives rise to the question of the existence of also MCRs, which are sequences of irreversible subreactions. The result of such questions is a new grammar and classification of MCRs:[5,24]

- Type IA: All starting materials, intermediate products and final products have mobile equilibria, so that the products are usually not isolable.
- Type IB: All starting materials, intermediates and products equilibrate, but the products are stable enough to be isolated.
- Type IIA: The pre-final products of type IB react with further multifunctional components and form irreversibly heterocyclic products, while the formal number of bonds does not change.
- Type IIB: The intermediate products of type I react with a further educt and form irreversibly pre-final or final products, so that the formal number of bonds increases.
- Type III: The educts of MCR form one-pot products by sequences of irreversible subreactions.

Most of the known MCRs belong to equilibria, so that their products are so unstable that they cannot be isolated (MCR of type IA). But they further react irreversibly, *e.g.* by α-additions onto further components such as isocyanides (MCR of type IIB; Figure 1 and Figure 2, **1**–**3** → **15** → **18**), or the equilibrating MCRs result in products that can be isolated (MCR of type IB), but they may also react as intermediate products and add further byfunctional reagents, forming irreversibly five- or sixmembered heterocyclic products.

The BB-4CR starts with a 3CR of type IB and forms its products by an irreversible final step of type Ia, whereas the U-4CR forms its products by a reaction of type IIB *via* a 3CR of type IA.

The MCRs of type III are much rarer and require special educts and sequences of subreactions. However, a few such MCRs can be carried out, like the recently described fivemembered cyclic P^{III}-reagent **19**,[25] which can undergo three or four steps of type III MCRs, forming products of type **23** and **25**.[25]

The chemical reactivity of these reagents is based on the difference in basicity of the groups attached to the phosphorus atom. Thus, they can be replaced successively in a one-pot reaction by different nucleophiles such as alcohols or phosphates leading to the P^{III}-triester **22**. Finally, they are oxidized by oxygen, sulfur or selenium to provide the P^{V}-product **23** (path a in Figure 2). Alternatively, biologically important phosphodiesters and their dinucleotides, phospholipids,[27] nucleopeptides and their analogs can be ob-

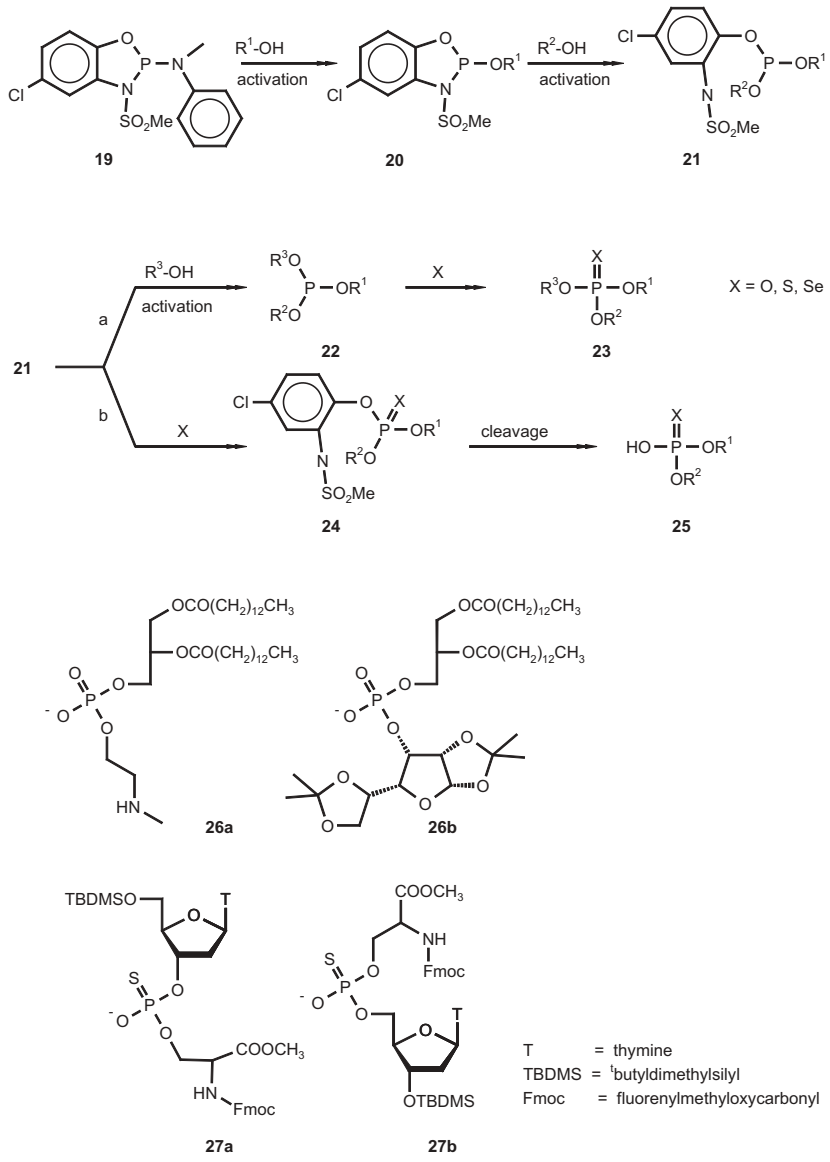


Figure 3

tained by a similar procedure (path b):[28] After two nucleophilic displacements, the oxidation step is carried out, followed by cleavage of the aryloxy group. Besides, nucleotide derivatives were recently also the first representatives of phospholipids like *e.g.* **26**[26a] and nucleopeptides like *e.g.* **27** (Ref. 26b). They have been synthesized according to this method.

The Variability of the Isocyanide Chemistry and the MCRs

It was realized in 1962 that it must be possible to prepare peptide derivatives by stereoselective U-4MCRs from aldehydes **1A** (R^1 = H), chiral

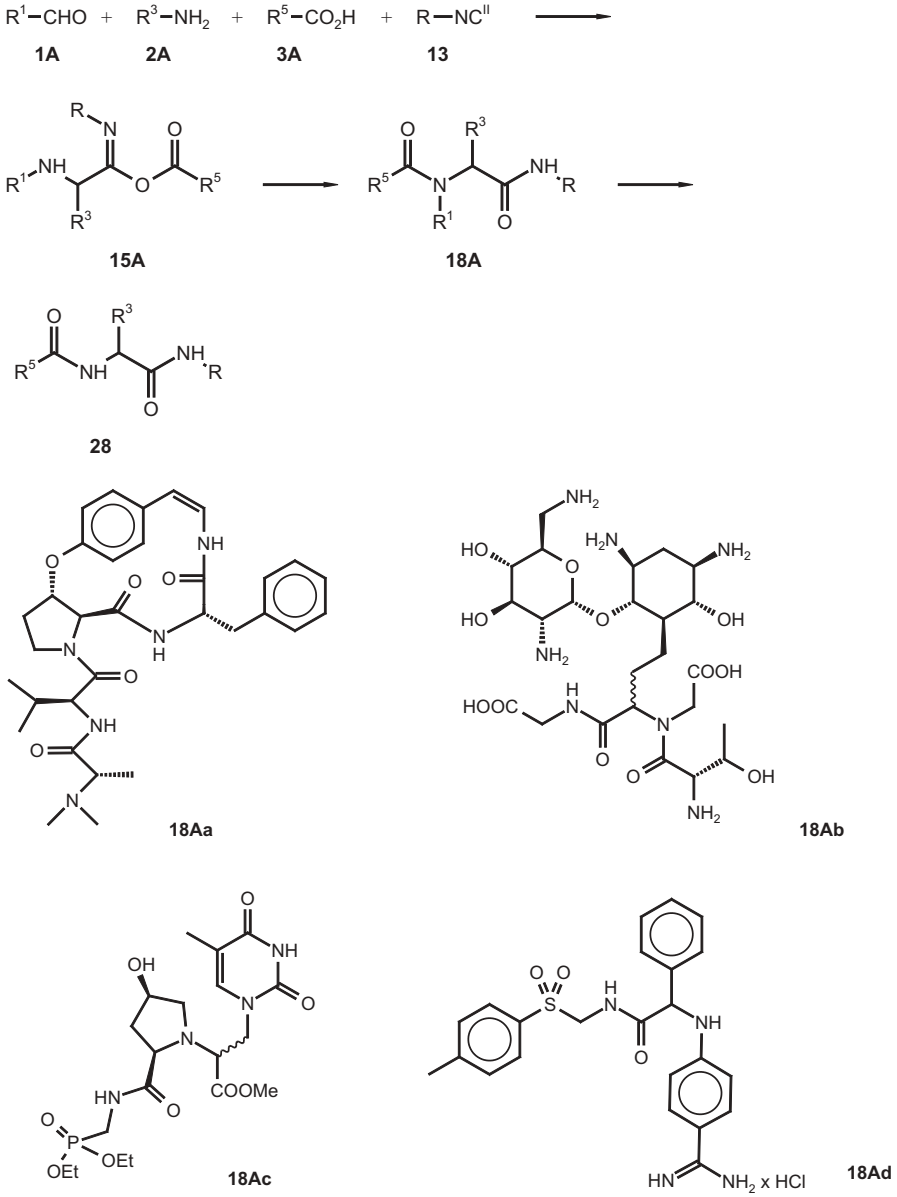


Figure 4

primary amines **2A** (R^3 = H), carboxylic acids **3A** and isocyanides **13**, which can be very widely used (Figure 5)[8f,18]. Since the advantage would be to produce peptide derivatives of three and more α-amino-acids, where new chiral R- or S-α-aminoacids could be formed, such syntheses of peptide derivatives do not only a high stereoselectivity of U-4MCRs by the asymmetric induction of chiral amines, but these products must also be cleavable according to **18A** → **28** (Figure 4). The syntheses of **18Aa**[29a], **18Ab**[30], **18Ac**[31] and **18Ad**[32] demonstrate that the wide variety of α-aminoacid and peptide derivatives and related products can be prepared by such one-pot U-4MCRs.

The first chiral amino components that could satisfy all necessary conditions were some α-ferrocenyl alkylamines, like **2b.**[8j,18] However, the formation of **18e** and **18f** does not proceed with sufficient stereoselectivity. The final yields of **28** and the re-synthesized amine **2b** were not high enough. Quite promising are the preliminary results of stereoselective formations of chiral products by U-4CR *via* chiral α-ferrocenyl-β-hydroxyethylamines.

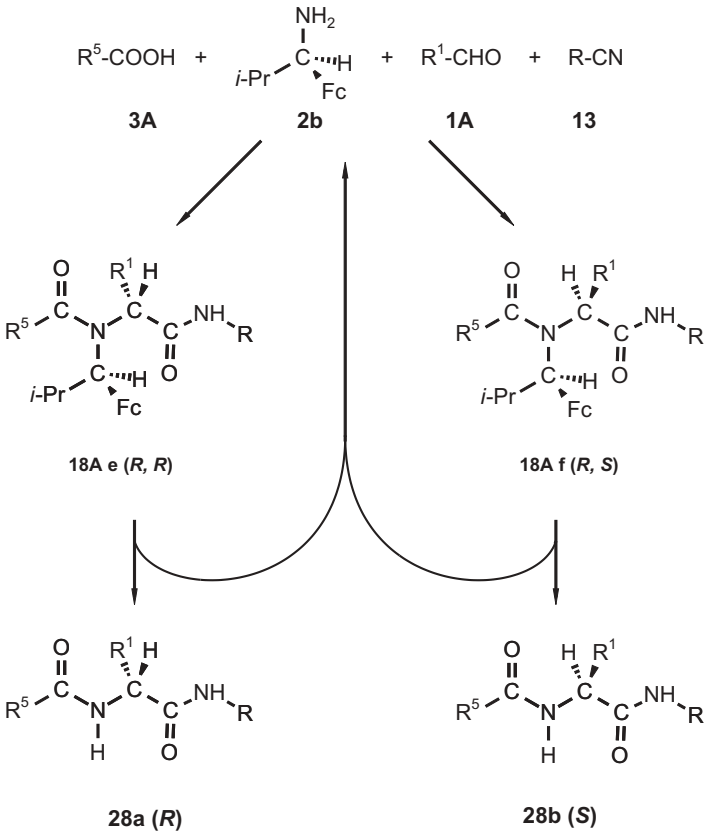


Figure 5

Kunz *et al.*[33] introduced the U-4CR with chiral *O*-acylated aminocarbohydrate into substituted α-aminoacid derivatives and other components of peptides, whose *N*-substituent could not be sufficiently removed under mild conditions. Later, several different types of amino carbohydrate derivatives were used in order to obtain peptide derivatives by the U-4CR. Their 4-CR-products could thus be cleaved more easily from the sugar-backbone, but not yet well enough.[34] Recently, several amine carbohydrates were introduced, whose endocyclic oxygen was also replaced by nitrogen derivatives (Figure 6). The amine components such as **31** seem to have the required properties (Figure 6).[35]

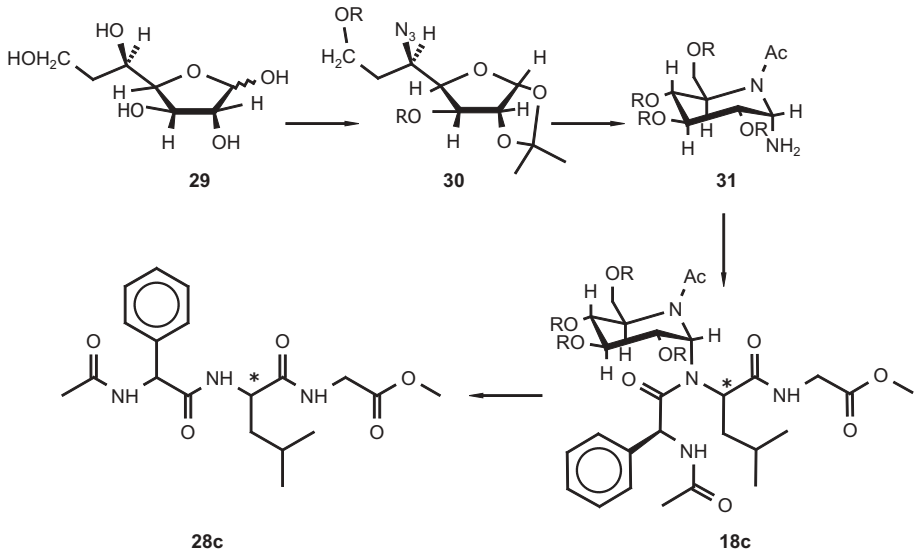


Figure 6

Already in the 1970s, Joullie *et al.*[29b] realized that many types of natural products can be prepared much easier by U-4MCRs than by the usual multistep synthesis. In the early 1980s, U-4MCRs of isocyanides were described, whose resulting Ugi products[32] with newly formed chiral α-aminoacids can be converted into activated carboxylic derivatives and can be combined with further α-aminoacid components,[36] forming higher peptide derivatives.

Armstrong[37] introduced removal of the *N*-Δ^1-cyclohexenyl group from the U-4CR Δ^1-cyclohexenyl-isocyanide products,[38] which can subsequently form a great variety of chemical compounds. In the last few years, new isocyanides have been introduced, whose products can be obtained in an even better way.[39]

Special Types of the U-4CR and Related MCRs of More than Four Educts

The four classes of participating U-4MCR components have their characteristic functional groups CO (of **1**), NH (of **2**), HX (of **3**) and NC (of **13**), if two or three of them exist in the same chemical compound. Then, in principle, six different pairs, or four trios of these differently active groups can be-

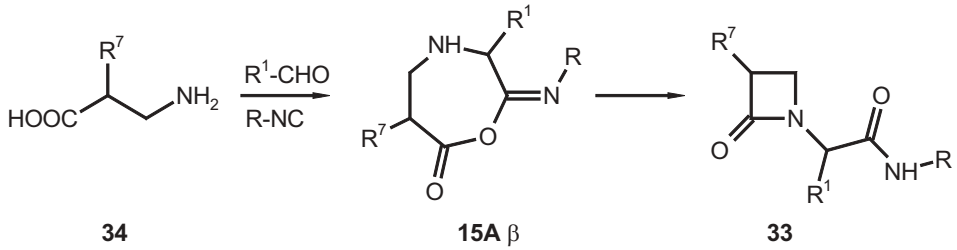


Figure 7

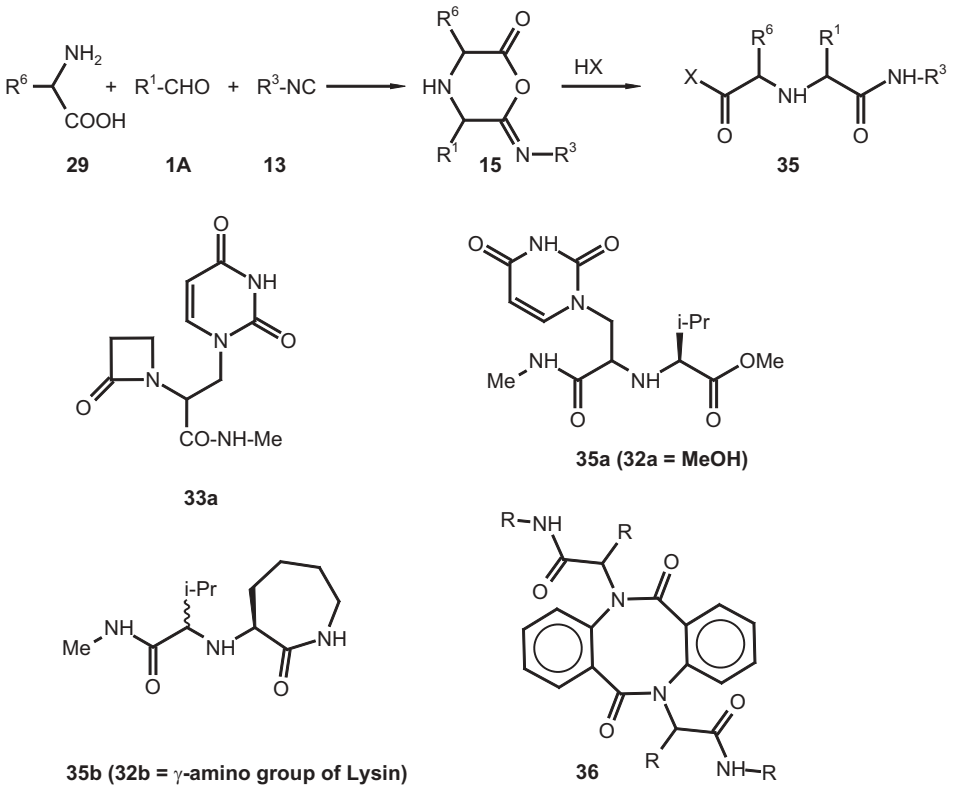


Figure 8

long to the same molecules. Thus, an even greater variety of U-4CR products can be created than by the usual U-4MCRs.

An exception is the combination of a primary amino group and the carbonyl group, since such components can be found together as Schiff bases, leading to the same products as those of **1** and **2A.**[8c,10]

Not only the most widely used U-4MCRs are those of primary amines **2A** and acids **3A** (Figure 4), but also the U-4MCRs of by-functional educts with amino and carboxylic groups are often applied. There even rather similar educts can react in very different ways. The cyclic α-adducts **15A**α of α-aminoacids[8f] (Figure 7) and **15A**ß of ß-aminoacids (Figure 8) rearrange into their different types of products **33**[8f,h,40–42] and **35** (Refs. 43,44). This is illustrated by their products **33a**[42] and **35a** (Ref. 43). The somewhat different product **36**[45] is formed from pairs of anthranilic acid, aldehydes and isocyanides. If one of the four components of the U-4CR does not only contain their usual functional groups, but also has other active parts, products like **35b**[44], are formed. This illustrates the variability of the U-4CR even for bi- and trifunctional educts.

Unions of such U-MCRs and the P-3CR can lead to products of six, seven and more components (Figure 9).[5,44]

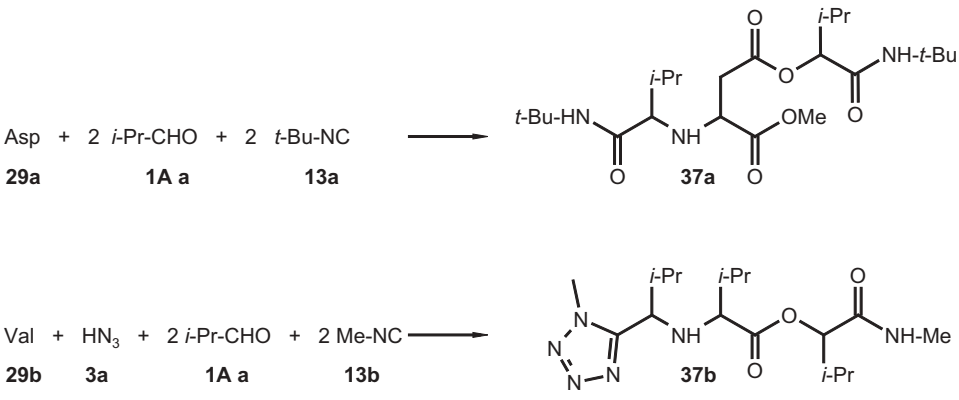
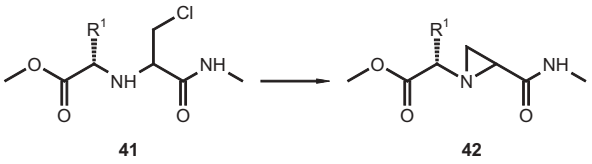


Figure 9

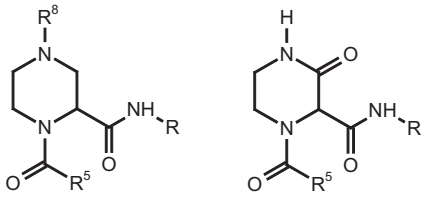
Thus, the U-4MCRs of α-aminoacids, chloro-acetaldehyde and isocyanides first form products **41** and then react further in basic media, ultimately forming aziridine derivatives **42.**[46]

Rossen *et al.*[47] formed many piperazine derivatives **43** from chloro-acetaldehyde, *N*-alkyl-ethylene-diamine, carboxylic acids and isocyanides. The hemiacetale of glyoxylic acid, a derivative of an α-carbonyl acid, reacts with ethylene-diamine and isocyanides into products **44.**[48]



41 **42**

Figure 10

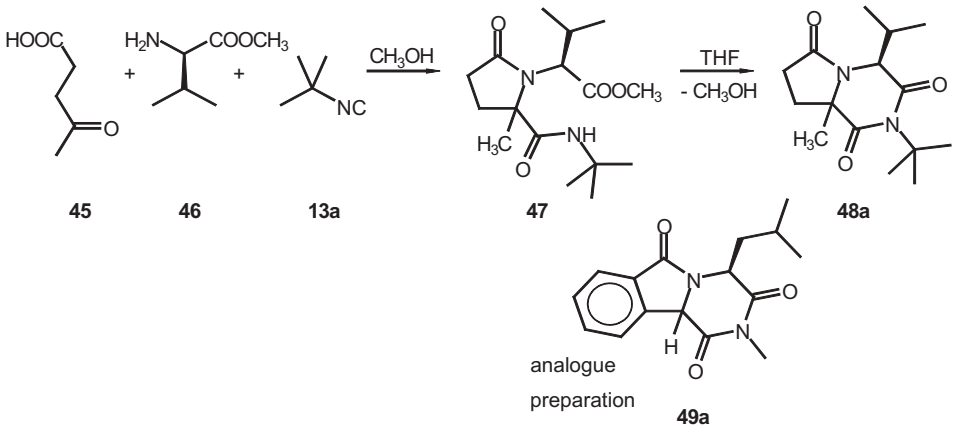


43 **44**

Figure 11

The U-4CR convert α-aminoacid-esters, γ-carboxylic acids and isocyanides first into fivemembered rings.[49,50] Their cyclization leads to additional sixmembered rings (Figure 12),[50] as it is illustrated by the reaction of **13a**, **45** and **46** *via* **47** to **48a** and the conversion of 2-carboxy-benzaldehyde into the di- and tricyclic compound **49a** and **b**.

After more than a century of HO-3MCRs and the chemistry of isocyanides, the new era of the U-4CR chemistry began. However, for more than



45 **46** **13a** **47** **48a** **49a**

Figure 12

three decades there was not much general chemical interest, but since 1993, the MCR chemistry of the isocyanides became an important part of organic chemistry, particularly in the chemical industry.[32,51]

This is probably due to the appearance of a publication about the first one-pot MCRs of seven different components that form their products much easier and in better yields of products than by the usual multistep sequences of conventional syntheses.[5,52] Several journals realized that this was not only an unusal entertaining event, but rather a potentially new profound progress in organic chemistry.[53,6a]

It was then realized that the MCRs of type IIA can form their heterocyclic products from three or four components, whereas the U-4CR is the union of the P-3CR and HO-3CR as the HO-3CRÈP-3CR that can form further unions with other chemical reactions or MCRs.[6,54] Such new types of MCRs can have, in principle, an unlimited number of components.[5]

The Chemistry of Libraries

As soon as organic chemistry started in this world, the MCR products and their libraries began to exist. Shortly later, the living cells and the biochemistry of the MCRs and their libraries came into existence.

The preparative chemistry of the MCRs was introduced around the middle of the last century, and preparation of their libraries was proposed more than a century later.[8e,32,5,55]

The solid phase peptide libraries were introduced by Furka in 1982.[51,56] Houghten[57] introduced further essential concepts, and he was particularly creative in the experimental production and investigation of peptide libraries. The recently published *Combinatorial Chemistry* volume of Wilson and Czarnik[58] illustrates this era of peptide libraries.

The essential background of the peptide chemistry was developed before 1962 (Ref. 59) and its last important progress appeared when Merrifield[60] introduced his solid-phase chemistry of the peptides. For one decade, the solid-phase libraries and their automated methodology were one of the most active parts of chemical research.[61] Solid phase syntheses of peptide derivatives can also be accomplished by U-4MCRs.[62] Such libraries were used mainly in the search for new pharmaceutical products. However, it was gradually realized that their library products were not sufficiently variable and were usually limited to injectionable products.[51] In the late 1980s, also solid-phase libraries of other multistep syntheses were introduced, but not sufficiently numerous types of chemical reactions could be carried out.

For more than three decades the isocyanide chemistry, their MCRs and their libraries were of little general interest. It was still at the GDCh-workshop conference of November 16–18, 1994, at Bitterfeld, Germany, that practically no attention was paid to the MCR libraries and their new mathe-

matically oriented computer methodology.[63] However, at the pharmaceutically oriented chemical conference of January 23–25, 1995, at La Jolla, California, very many colleagues were interested in the progress of the MCR and their libraries, demonstrated by Dömling and Gruber.[64] Soon after that, Armstrong[38] described his contribution the solid-phase MCR libraries, and Weber *et al*.[32] introduced the first successful union of many different types of industrial research, sophistically planning their preparative, analytical and computer-oriented, maximally automated chemical methods that proceed much more efficiently than separate activitie.[51]

The production of peptide libraries is limited to solid-phase procedures, which often large amounts of educts. These usually require sophisticated multistep procedures whereas the libraries of their products are rather narrow. Also other libraries of multistep procedures like the DNA/ RNA and the PNA libraries, have the same limitations and disadvantages.[58] Also the more generally applicable libraries of multistep syntheses have similar disadvantages, whereas the MCR libraries are extremely variable. Their MCRs can take place in solid and liquid phases, and in the latter they can be produced together as one-pot libraries (or in many different vessels), so that each compound of such a library corresponds to a collection of separate products.[64] This is partly due to the possibility of formimg relatively high yields of rather pure products. Many of such MCR events proceed very quickly and can be automated much easier than those of multistep libraries.

Perspectives

In recent years, the combinatorial chemistry and related subjects have been among the most widely used areas of the industrial chemical research. This is due to the search for methodological planning, investigation and production of improved products. These completely new products can be nowadays formed much faster and more efficiently than by any of the previous methods. This is certainly one of the essential parts of theoretical and applicable areas of chemistry, which has been very active in the last four years and will also be important in the next century.

This almost sudden progress is mainly due to many long-known ideas, concepts, methods and techniques of various fields of science and technology in the chemical industry. Many groups have suddenly realized that this methodology has many advantages over all previous methods of chemistry. But still a great deal of further profound progress will be necessary.

This MCR chemistry is due to different, rather old and also several newer results and methods of science and technologies. Thus, the preparative chemistry of the MCRs, the isocyanides, has been known since the middle of the last century. In the 1960s the mathematically oriented chemical computer-technology and the important modern methods of preparing het-

erocycles by MCRs and the modern chemistry of the isocyanides became known, but the modern MCR chemistry with unlimited numbers of components began in the 90s.

The chemistry and related sciences of the MCRs and their libraries had a very fast and productive industrial progress. Still, a great variety of not yet generated new types of MCRs should be developed so that an even greater variety of further chemical compounds can be produced. Most MCRs can lead to almost quantitative yields of products, and if chiral educts are used, even highly stereoselective MCRs can be carried out. But such favourable procedures take place only if the optimal components and reaction conditions are found.[65]

The optimal exploration and application of the MCR libraries require a variety of mathematically oriented computer-assisted procedures to be developed,[32,63a,66] including new automatic equipment used in the mechanical, mathematical and computer oriented studies.

It is quite certain that the chemistry of the MCRs and their libraries will not be given up, or replaced by some other methodology, but it will be improved continuously and this field of science will be also topical in the next century.

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SAŽETAK

MCR XVII. Tri tipa multikomponentnih reakcija (MCR) i biblioteke spojeva – kemija prirodnih događaja i preparativna kemija

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U multikomponentnim reakcijama u jednom stupnju (MCR) (1) pretvaraju se više od dvije različite komponente u produkte s najmanje dvije novonastale kemijske veze pri čemu produkti sadrže sve edukte ili barem njihove dijelove. Mnoge kemijske reakcije imaju nekoliko ali ne i sve aspekte MCR. Postoje tri različita osnovna tipa (I-III) i dvije podklase (A i B) multikomponentnih reakcija.

U prirodi, odprilike prije 4,6 milijardi godina započela je kemija na našoj planeti uključujući MCR tipa I i II koje su dale biblioteke različitih spojeva. Nešto kasnije nastale su žive stanice i njihove biokemijske MCR sva tri tipa. U njihovim različitim dijelovima selektivno nastaju biokemijski produkti uz pomoć enzima no većina njihovih MCR pripada tipu III.

Sintetska kemija temeljem MCR započinje sredinom prošlog stoljeća kada se izoliraju produkti ravnotežnih trokomponentnih reakcija tipa IB. Predzadnje reakcije tipa I daju spojeve koji dalje reagiraju MCR tipa II dajući konačne produkte. Produkti MCR tipa IIA obično su heterociklički spojevi dok su oni nastali reakcijama tipa IIB produkti izocijanida. Otkrićem U-4CR (U-četverokomponentnih reakcija) nastaje nova sintetska kemija MCR. Nastali edukti i intermedijarni produkti su u ravnoteži (tip IA) i podliježu dalje ireverzibilnim α-adicijama izocijanida CII $\rightarrow$ CIV, koje slijede različita pregrađivanja u konačne produkte (tip IIB). U posljednje vrijeme uvedene su reakcije s još većim brojem komponenata koje daju još više različitih vrsta produkata. 1961. predloženo je stvaranje biblioteka spojeva nastalih MC reakcijama, a od 1995. ta kemija postaje bitan dio kemijskih istraživanja u industriji, usmjerenih prema pronalasku novih produkata. Ta metodologija zahtijeva znatno manje sintetskog rada i za nekoliko je redova veličine brža nego sve prijašnje metode.