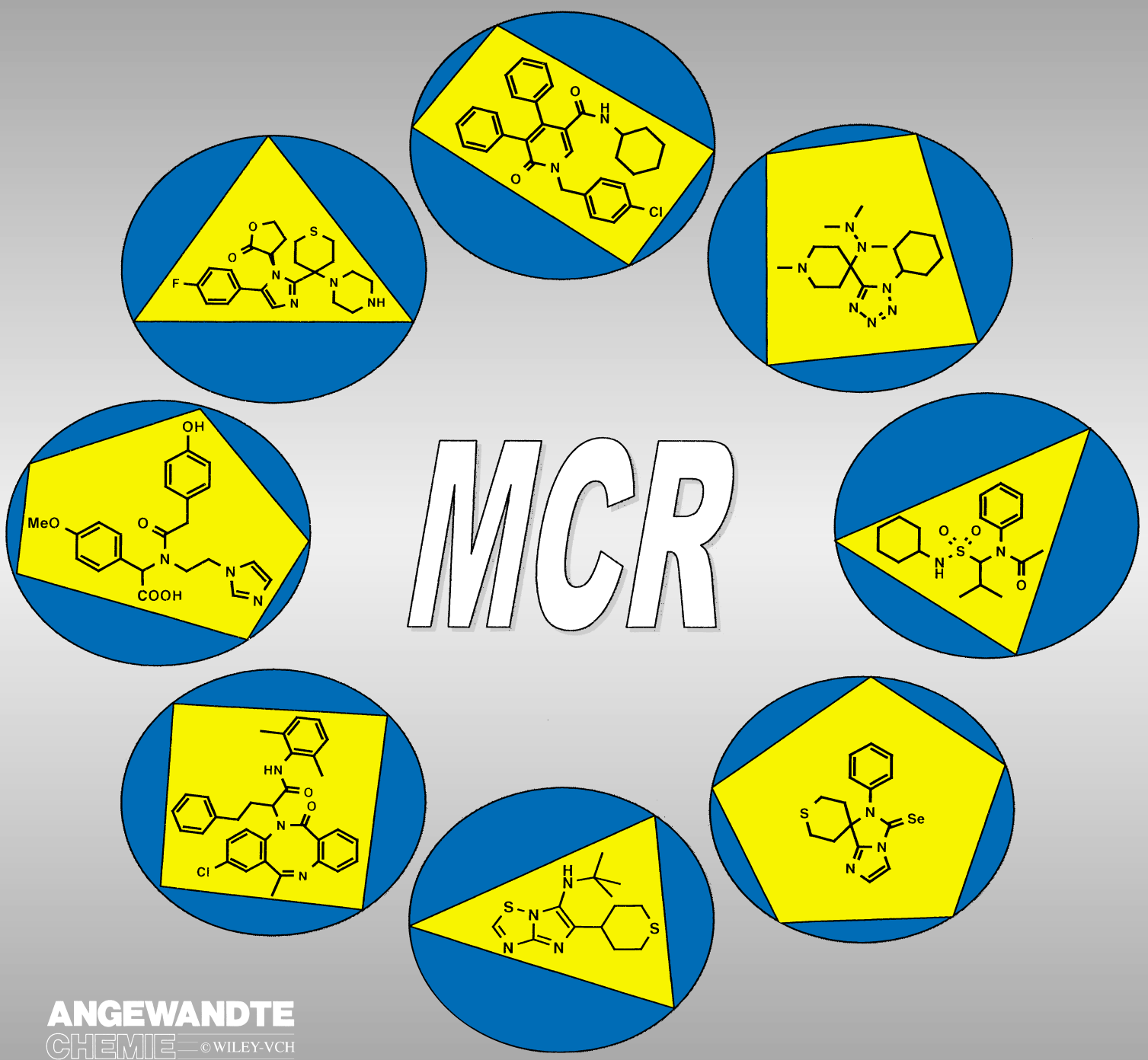

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Multicomponent Reactions with Isocyanides

Alexander Dömling* and Ivar Ugi

Multicomponent reactions (MCRs) are fundamentally different from two-component reactions in several aspects. Among the MCRs, those with isocyanides have developed into popular organic-chemical reactions in the pharmaceutical industry for the preparation of compound libraries of low-molecular druglike compounds. With a small set of starting materials, very large libraries can be built up within a short time, which can then be used for research on medicinal substances. Due to the intensive research of the last few years, many new backbone types have become accessible. MCRs are also increasingly being employed in the total synthesis of natural products. MCRs and especially MCRs with isocyanides offer many opportunities to attain new reactions and basic structures. However, this requires that the chemist learns the "language" of MCRs, something that this review wishes to stimulate.

Keywords: combinatorial chemistry · isocyanides · multicomponent reactions · synthetic methods

1. Introduction

Organic-chemical syntheses have reached a high degree of skilfulness. There is hardly a complicated natural product that escapes a multistep total synthesis, in which the target molecules are often synthesized divergently rather than convergently, or sequentially, in many steps according to their complexity. The progress made in the last decades in the total synthesis of natural products becomes visible when Woodward's strychnine synthesis is compared with newer syntheses.[1] It is founded in part on the optimization of synthetic operations and reactions. For example, organometallic variations of classic reactions often are more diastereo-, enantio-, regio-, and/or chemoselective and often afford the products in higher yields. Improved analytical and separation methods contribute to more efficient synthetic steps. Whereas Woodward obtained strychnine from his 28-step synthesis in 6×10^{-5}% overall yield, the groups of Magnus, Overman, Kuehn, and Rawal were able to produce this complex compound in less synthetic steps and with 10^3 to 10^4 times higher total yield.

The "ideal synthesis" (Figure 1) should lead to the desired product in as few steps as possible, in good overall yield and by using environmentally compatible reagents.[2] The synthetic variables that have to be optimized are time, costs, overall yield, simplicity of performance, safety, and environmental acceptability. In multistep syntheses the temporal and preparative complexity increases in proportion to the number of steps in a first approximation. It is reflected in many isolation and purification operations, such as crystallization, extraction, distillation, or chromatography.

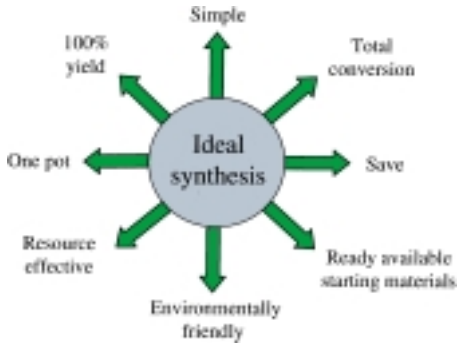

Figure 1. The ideal chemical synthesis (adapted from Wender et al.).[2] Although virtually no natural product, however complex it may be, escapes a chemical total synthesis, the organic synthesis is far from the elegant, effective and economical biosynthesis.

Besides the multistep, sequential synthesis of a target molecule, the desired product can also be obtained in one-pot reactions of three or more starting compounds, the multicomponent reactions (MCRs), in many cases. Here the starting materials do not react simultaneously in one step, but rather in a sequence of elementary steps according to a program. Reactions with an irreversible step, which drives the

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preceding equilibrium to the product side, are especially favorable. In contrast to two-component reactions, MCRs are especially variable. Very many products can be synthesized from only a few starting substances. Many common MCRs fall back on easily accessible, archetypical functional groups, which are available in a great variety, that is an MCR is economical with resources. As MCRs, being one-pot reactions, are practically single-step conversions, they are easier to carry out than multistep syntheses. Thus, the MCRs already come quite close to the idea of an "ideal synthesis". If a product can be synthesized by means of an MCR, this procedure offers many advantages.

A large and important class of MCRs are the isocyanide multicomponent reactions (IMCR). The chemistry of isocyanides began in 1838. Apart from short active periods, isocyanide chemistry has slumbered for more than a century (Figure 2).

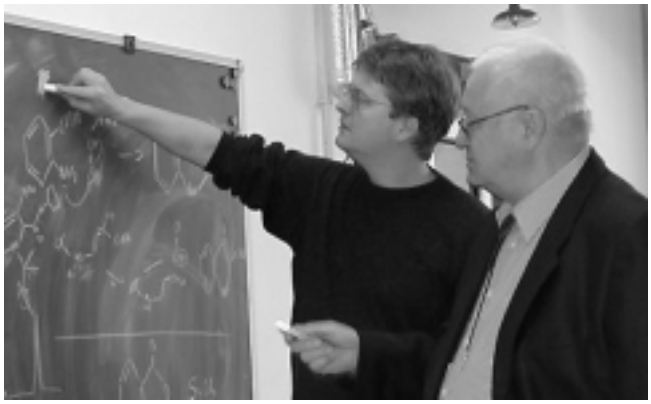
In the last 150 years, the classical MCR chemistry was developed, which is summarized in 1960 in the book "α-Aminoalkylierung" by Hellmann and Opitz.[3] Many of these classical MCRs are name reactions, among them well-known classics, such as the Mannich reaction (a three-component reaction, M-3CR) or its intramolecular variant, the Pictet–Spengler reaction (a two-component reaction, PS-2CR).

A short time after the Ugi four-component reaction (U-4CR; January 1959) was discovered, it was found that xylocain **4**—an important local anaesthetic then as well as now—could be synthesized in only one step from 2,6-dimethylphenyl isocyanide (**1**), formaldehyde (**2**), and diethylamine (**3**) with good yield (Scheme 1). Ownership of the patent which was immediately applied for[4] changed over to the company A.B. Astra. At that time, Ivar Ugi was scientific consultant for the Swedish company. He recommended to the synthetic chemists and research heads to produce whole collections[5] of different α-amino amides, based on the four-component reaction which is highly variable and easy to carry out in one pot, and to test them for their anaesthetic effect. Later, more than a dozen local anaesthetics based on the xylocain structure were developed and marketed by various pharmaceutical companies.

In the last decade a change of thought has taken place in the pharmaceutical industry which has led to a renaissance of the MCRs. Characteristic for this paradigm change in pharmaceutical research are the fields of combinatorial chemistry, high-throughput screening, and genome and proteome analysis.[6] Whereas only a few years ago the substance productivity of a medicinal chemist was relatively low, today thousands of substances can be produced and characterized every day by means of automated methods.

Although the suitability of the MCRs for building up large compound libraries was published as early as 1961,[7] these reactions were of little interest in the following decades.

Alexander Dömling, born in 1964, studied biology and chemistry at the Technische Universität München and completed his doctorate in chemistry under the supervision of Prof. Ivar Ugi in 1994. As holder of a Humboldt fellowship he spent one year at the Scripps Research Institute in the group of Barry Sharpless. Then he began his habilitation at the TU München. In 1996 he founded the company Morphochem AG with Wolfgang Richter. In the same year he was awarded the Friedrich-Weygand prize by the Max Bergmann circle. His research interests are the discovery of new multicomponent reactions and their application in total syntheses of natural compounds, ideally in one step (one-pot syntheses). Further interests are in "other forms of life" and complex artificial enzymes



A. Dömling I. Ugi

Ivar Ugi, born in 1930 in Estonia, studied chemistry at the Universität Tübingen from 1949 to 1952. In 1954 he obtained his doctorate at the Universität München. His habilitation on aryl pentazoles and isocyanides followed in 1959. From 1962 to 1968, he worked in the Central Research Laboratories of the Bayer AG in Leverkusen, where he was the chairman of the commission for basic research and head of research for the last three years. In 1964 he was awarded the research prize of the scientific academy in Göttingen. From 1968 to 1971 he was a professor at the chemical institute of the University of South California, Los Angeles (USA), and then became a professor for organic chemistry at the Technische Universität München in Garching (Germany), holding the Hans Fischer chair, where he remained until 1999. He is a member of the Royal Swedish Academy of Science in Uppsala (since 1987), the Estonian Academy of Science (since 1991), and the US Academy of Science in New York (since 1994). In 1988 he received the Challenge Future Prize from the Philip Morris Foundation, in 1992 the Emil Fischer Medal from the Gesellschaft Deutscher Chemiker for his discovery of the four-component condensation and the development of mathematical models for the logical structures of chemistry, in 1995 the Ugi-Dugundji-Medal, awarded for the first time, to honor his achievement in applying mathematics and information technology to chemistry, and in 1999 he was awarded the Max Bergmann Medal.

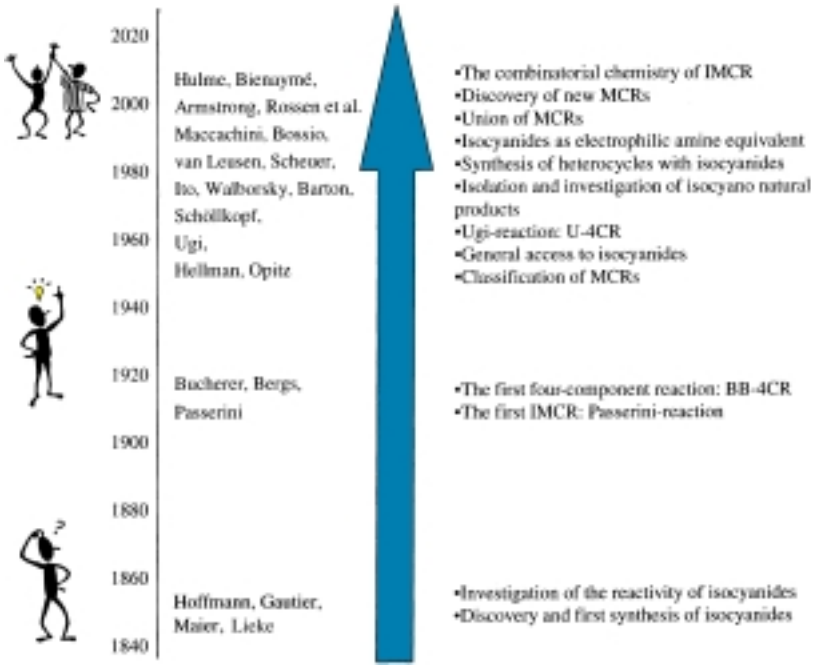
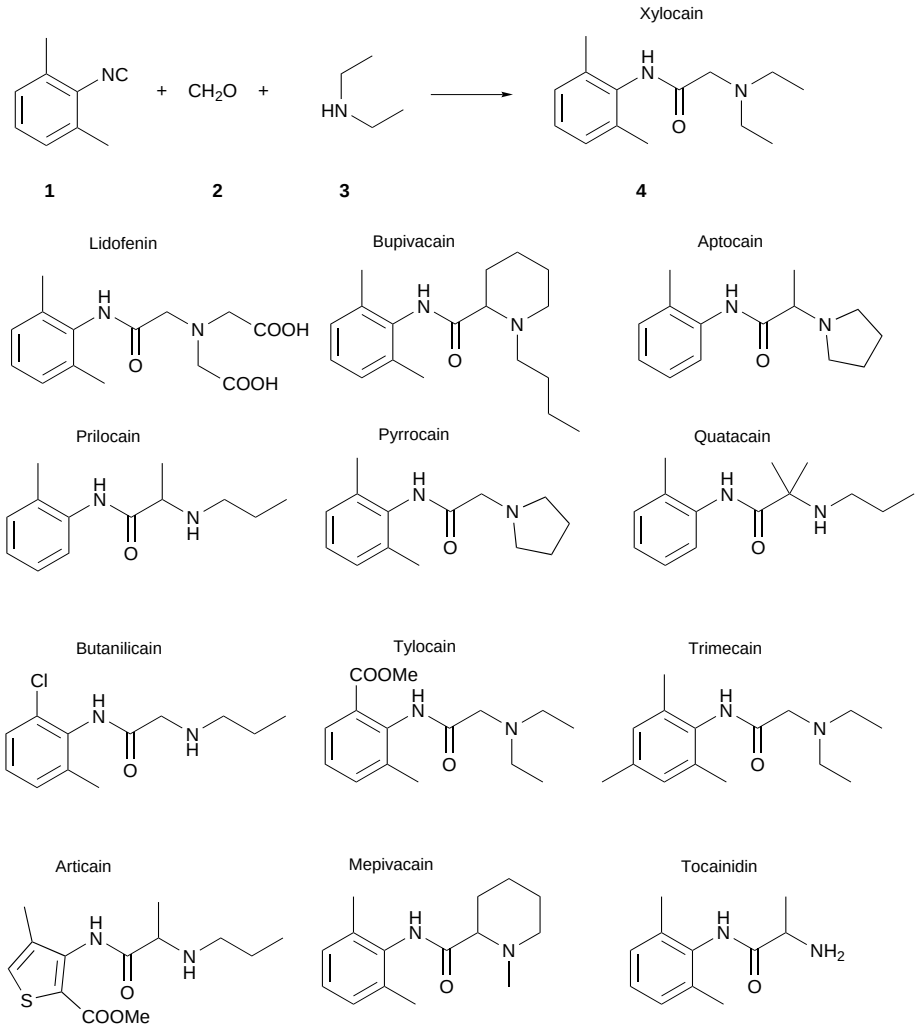


Figure 2. The history of the isocyanides and that of their MCRs took place in three large, parallel waves. The first wave was the constituting one, in which the isocyanides were discovered and their structure and identity recognized, some properties were examined and limited preparative access was found. In the following, research on this area was sporadic with only a few publications until the Italian Passerini discovered the self-named, first IMCR and investigated it for many years (the second wave). It grew silent again for many decades until a general and good appproach to the class of the isocyanides was found. In this third wave, the largest so far, which may not even have reached its climax yet, the Ugi reaction and many new IMCRs, many biologically active natural compounds, new heterocycle syntheses with isocyanides and other important synthetic applications of isocyanides were described. Finally, the immense advantages of the IMCRs in drug research were recognized (the figures at the edge of the diagram were taken from Microsoft ClipArt).



Scheme 1. One-pot synthesis of xylocain (**4**) and a selection of commercial analogues based on the α-aminoamide structure.

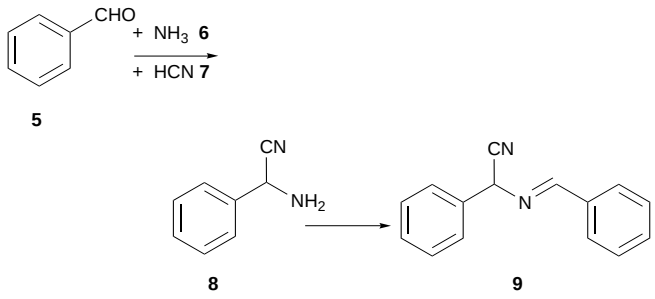
Especially due to their efficiency, the ease of their automation, and the enormous number of possible products, they have moved into the focus of contemporary endeavors to find new active substances in shorter periods of time. Great efforts have been and still are being made to find and develop new MCRs.[8h] With the concept of unions of MCRS described in Section 7, new reactions of even more components have been and will in future be described.

In the following the history and the historical development of the MCRs in the last one and a half centuries are presented. The overview pays special attention to new aspects and applications of the MCRs of isocyanides;[8] other MCRs are only mentioned in passing. The new IMCR literature is summarized and discussed with special emphasis on combinatorial applications, and new concepts of the MCRs are introduced.

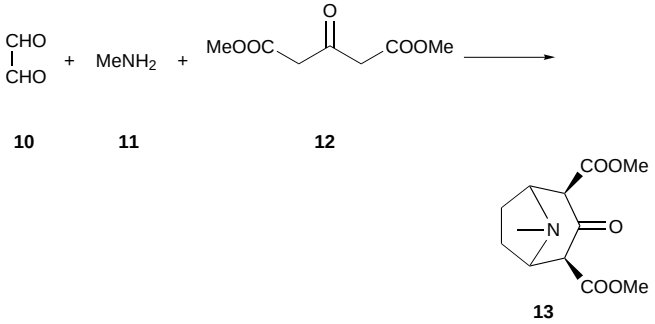
1.1. History of the MCRs

The general ordering principle of MCRs is followed by the α-amino alkylation, in which an oxo compound and a primary or secondary

amine undergo electrophilic addition to an electron-rich position of a molecule.[3, 9, 10] The Strecker synthesis of α-amino acids via α-amino cyanides was first published in 1850 and is generally considered to be the first MCR.[11] However, in the reaction of bitter almond oil and ammonia 12 years earlier, Laurent and Gerhardt isolated a poorly soluble product that had evolved in an MCR.[12] In this reaction, the crude product, hydrocyanic acid-containing benzaldehyde(**5**/**7**), reacts in a Strecker reaction with ammonia (**6**), giving aminobenzyl cyanide (**8**), whose Schiff base with benzaldehyde was called "benzoyl azotide" **9**.

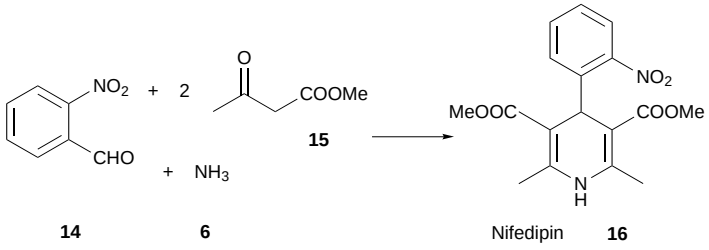


Robinson's synthesis of the alkaloid tropinone (**13**) from succinic dialdehyde (**10**), methylamine (**11**), and dimethyl acetonedicarboxylate (**12**), carried out in 1917, is the first important application of MCRs in natural product synthesis.[13] Two decades later, Schöpf was able to carry out analogous syntheses under physiological conditions.[14] Mannich-type reactions (M-3CR) proved in the following to be extremely valuable for the total synthesis of natural products.[10]



Many important heterocycle syntheses are MCRs. 1,4-Dihydropyridines such as **16** were first synthesized over one hundred years ago in a four-component reaction by Hantzsch (H-4CR) from ammonia (**6**), aldehyde **14** and acetoacetic ester **15**.[15] As this preparation is particularly simple to carry out, it was listed in the popular laboratory manual by Gatterman for half a century.[16] Finally, at the Bayer AG company, a very successful dihydropyridine preparation for the therapy of cardiovascular disease named Nifedipin was developed, based on the Hantzsch synthesis.[17]

The first MCR with isocyanides was described in 1921 by the Italian Passerini (P-3CR).[18] In many publications, he was able to show the preparative possibilities of this reaction.[19a]



A further important MCR is the Bucherer–Bergs reaction (BB-4CR).[20] It can be understood as an extension of the S-3CR by one component (CO_2). Whereas the Strecker three-component reaction (S-3CR) is an equilibrium reaction and often delivers the products in unsatisfactory yields, the BB-4CR is practically irreversible upon addition of CO_2. It still is an important method for the synthesis of unnatural α-amino acids.

Some more important MCRs leading to heterocycles are listed in Table 1.

1.2. Isocyanides

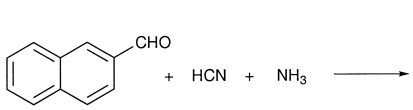
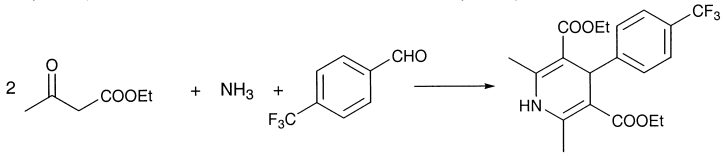
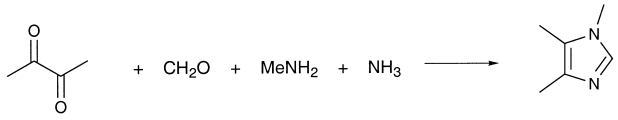
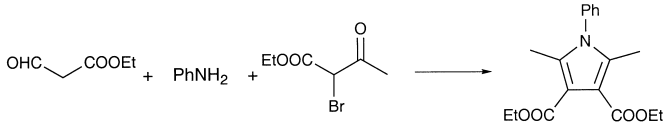
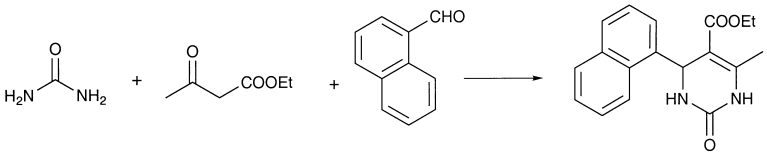
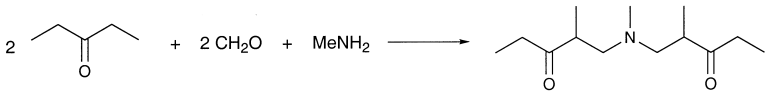
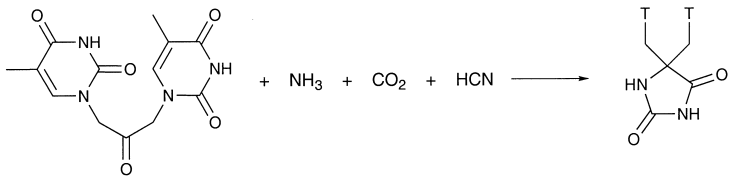
Isocyanides, formerly known as isonitriles, are compounds with an extraordinary functional group. Its unusual valence structure and reactivity were discussed for over one and a half centuries. Isocyanides are the only class of stable organic compounds with a formally divalent carbon.[27] In exothermic reactions C^{II} is oxidized to C^{IV}. This was already noted in 1892 by Nef.[28] Owing to its reactivity the isocyanide group differs fundamentally from other functional groups.

Hundreds of isocyano group containing natural products were isolated, above all from marine species. The name Scheurer is synonymous for the investigation of natural isocyanides from marine sources.[29] Many natural isocyanide show a strong antibiotic, fungicidal, or antineoplastic effect. The potential of isocyanides as possible agents for crop protection, discovered as early as the 1960s, also found its way into the patent literature,[30] in which the antibiotic, acaricidal, fungicidal, or insecticidal activity with simultaneous low toxicity for warm-blooded animals is described. Di- and triisocyanides stand out because of their extraordinary antibiotic activity and often show no signs of resistance even after hundreds of generations.[31] Antifouling properties similar to those of copper sulfate were recently described for marine, terpenoid isocyanides.[32]

Many natural products are isolated as *N*-formamides. As these can be regarded either as precursors or as products of the hydrolysis of isocyanides, presumably many more isocyanides occur naturally than is generally assumed. A small selection of bioactive natural products with isocyanide functionality, **17**–**28**, is shown in Scheme 2.

Isocyanides were first synthesized in 1859 by Lieke, who did not recognize them as such and first believed them to be nitriles.[33] He tried to transform the putative nitriles into the corresponding carboxylic acids by means of hydrolysis, but obtained formamides instead. At the time, isocyanides were

Table 1. Many of the historically significant MCRs are based on the reactivity of carbonyl or imine groups.

Name of the reaction	Year of discovery	Example[a]
Strecker synthesis[10]	(1838) 1850	
Hantzsch dihydropyridine synthesis[15]	1882	
Radziszewski imidazole synthesis[21]	1882	
Hantzsch pyrrole synthesis[22]	1890	
Biginelli reaction[23, 24]	1891	
Mannich reaction[25]	1912	
Bucherer–Bergs hydantoin synthesis[20, 26]	1941	

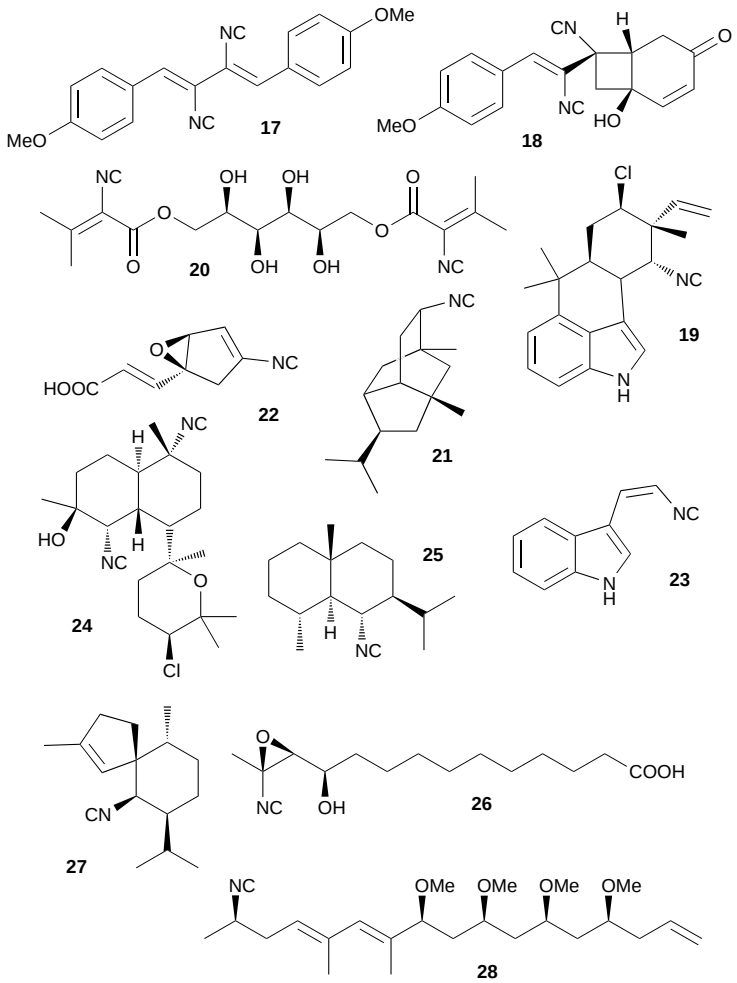
[a] T = thymine.

produced in substitution reactions of reactive alkyl halides with silver cyanide. Owing to the poor scope of substrates for this reaction, only few isocyanides were available. The isocyanides stood out because of their strange odour which forced the chemists to work outdoors. Almost all commercially available isocyanides are volatile and carry this repulsive odor "which is reminiscent of artichokes and phosphorus at the same time."[34] People who have inhaled volatile isocyanides such as allyl, benzyl, methyl, or *tert*-butyl isocyanide over a longer period of time report the sensory perception of the smell of hay.[35] The more long-term inhalation of isocyanides is also said to increase the intensity of dreams at night. Other liquid isocyanides, such as the position isomeric picolyl isocyanides, on the other hand, do not smell. The isocyanide derived from L-phenylglycine methyl ester smells of rhubarb. In fact most isocyanides are solid and odorless. Gautier already investigated the toxic properties of isocyanides by dribbling them into the eyes of dogs.[34] However, according to toxicological examinations of hundreds of isocyanides carried out in the 1960s by the Bayer AG company, this class of compounds is only slightly toxic, apart from few exceptions.[36]

Once again, it was Gautier who first discovered the isomeric nature of relationship between the isocyanides and the nitriles.[37] At the same time, Hoffmann found a new approach to isocyanides with the reaction of primary amines with potash and chloroform. All methods for the preparation of isocyanides known at the time were, however, complicated, poorly generalizable, and delivered the products in low yields. Often the isocyanides could not be separated from the accompanying nitriles. The preparative availability and their bad odor may have been the reasons why the chemistry of isocyanides was investigated only sporadically and not very intensely for 100 years. Whereas only twelve isocyanides were known in the first 100 years, 325 isocyanides were described by 1971.

1.2.1. Methods for the Preparation of Isocyanides

Even though dozens of methods for the preparation of isocyanides have been described,[38] the reaction of the *N*-formamides with phosgene or phosgene surrogates such as di- and triphosgene or other inorganic dehydratants and matching bases is the method of choice regarding cost, yield, and



Scheme 2. Examples of naturally occurring isocyanides: the antibiotic xanthocillin (**17**) from *Penicillium chrysogenum*, leptocillin (**18**), hapalindole A (**19**), the antibiotic, antimycotic, and antihypertensive compound A-32390 (**20**) from the fungus *Pyrenochaeta spaeropsidales*, isocyanopupukean (**21**) from *Phylliadia variosa*, 4-((*E*)-2-carboxyvinyl)-3,4-epoxy-1-cyclopentenyl isocyanide (**22**), B 371 (**23**) from *Pseudomonas sp.*, the antimalarial kalihinol A (**24**) from *Chromobacterium spec.*, acenthellin-1 (**25**), aerocyanidine (**26**), axisonitrile-3 (**27**), and mirabilene isonitrile A (**28**).

execution in most cases.[39] Another convenient and advantageous method of preparation is the dehydration with $POCl_3$.[40] Racemization-sensitive α-amino acid isocyanides can be synthesized with oxomethylenebis(3*H*-imidazolium)-bismethanesulfonate.[41]

In the last century Gautier already attempted to obtain isocyanides from *N*-formamides.[42] As he omitted to add appropriate equivalents of base to the reaction mixture, the isocyanide formed in situ soon was converted back to the *N*-formamide.[43] The use of various organic bases such as triethylamine, pyridine, quinoline, 1,4-diazabicyclo[2.2.2]octane (DABCO), or diisopropylamine has been described. Depending on which further functionalities are present, many alternative production methods can be drawn upon (Table 2). Very sensitive isocyanides, such as the isocyano analogue 3′-azido-3′-deoxythymidine (AZT), can only be synthesized under special precautions.[44] Finally, isocyanides were linked to the solid phase very early on.[45]

Despite the obviously easy availability of isocyanides from accordingly variable precursors, only a few are commercially available. However, for the combinatorial application of MCRs, all classes of starting materials should ideally be present with a great scope of compounds. An interesting solution to the problem is the combinatorial formation of isocyanides.

One possibility for the diversification of the isocyanide group was described by Bienaymé with the P-3CR. In the course of this the expression "reagent explosion" came up. He describes the synthesis of various β-dialkylamino α-isocyanoacrylates.[58] *N*-imidazomethyl diethyl acetal (**29**) was treated with methyl isocyanoacetate (**30**) and primary as well as secondary amines to give the β-substituted isocyanoacrylates **31**–**36**.

Bossio's group, which is very productive in the field of IMCR, described the two-step synthesis of isocyanides by means of a U-4CR with ammonium formate and subsequent dehydration (Scheme 3).[59] This method allows the combinatorial production of isocyanides from other isocyanides and aldehydes.

Based on the work by Schöllkopf, Armstrong et al. have developed an in situ method in which isocyanides are obtained from α-alkylations and employed in MCRs without former isolation.[60] Different benzylisocyanides are first treated with BuLi and alkylating reagents, then with aldehydes, carboxylic acids, and amines. This way the limited number of commercially available isocyanides can be increased significantly with little preparative effort.

Finally, the problem of isocyanide diversity and availability can also be circumvented by linking the isocyanide group to a solid phase. Many such examples are discussed in the following.

1.2.2. Chemistry of Isocyanides

The chemistry of isocyanides is characterized by three properties: the α-acidity, the α-addition, and the easy formation of radicals.

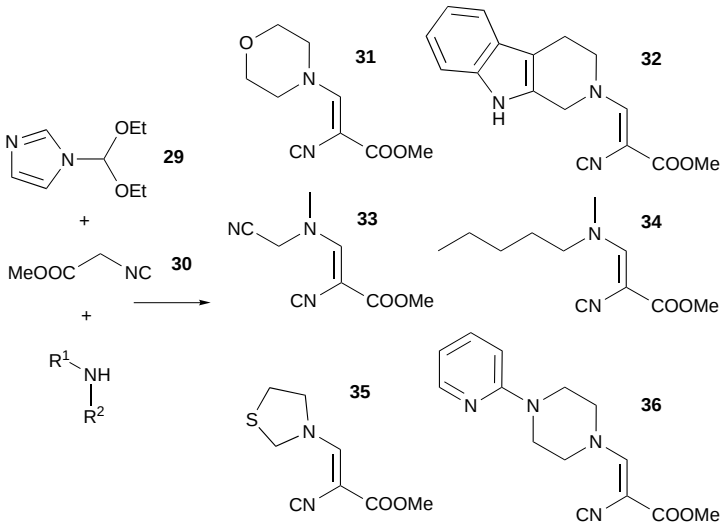
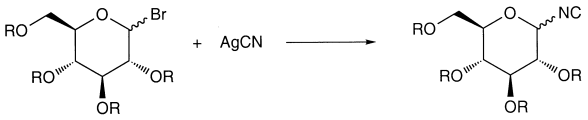
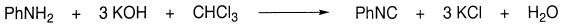
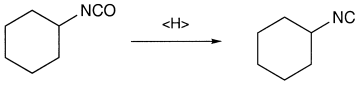
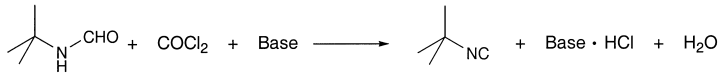
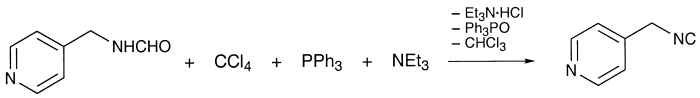
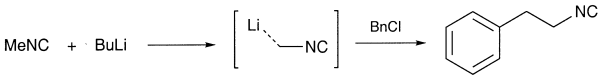
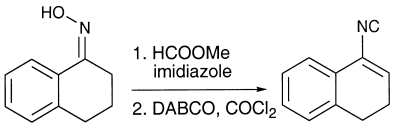
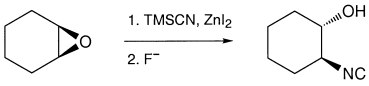
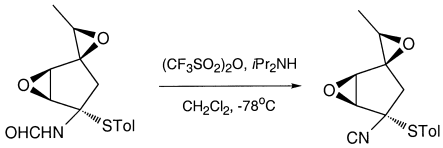
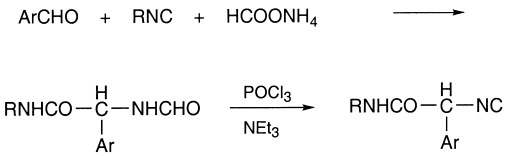


Table 2. Important preparative isocyanide syntheses with examples.

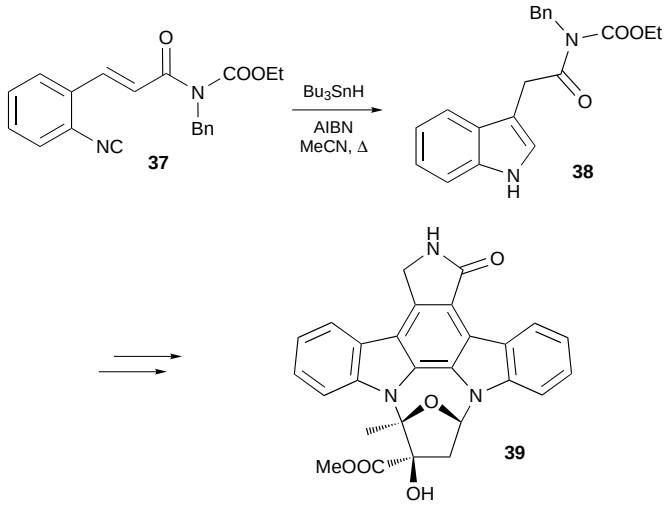
Method	Example[a]	Ref.
Lieke, 1859		[33]
Meyer, 1866		[46]
Gautier, 1867	the silver cyanide method, often referred to as the Gautier method, was first described by Lieke and Meyer.	[47]
Hoffmann, 1867		[48]
Hoffmann, 1870		[49]
Ugi, 1958		[50]
Ugi, Weber, Gockel, 1972	improved Hoffmann carbylamine method, in $CH_2Cl_2/CHCl_3/H_2O$ with phase transfer catalyst	[51]
Appel, 1972		[52]
Schöllkopf, 1971		[53]
Barton, 1988		[54]
Gassman, 1982		[55]
Baldwin, 1990		[56]
Kitano, 1998		[57]

[a] DABCO = 1,4-diazabicyclo[2.2.2]octane, TMS = Me_3Si, Tol = tolyl.



Scheme 3. Two-step isocyanide synthesis by means of a U-4CR and subsequent dehydration. This method allows the combinatorial preparation of isocyanides from other isocyanides and aldehydes.

Isocyanides and especially phenyl isocyanides are substrates for radical-induced cyclizations. Complex indole-containing natural products like the kinase inhibitor (+)-K252a (**39**) can be synthesized starting from *o*-isocyanocinnamic acid amides such as **37** (via **38**) by means of radical cyclizations (AIBN = α,α'-azoisobutyronitrile).[61] A further famous example is the synthesis of the ABCD ring moiety of the



topoisomerase II inhibitor camptothecin and numerous derivatives by Curran et al.[62]

The α-acidity as a striking feature of the isocyanides is increased by further electron-withdrawing substituents in the α-position such as carboxylic esters, nitriles, phosphonic esters, or sulfonyl groups. α-Metalated isocyanides are versatile starting materials for the synthesis of α,β-unsaturated isocyanides, heterocycles or amino acids.[63] Schöllkopf found that α-metalated isocyanides are easy-to-handle α-amino anion equivalents.

Isocyanides polymerize under Lewis acid catalysis to polyiminomethylenes. The corresponding polymers have the structure of cylindrical helices.[64]

The synthetically most important property of isocyanides is the reaction with nucleophiles and electrophiles at the isocyanide carbon atom. The α-addition of nucleophiles and electrophiles leads to the α-adduct (Figure 3). Most other

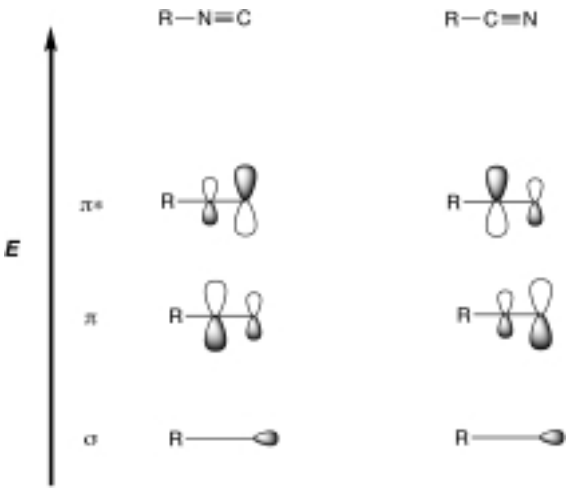


Figure 3. Qualitative comparison of the frontier orbitals of isocyanides and nitriles, showing the different reactivities of the two isomeric functional groups. Compared to the nitriles, the orbital coefficient of the isocyanides at the carbon atom in the π* orbital is higher, leading to nucleophilic attack of the carbon atom. Electrophiles react with the σ orbital of the HOMO-1 and therefore also with the carbon atom. Nitriles, on the other hand, are attacked by nucleophiles at the carbon atom (higher π* orbital coefficient) and by electrophiles at the nitrogen atom (higher π orbital coefficient).

functional groups in organic chemistry react with nucleophiles and electrophiles at different centers. Only carbenes and carbon monoxide share this property with the isocyanides. Thus, many parallels can be found in the chemistry of these classes of compounds.

One of the classic themes in the chemistry of isocyanides is heterocycle synthesis. The names of Schöllkopf and van Leusen stand for many pioneering developments in this field.[65] Among others, useful imidazoline, oxazoline,[66] thiazoline, pyrrole,[67] imidazole,[68] oxazole,[69] and thiazole syntheses[70] have been described. Enantioselective methods for the preparation of dihydrooxazoles and therefore of hydroxy-amino acids were elaborated by Ito and Togni with planar-chiral ferrocene catalysts.[71] A comprehensive review of heterocycle syntheses with isocyanides has been published.[72]

1.3. Definitions of MCRs

Reactions in which more than two starting compounds react to form a product in such a way that the majority of the atoms of the starting material can be found in the product are called multicomponent reactions. This rough definition is suitable to distinguish traditional two-component reactions and domino reactions, in which usually only one or two starting compounds are converted, from MCRs. A more sophisticated view is introduced in the following (Table 3).

Table 3. The basic types of MCRs.

MCR type	General reaction scheme
I	A + B ⇌ C ⇌ ... O ⇌ P
II	A + B ⇌ C ⇌ D ... O → P
III	A → B + C → D → ... O → P

MCRs whose starting compounds, intermediates, and products are in a mobile equilibrium are classified as type I MCRs. As different states of balance can prevail, yields between 0 and 100 % are possible. In most cases the products occur as mixtures with the intermediates and/or starting materials and are difficult to isolate. As the reaction often is incomplete, side reactions are possible which lead to further impurities.

MCRs whose elementary reactions are equilibria and irreversible partial reactions and whose last reaction step is irreversible belong to type II. Reactions of this type are preparatively advantageous as the total equilibrium is shifted to the side of the products by the last irreversible step. Such irreversible steps are, for example, the result of strongly exothermic reactions, such as the $C^{II} \rightarrow C^{IV}$ conversion of the isocyanides, a ring-closure reaction, or an aromatization.

MCRs of the type III are sequences of irreversible elementary reactions. They seldom occur in preparative chemistry. On the other hand, biochemical reactions in the living world fall into this category. Many of these reactions are de facto irreversible partial reactions, either due to the thermodynamic circumstances or due to the combination of endothermal with exothermal reactions (e.g. ATP coupling). These reactions correspond to enzymatically accelerated and mostly highly selective reactions so that significant amounts of side products are seldom formed. Should this nevertheless be the case, the side products are eliminated enzymatically and returned to the circuit.

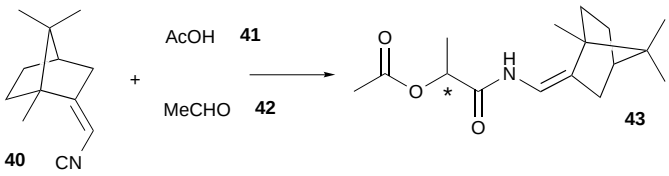
It must be considered in the above classification that these are idealizations. Many reactions can not be counted to one of the classes, rather the transitions are fluid.

In the following the Passerini reaction, the Ugi reaction, and other IMCRs as well as their new variants shall be introduced. It will be attempted to subdivide the presentation of the examples according to reaction as well as to structure features.

2. The Passerini Reaction

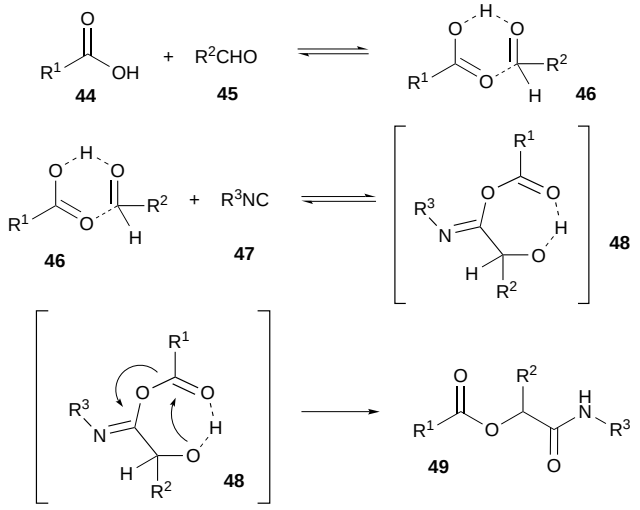
The classic reaction between carboxylic acids, oxo compounds and C-isocyanides, described by Passerini in 1921 and

later given his name, opens the access to α-acyloxycarboxamides in one step.[18] The mechanism of the reaction has often been discussed.[19] Kinetic and preparative investigations have led to different mechanistic suggestions.[73] In contrast to the Ugi reaction, the Passerini reaction is accelerated in aprotic solvents, indicating a nonionic mechanism.[74] The results concerning the influence of chiral isocyanides on the stereochemical course of the P-3CR seem contradictory. Mostly it was stated that chiral isocyanides have no influence on the diastereoselectivity of the P-3CR. The α,β-unsaturated isocyanide **40** derived from camphor is an exception. Thus, the P-3CR of the chiral isocyanide **40** with acetic acid **41** and acetaldehyde **42** yielded one diastereomer **43** with 93% *de*.[75]



Passerini himself postulated hemiacetals between the carboxylic acid and the oxo compound as intermediates. From kinetic studies and the observation of a third-degree reaction order, bipolar intermediates were assumed.[19c] Other authors have discussed N-protonated isocyanides as reactive intermediates.[19d] A P-MCR in the ligand sphere of organometallic catalysts has also been described.[19e]

A plausible mechanism which agrees with the experimental data is the formation of a loosely hydrogen-bonded adduct **46** from a carbonyl compound **45** and a carboxylic acid **44**, followed by the α-addition of the electrophilic carbonyl carbon and the nucleophilic oxygen atom of the carboxylic acid to the isocyanide carbon of **47** (Scheme 4) under formation of a cyclic transition state with all three parent compounds. The α-adduct **48**, which cannot be isolated, rearranges in an intramolecular transacylation to the stable α-acyloxy carboxamide **49**.

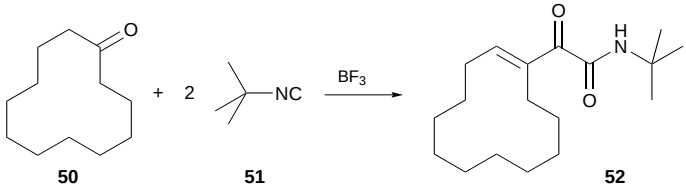


Scheme 4. Suggested mechanism of the P-3CR.

The Passerini reaction is carried out at high concentrations of the starting materials and in inert solvents at or below room temperature. There rarely are limitations concerning the oxo compound; thus, perfluorinated aldehydes and ketones also react, for example.[76] Some sterically hindered and α,β-unsaturated ketones obviously are no substrates of the P-3CR.[77] Bicyclic, sterically extremely hindered ketones such as camphor or bicyclo[3.2.1]octanone-2 do not react with isocyanides in a Passerini reaction, even in the presence of $BF_3 \cdot OEt_2$.[78]

Besides normal C-isocyanides, Me_3SiCN (TMSCN), which is in equilibrium with TMSNC and is a formal derivative of the most basic isocyanide, namely isocyanic acid, also reacts with mineral acids in the presence of ZnI_2 to give 2-hydroxycarboxylic acid amides.[79]

If the ketone **50** is treated with two equivalents of the isocyanide **51** in the presence of $BF_3 \cdot OEt_2$ in nonpolar solvents, the β,γ-unsaturated α-oxocarboxylic amide **52** is formed.[80] One equivalent of the isocyanide is the source of the α-C atom in this reaction.



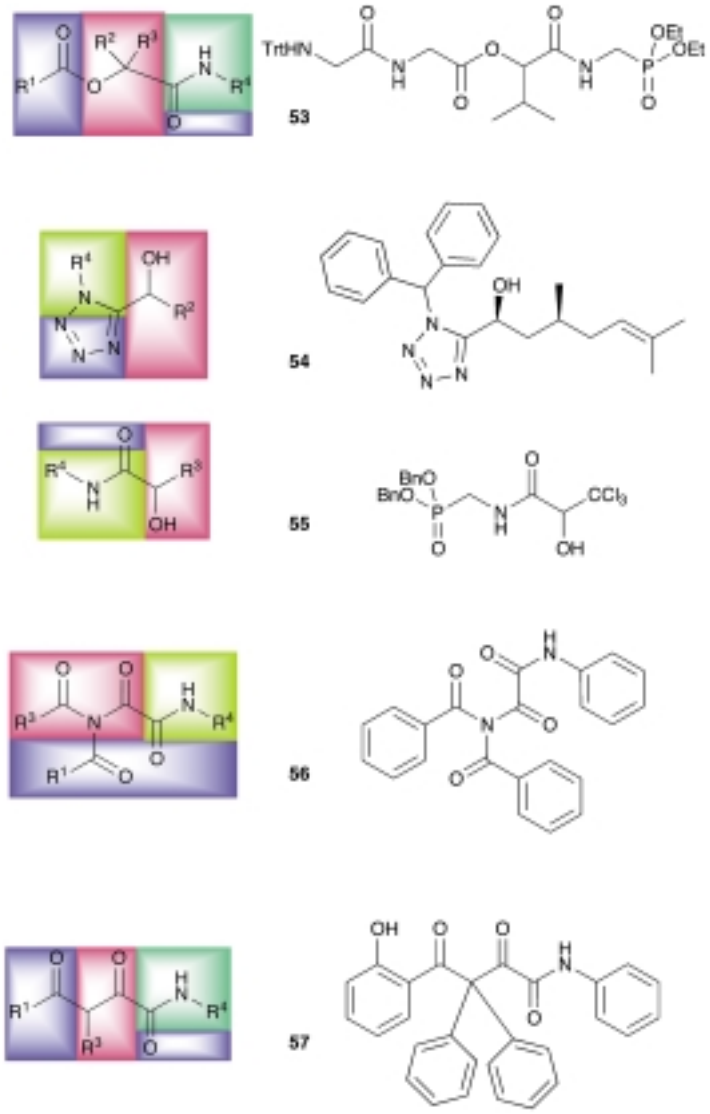
The α-acyloxy carboxamide group is a frequently recurring motif in many natural products, for example in the pharmacologically interesting depsipeptides. Thus, the P-3CR is particularly suitable for the synthesis of many compounds of this class and their derivatives. As an example, the synthesis of the complex phosphonic acid derivative **53** was achieved in one step from commercially available starting materials in 60% yield (Scheme 5).[81]

Lewis and Brønstedt acids catalyze the formation of α-hydroxytetrazoles such as **54** from isocyanides, HN_3, and oxo compounds.[82, 83] Highly chlorinated oxo compounds are converted to α-hydroxycarboxamides such as **55**, even without catalysts.[84] A little-known variant of the P-3CR is the reaction of aryl isocyanates with carboxylic acids and isocyanides under formation of *N*-alkyl or *N*-aryl *N*′,*N*′-diacyloxamides such as **56**.[85] The reaction of ketenes with isocyanides and carboxylic acids to α,γ-dioxocarboxylic amides such as **57** is also counted among the P-3CRs.[86, 94]

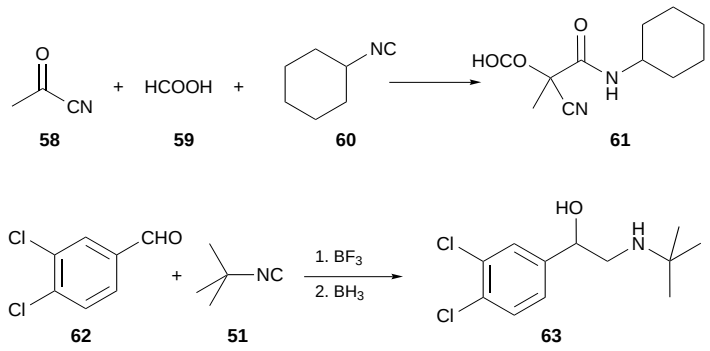
Acetyl cyanide (**58**) as the oxo component was transformed into α-cyano-α-alkyloxyamides in several examples in 75–89% yield.[87] Compound **61** can be isolated in 58% yield after the reaction of formic acid **59** and isocyanide **60**.

The easily performed reduction of Passerini products opens the way to a multitude of N-substituted β-hydroxyamines. In this way, **63** can be isolated in a one-pot reaction without isolation of the Passerini product in quantitative yield over both steps! Many analogous examples have been described.[88]

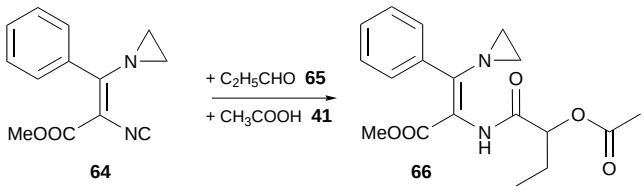
The parallel synthesis of dehydroamino acid derivatives such as **66** has been described.[89] The alkene geometry



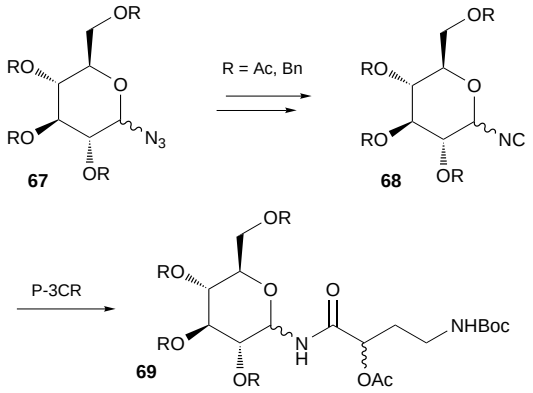
Scheme 5. Classic variations of the Passerini reaction. The components are color-coded: The acidic component is blue, the oxo component red, and the isocyanide component green or yellow. Trt = Ph_3C.



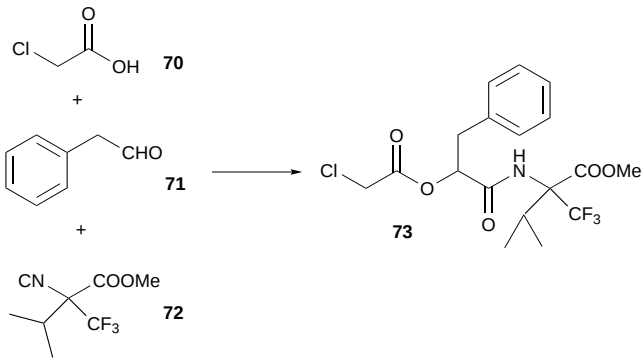
brought in by the isocyanides is retained in the target molecule. The dehydroamino acid moiety is introduced by α,β-unsaturated isocyanides like **64**. The dehydroamino acid motif occurs in many pharmacologically interesting natural products. Therefore, this reaction was also used for the synthesis of corresponding libraries.[8b]



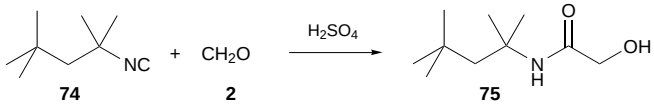
With anomeric glycosyl isocyanides **68** as isocyanide component in the P-3CR, the one-pot synthesis of very complex glycopeptide building blocks **69** (Boc = *tert*-butoxycarbonyl) is achieved. Even when one takes into consideration the two-step synthesis of the C-isocyanoglycals from the azides **67**, this entry to glycopeptide building blocks is without rival in its brevity and versatility.[90] The diastereoselectivities of the five cases described lie between 50:50 and 58:42 with yields of 23 to 80%.



Partly or perfluorinated fragments can easily be introduced into a desired target molecule. For example, **73** was synthesized from chloroacetic acid (**70**), phenyl acetaldehyde (**71**), and the 2,2,2-trifluoroethyl isocyanide **72** in 47% yield.[76b]

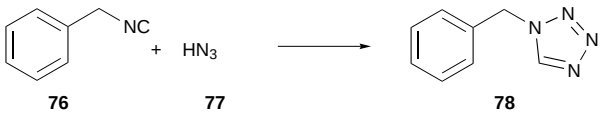


Finally, otherwise elusive *N*-*tert*-alkyl glyoxylic acid derivates such as **75** can be obtained elegantly in one step in a P-3CR of tetramethylbutyl isocyanide **74** with formaldehyde **2** under acidic conditions.[91]

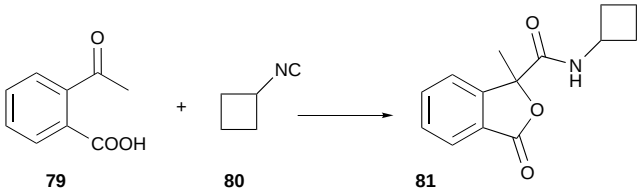


2.1. Cyclic Variations of the P-3CR

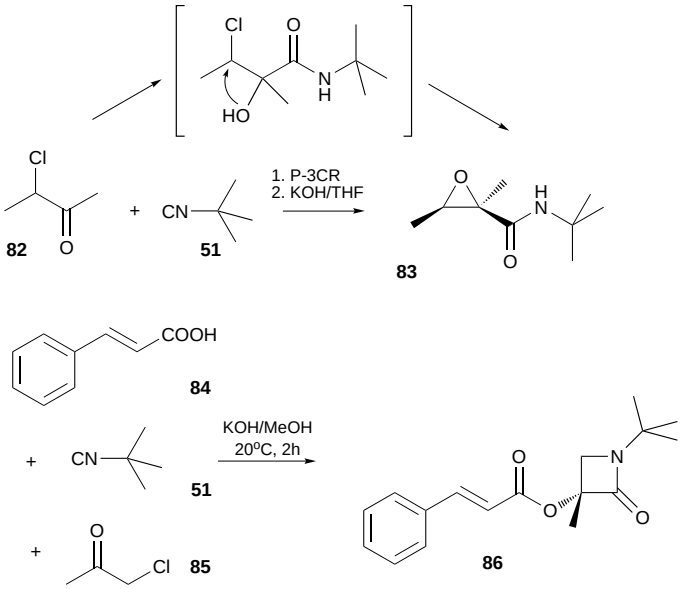
α-Hydroxytetrazoles such as **54** were described as early as 1931 as products of the reaction between hydrazoic acid, oxo compounds, and isocyanides.[92] With less reactive oxo compounds, the well-known tetrazole formation due to the reaction of the isocyanide **76** with HN_3 **77** to **78** according to Oliveri-Mandala and Alagna comes to the fore.[93] If $Al(N_3)_3$ is used as the azide source, unreactive oxo compounds can also be brought to react.[73]



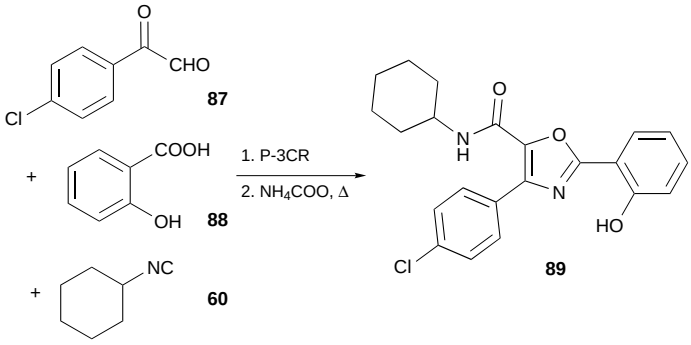
If bifunctional starting materials such as **79** with a ketone or aldehyde function and a carboxyl group are used in the P-3CR, lactones of various ring sizes, such as **81**, are obtained depending on the carbonyl–carboxylic acid distance.[95]



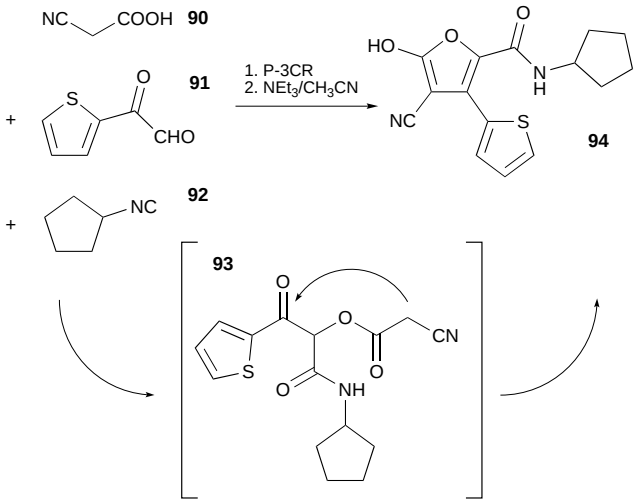
α-Epoxyamides such as **83** and 3-acyloxy-2-azetidinones like **86** can be synthesized from α-chloroketones (**82** and **85**, respectively), isocyanides (**51**) and carboxylic acids (**84**) depending on the conduction of the reaction.[96, 97]



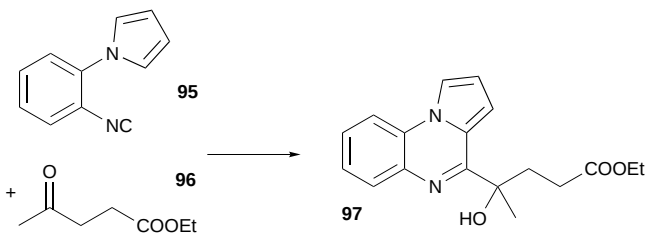
Oxazoles such as **89** can be generated very elegantly and with high diversity from α-oxoaldehydes (**87**), carboxylic acids (**88**), and isocyanides (**60**). The *N*-alkyl-2-acyloxy-3-aryl-3-oxopropionic amides formed intermediately react smoothly and with good yields with ammonium formate in acetic acid under reflux, leading to the 2,4,5-trisubstituted oxazoles.[98] All three substitutable positions of the oxazole can be varied independently in this two-step sequence.



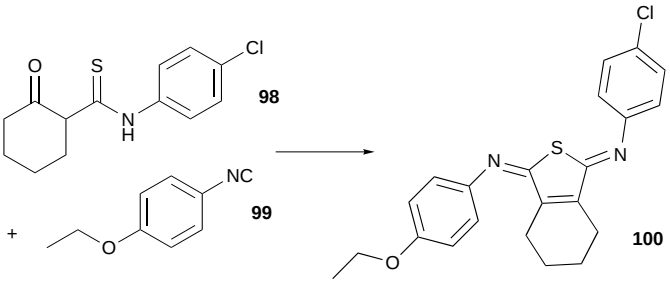
Cyanoacetic acid **90** as acid component, α-oxoaldehydes (**91**), and isocyanides (**92**) lead to the expected Passerini products (**93**), which cyclize to 2-hydroxyfurans such as **94** upon the addition of base in a Knoevenagel condensation.[99]



A Japanese group has described an interesting intramolecular variation of the P-3CR which leads to heterocyclic CNS-active substances: The 1-(2-isocyanophenyl)pyrrole **95** obtained from 1,2-phenylenediamine reacts with oxo compounds (**96**) in the presence of $BF_3 \cdot OEt_2$, leading to 4-(1-hydroxyalkyl)pyrrolo[1,2-*a*]quinoxalines like **97**.[100] Optimum catalytic properties were shown by $BF_3 \cdot OEt_2$ towards $TiCl_4$, $SnCl_4$, $AlCl_3$, and $ZnCl_2$. The pyrrole-CH group in 2-position reacts as a nucleophile or as the acid component.



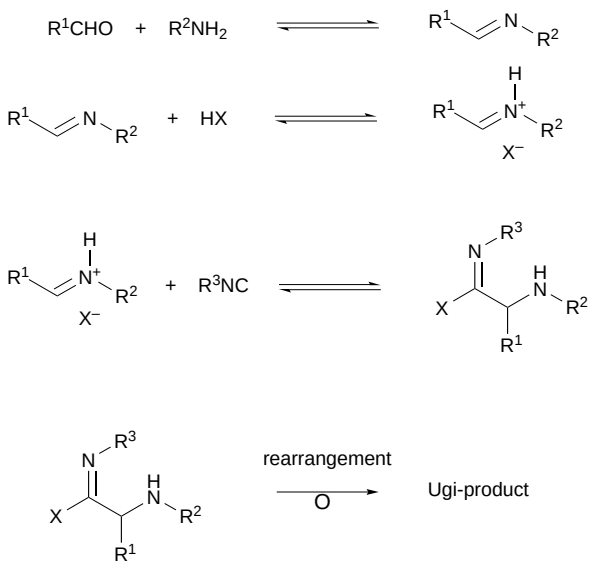
In another cyclic variation of the P-3CR, a β-oxothioamide (**98**) reacts intramolecularly as the acid and the oxo component to give benzo[*c*]thiophenes like **100**.[101] The tautomeric pair thioamide $\rightleftharpoons$ α-sulfanylimide functions as the acid component.



The Passerini reaction has had a renaissance in the last few years. Compared with the Ugi reaction, however, the number of different suitable types of acid components is modest. The carbonyl group of the ketones and aldehydes in the P-3CR and the imine group of the imines in the U-4CR are isoelectronic. Thus, the chances of finding further new acid components that can be utilized in the P-3CR are high. Generally, many variations of the U-4CRs should also be possible as P-3CRs under accordingly modified reaction conditions. Finally, there are many as yet undiscovered ways to reach new basic structures starting from bifunctional compounds and using secondary reactions.

3. The Ugi Reaction

In 1959, Ugi et al. described the most important variants of the four-component condensation, the U-4CRs.[102] Within a few weeks most of the condensation types known today were discovered. Carboxylic acids, hydrazoic acid, cyanates, thiocyanates,[103] carbonic acid monoesters, salts of secondary amines, water, hydrogen sulfide as $Na_2S_2O_3$ and hydrogen selenide as the acid components in the U-4CR react with ketones or aldehydes, primary and secondary amines, hydrazines, and hydroxylamines as the amine components, and C-isocyanides.[104] The Bayer AG company carried out investigations on the reaction mechanism and the theory of the stereoselectivity of the U-4CRs. In these investigations, extensive, analytically insoluble systems of equations were solved numerically with one of the first Zuse computers that were commercially available at the time.[105] A strongly simplified reaction mechanism for U-4CRs with carboxylic acids as the acid component is shown in Scheme 6. In the first step the oxo component and the amine condense to the imine, the Schiff base, via a hydroxy aminal. It is also possible that the hydroxy aminal can be transformed directly in the course of the reaction without formation of a Schiff base under certain circumstances. Imines can be understood as carbonyl analogues. Like most imine reactions, the U-4CR runs better upon activation of the Schiff base. For this, the acid component protonates the nitrogen atom of the Schiff base,



Scheme 6. Simplified mechanism of the U-MCR and its main variants: The variability of the basic structures of the U-MCR depends above all on the acid component, but also on the properties of the other components.

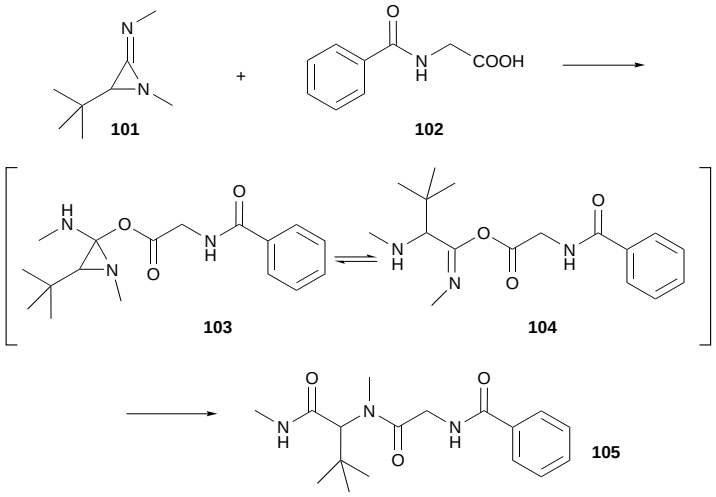
thus increasing the electrophilicity of the C=N bond. Another way to increase the electrophilicity of the imines is the addition of Lewis acids such as $TiCl_4$ or $BF_3 \cdot OEt_2$. Depending on the solvent, the ions can be present as a salt pair or separately. The electrophilic iminium ion and the nucleophilic acid anion add to the isocyanide carbon atom. The α-adduct thus formed can be seen as a hetero analogue of an acid anhydride in which an *exo*-oxygen atom has been substituted by an NR group. Acid anhydrides are strong acylating agents, as are their heteroanalogues formed here. The closest acylable atom is the nitrogen of the former amine. After an intramolecular acylation and subsequent hydroxylimine $\rightarrow$amide rearrangement the stable Ugi product is obtained. This type of intramolecular acylation was first described in 1910 by Mumm and was subsequently called the Mumm rearrangement.[106] All elementary steps of this reaction sequence are equilibria; however, that of the last step, the rearrangement to the stable α-acylaminoamide, lies exclusively on the product side. In this respect this type II MCR is very different from other MCRs. The driving force of the total reaction sequence is the oxidation of the isocyanide C^{II} atom to the amide C^{IV} atom.

It is instructive to follow the changes in nucleophilia and electrophilia of the components during the U-4CR. In the course of the individual steps the reactive centres of the acid component and the imines change the sign of their reactivity several times. At first the C=N bond of the imine behaves like a base towards the acid component. Then the protonated Schiff base functions as the electrophilic and the acid anion as the nucleophilic component of the α-addition. Due to the α-addition to the isocyanide, the amine nitrogen atom becomes the nucleophilic reaction partner of the electrophilic *O*-acylcarboxylic acid amid system in the α-adduct. In the course of the cycloaddition and the elimination, the reactive centres change their philia signs once again.

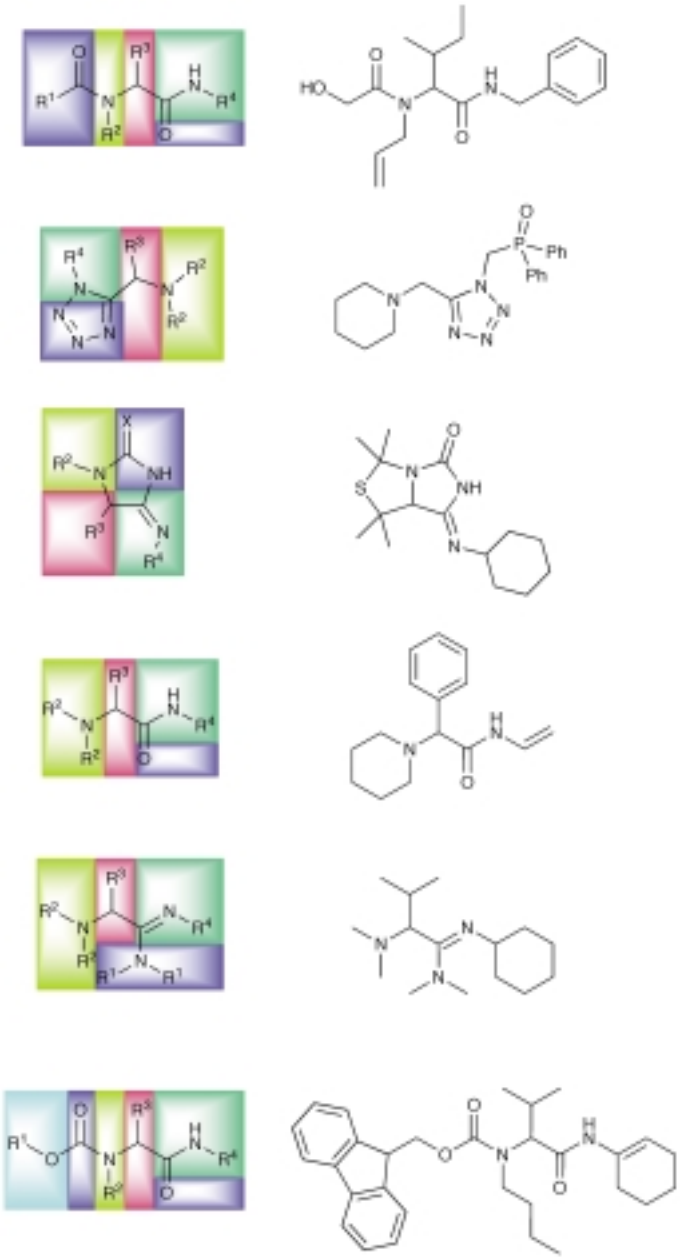
In the course of the U-4CR, one C–C bond and several heteroatom-C bonds are newly formed.

Reactivity series for isocyanides have been set up. In competitive experiments, the product distribution of different isocyanides was examined in the U- and the P-MCR as a function of the solvent and the concentration.[107] The reactivity is mainly influenced by inductive and mesomeric and to a lesser extent by steric effects. The reactant concentration is much more important for the reactivity than the properties of the solvent! McFarland was the first to examine the product distribution of the U-4CR depending on different reaction conditions systematically.[83]

Iminoaziridines such as **101** also react with carboxylic acids like **102** to give the Ugi products (**105**). They are known to decompose to isocyanides and imines under thermal conditions or acid catalysis. In this work, detailed spectroscopic examinations of the elusive α-adducts (**104**) were carried out for the first time.[108]



The diversity of the basic structures of the U-4CR depicted in Scheme 7 is primarily due to the variety of the acid components and their rearrangement opportunities, but also to the structures of the amines as well as the many intramolecular variations. The classic U-4CR can be carried out in solution as well as on a solid phase. The following experiences made in over 40 years are valid for the reaction in solution: Low-molecular-weight alcohols, such as methanol, ethanol, or trifluoroethanol[109] are used as solvents. Aprotic polar solvents like DMF, chloroform, dichloromethane, THF, or dioxane have also been described as advantageous. In addition, the U-4CR can be performed in biphasic, aqueous solvent mixtures. The exothermic U-4CR usually proceeds fast, within seconds or a few minutes at room temperature or below. Therefore, external cooling is recommended for large batches. Generally the reaction proceeds better if the reactants are present in high concentrations, that is 0.5 to 2 molar. The precondensation of amine and oxo compound usually has a positive effect on the yields. The addition of Lewis acids can be advantageous, which is understandable according to the mechanism of the U-4CR discussed above. This is especially the case for electron-rich, weakly electrophilic Schiff bases. Recently, the rate-accelerating effect of microwaves on the U-4CR was described.[110]



Scheme 7. Diversity of the basic structures obtained in U-MCRs by varying the acid component. The components are color-coded: The acid component is blue, the oxo component red, the amine component yellow, and the isocyanide component green. N=N–N and R^1_2N in the second and fifth formulas, respectively, stem from the acids HN and $H_2NR^1_2Cl$, respectively; in the sixth example the acid R^1OCOOH comprises CO_2 (blue) and R^1OH (light blue).

3.1. Peptides, Peptoids, and Stereoselective U-4CRs

The classic version of the U-4CR described in many textboooks is the reaction of a primary amine, an oxo component (aldehyde or ketone), an isocyanide, and a carboxylic acid to give an α-amino acylamide. Two amide bonds are formed in the course of this reaction. The possibility of a peptide synthesis with the U-4CR was therefore recognized and discussed early on. Two strategies were followed, namely peptide segment coupling with U-4CR (4CC-SC) and the synthesis of peptide fragments by means of

stereoselective U-4CR (4CC-SSS), which were both discussed in detail in a review.[111]

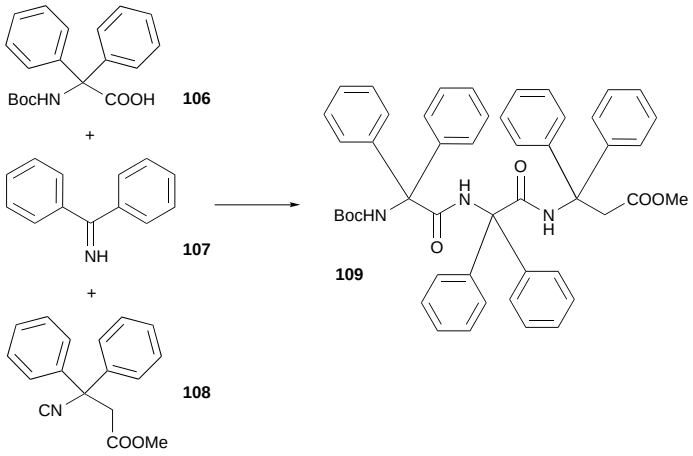
In the 4CC-SC, suitable peptide fragments with protected carboxy and amino termini are brought to react with an aldehyde and an isocyanide, in the course of which a cleavage point is inserted, for example by using *o*-nitrobenzaldehyde. After the U-4CR the coupling ballast is removed.

In the 4CC-SSS an aminoterminally protected peptide fragment is brought to react with a chirality-inducing amine, serving as a chiral ammonia equivalent, an isocyanopeptide, and an aldehyde. The directive amine residue is cleaved after the U-4CR. By repeating this sequence several times a peptide can be built up.

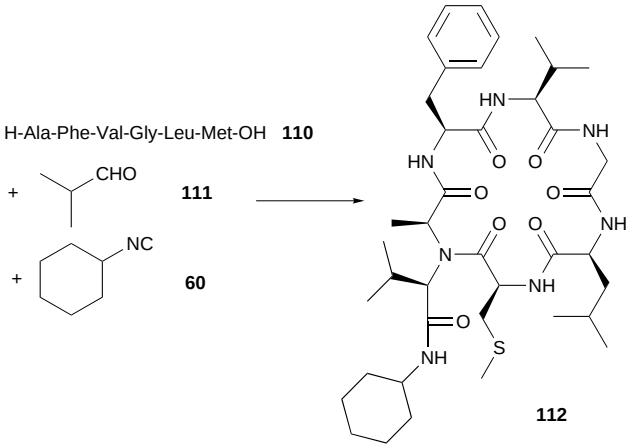
Until today the problem of control of the newly formed stereocenter has not been solved conclusively. Many paths were followed: So far, sugar amines and α-ferrocenyl alkylamines, which can be cleaved and in principle recycled after the U-4CR, have shown themselves to be the most promising reagents.[112]

The potential of the Ugi reaction for the production of nonnatural α-amino acids was recognized very early. For example, Joullié et al. reported the synthesis of enantiopure heterocyclic α-amino acids by using chiral phenylethylamine.[113]

The U-4CR has also proved itself in the synthesis of α,α-dialkyl or -diaryl dipeptide fragments. In this way, α,α-diisopropyl and α,α-diphenyl dipeptides were synthesized, among others.[114] To our knowledge, this is the only method to obtain such sterically hindered peptide building blocks. The great steric strain becomes especially obvious when one attempts to build space-filling models of these compounds. A Japanese group has synthesized α,α-diphenyl dipeptides in a U-4CR under very high pressure.[115] The same group also synthesized compounds of this type under normal pressure and at room temperature: Precondensed diphenylimine (**107**) was treated with N-protected α,α-diphenylglycine **106** and methyl α,α-diphenyl isocyanopropionate (**108**), and the resulting tripeptides such as **109** were obtained at room temperature after 14 h in 55% yield following chromatography.[116]



Linear hexapeptides such as **110** can be cyclized to give 18-membered cyclohexapeptides such as **112** by means of the reaction of isocyanides (**60**) and aldehydes (**111**) in good yields.[117] This reaction proceeds via a 21-membered α-adduct.



If further reactions are to be carried out with the primary U-4CR product, preformed cleavage points play an important part. At these predetermined breaking points, new functional groups for follow-up reactions evolve. The development of such cleavable reagents has been worked on since the beginnings of the U-4CR. Table 4 gives an overview over the cleavable reagents described so far.

In 1996, Armstrong et al. described further applications for cyclohexenyl isocyanide (**113**) introduced by Ugi in 1961 as an isocyanide for subsequent cleavage to primary amides **114**. With this reagent, derivatizations to carboxylic acids, esters **115**, thioesters **116**, pyrroles **117**, and benzodiazepines **118** can be carried out after the U-4CR (Scheme 8).[118, 134] A münchnone[135] is discussed as an intermediate in this reaction. Because of the versatile transformation possibilities, Armstrong introduced the term "universal isocyanide" for **113**.[136]

Generally, one dimension is lost with invariable (e.g. resin-bound) components, that is with a "universal isocyanide" a U-4CR in fact becomes a reaction in which only three components and therefore only three substituents are variable. The cyclohexenyl isocyanide only provides one C atom in the product molecule.

Peptidomimetic libraries of α-methylated amino acid derivatives were described from the corresponding methyl ketones in solution as well as on Rink resin in 31–71% yield.[137] The corresponding α-methyl-α-alkyl(di)peptides are expected to show better pharmacokinetic properties than the natural peptides.

N-protected α-amino acids react with cyclic thiazolidines, 2*H*-1,3-oxazines[138] and 2*H*-1,3-benzoxazines of the Asinger type to give unusual peptide fragments containing nonproteinogenic α-amino acids.[139] The reaction of precondensed Schiff bases, for example of Asinger heterocycles, with unprotected amino acids, di- or tripeptides, and isocyanides is suitable for the one-step synthesis of unprotected oligopeptides. This constitutes a protecting-group-free peptide synthesis.[140]

A repetitive U-4CR with multifunctional N-protected α-isocyanamines such as **122**, opening a short route to Nielsen's polyamidonucleic acid (PNA), has been described.[141] This route is also suitable for the synthesis of highly diverse PNA

Table 4. Cleavable reagents for IMCRs described so far. One example each is listed with reaction conditions and yields.

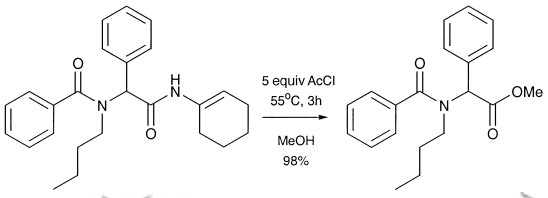
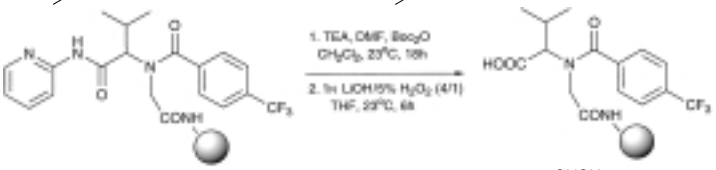
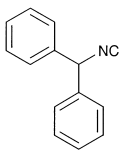
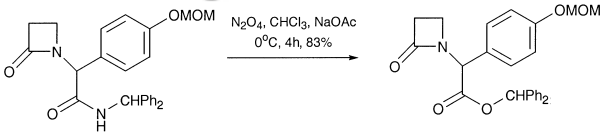
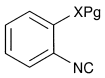
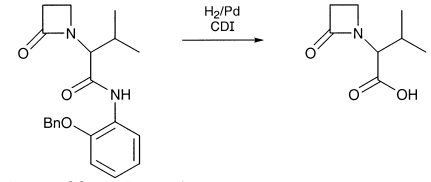
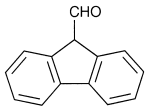
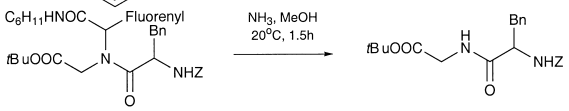
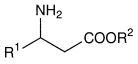
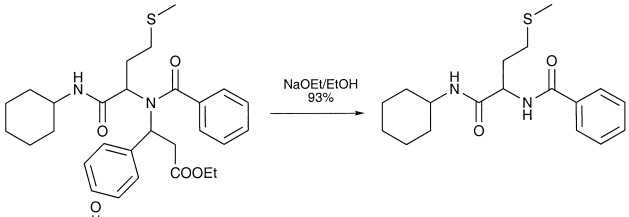
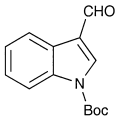
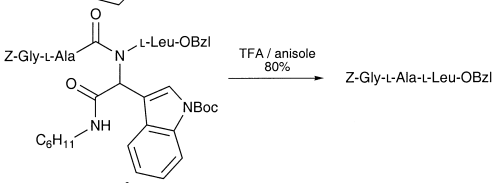
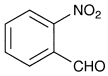
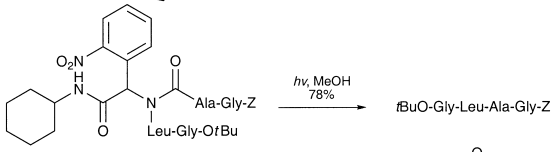
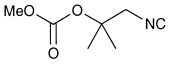
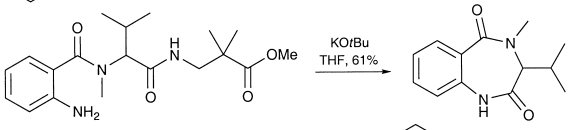
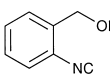
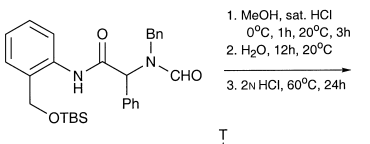
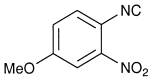
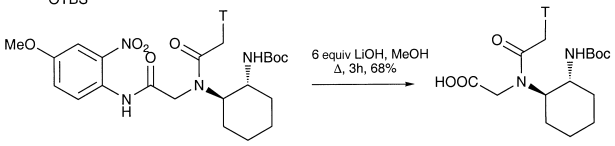
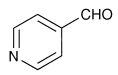
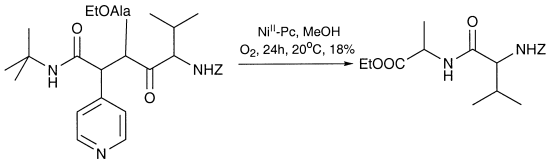
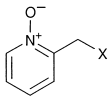
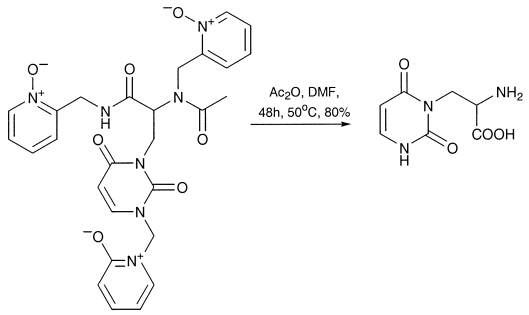
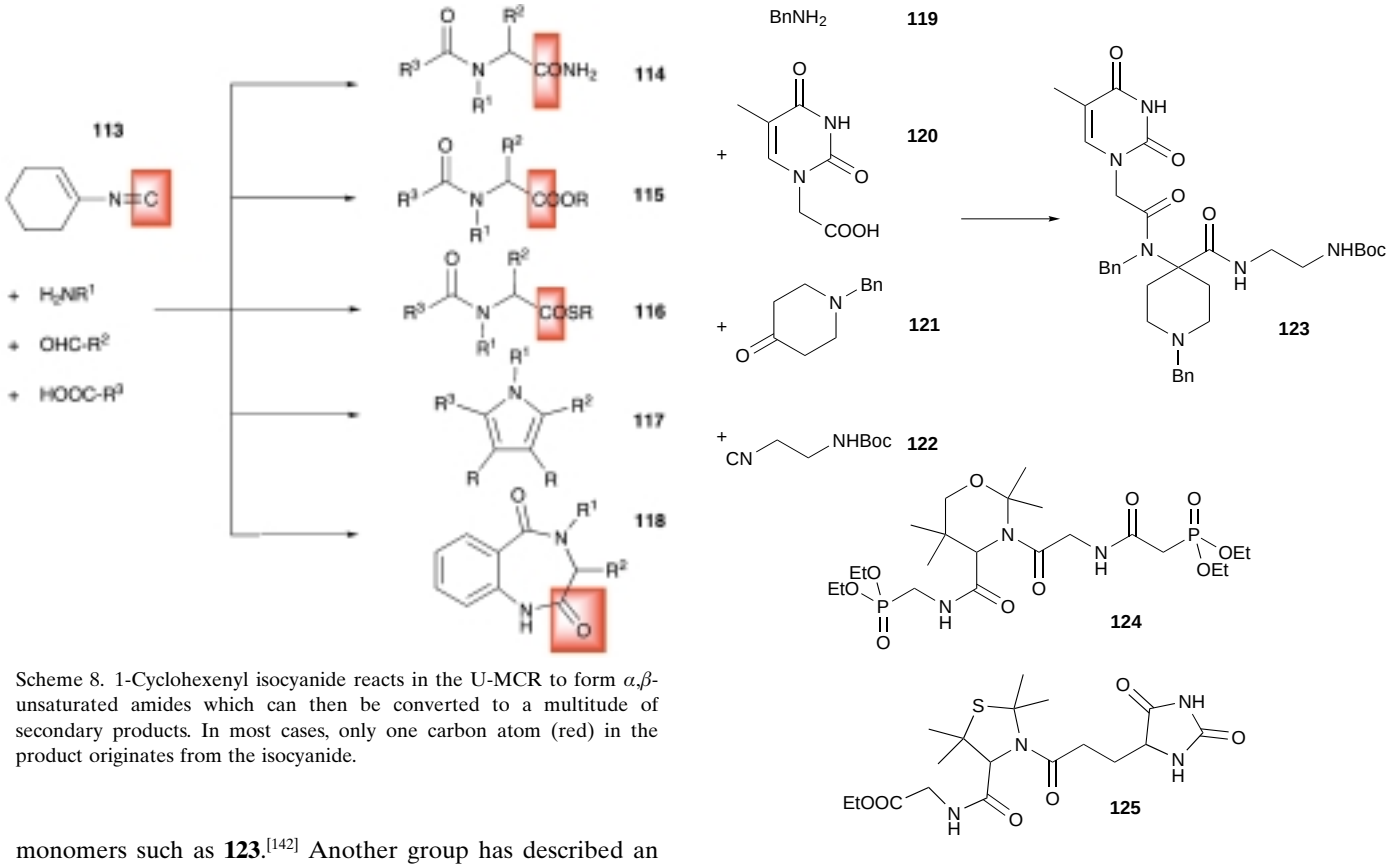
Entry	Cleavable reagent	Example[a]	Comment	Ref.
1			cleavable to various functional groups via münchnones (see Scheme 8); alternatively, benzyl isocyanides can be used	[118]
2			2-pyridinamides which can be hydrolyzed on solid phase and lead to pyrroles via münchnones or to carboxylic acids	[119, 120]
3			oxidative cleavage with N_2O_4 to the Ph_2CH esters is possible; in the same way *p*-nitrophenyl(PNP) isocyanide can oxidatively be converted to PNP esters	[121, 122]
4			U-4CR, cleavage of the protecting group with H_2/Pd and condensing cleavage with CDI	[123]
5			cleavage of the aldehyde–isocyanide moiety with NH_3 in MeOH at room temperature	[124]
6			mild cleavage of the amine residue, good ammonia equivalent	[125]
7			acidic removal of the aldehyde–isocyanide moiety	[126, 127]
8			photochemically cleavable	[128]
9			basic cleavage of the secondary amide bond to form esters and carboxylic acids with KO*t*Bu	[129]
10			cleavable isocyanide which leads to a high diastereoselectivity with sugar amines	[130]
11			isocyanide cleavable to the carboxylic acid	[131]

Table 4. (Continued).

Entry	Cleavable reagent	Example[a]	Comment	Ref.
12			O_2/Ni^{II} – phthalocyanine(Pc)	[132]
13			2-picolylamine-1-oxide (X = NH_2) and 2-picolylisocyanide-1-oxide (X = CN) as components of the U-4CR with subsequent acidic cleavage to the primary amine or the acid, respectively	[133]

[a] TEA = triethylamine, MOM = CH_2OCH_3, CDI = carbonyl imidazole, Bn = benzyl, Bzl = benzoyl, Pg = protecting group, TBS = tBuMe$_2$Si, T = thymine.



Scheme 8. 1-Cyclohexenyl isocyanide reacts in the U-MCR to form α,β-unsaturated amides which can then be converted to a multitude of secondary products. In most cases, only one carbon atom (red) in the product originates from the isocyanide.

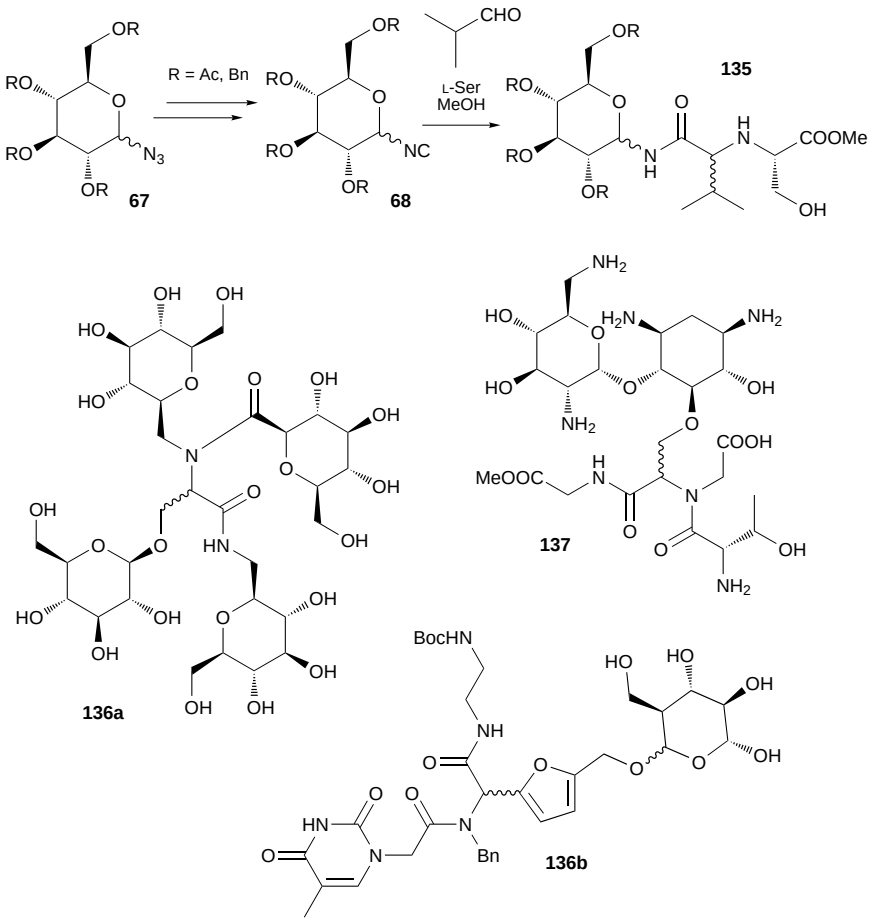
monomers such as **123**.[142] Another group has described an alternative route to PNA monomers.[131] In this reaction, nucleobase acetic acids are treated with amines, oxo compounds and cleavable isocyanides. After the cleavage of the amide group, PNA monomers result (Table 4, entry 11). This monomer synthesis is highly convergent, short and very variable, compared to the classic monomer synthesis.[143] In the same paper, the synthesis of phosphonopeptides like **124** as well as glutathione derivatives such as **125** by means of U-4CR was also published.

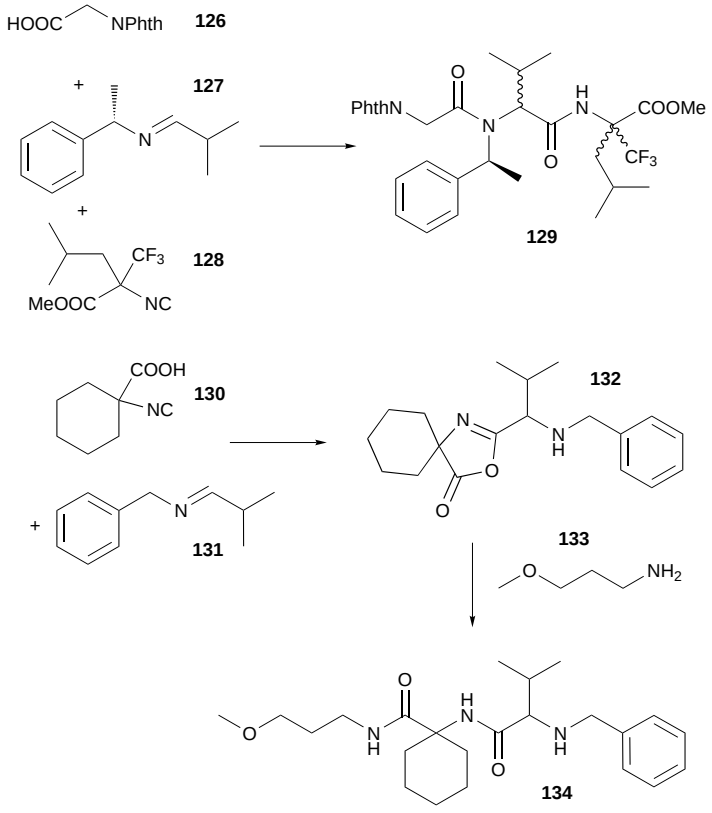
Fluorinated α-amino acid derivatives, which are otherwise hard to synthesize but pharmacologically very interesting, can be obtained with partly or perfluorinated oxo compounds. α-Trifluoromethyl-substituted α-amino acids such as **129** (PhthN = phthalimidyl) were inserted at the C and N termini of peptides by means of U-4CR.[76b]

When the bifunctional starting material 1-isocyanocyclohexane-1-carboxylic acid (**130**) is treated with the Schiff base

131 in the U-4CR,[144, 145] the intermediary α-adduct **132** can be isolated and treated with a further nucleophile, for example a second amine **133**, in the same reaction vessel to yield **134**. In sum, this synthesis of **134** corresponds to a U-5CR. The intermediate **132** is the first stable α-adduct to be isolated and described.

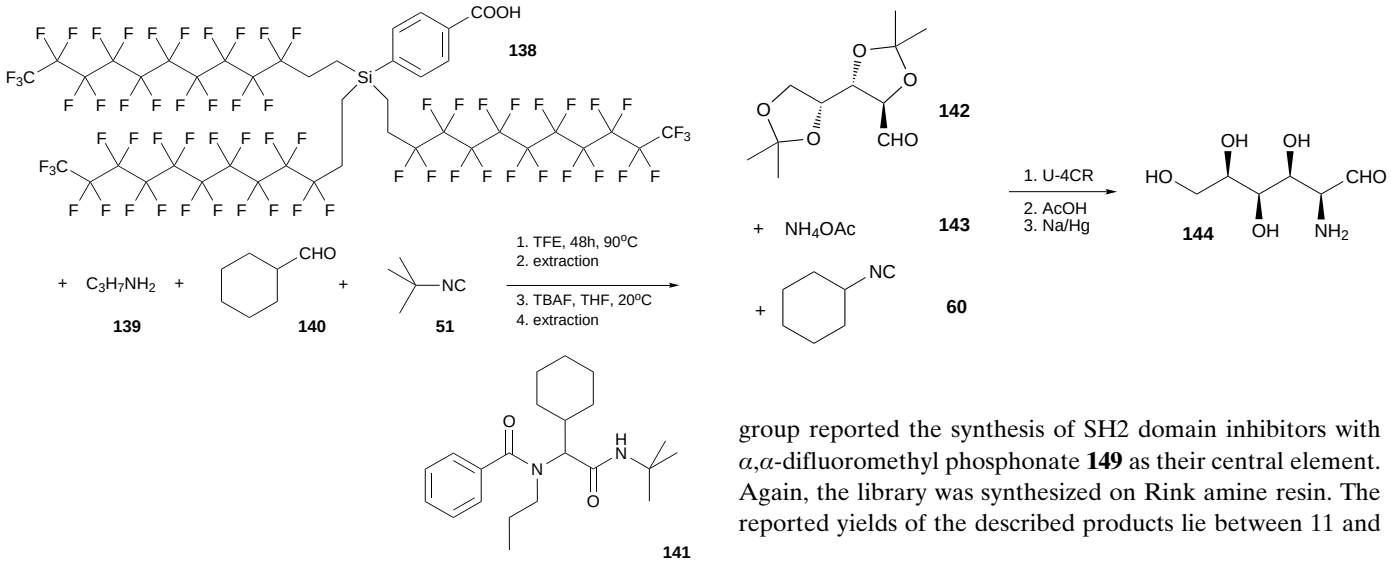
The fast and diverse construction of glycopeptide libraries is achieved with glycosyl isocyanides as U-4CR components. As was to be expected, the diastereoselectivity is very low.[90, 146] On the other hand, highly complex glycopeptide fragments were built up in one step and with satisfactory yields considering the complexity, whereas the time-consuming conventional synthesis would go over many steps. Thus, **135** was obtained in a U-3CR of serine methyl ester, the glycosyl isocyanide **68** and isobutyroaldehyde in 15% yield after chromatography. Another paper and a patent describe the utilization of the U-4CR for the synthesis of glycoconjugates.[147, 148] In this way, glycosyl derivatives of all four components were synthesized and successfully converted to the expected tetrapseudoglycoside **136a**. All glycosyl derivatives used were protected. In our experience this is often unnecessary as





the reaction also takes place in the presence of free hydroxy groups with very good yields. For example, the nucleobase glycoconjugate **136b** can be synthesized from the corresponding unprotected furfural sugar, benzyl amine, thyminoacetic acid and 2-Boc-1-isocyanoethylamine in nearly quantitative yield.[148] Park et al. synthesized Ras-Raf protein-binding Ugi libraries that were active against HIV such as **137** on polyethylene glycol (PEG) and in solution. The yields of the compounds synthesized in solution were no better than on PEG; however, the purification of the libraries was less complicated, being a simple precipitation with diethyl ether.[149]

Curran et al. emphasize the advantages of components with long-chained perfluorinated residues, for example **138**, in the U-4CR (TFE = tetrafluoroethylene; TBAF = tetrabutylammonium fluoride).[150] These fluorous labels make the purification of the substance libraries easier. The products of Ugi reactions ("Ugis") with fluorinated substrates (these reactions are also called "Flugis") can be liberated from excess reagent by means of liquid–liquid extraction with fluorous phases. Subsequently the fluorous tags are eliminated from the product. Analogous methods have also been described for the Biginelli reaction ("Fluginelli" reactions). So far the conventional method has not been compared to the "Flugi" method concerning purity and yield as well as synthetic complexity and reagent costs. It remains to be seen whether this technique achieves greater importance.



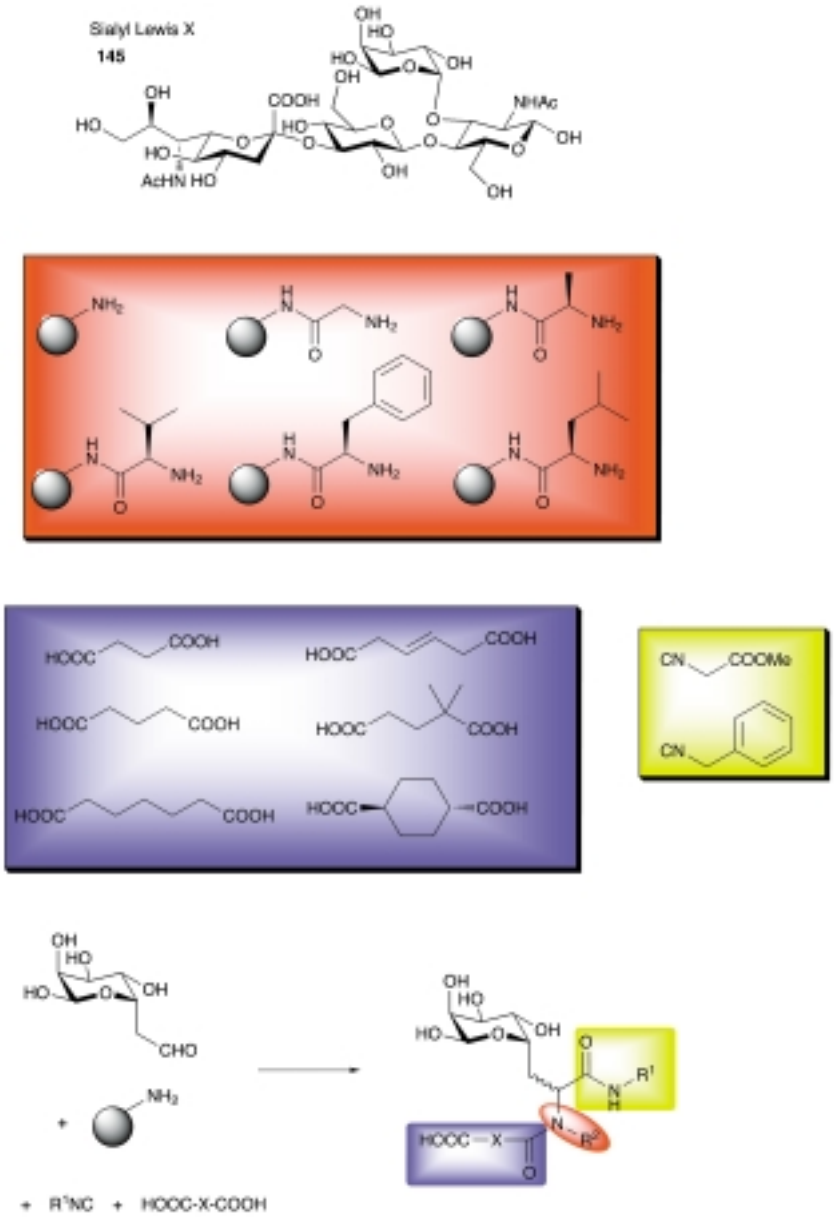
141

Russian authors have utilized the U-4CR in the synthesis of glucosamine **144**. Ammonium acetate reacted with the isocyanide **60** and the chiral aldehyde **142** derived from glucose to give the Ugi product. Acidic cleavage of its acetal functions and reductive cleavage of its amide functions then yielded **144**.[151]

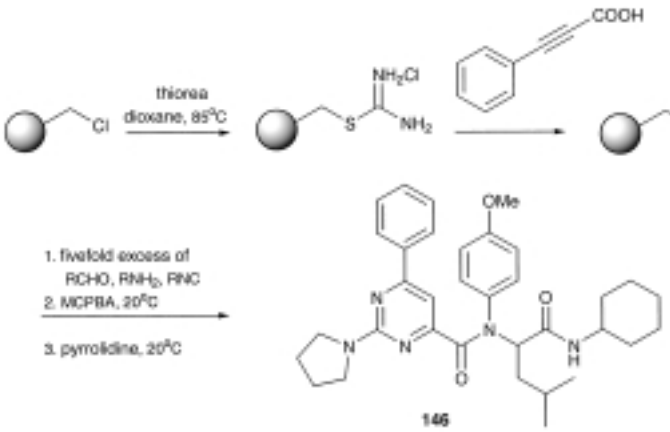
Sialyl-Lewis-X **145** plays a prominent role in cell–cell recognition. Therefore, libraries of sialyl-Lewis-X mimetics are the goal of diverse synthetic efforts. *C*-Glycoside-peptide ligands were prepared by means of U-4CR on Rink resin (Scheme 9).[152] With the resin-bound amine component, remarkably, it is possible to use the unprotected dicarboxylic acids, which react only once on the solid phase due to the high degree of dilution. A corresponding direct synthesis with unprotected dicarboxylic acids is impossible in solution.

The application of resin-bound starting materials in MCRs has been described by various authors. Besides Merrifield resin, the preferred resins are Wang, Tentagel, and Argogel. The Ugi reaction for the synthesis of pyrimidines such as **146** on highly loaded Merrifield resin was described by a group at Hoffmann–LaRoche (Scheme 10).[153]

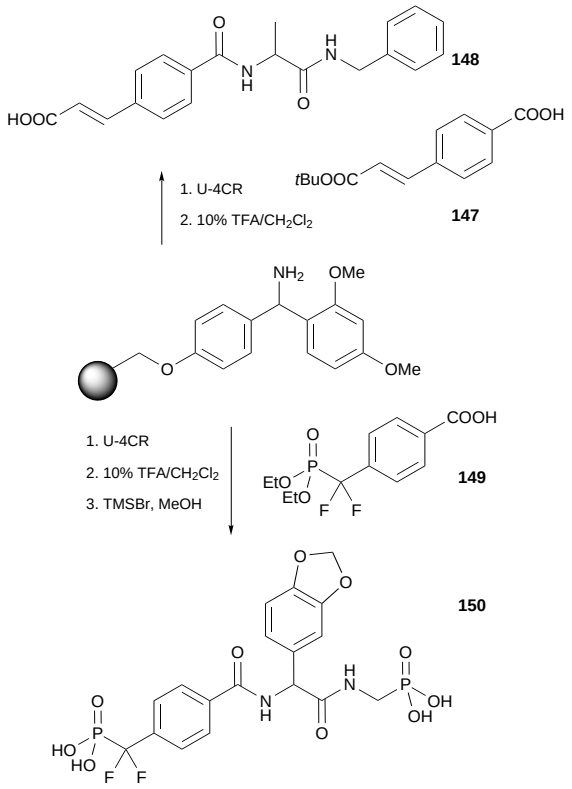
The production of potent inhibitors of the hematopoetic (blood-forming) protein-tyrosine phosphatase by means of U-4CR was described by a group at the company Ontogen. The overexpression of the enzyme occurs in acutely leukaemic cells. A common element of the library is *tert*-butyl-4-carboxycinnamate (**147**), which appears in all compounds, for example **148**. The library was again built up on Rink resin (TFA = trifluoroacetic acid).[154] The application of radio frequency tags was described for an analogous U-4CR library.[155] Another research group reported the synthesis of SH2 domain inhibitors with α,α-difluoromethyl phosphonate **149** as their central element. Again, the library was synthesized on Rink amine resin. The reported yields of the described products lie between 11 and



Scheme 9. Synthesis of sialyl-Lewis-X analogues by solid-phase U-4CR.

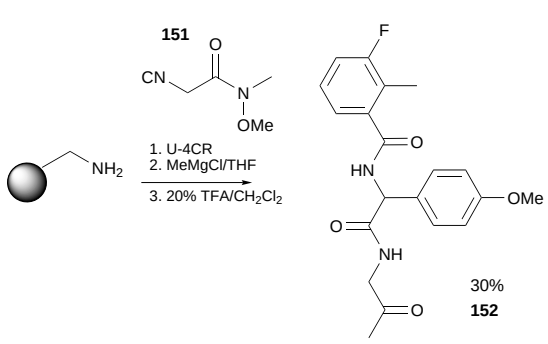


Scheme 10. Synthesis of **146**; MCPBA = *meta*-chloroperbenzoic acid.



95 % with an HPLC purity of usually far beyond 80 %.[156] For example, **150** was isolated in 77 % yield.

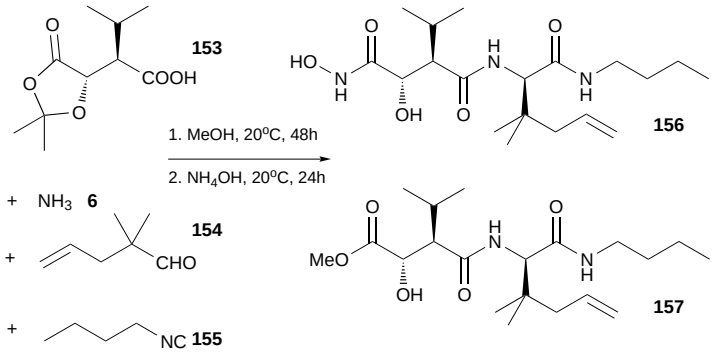
The build-up of α-oxodipeptides **152** as serine proteinase inhibitors is achieved by introduction of Weinreb's amido isocyanide **151** into a U-4CR library and subsequent derivatization with Grignard reagents on Rink amine resin. Compounds of this type are interesting as anticonvulsants.[157]



3.2. Variation of the Amine Component

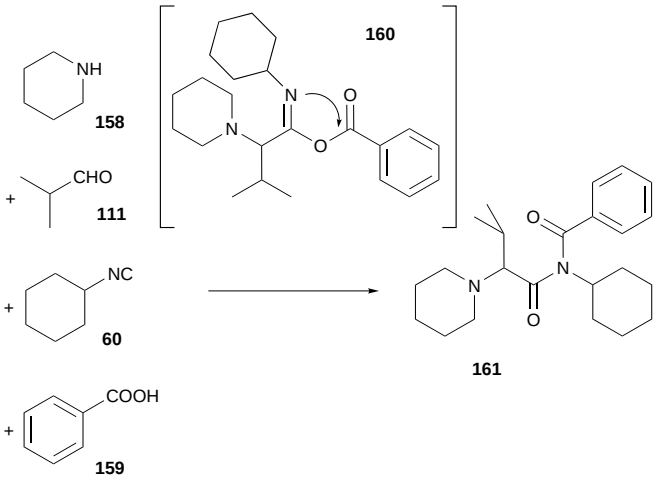
The structural diversity of the U-MCRs is brought about by the different types of acid compounds used, but also by the multitude of "amine-like" components.

Ammonia as the simplest amine reacts in the U-4CR. Libraries of analogues of the naturally occurring metalloproteinase inhibitor marimastat were described by a group at the company British Biotech. In a two-step reaction, ammonia (**6**), the carboxylic acid **153**, the aldehyde **154**, and the isocyanide **155** were converted in a U-4CR and transformed to the hydroxamic acid **156** with hydroxylamine without isolating the intermediate. The product was isolated in moderate to good yields. The side reaction is the ammonia-catalyzed formation of the methyl ester **157**, which can be suppressed by means of precondensation of the Schiff base.[158] In some cases, however, the turnovers and yields are low with ammonia as the amine component. Alternatively, 2,4-dimethoxybenzylamine, for example, can be used as the amine component and the corresponding amide cleaved in the familiar way with acid catalysis.[159]



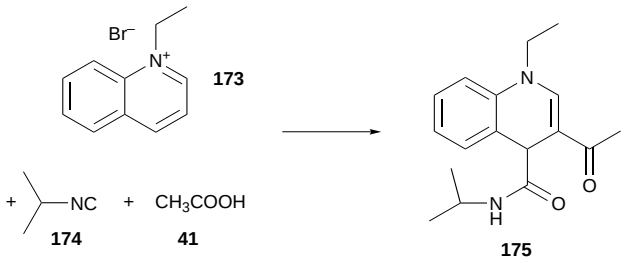
Primary amines react as described above to afford the corresponding α-amino acylamides. When secondary amines such as **158** are used in the place of primary amines, the amine nitrogen of the α-adduct (**160**) cannot be acylated anymore. Instead, the former isocyanide nitrogen atom is acylated, and α,α'-diacylimides such as **161** result. This reaction variation proceeds much faster if the enamines are precondensed.[83, 160]

Ammonia derivatives, such as hydrazine, hydrazides, or hydroxylamine, react in an analogous way to yield the expected products, for example **163** and **166**. Hydrazine leads to the mono, bis, tris, and tetrakis products as well as mixed Ugi – Mannich products in reactions that are hard to control (UM-5CR). On the other hand, monoacylate hydrazines can be converted selectively only once to the highly substituted

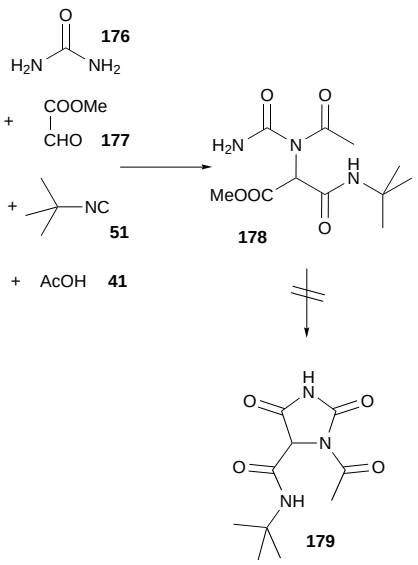


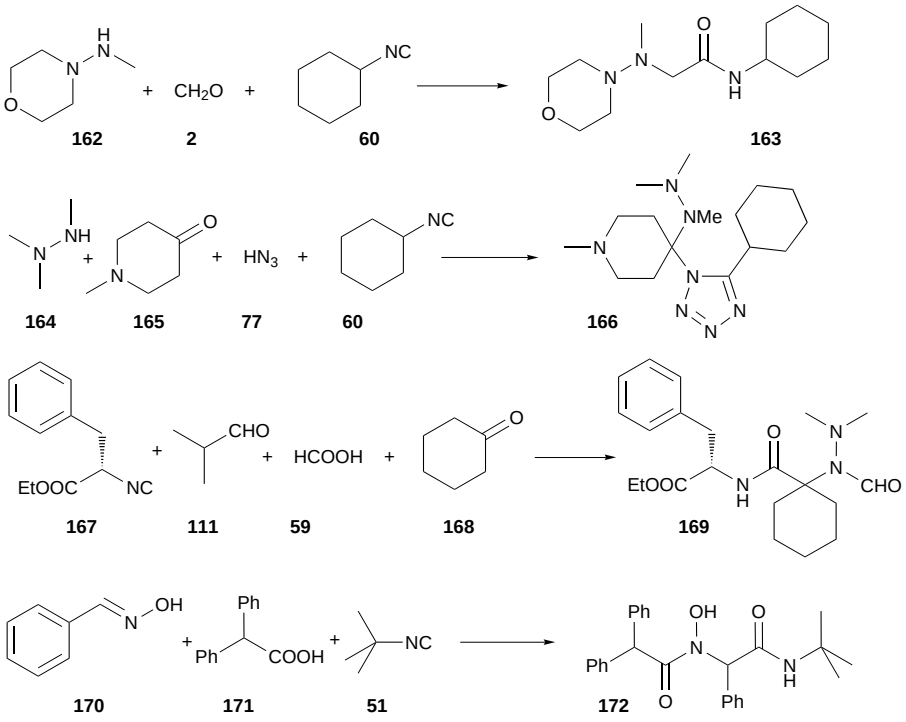
hydrazines in an Ugi reaction.[161] Not only unnatural amino acids are easy to build into peptides, *N*-aminopeptides like **169** are also accessible in one step with the hydrazine variant of the U-4CR.[162] Depending on the reaction conditions, hydroxylamine leads to substituted hydroxylamines, α-hydroxylamino-*N*-hydroxyamidines, 2-hydroxylaminoamides, or 2,2-iminodicarboxdiamides.[38d] Sterically extremely hindered *N*-hydroxypeptides are accessible by means of an oxime U-4CR. The resulting *N*-hydroxy group can easily be reduced to the amide with $TiCl_3$.[163] Hydroxylamine and oximes such as **170** open routes to the pharmacologically extremely interesting class of hydroxamic acids (**172**). Hydroxamic acids are potent metalloproteinase inhibitors with possible applications in the therapy of proliferative and inflammatory diseases.[164] The hydroxamic acids available through U-4CR are otherwise hard to obtain with this substitution pattern and in this multitude.[104, 165]

Like conventional immonium ions, *N*-alkylquinolinium compounds such as **173** react in the U-4CR according to their electrophilic character. Theoretically, two isomeric products can arise through the reaction in the 2- or 4-position. In fact, the addition in 4-position leading to the formation of **175** takes place exclusively.[166]



Recently it was shown for the first time that urea (**176**) is also basic enough to function as the amine component in the U-4CR. However, under the experimental conditions the desired cyclization of **178** to **179** did not take place.[167]

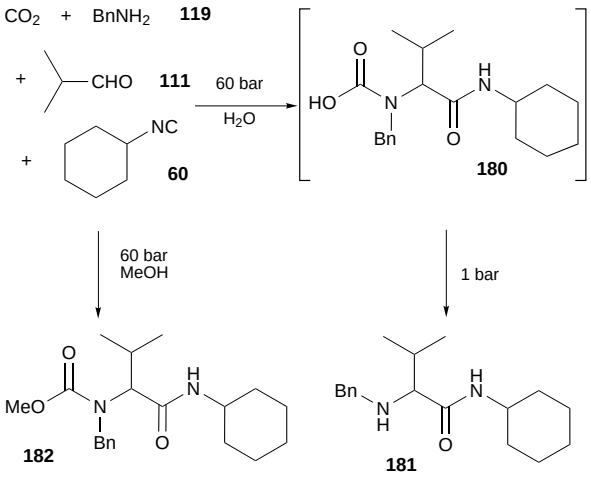




3.3. Variation of the Acid Component

The great structural variety of the U-MCRs is primarily due to the variety of the acid components (see Scheme 7). Aqueous mineral acids react with amines, oxo components, and isocyanides to give α-amino alkylamines. In this reaction, water formally reacts as the acid component.[83, 160, 168, 169]

An alternative and complementary method for the preparation of α-amino amides like **181** is the reaction of isocyanides with an amine, an oxo compound, and CO_2 under pressure. The carbamido

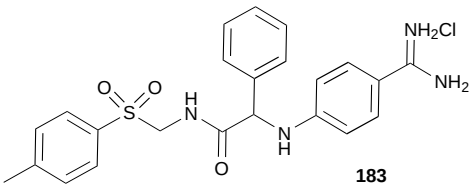


acid (**180**) formed intermediately is hydrolyzed after expansion of the pressure reactor.[170]

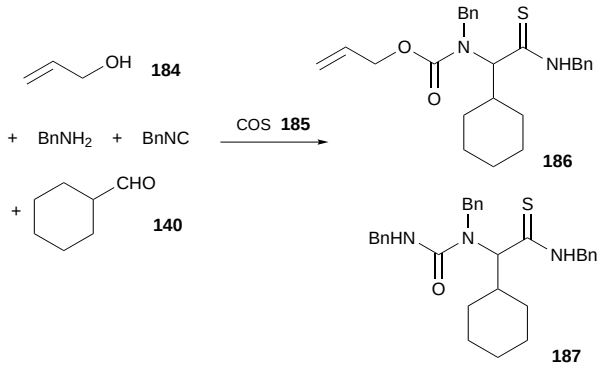
Whereas hydrogen sulfide can only be converted to α-amino thioamides as the acid component in the shape of thiosulfate, hydrogen selenide reacts smoothly to the α-amino selenoamides.[102]

In a CO_2 atmosphere, alcohols are in equilibrium with their monoalkyl carbonates. These can function as the acid component in the U-MCR (for example, see the formation reaction of **182**). As the carbonic acid is formed in situ, this reaction corresponds to a U-5CR.[102, 171] Whereas the yields are good with low-molecular-weight, liquid alcohols, they decrease sharply with higher molecular weight, solid alcohols. Nevertheless, 9-fluorenyl methanol can serve as the alcoholic component for the introduction of the 9-fluorenyl methoxycarbonyl(Fmoc) protecting group into amines.[172]

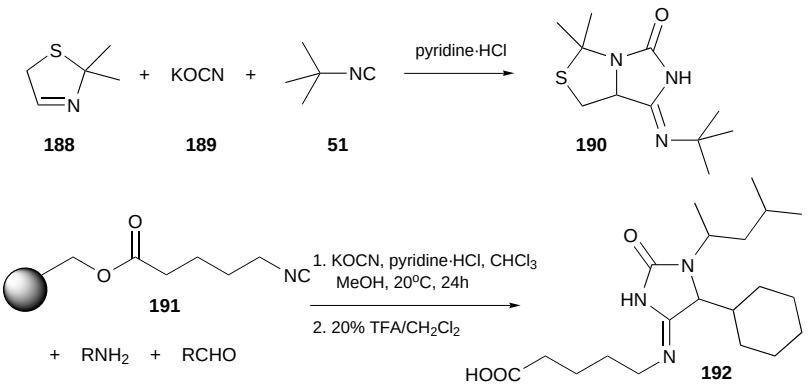
Weber et al. have described the synthesis of very potent thrombin inhibitors with water as the acid component. For this, they used a novel technique to discover new active substances, the Genetic Algorithm.[173] This way the most potent substance in a large collective of compounds can be found within a short space of time. The described virtual library comprised 160000 compounds. Within a few synthesis and screening cycles, the inhibitor **183**, which is effective in nanomolar concentrations, was found.[174]



It was also researched whether dithio- and thiocarbonic acids can be used as acid components in the U-4CR instead of carbonic acids. In analogy to the formation of the carbonic acids from carbon dioxide and alcohol, CS_2 and COS were treated with alcohols. With CS_2, mixtures of α-aminothioamides, thioureas and α-thioacylamide thioureas evolve. The authors discuss several mechanisms for their formation.[172] In the case of carbon oxide sulfide **185**, the expected product **186** can be isolated besides the α-thioacylamide urea **187** and the corresponding α-aminothioamide. In the case of the urea, a second equivalent of the amine reacts with the α-adduct. The reaction seems to be useful for the synthesis of α-amino-thioamides and α-amino thioacylcarbamates.



Cyanic acid and hydrogen thiocyanate react as acid components with primary amines, oxo components and isocyanides, yielding iminohydantoins and thioiminohydantoins, respectively.[103] The reaction is generally carried out with amine hydrochlorides and cyanate or thiocyanate salts, respectively; alternatively the amines, the cyanate- (**189**) or thiocyanate salts, respectively, and pyridinium chloride can also be used. Often the pure products precipitate from the reaction solution. With cyclic imines such as **188**, bicyclic hydantoins such as **190** are formed.



The synthesis of hydantoins such as **192** from the four components isocyanide, amine, aldehyde, and cyanate has also been described on solid phase. Wang resin-bound isocyanide **191** is treated with pyridinium chloride and potassium cyanate at room temperature. After removal of the products with 20% TFA in dichloromethane, the hydantoins can be isolated in 41–81% yield. The analogous thiohydantoin synthesis on Wang resin led to unsatisfactory results, compared to the synthesis in solution.[175]

Hydrazoic acid reacts as the acid component with primary or secondary amines and oxo compounds as well as isocyanides, affording 1,5-disubstituted tetrazoles.[103, 161a, 168, 176]

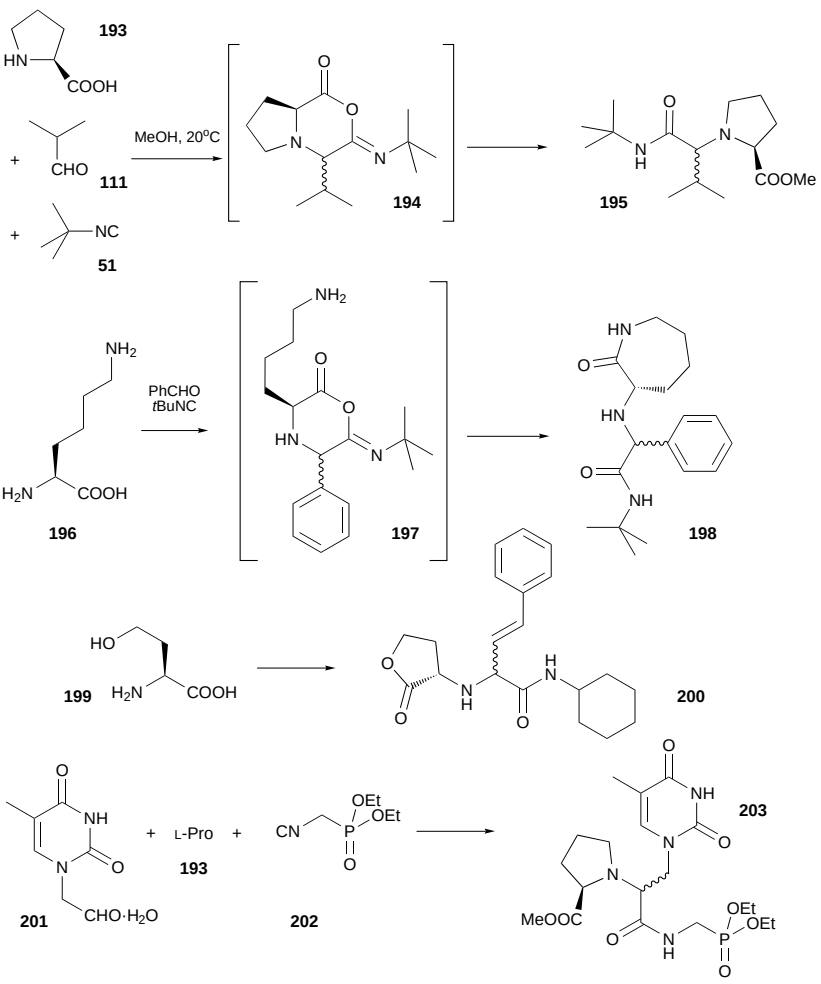
Formaldehyde and primary amines can react with each other twice and yield bistetrazolyl amines. With ammonia and small aldehydes like formaldehyde, tristetrazolyl amines are obtained. The solution of HN_3 in benzene which is often described can be replaced advantageously by $TMSN_3$ in methanol, which is easy to handle and less toxic.[177]

The solid-phase (Wang resin) synthesis of tetrazoles and α-alkylamino amides is achieved with moderate yields. The corresponding syntheses in solution proceed with much better yields.[178]

An important group of U-MCRs runs via bifunctional carboxylic acids.

In analogy to the synthesis of β-lactams from β-amino acids by means of U-4CR, it was attempted to prepare α-lactams from α-amino acids in the initial phase of the 4CR. However, iminodicarboxylic acid derivatives were isolated instead of the expected α-lactams.[179]

The nonisolable, six-membered intermediate **194** from the α-amino acid **193**, the aldehyde **111**, and the isocyanide **51** is transformed to the stable product **195** by the solvent alcohol in a nucleophilic reaction. The new-formed stereocenter is often generated with surprisingly high diastereoselectivity. The selectivity can be reversed by addition of metal salts.[180] Apart from cysteine, all known natural and many unnatural α-amino acids can undergo this reaction with aldehydes, mostly with good to excellent yields.[181]

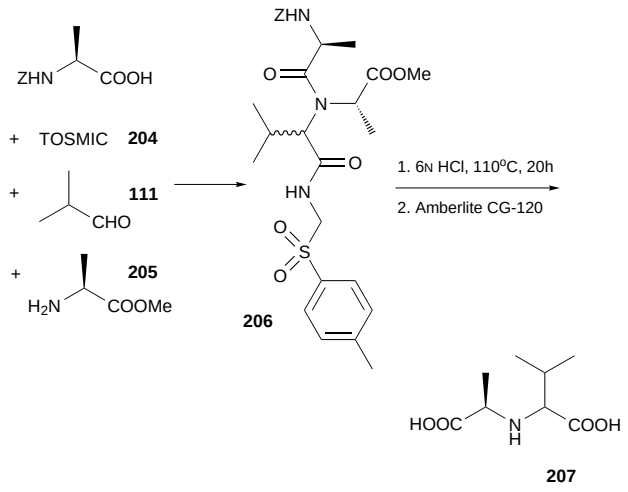


α-Amino acids with nucleophilic side groups, such as lysine (**196**) and ornithine, react intramolecularly via the elusive cyclic intermediate (**197** in the case of **196**), affording the corresponding seven- (**198**) or six-membered α-aminolactam.[182] Whereas serine and threonine are transformed intermolecularly to the corresponding iminodicarboxylic acid derivatives without participation of the hydroxy function, homoserine (**199**) as the α-amino acid component leads to the α-amino-γ-lactam **200** in the solvent trifluoroethanol.[183] Hundreds of potential virostatics, for example **203**, were synthesized with nucleobase-derived aldehydes (**201**), α-amino acids (**193**), and isocyanides (**202**), and screened for their activity.[184]

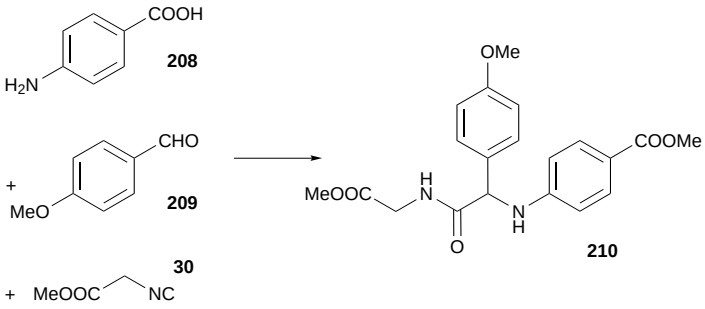
The methods impress with their simplicity: After the insoluble α-amino acid is dissolved through the reaction with aldehyde and isocyanide in alcohol, the conversion is finished and surplus solvent is removed. The reactions are fast and take place at room temperature. In this way many thousands of iminodicarboxylic acid derivatives were synthesized and screened.

With this reaction type, mixing libraries were synthesized in solution.[185] Three each α-amino acids, aldehydes, and isocyanides,respectively, were converted in one reaction vessel. Of the expected 54 compounds ($3 \times 3 \times 3 \times 2$), 39 were identified by means of GC-MS analysis of the mixing library and corresponding daughter libraries.[186]

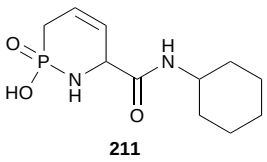
Besides the similarity of these Ugi products to commercial acetylcholine esterase(ACE) inhibitors, the iminodicarboxylic acids are important natural compounds: The opines are constituents of many poisonous fungi. They are also isolated from virus-induced plant galls. Owing to the pharmacological importance, many efforts towards the synthesis of opines were made. An alternative, multistep synthesis of the opine **207** by means of a classical U-4CR with benzyloxycarbonyl(Z)-protected l-alanine and tosylmethyl isocyanate (TOSMIC) **204** and subsequent secondary transformations was described by a Japanese group.[187]



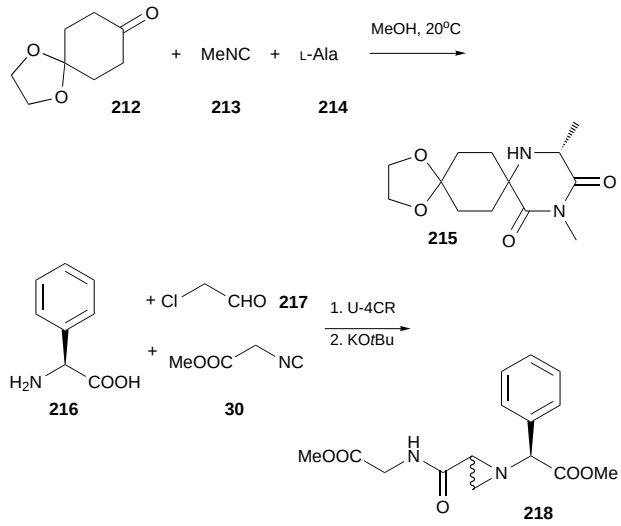
Another unnatural amino acid, 4-aminobenzoic acid (**208**), reacts with oxo compounds and isocyanides in methanol,affording *N*-carbamoylmethyl *p*-aminobenzoates, as shown for **210** (37% yield).[188]



Phosphonic acids react as the acid component in the U-4CR. In a cyclic variant, ω-oxophosphonic acids as bifunctional parent compounds were treated with isocyanides and amines, leading, for example, to the aminophosphonate **211**.[189]

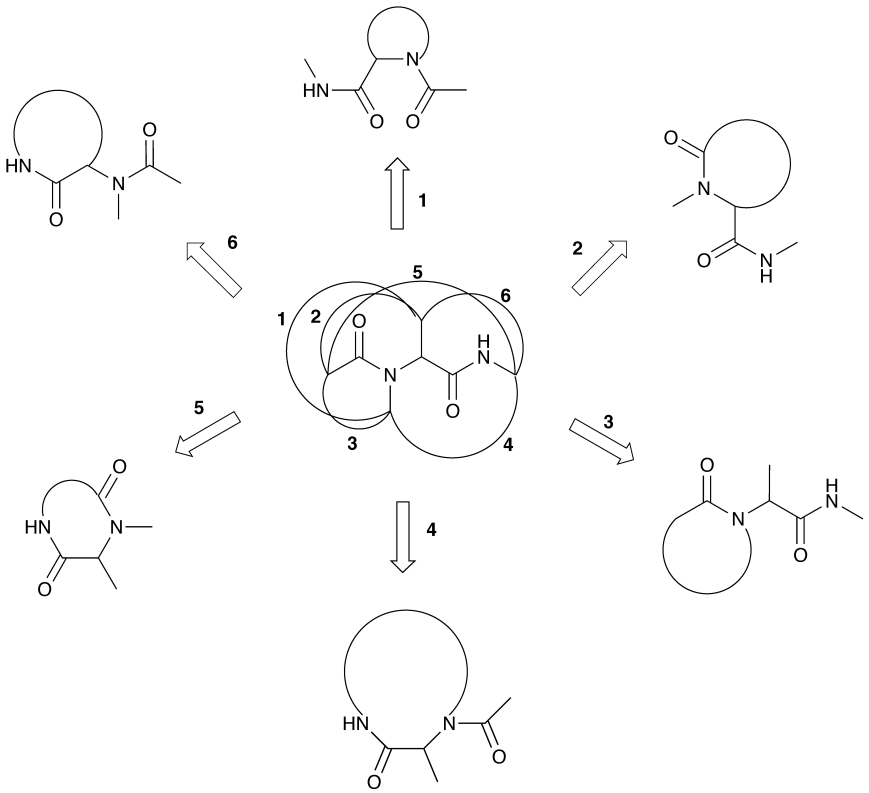


When α-amino acids (**214**) are treated with ketones (**212**) and isocyanide (**213**) in the presence of triethylamine in methanol, the main products are bispirocyclic 2,6-piperazine diones like **215**.[190] The iminodicarboxylic acid derivatives formed with aldehydes can also cyclize to 2,6-piperazine diones in THF/*t*BuOK in good yields. In an interesting variant, α-amino acids like **216** react with α-haloaldehydes such as **217** and isocyanides to form aziridine derivatives (**218**).[191]



3.4. Cyclic Variants of the U-MCRs with Bifunctional Parent Compounds

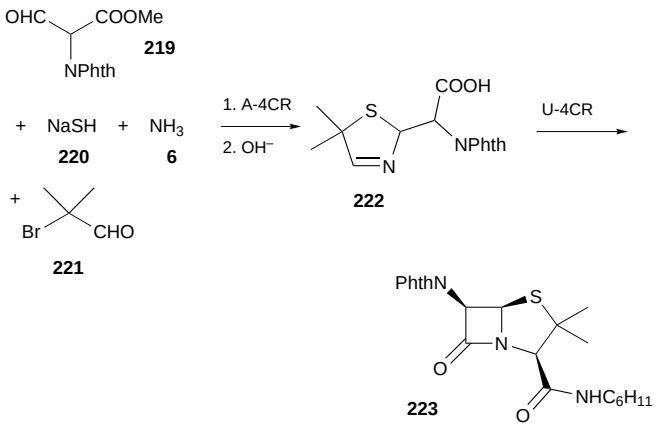
Cyclic products can be obtained in U-MCRs with bifunctional starting compounds or in secondary reactions. Cyclic variants of the MCRs are interesting for several reasons. On the one hand, they lead to new types of structures, on the other hand they increase the stiffness of an open-chained basic structure so that the product often shows improved pharmacological properties. Formally, mono-, bi-, or oligocyclic compounds can evolve depending on the number of intramolecular binding sites (Scheme 11).

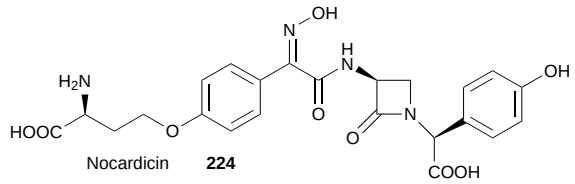


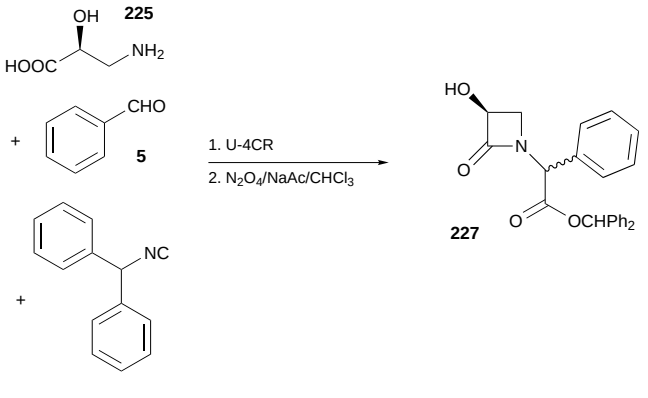
Scheme 11. All topologically feasible combinations of bifunctional parent compounds which can lead to cyclic structures in the carboxylic acid variant of the U-4CR. The variants 1 (cyclic imines), 2 (ω-oxocarboxylic acids), 3 (ω-aminocarboxylic acids), and 5 (ω-isocyanocarboxylic acids) have already been realized.

The one-step formation of the β-lactam ring starting from β-amino acids, oxo compounds, and isocyanides is a very early and interesting application of the U-4CR.[192, 193] Penicillin derivatives such as **223** were already produced by means of U-4CR in the early 1960s.[194] A central parent compound, the thiazolidine derivative **222**, was generated by means of another MCR, the A-4CR, from NaSH (**220**), the α-bromoaldehyde **221**, the aldehyde **219** and ammonia (**6**). According to NMR studies, the product has the same relative configuration as natural penicillin G. This synthesis is therefore the shortest known synthesis of a penicillin derivative.

In a similar fashion, carbapenems,[195] carbacephems,[109, 196] carbacephams,[197] and cephalosporin derivatives were syn-

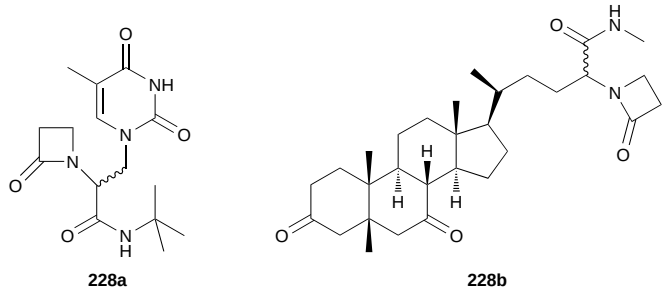






thesized by means of U-4CR. Remarkably, Hatanaka et al. were able to hydrolyze the exocyclic amide bond of β-lactams with PCl_5/MeOH without cleavage of the β-lactam ring of the oxacepham.[121] The synthesis of the 2-isocephem and the 2-isooxacephem skeleton was achieved with *p*-nitrophenyl isocyanide and subsequent nitrating cleavage with N_2O_4, affording the *p*-nitrophenyl ester.[198]

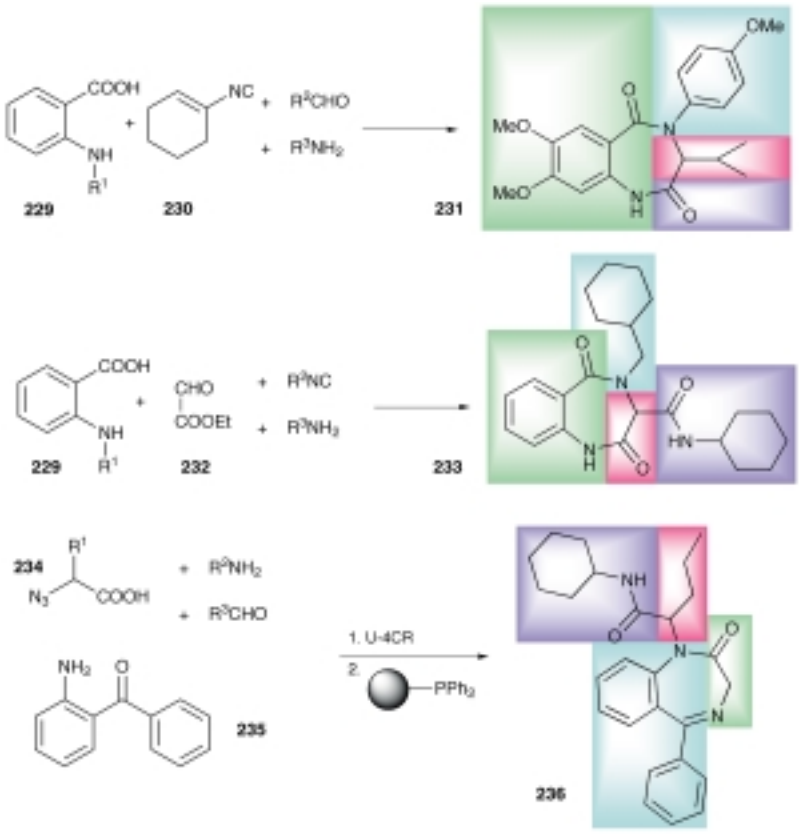
The first library of low-molecular-weight organic compounds known to us was produced in 1981 by Hofheinz and Isenring at Hoffmann – LaRoche: The library of nocardicin-A (**224**) derivatives contained several hundred compounds, for example **227**. Different β-amino acids (**225** in the case of **227**) were treated with oxo compounds (**5**) and diphenylmethyl isocyanide (**226**). Subsequently, the DPM amide was transformed into the carboxylic acid by means of oxidation and hydrolysis.[122] Enantiomerically pure α-amino acids allow a facile synthesis of stereochemically uniform monocyclic β lactams substituted in the 4-position.[199]



Chimeric monocyclic β-lactams with nucleobases or steroid skeletons in the side chains, like **228a** and **228b**, respectively, were also prepared.[200, 201] No other method allows such a fast and elegant synthesis of a multitude of unusual β-lactams.

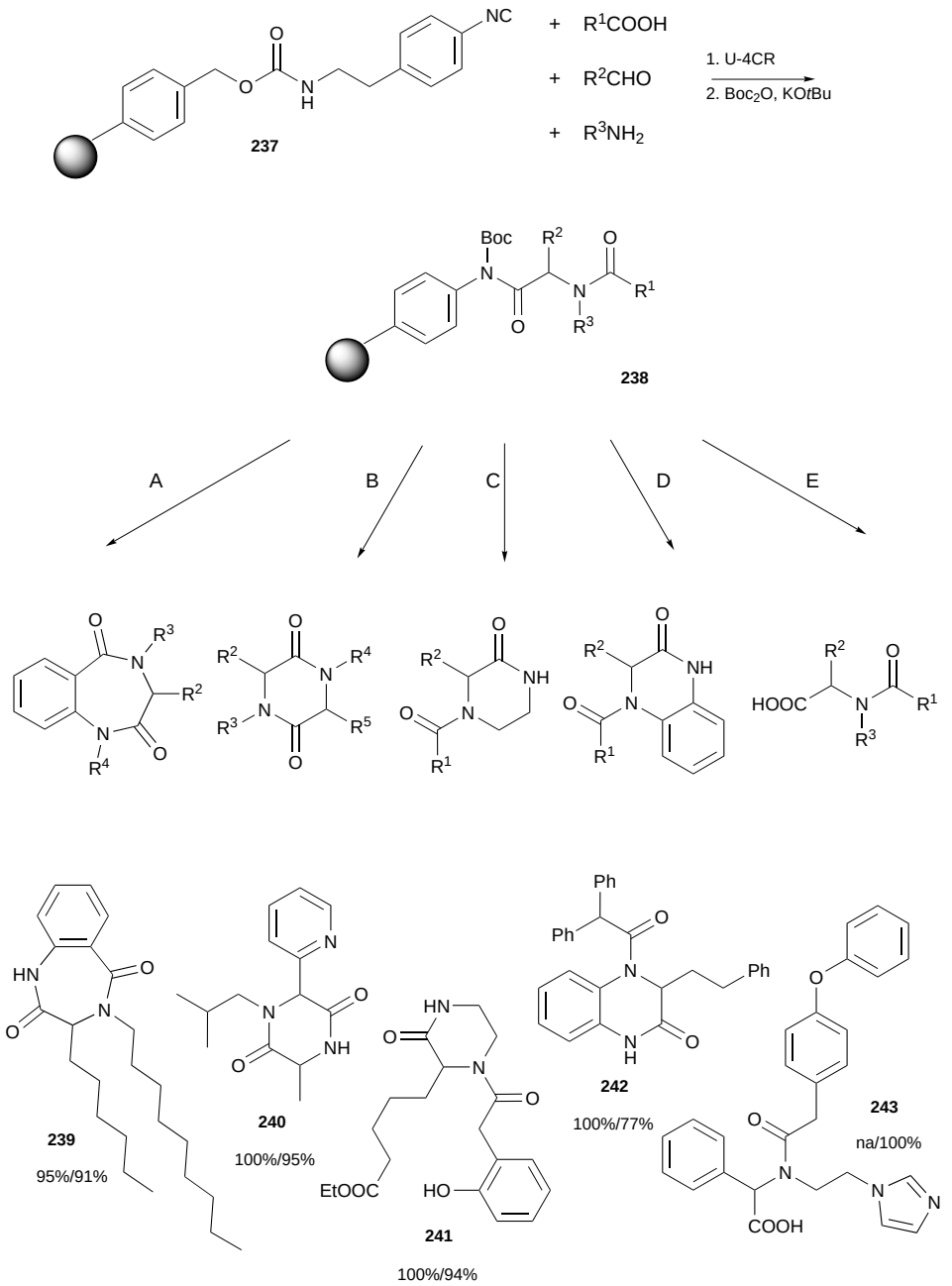
Libraries of monocyclic β-lactams, which are of interest as potential serine protease inhibitors, were synthesized in solution with a U-4CR. In this way, 126 β-lactams were described that were characterized by means of EI-MS.[202] Such β-lactams could be useful as inhibitors of the CMV protease, as HLE inhibitors, and as chymotrypsin inhibitors.[203]

Hardly any other type of skeleton has been subject to more intense pharmacological investigations than that of the benzodiazepines. Armstrong et al. were first to describe the synthesis of 1,4-benzodiazepine-2,5-diones such as **231** by means of U-4CR. Anthranilic acids **229** react with oxo compounds, amines, and cyclohexenyl isocyanide to give the corresponding open-chained α-benzoyl aminoamides. In acid solution the cyclization to **231** takes place. The authors suggest münchnones as intermediates of the cyclization.[204] Chemists from the company Affymax improved the method by linking silyl groups to the anthranilic acids, thereby rendering them soluble in organic solvents.[205]



Alternatively benzodiazepine **233** as well as others described below can be prepared from glyoxal ethyl ester **232**. A group at Hoffmann–La Roche treated α-azidocarboxylic acids (**234**) and *o*-azidobenzoic acids with *o*-aminobenzophenones like **235**, isocyanides, and oxo compounds and then effected ring closure to the benzodiazepines (**236**) and the benzodiazocines, respectively, by means of an aza-Wittig reaction.[206] In that reaction, polymer-bound triphenylphosphane was used, so that the product could be purified by means of resin-capture. It is noteworthy that there are different, complementary entries to the basic benzodiazepine skeleton.

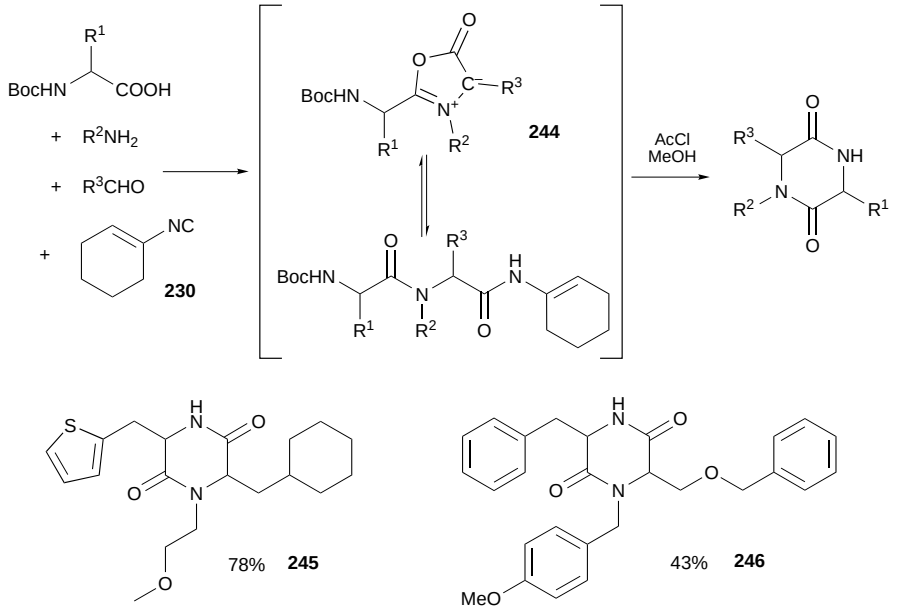
A group at Rhône–Poulenc–Rorer reported the solid-phase synthesis of 1,4-benzodiazepines, dioxopiperazines, oxopiperazines, and dihydroquinoxalinones by means of U-MCR (Scheme 12).[207] The application of Boc-protected building blocks and subsequent Boc cleavage allow all sorts of cyclizations. The isocyanide component is bound to Wang resin in this reaction (**237**). After the U-4CR with an oxo compound, an amine, and a carboxylic acid, the secondary amide of the former isocyanide is provided with a Boc group, affording **238**, and then intramolecularly cleaved by a functional group of the other components. Thus, Boc-protected anthranilic acids lead to benzodiazepines (route A, e.g. **239**), Boc-protected α-amino acids to dioxopiperazines (route B, **240**), singly Boc-protected ethylene diamines to oxopiperazines (route C, **241**), and singly Boc-protected 1,2-phenylenediamines to dihydroquinoxalinones (route D, **242**). If the primary Ugi product is removed from the resin with LiOH, N-alkylated and -acylated α-amino acids result (route E, **243**). The striking abbreviation UDC (*U*gi/*D*eboc/*C*leavage) was introduced for the sequence of Ugi reaction, linking of the Boc group and cleavage. The same strategy for the removal of an amide group from a U-4CR product by bonding of the Boc group and basic cleavage was already applied some years before in the synthesis of bicyclic β-lactams.[109, 208]



Scheme 12. By using protected starting materials and a bifunctional component, many interesting classes of heterocyclic compounds, such as benzodiazepines, oxopiperazines, dioxopiperazines, or dihydroquinoxalinones are accessible in a one-pot reaction. In each case the yield and HPLC purity is given. na = not available.

A variation for the preparation of dioxopiperazines in solution was described by the same group. In this reaction, Boc-protected α-amino acids and cyclohexenyl isocyanide (**230**) were converted (Scheme 13). The U-4CR products were treated with acetyl chloride in methanol or with TFA, and the cyclization affords dioxopiperazines such as **245** and **246** in satisfactory to good yields. A possible substitute for the sensitive cyclohexenyl isocyanide (**230**), which is difficult to prepare and to store, is the stable and commercially available benzyl isocyanide. The cyclization takes place via the münchnone **244**. A side product is the noncyclized amine.[209, 210]

Szardenings et al. from the company Affymax have described another route to dioxopiperazines by means of U-4CR (Scheme 14).[211] An α-amino acid anchored to the resin with its carboxyl group as the amine component, a Boc-protected

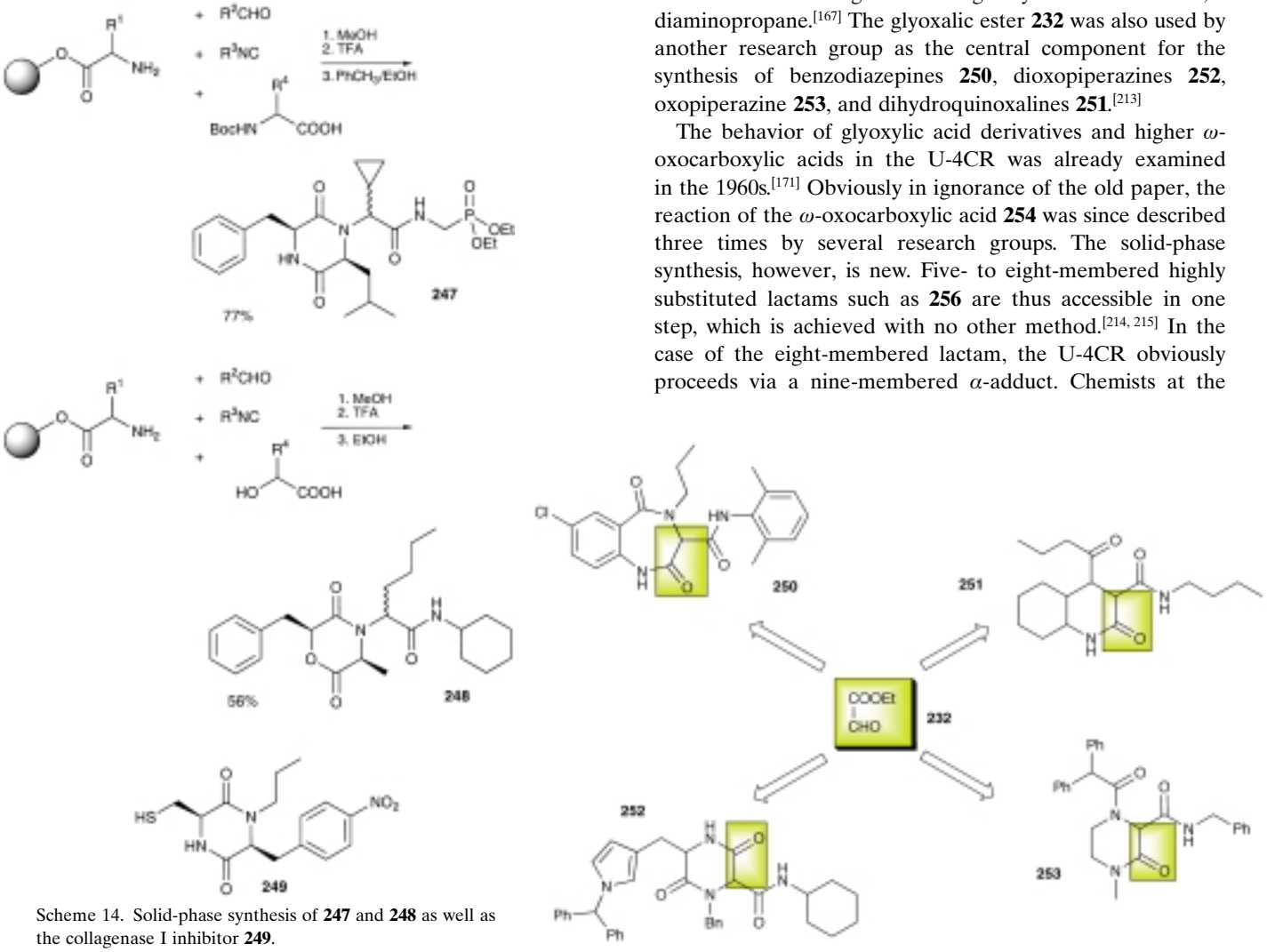


Scheme 13. The reaction of Boc-protected parent compounds with cyclohexenyl isocyanide (**230**) to form dioxopiperazines in solution. A münchnone (**244**) is discussed as the intermediate of the acidic cyclization.

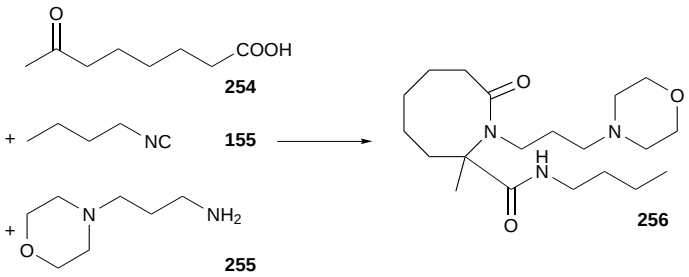
α-amino acid, an oxo component, and an isocyanide react in a U-4CR and can then be cyclized to dioxopiperazines such as **247** under acidic conditions. In contrast to the variants described before, which are only 3CRs, this is a genuine 4CR in which all four components, including the resin-bound amino acid, can be varied independently. When α-hydroxycarboxylic acids are used instead of the Boc-protected α-amino acids, dioxomorpholines like **248** are also accessible. With this Ugi variant, highly selective and potent collagenase I inhibitors were found. Thus, the dioxopiperazine **249** inhibits collagenase-I with an IC_{50} value of 65 nM and a selectivity towards the enzymes gelatinase B (1) and stromelysin of 1:45: $> 10^3$.[212]

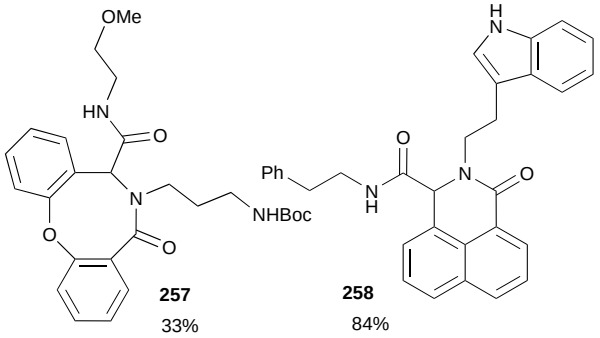
Oxopiperazines can also be synthesized from glyoxalic esters, diamines, carboxylic acids, and isocyanides in 60–90% yield. The corresponding seven-membered rings are analogously available from 1,3-diaminopropane.[167] The glyoxalic ester **232** was also used by another research group as the central component for the synthesis of benzodiazepines **250**, dioxopiperazines **252**, oxopiperazine **253**, and dihydroquinoxalines **251**.[213]

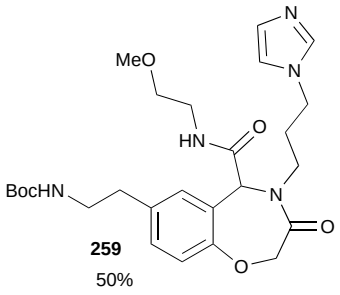
The behavior of glyoxylic acid derivatives and higher ω-oxocarboxylic acids in the U-4CR was already examined in the 1960s.[171] Obviously in ignorance of the old paper, the reaction of the ω-oxocarboxylic acid **254** was since described three times by several research groups. The solid-phase synthesis, however, is new. Five- to eight-membered highly substituted lactams such as **256** are thus accessible in one step, which is achieved with no other method.[214, 215] In the case of the eight-membered lactam, the U-4CR obviously proceeds via a nine-membered α-adduct. Chemists at the

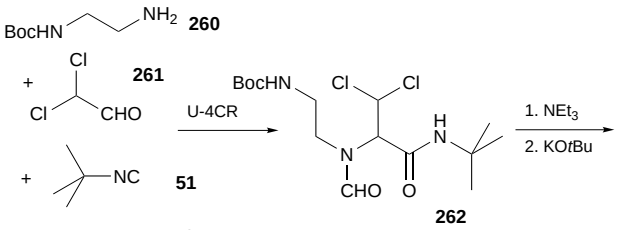


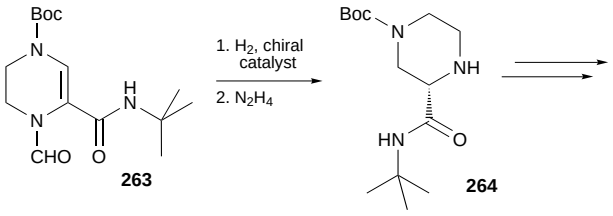
Scheme 14. Solid-phase synthesis of **247** and **248** as well as the collagenase I inhibitor **249**.

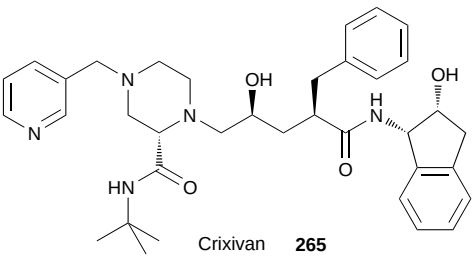






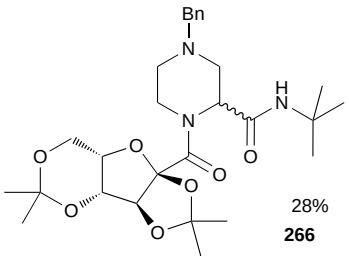


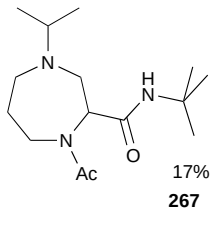




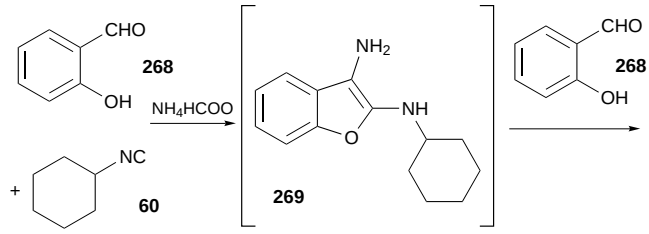
company Repligen have described many heterocyclic analogues, for example **257**–**259**, which contain exactly that lactam motif.[216]

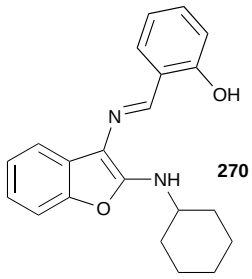
Piperazines such as **266** and their seven-membered analogues (e.g. **267**) can be synthesized from monoalkylated (-arylated) ethylenediamines and propylenediamines, chloroacetaldehyde, carboxylic acids, and isocyanides in one step and with great diversity. Piperazine-2-carboxamides are the central elements of many drugs.[217]

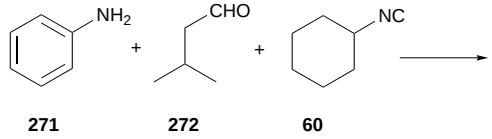


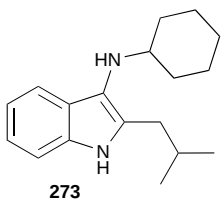


The enantioselective four-step synthesis of the precursor **264** of the HIV protease inhibitor crixivan (**265**) on a gram scale was described by a group at Merck. *tert*-Butyl isocyanide was treated with formic acid, dichloroacetaldehyde (**261**), and mono-Boc-protected ethylenediamine **260** to form **262**. After the Ugi reaction of **262**, base-supported cyclization of **263**, racemization, and enantioselective hydrogenation, the crixivan precursor **264** was isolated with good overall yield and



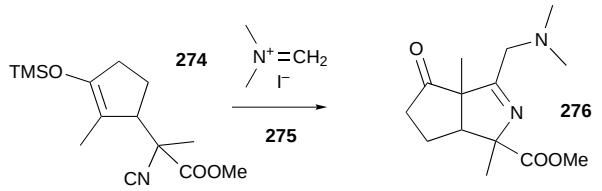




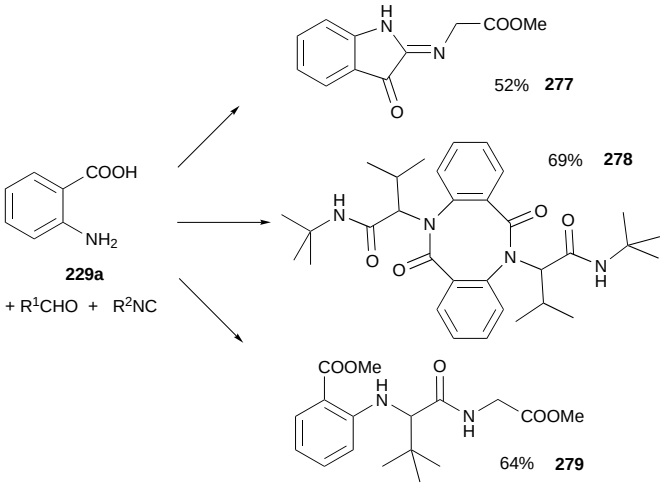


excellent enantioselectivity.[218] The described synthesis is an advantageous alternative to the classic route.[219]

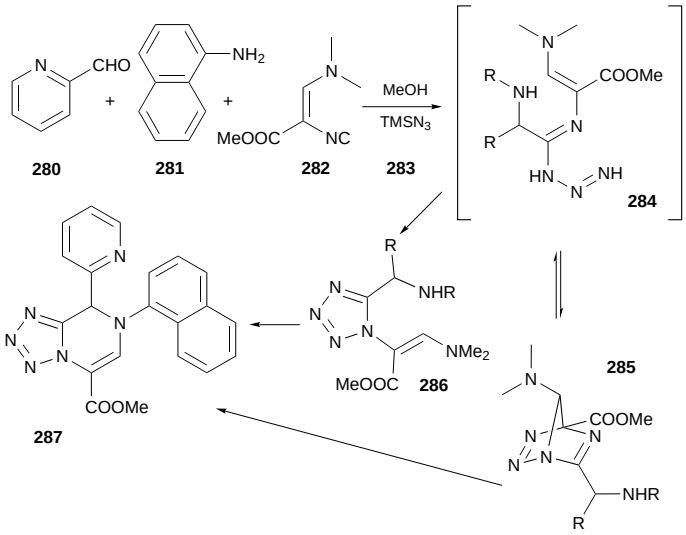
The phenol moiety of salicylaldehydes can serve as the acidic function in the U-4CR. Salicylaldehydes like **268** react with ammonium formate and isocyanides (**60**) to form benzofurans. The intermediate 2,3-diaminobenzofuran (**269**) finally reacts with a further equivalent of salicylaldehyde to the Schiff base (**270**).[220] Anilines (**271**), isocyanides (**60**), and aldehydes (**272**) react to form 3-aminoindoles (**273**). Interestingly, the acidic function here is the CH-acidic *ortho*-CH group in the aniline.[221] A case of C-nucleophiles in the U-4CR with five examples was described for the reaction of 4-isocyano-1-silenyl ethers like **274** (TMS = Me_3Si) with Eschenmoser's salt. The resulting pyrroline derivatives such as **276** can be isolated in 82–94% yield.[222]



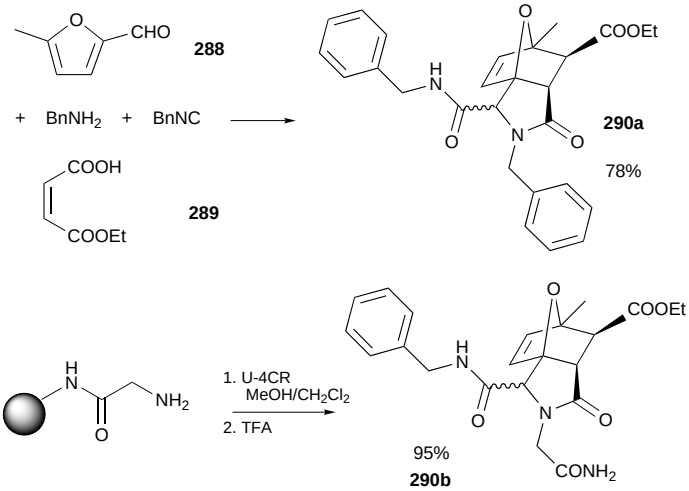
Since the beginnings of the U-4CR efforts have been made to elucidate how anthranilic acid **229a** reacts. Studies in our laboratory[223] have shown that anthranilic acid is an unstable system in the U-4CR, leading to the formation of different products depending on the reaction conditions and the starting materials. Under reflux conditions in the presence of ketones, **229a** reacts with isocyanides to form 2-iminoindoline-3-ons such as **277**. The ketone is not incorporated into the product. Two equivalents each of anthranilic acid, isocyanide, and aldehyde lead to eight-membered 1,5-diazocine-2,6-diones, e.g. **278**. Finally, *N*-carbamoylmethyl anthranilic esters such as **279** can also be isolated with sterically hindered aldehydes.



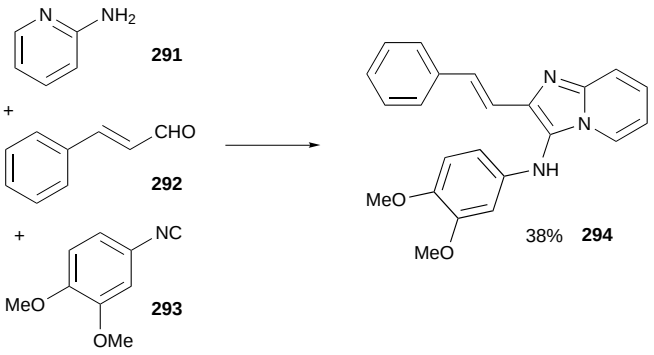
In a variant of Ugi's classic tetrazole synthesis, bicyclic, stiffened tetrazoles such as **287** were synthesized by utilizing the alkyl-β-(*N*,*N*-dimethylamino)-α-isocyanoacrylates (**282**) described by Schöllkopf. Depending on the starting materials, acyclic products (**286**), [3+2]cycloadducts (**285**), or bicyclic products (**287**) were isolated in varying ratios. The bicyclic compounds were purified in parallel by acidic extraction and isolated with a purity >80% in most cases. $TMSN_3$ **283** in MeOH was applied as a convenient in situ source of HN_3. Thousands of conformationally limited bicyclic tetrazoles were synthesized this way and tested for their biological activity.[177]



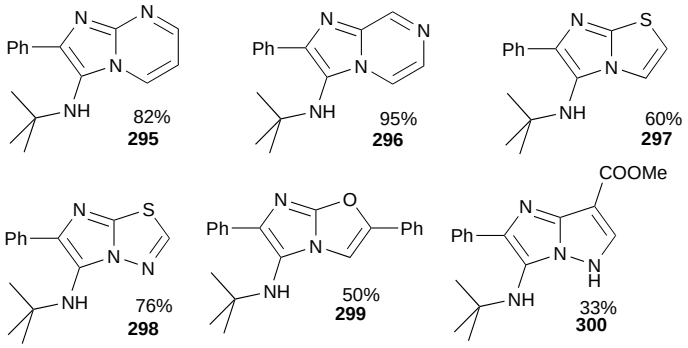
Chemists at the company Affymax treated furan aldehydes like **288** with maleic acid derivatives (**289**), amines, and isocyanides to obtain the tricylic compounds **290a** and **290b**. The initially formed Ugi product is converted in one pot in an intramolecular Diels–Alder reaction. Variants in solution as well as on a solid phase (ArgoGel Rink resin) have been described.[224] The mild conditions required for this transformation are remarkable.



Since 1996, Weber has reported on a new variant of the U-4CR at several congresses on medicinal chemistry.[225] In this intramolecular reaction, heteroarenes such as **291** with an H_2N–C=N group are treated with oxo compounds like **292**

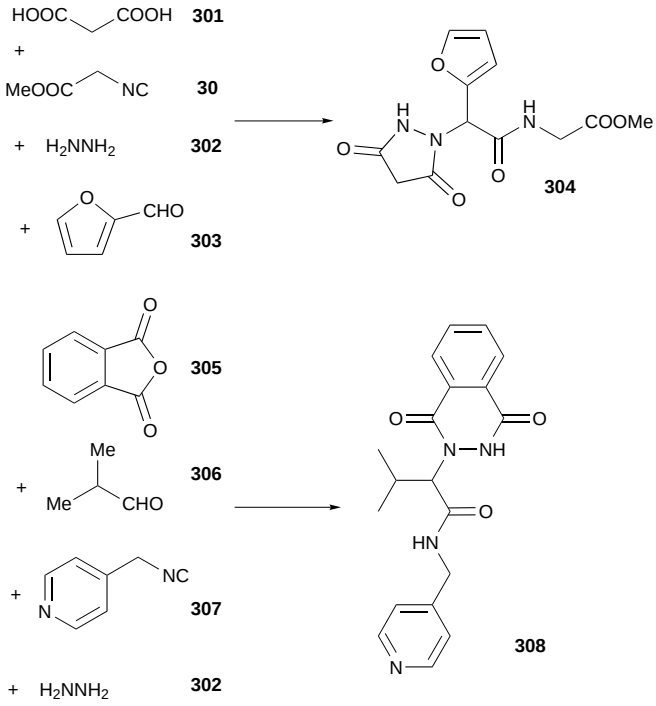


and isocyanides such as **293** to form annelated 3-aminoimidazoles (**294**).[226] This reaction type was recently published simultaneously by three groups from the pharmaceutical companies Hoffmann–LaRoche, Millenium Pharmaceuticals, and Rhône–Poulenc–Rorer. The reaction can be carried out in solution or on solid phase (Wang resin). No limitations were found either concerning the isocyanide component or concerning the aldehyde component. The reaction is catalyzed by Lewis ($Sc(OTf)_3$; $Tf = SO_2CF_3$) or Brønstedt acids ($HClO_4$, acetic acid). The range of applications for this reaction is very wide (see the different products **295**–**300**). Many tens of thousands of products were obtained from this versatile reaction and were tested.[227]

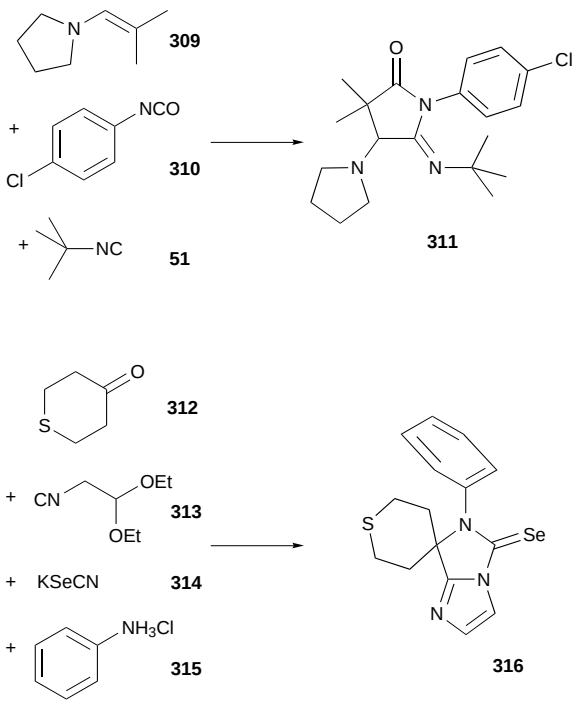


Another variant is the reaction of hydrazine with cyclic carboxylic acid anhydrides (**305**), oxo components (**306**), and isocyanides (**307**), leading to novel cyclic dioxohydrazine derivatives such as **308**. Malonic acid (**301**) reacts analogously to the cyclic anhydrides under formation of **304**. The reaction takes place at room temperature and affords the desired products from a wide range of starting compounds. Starting from malonic acid and five- to seven-membered anhydrides, the corresponding five- to eight-membered products are obtained. Accordingly, the intermediary cyclic α-adducts are eight- to eleven-membered rings.[228]

Iminopyrrolidones such as **311** and -thiopyrrolidones can be obtained starting from isocyanides, enamines (**309**), and isocyanates (**310**) or isothiocyanates, respectively. The reaction proceeds with good yields and was used for the gram-scale production of the corresponding pyrrolidines.[229] For example, **311** was obtained in 90% yield. A row of ketones like **312** and amine hydrochlorides like **315** was converted to the Ugi products with potassium cyanate, thiocyanate, and

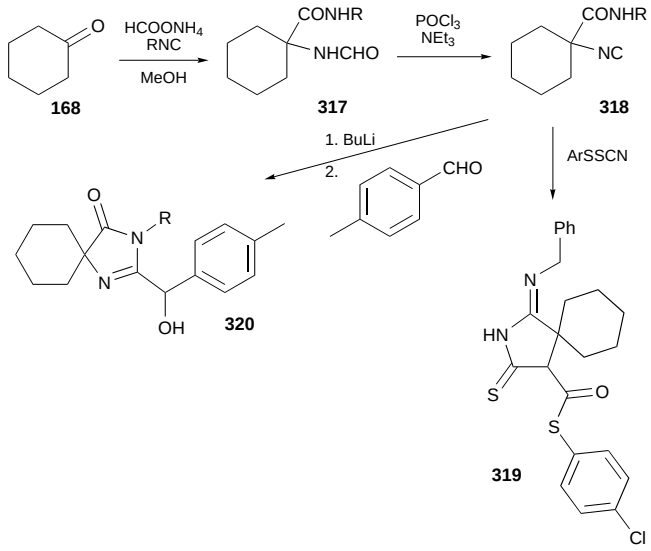


selenocyanate **314**, and 1,1-diethoxy-2-isocyanoethane (**313**) and subsequently cyclized under acidic conditions to the bicyclic imidazo[1,5-*a*]imidazoles (**316**).[230]

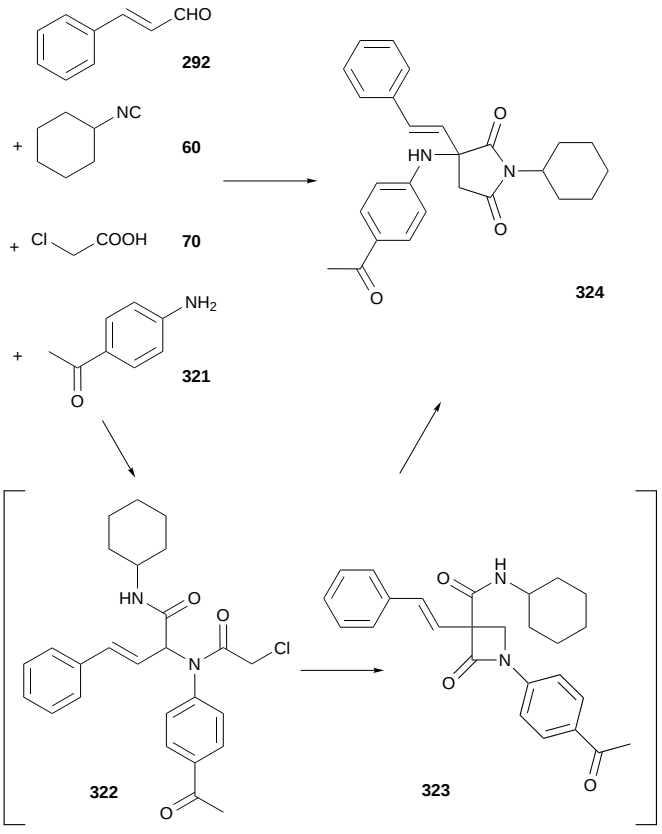


Cyclic ketones such as **168** react with ammonium formate and isocyanides to yield formamides such as **317**. Dehydration leads to α-isocyanocarboxylic acid amides (**318**), which form 1,3-diazaspiro-2-thiones (**319**) with arylsulfenyl isocyanates.[231] When the α-isocyanocarboxylic amide is treated with butyllithium, the intermediately formed carbanion can

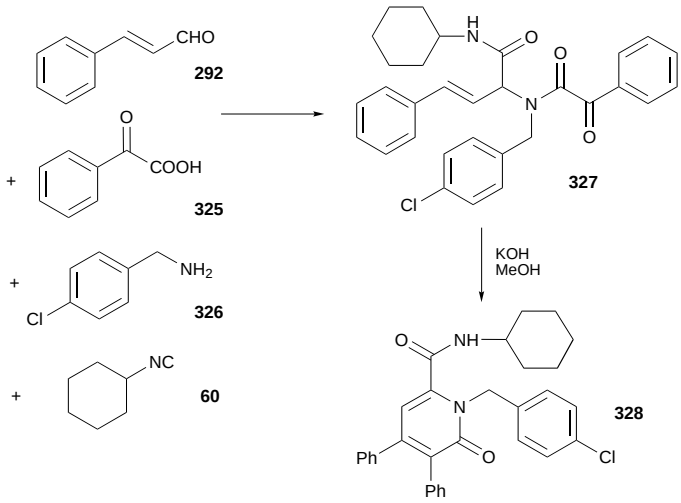
be trapped, for example, with aldehydes under formation of 2,3-disubstituted spiroimidazolones (**320**).[232]



The reaction of cinnamic aldehyde **292**, chloroacetic acid **70**, amines like **321**, and isocyanides like **60** allows the one-step synthesis of highly substituted succinimides like **324** in modest to good yields via the Ugi product **322**, and the elusive β-lactam **323**.[233]

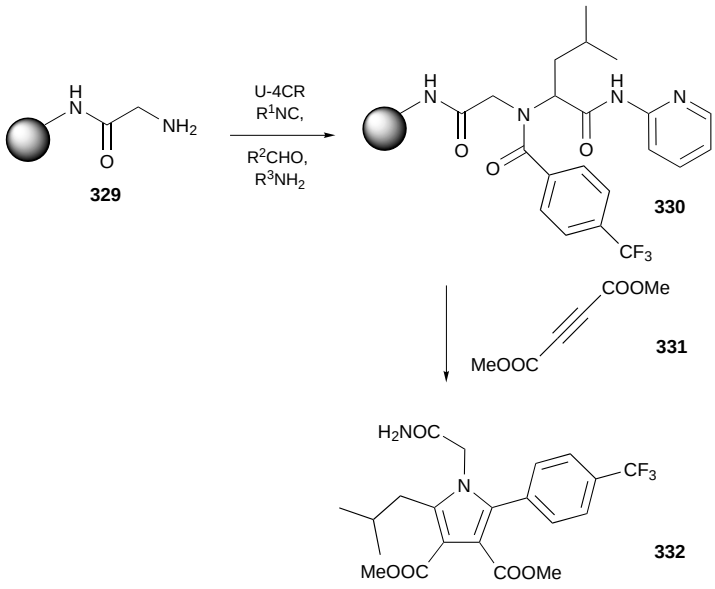


In contrast, **292** reacts with the α-oxocarboxylic acid **325**, the amine **326**, and the isocyanide **60** to form **327**, which cyclizes to the 1,6-dihydro-6-oxopyridine-2-carboxylic acid derivative **328** with KOH in methanol. Corresponding structures occur in natural products such as acromelic acid.[234]



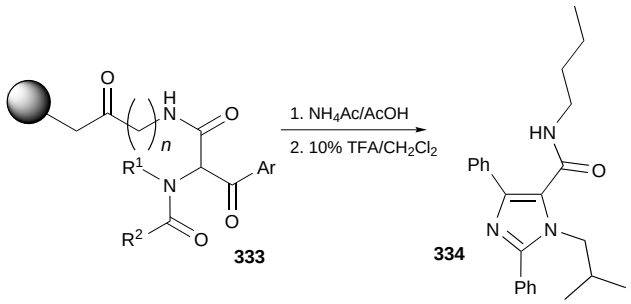
For the synthesis of α-acylamino esters and pyrroles on Rink and Wang resins, cyclohexenyl isocyanide was used and the carboxylic acid linked to the solid phase with succinic anhydride.[119]

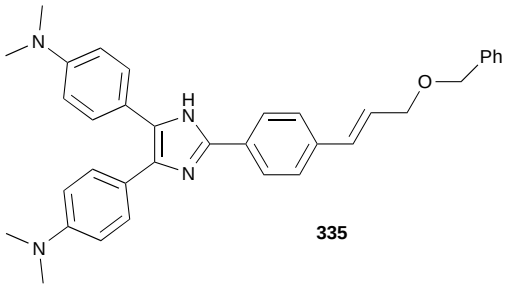
At the same time, chemists from the company Ontogen reported the synthesis of pyrroles such as **332** by means of U-4CR on NH_2-functionalized Rink resin **329** and subsequent cycloaddition with alkynes (**331**) in good yields and with excellent purities after removal from the resin.[120] They applied highly reactive 2-isocyanopyridine as a convertible isocyanide (see also Table 4, entry 2).



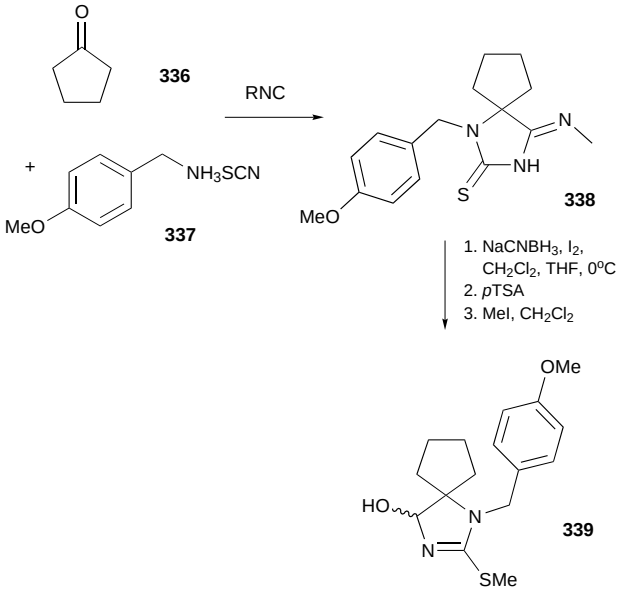
Tetrasubstituted imidazoles like **334** were synthesized by means of U-4CR of α-oxoaldehydes, amines, and carboxylic acids on isocyanide-functionalized Wang resin, affording **333**, and subsequent ring closure with ammonium acetate in 16–56% yield. In the first step an α-(*N*-acyl-*N*-alkylamino)-β-

oxoamide is formed. The corresponding two-step reaction to form **334** in solution proceeds with 47% yield.[235] It was shown that analogous compounds such as **335** were able to sensitize MDR cells for a treatment with chemotherapeutic agents.[236]



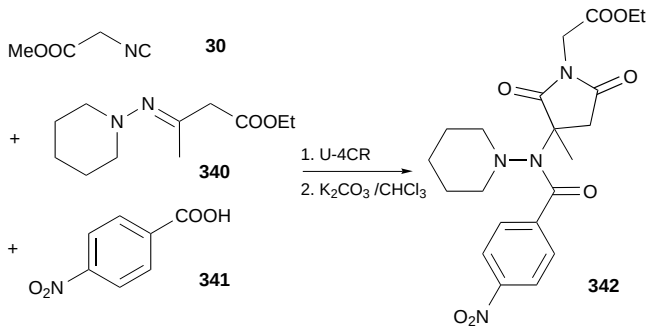


A method was introduced for the synthesis of spiro-α-hydroxyguanidines such as **339**, which occur in many natural products, for example tetrodotoxin or crambin B.[237] The

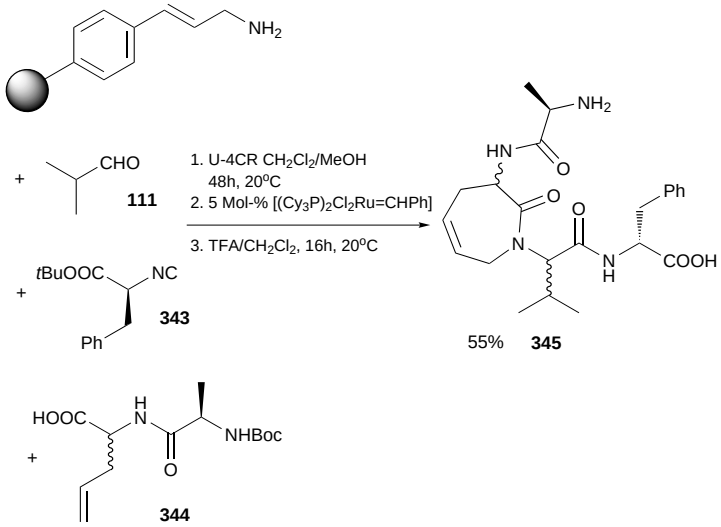


2-thiohydantoin-4-imines (**338**) synthesized from ketones, isocyanides and benzylaminothiocyanate **337** have to be reduced to the α-hydroxyguanidines with sodium cyano hydridoborate (pTSA = p-toluenesulfonic acid).

1,1-Disubstituted hydrazine react with acetoacetic ester to form imines such as **340**. These lead to the usual U-4CR products with isocyanides and carboxylic acids such as **341**, which can then be cyclized to 2,5-dioxopyrrolidines (**342**) under mild basic conditions with good yields.[162]



A topical example of how the choice of suitable parent compounds for a U-4CR and subsequent secondary reactions led to novel types of compounds is the synthesis of β-turn mimetics of the Freidinger lactam type (**345**). The cyclization by ring-closing metathesis takes place after the U-4CR. The resin-bound 3-phenylallylamine serves as traceless linker.[238]

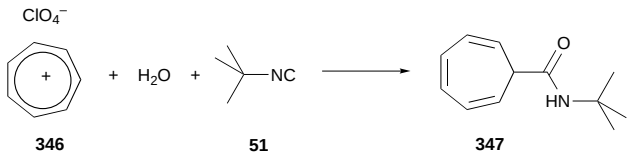


4. Other MCRs with Isocyanides

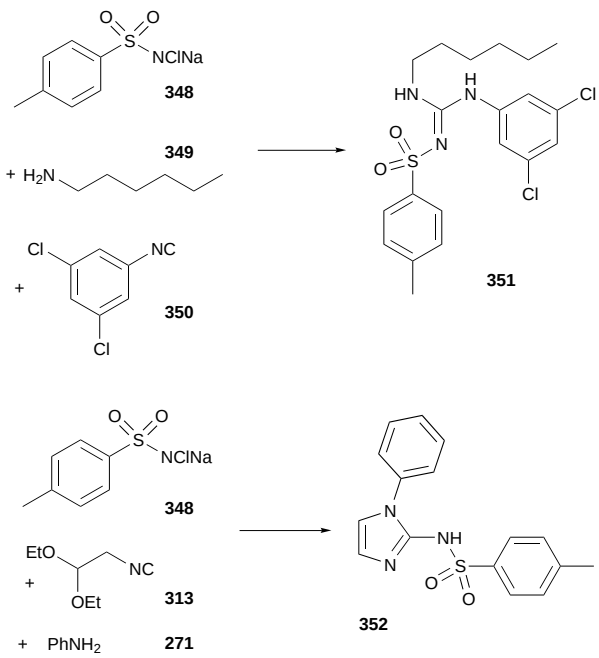
There are some IMCRs that cannot be classified as P- or U-MCRs.

Thus, the reaction of tropylium perchlorate (**346**) with isocyanide **51** and water to the tropylium derivative **347** has been described.[239] This is a 3CR in which the tropylium ion serves as the electrophile instead of a Schiff base or an enamine.

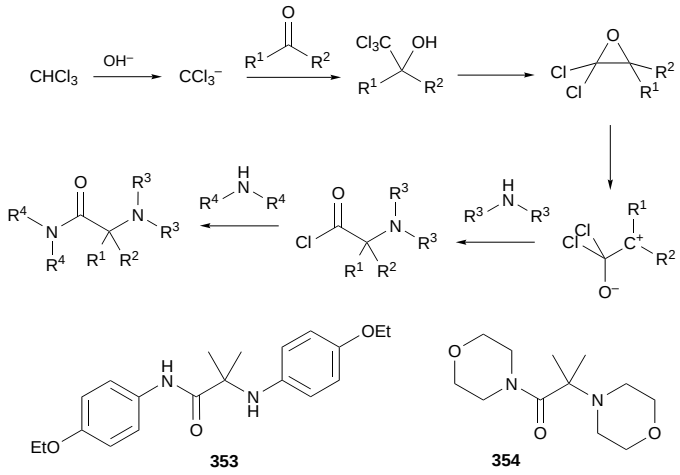
In a 3CR, chloramine T **348** and the amine **349** react with α-addition to the isocyanide, leading to the guanidine **351**.[240] Analogously, the synthesis of highly substituted imidazoles is effected by the reaction of **348** with anilines (**271**) and 2,2-



diethoxy-1-isocyanoethane**313** and subsequent ring closure in boiling acetic acid. The two-step synthesis via the isolable *N*-tosylguanidines leads to the *N*-aryl-2-tosylamino-1*H*-imidazoles (**352**) in 40 – 75 % yield.[241]

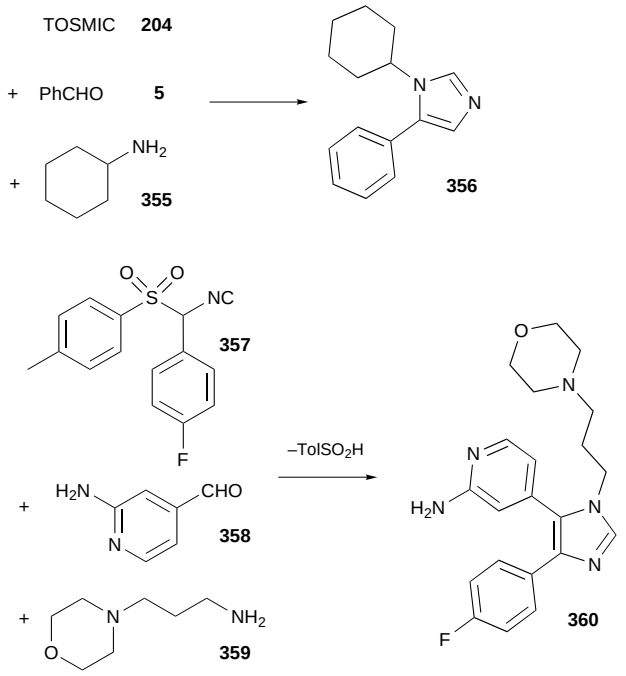


α-Amino amides are the U-3CR reaction products of amines, oxo compounds, and isocyanides in a mineral acidic medium. Interestingly, α-amino amides like **353** or **354** can be synthesized in a 4CR which obviously follows a completely different mechanism (Scheme 15): Chloroform is treated with two primary or secondary amines and an oxo compound in the presence of a phase-transfer catalyst.[242] As secondary amines (which cannot be converted to isocyanides) also react, the mechanism cannot proceed as for the Ugi reaction.[243]



Scheme 15. Possible mechanism of a different MCR of amines, ketones, and chloroform which also leads to α-amino amides.

Van Leusen et al. have described the 3CR of TOSMIC **204**, aldehydes, and primary amines, leading to 1,4-disubstituted imidazoles (**356**).[68] Alternatively, the intermediately formed α,β-unsaturated isocyanide can also be isolated and treated with amines.[68] 1,4,5-Trisubstituted imidazoles (**360**) were described by the same group: 2-Substituted TOSMIC derivatives like **357** are treated with primary amines and aldehydes. The reaction can be described as a dipolar [2+3]cycloaddition of the Schiff base and the isocyanide followed by sulfinic acid elimination (Tol = tolyl). Compound **360** and similar ones have been described as highly potent P38 MAP kinase inhibitors.[270]

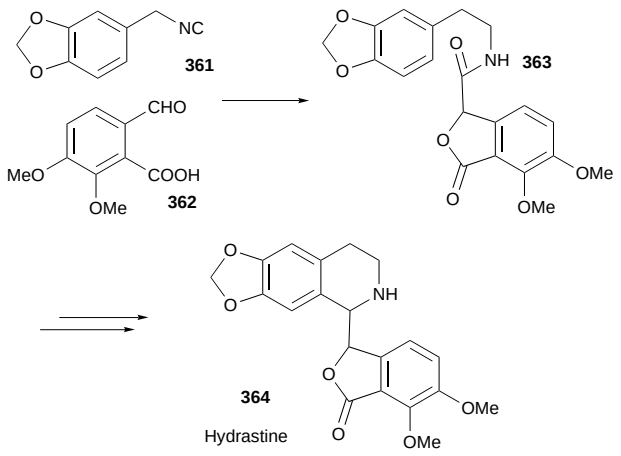


5. IMCRs in the Total Synthesis of Natural Compounds

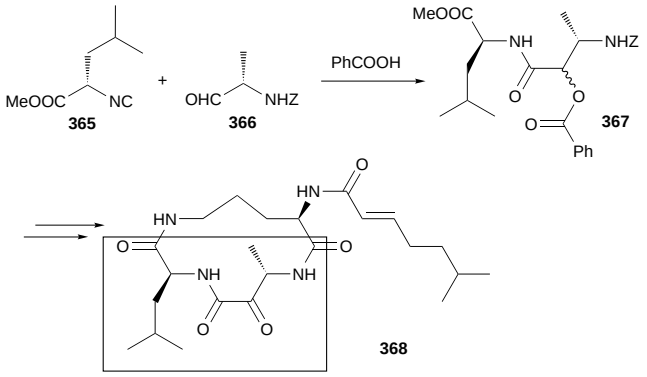
MCRs with isocyanides were often used in the total synthesis of natural products. This can be advantageous, as several starting materials are combined to very complex products in one step, which makes analogues of the corresponding natural compounds available. In the following, several total syntheses are introduced in which MCRs were used as the key steps.

Based on the lactone variant of the P-3CR to **363** with the bifunctional ω-oxocarboxylic acid **362** and the isocyanide **361**, a two-step total synthesis of the alkaloid hydrastin **364** was carried out.[244]

The synthesis of the natural product and prolyl endopeptidase inhibitor eurystatin A **368** by Schmidt et al. uses the

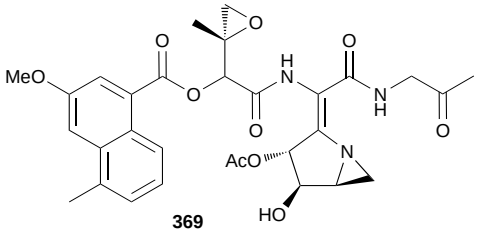


P-3CR as a build-up reaction. Eurystatin A, like the prolyl endopeptidase inhibitors postatatin,[245] rapamycin, and FK 506 contains an essential α-oxoamide unit. In the P-3CR, the enantiopure α-isocyano ester **365** derived from an α-amino acid and the amine-protected α-amino aldehyde **366** are treated with benzoic acid. No diasteroselectivity was observed. As the hydroxy group formed here is oxidized to a

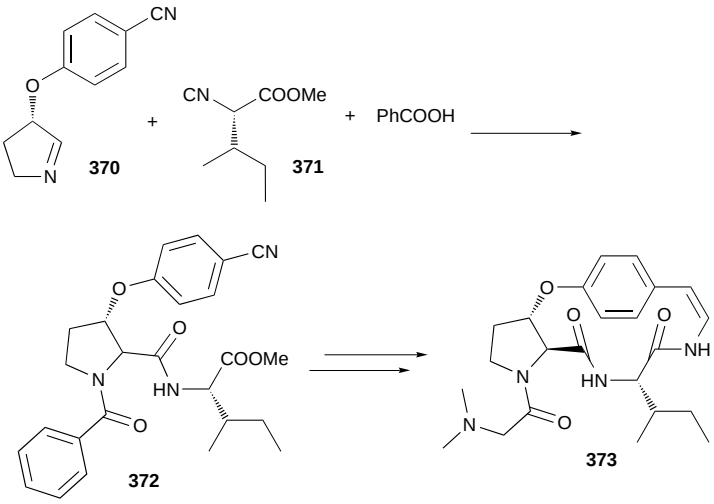


carbonyl function later in the synthesis, the missing diastereoselectivity of the Passerini reaction is of no importance. Overall, the complicated 13-membered natural product was synthesized in a short sequence.[246]

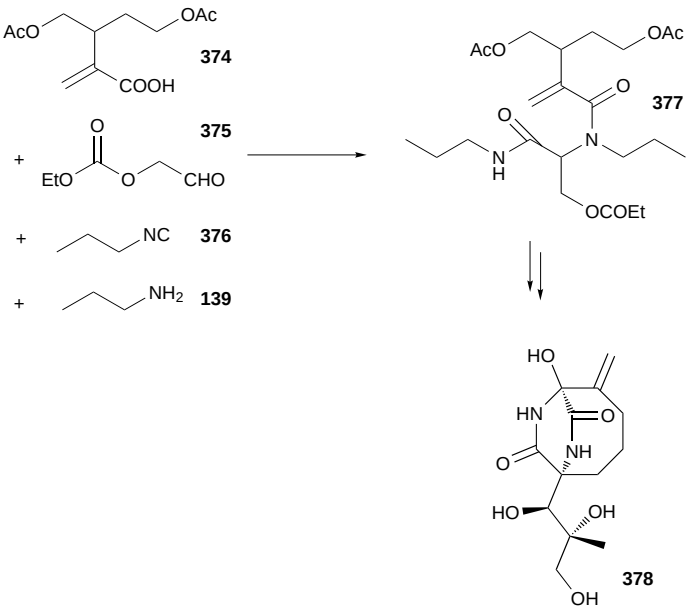
Armstrong et al. have described the synthesis of the DNA-binding and alkylating antibiotic azinomycin **369** and of libraries of analogues by means of the P-3CR of appropriate α,β-unsaturated isocyanides, aldehydes, and carboxylic acids.[8b]



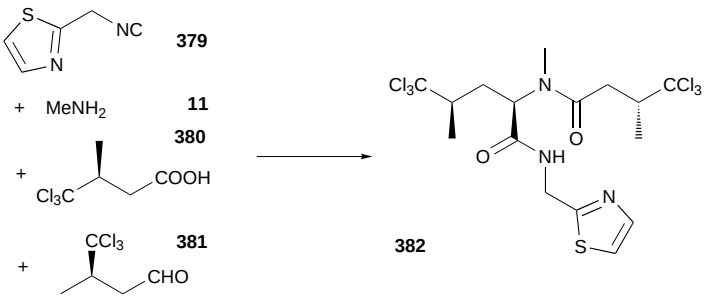
The large group of cyclic peptide alkaloids has been the object of numerous synthetic efforts since the first description in 1963. They usually are 13- to 15-membered macrocycles with para- or metacyclophane units and characteristic aryl ether bonds. Joullié et al. chose the U-4CR as the central step in the total synthesis of the 14-membered cyclopeptide alkaloid **373**.[247]



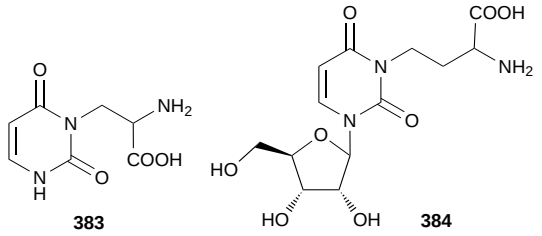
The antibiotic bicyclomycin **378**, which was isolated from *Streptomyces sapporonensis* and is very active against gram-negative bacteria, and many derivatives were synthesized by Fukujama et al.[248] A key position in the synthesis of numerous analogues is taken by the U-4CR of the α,β-unsaturated carboxylic acid **374**, the amine **139**, the α-hydroxy aldehyde **375**, and the isocyanide **376** to form **377**.



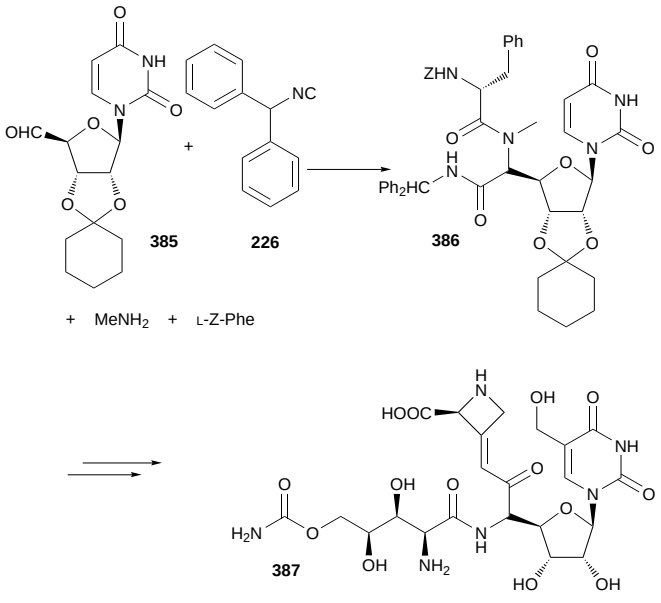
Dysidenin, isolated from the sponge *Dysidea herbacea*, is an unusual, highly chlorinated toxin which in its demethyl variant **382** could be synthesized in virtually one step by U-4CR from the appropriate starting compounds **379** – **381** and **11**. The two possible diastereomers are formed in a ratio of 17:13 and can easily be separated chromatographically.[249]



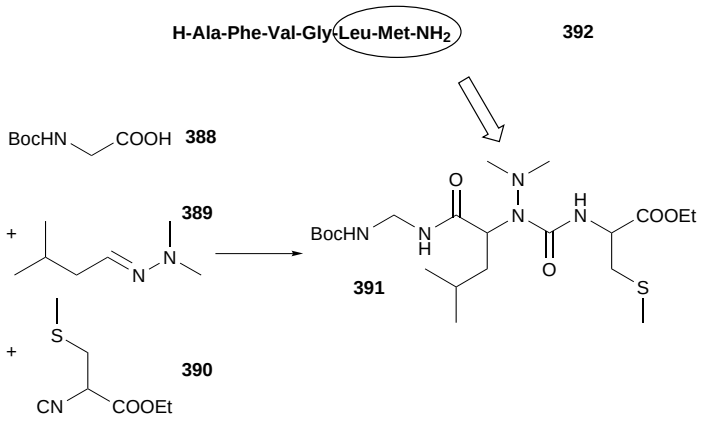
Naturally occurring antimetabolites such as isowillardiine (**383**), nikkomycin (**384**), and sinfugin were synthesized by Japanese research groups on a 20 g scale, a U-4CR being the key step.[133, 250]



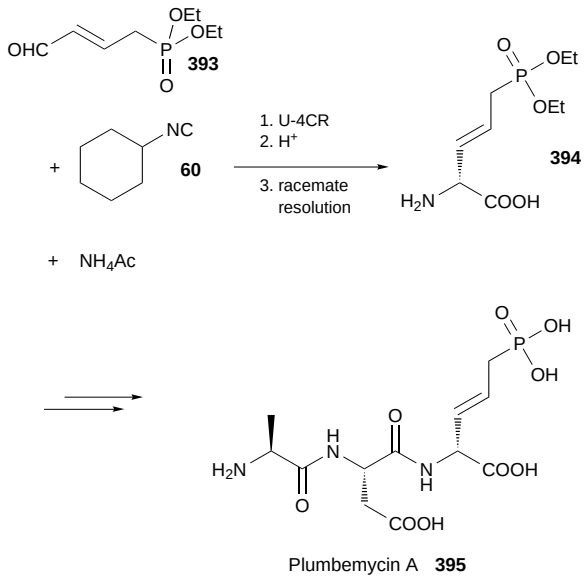
The total synthesis of various highly active fungicidal polyoxins like **387** was described by Boehm et al. A U-4CR with diphenylmethyl isocyanide and the aldehyde **385** was used as the central step. The resulting amide was oxidatively converted to the diphenylmethyl ester with N_2O_4.[251] The product of the U-4CR with amino-protected α-amino acids and diphenylmethyl isocyanide (**226**) was transformed to the corresponding oxopiperazines by means of hydrogenation. In another variant, cyclohexenyl isocyanide was used, which was transformed to the carboxylic acid via the primary amide.[252]



The modified analogue **391** of the antihypertensive hexapeptide eledoisin (**392**) was synthesized in a U-4CR and screened pharmacologically. For this reaction, the dimethylhydrazine Schiff base **389** as the amine component was treated with N-protected glycine **388** and methionine isocyanide (**390**).[253]

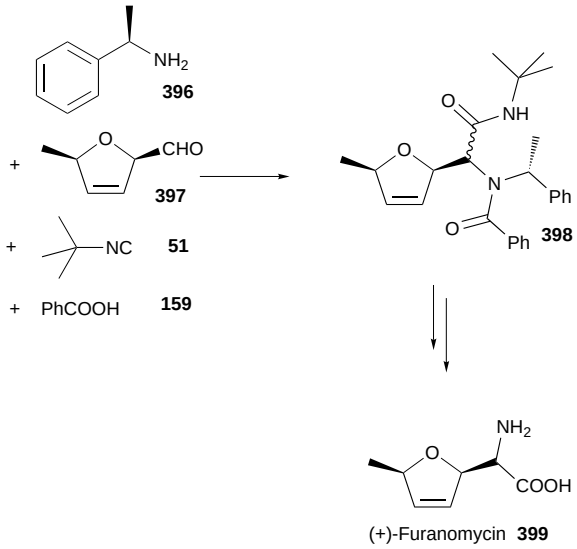


The antibiotics plumbemycin A (**395**) and B, as well as some analogues, were obtained in a synthesis which used the U-4CR as its key reaction. The unusual amino acid 3,4-didehydro-5-phosphono-D-norvaline (**394**) was obtained in a one-pot synthesis by means of U-4CR of cyclohexyl isocyanide, ammonium formate, and the aldehyde **393** and subsequent hydrolysis in 80% yield.[189] The resolution of the racemate was carried out enzymatically.



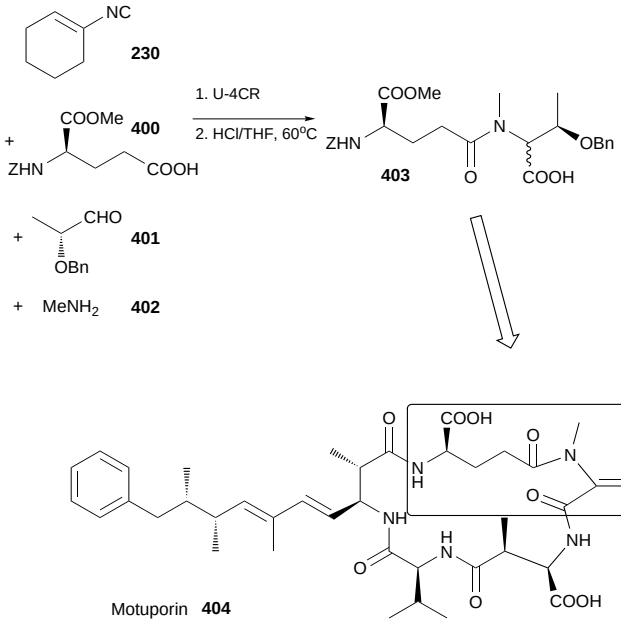
Furanomycin is a rare example of a triketide consisting of two acetate and one propionate unit. The stereoselective total synthesis of (+)-furanomycin (**399**) and its stereoisomers by means of U-4CR of **396**, **397**, **51**, and **159** to form **398** was achieved by Joullié et al.[254]

Recently, the total synthesis of the complex protein phosphatase (PP) inhibitor motuporin (**404**) was described.[255] The part of this cyclic peptide, consisting of a didehydro amino acid, an α-, two β-, and one γ-amino acid, which is of



(+)-Furanomycin **399**

interest for the bonding to PP1, was synthesized by means of a U-4CR and is therefore easily accessible for diversification. Both of the diastereomers **403** formed in the U-4CR in a ratio of 1:1 are converted into the didehydro amino acid fragment in a later stage of the total synthesis.

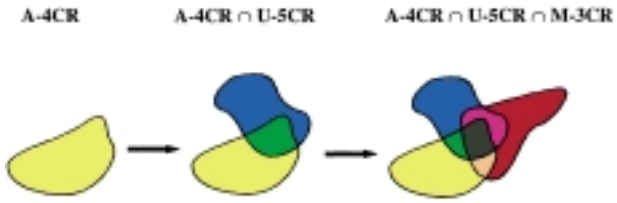


In this section, several examples for the application of the U-4CR in the synthesis of unnatural α-amino acids were presented. A series of different auxiliaries which can be removed in mild conditions is available today so that the IMCR should always be considered as a possibility for the synthesis of α-amino acids.

6. The Union Concept

Of all the combinatorial techniques, only split-and-combine methods[256] and MCRs give the chemist the opportunity to examine very large structural space. With the entirety of all organic-chemical reactions (two-component reactions), far fewer compounds can be synthesized than with MCRs by several orders of magnitude. If conventional reactions are to lead to large, highly diverse libraries, sequential work is necessary and the chemist inevitably has to go over to solid-phase syntheses—with all their advantages and disadvantages. Not so in MCRs, which often also proceed well in solution, but nevertheless open large structure and substance space.

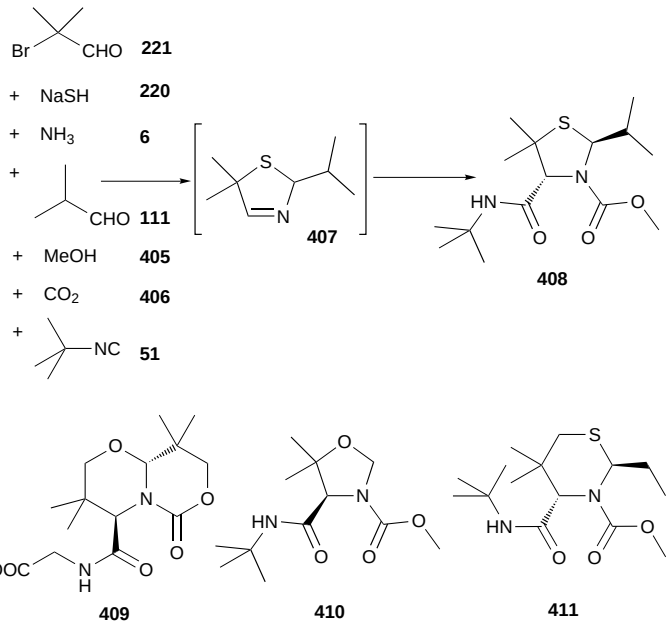
A few years ago, we asked ourselves how many starting materials can at most be converted to a product in a one-pot reaction. Our answer was: seven.[257] We were able to show that the A-4CR can be combined with the U-5CR: A-4CR ∩ U-5CR ≡ AU-7CR (Scheme 16).[258] The concept of unions of



Scheme 16. Schematic representation of the combination concept. The colored areas correspond to MCRs and the overlaps to new combinations of MCRs.

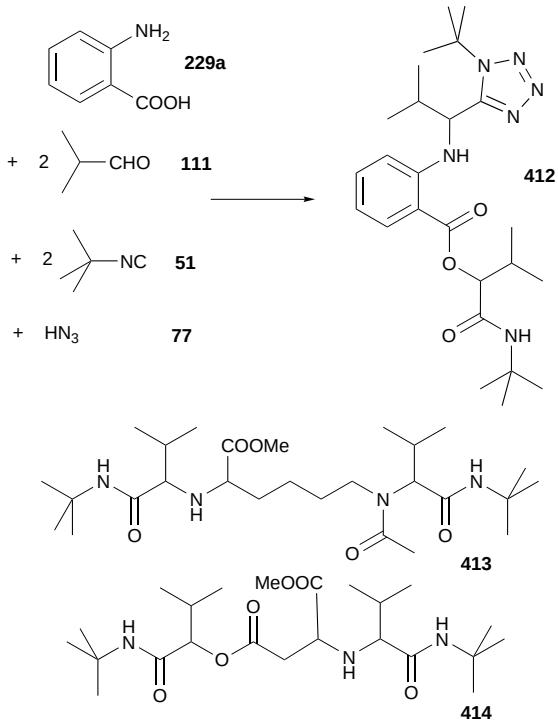
two or more (M)CRs proved to be productive in the following years, and further examples were described. It has turned out that many such combinations of MCRs are possible if the starting materials are well-chosen. Ideally, the elementary steps of the reactions take place acccording to a program. It is to be expected that many more examples are to come in the next few years. The reactions resulting from the union concept offer a greater structural variety than the simple MCRs.

A remarkable "seven-component reaction" is, for example, the transformation of the α-bromoaldehyde **221** with NaSH (**220**), another oxo component (**111**), and ammonia (**6**) in an



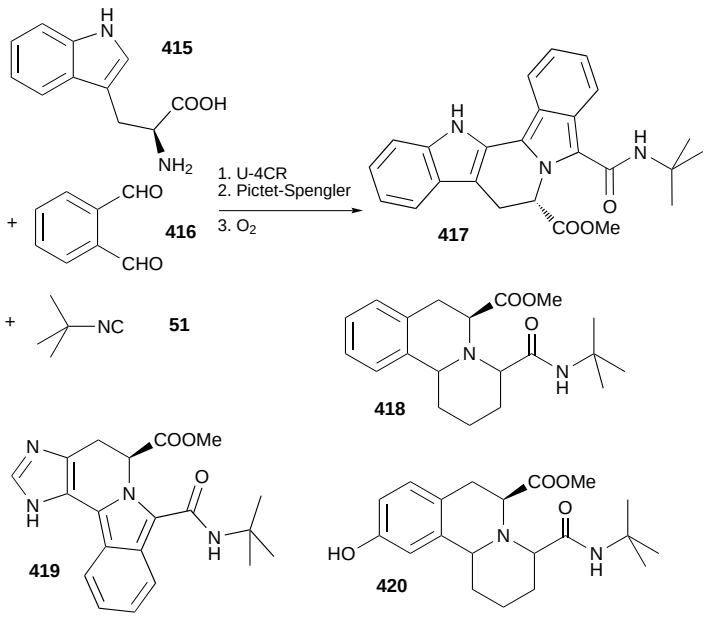
Asinger four-component reaction (A-4CR) to form the thiazoline **407**, which undergoes a U-4CR with the isocyanide **51** in methanol (**405**) and under CO_2 (**406**), affording the thiazolidine **408**. After optimization of the reaction, **408** was obtained in up to 45% yield.[257] Oxazine, oxazolidine, and thiazine derivatives (**409**–**411**) were also synthesized in this fashion.

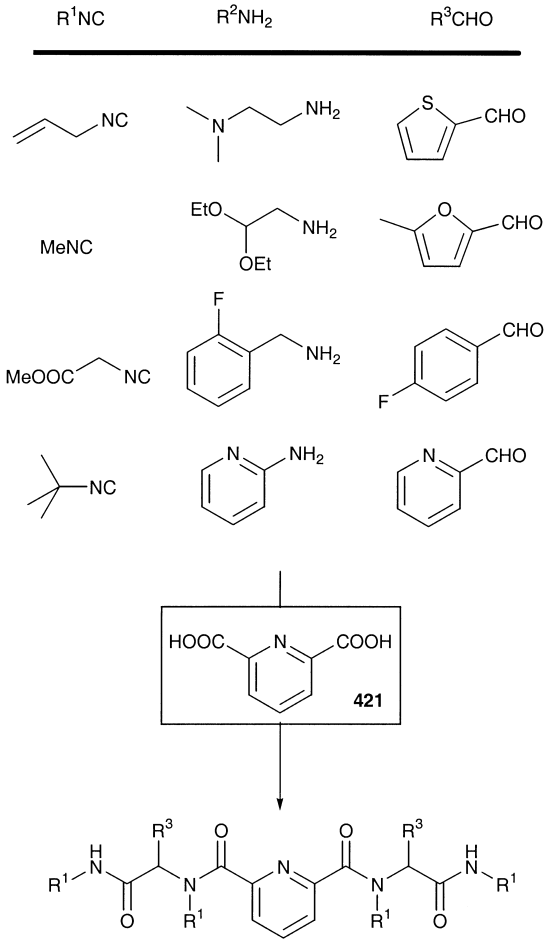
Further such combinations of MCRs were achieved with multifunctional parent compounds. Thus, anthranilic acid reacts with two equivalents of isobutyric aldehyde, two equivalents of isocyanide, and hydrazoic acid in a Passerini and Ugi reaction (U-4CR ∩ P-3CR ≡ UP-5CR) to form **412**. Compound **413** is obtained from lysine and a further six components (U-4CR ∩ U-4CR ≡ UU-7CR) and **414** from glutamic acid and five other components (U-4CR ∩ U-5CR ≡ UU-6CR).[259]



Recently the combination of the Pictet–Spengler reaction with the Ugi reaction succeeded: U-4CR ∩ PS-2CR. Here, electron-rich aromatic ethylamine derivatives react with dialdehydes and isocyanides, forming structures similar to alkaloids. In the example shown, tryptophane **415** first reacts with phthalic dialdehyde **416** and the isocyanide **51** in an Ugi reaction, the α-amino acid variant, to a nonisolable intermediate which finally affords the pentacycle **417** after a Pictet–Spengler reaction and subsequent oxidation. Other aromatic amino acids, such as phenylalanine, histidine, 3,4-dihydroxyphenylalanine (DOPA), or tyrosine, were also converted to the products **418**–**420** in this fashion.[260]

An interesting example of how the combination of U-4CRs can lead to very many products is the reaction of a dicarboxylic acid with four each amines, aldehydes, and isocyanides. In view of the construction of pseudo-C_2-symmetric protease inhibitors, pyridine-2,6-dicarboxylic acid (**421**) was treated with aldehydes, amines, and isocyanides. In this way, 13 starting materials lead to 8256 products (Scheme 17).[186]



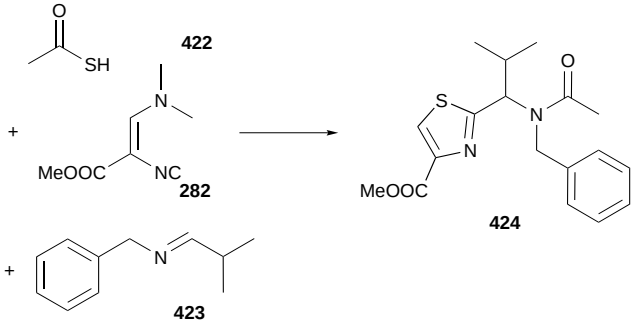


Scheme 17. Construction of pseudo-C_2 symmetric protease inhibitors from pyridine-2,6-dicarboxylic acid (**421**), aldehydes, amines, and isocyanides. A total of 8256 compounds are accessible from only 13 starting materials.

7. Outlook or Can New MCRs Be Found?

Basically, new MCRs can be found in different ways: by reflection (reaction design) or by applying combinatorial techniques (combinatorial reaction finding).[261]

Some time ago we discovered that thiocarboxylic acids react in a U-4CR. Interestingly, only one of the two possible regioisomers α-amino thioacylamide and α-aminoacyl thioamide is formed. X-ray analyses prove that the α-amino thioacylamide is the exclusive product. This is in harmony with the different bond strengths (C-S < C-O). Thioamides are known as parent compounds for diverse thiazol syntheses. However, the thioamide obtained in this U-4CR variant is not suitable for any of the known thiazole syntheses due to its substitution pattern. Nevertheless, when methyl β-dimethylamino-α-isocyanoacrylate **282** as the isocyanide component is treated with Schiff bases and thiocarboxylic acids, 2,4-disubstituted thiazols such as **424** are formed in one step.[262] It is of great importance that only one of the two possible



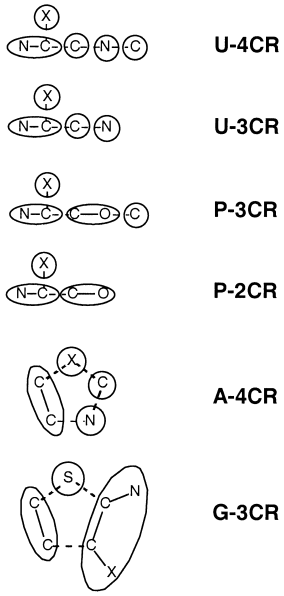
isomers is formed in the rearrangement in the U-4CR. The other theoretically possible isomer cannot cyclize with β-dimethylamino-α-isocyanoacrylic acid derivatives to form a thiazole, as this would lead to a tertiary thioamide and no aromatization could take place. Thus, by choosing a suitable bifunctional parent compound in combination with a new selective acid component, a multicomponent thiazole synthesis was designed and carried out.

Can the chemist be given a set of rules or even algorithms and therefore programs which enable him to use MCRs for the total synthesis of natural and medicinal products and in the search for new drugs?

The intuitive method of synthesizing desired target molecules by means of MCRs is shown in Scheme 18. The smallest common structural element of a MCR is searched for in the molecule to be synthesized.

A combinatorial way of finding new MCRs was presented by Weber et al.[263] A collection of ten compounds with different functional groups was provided (Scheme 19). Then, all MCR combinations of the ten parent compounds were pipetted together automatically, a 10CR variant, ten 9CR variants, etc. In the HPLC analysis, the signals for the starting substances and those from obvious 2CR products were ignored in the evaluation. Reaktions whose product signals passed a predefined threshold value (here: 30%) were repeated on a preparative scale and analyzed in detail. In this way, many classic MCRs were found, but many new MCRs were also discovered. For example, cyclohexanone reacts with benzyl isocyanide, acetic acid, and *p*-methoxyphenyl hydrazine hydrochloride to form 2,3-dihydrocinnoline **425**.

The chemistry of the MCRs is more varied than that of the 2CRs by several orders of magnitude. Whereas mainly the chemistry of 2CRs was examined ever since the beginnings of organic chemistry, MCRs were only researched sporadically and only by a few groups. Therefore, the chemistry of the MCRs presents itself rather like a map of the world before the times of the great discoverers: full of white areas. Thus, MCRs offer a large field for diverse and important new discoveries.[264–282]



Scheme 18. In the products of every MCR, common basic structures can be found. These smallest common atom connectivities can help the synthetic chemist discover an MCR for his target molecule that can simplify its total synthesis.

8. Appendix: Abbreviations

MCR	multicomponent reaction
IMCR	isocyanide MCR
M-3CR	Mannich three-component reaction
A-4CR	Asinger four-component reaction
PS-2CR	Pictet – Spengler two-component reaction
U-4CR	Ugi four-component reaction
P-3CR	Passerini three-component reaction
BB-4CR	Bucherer – Bergs four-component reaction
UM-5CR	Ugi – Mannich five-component reaction
G-3CR	Gewald three-component reaction
4CC-SSS	four-component condensation with stereoselective segment coupling
4CC-SC	segment coupling by means of four-component condensation
HLE	human leukocyte elastase
MDR	multiple drug resistance
CMV	cyto-megalo virus

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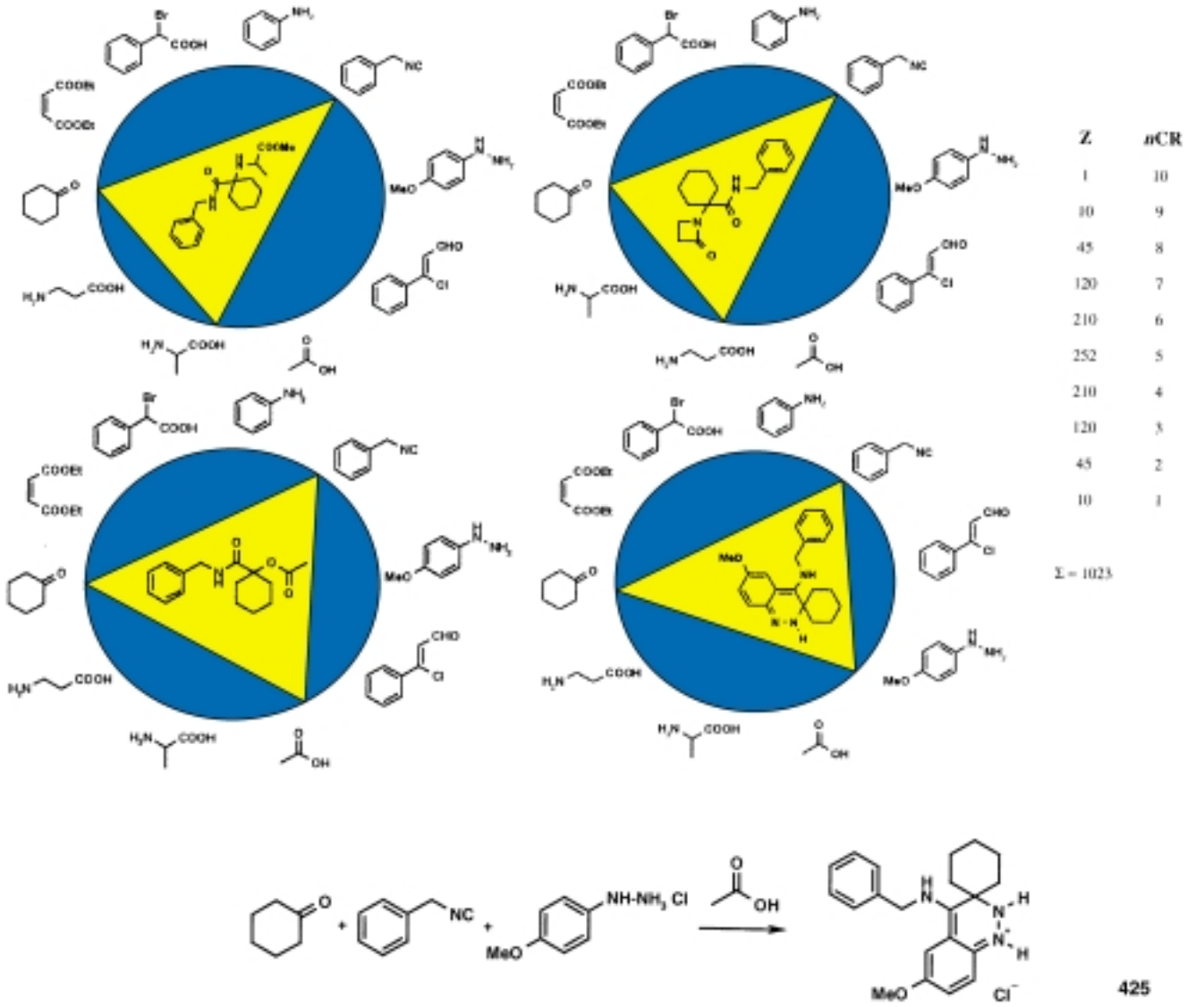
[1] a) R. B. Woodward, M. P. Cava, W. D. Ollis, H. Hunger, H. U. Daeniker, K. Schenker, *J. Am. Chem. Soc.* **1954**, *76*, 4749; b) P. Magnus, M. Giles, Bonnert, C. S. Kim, L. McQuire, A. Merritt, N. Vicker, *J. Am. Chem. Soc.* **1992**, *114*, 4403; c) S. D. Knight, L. E. Overman, G. Pairaudeau, *J. Am. Chem. Soc.* **1993**, *115*, 9293; d) M. E. Kuehne, F. Xu, *J. Org. Chem.* **1993**, *58*, 7490; e) V. H. Rawahl, Iwasa, *J. Org. Chem.* **1994**, *59*, 2685.



Scheme 19. Finding MCRs by means of combinatorial methods: Ten parent compounds with different functional groups are depicted on the rim of a circle. In principle there are 1023 possibilities for these compounds to react with each other if each compound is to react only once. Interestingly, there are many more possibilities for MCRs than for 2CRs with a maximum at 5CRs. Analysis of all combinatorial reaction possibilities led to the discovery of new MCRs, but also the rediscovery of old ones: the MCR of β-amino acids, ketones, and isocyanides to β-lactams (top right), the reaction of α-amino acids, isocyanides, and ketones to give iminodicarboxylic acid derivatives (top left), the classic Passerini reaction of isocyanides, carboxylic acids, and ketones (bottom left) and an example of a new 3CR of aromatic hydrazines, ketones, and isocyanides, which cyclize to dihydrocinnolines in the presence of acetic acid (bottom right).

[2] "Towards the ideal synthesis": P. A. Wender, S. T. Handy, D. L. Wright, *Chem. Ind*. **1997**, 765.

[3] G. Hellmann, H. Opitz, *α-Aminoalkylierung*, Verlag Chemie, Weinheim, **1961**.

[4] I. Ugi, C. Steinbrückner, DE-B 1,103,337, **1959**.

[5] At the time, the term "collections of compounds" was used instead of "libraries".

[6] J. Drews, *Die verspielte Zukunft*, Birkhäuser, Basel, **1998**.

[7] I. Ugi, C. Steinbrückner, *Chem. Ber*. **1961**, *94*, 734.

[8] Other new reviews: a) I. Ugi, A. Dömling, W. Hörl, *Endeavour* **1994**, *18*, 430; b) R. W. Armstrong, A. P. Combs, P. A. Tempest, S. D. Brown, T. A. Keating, *Acc. Chem. Res.* **1996**, *29*, 123; c) I. Ugi, *J. Prakt. Chem*. **1997**, *339*, 499; d) I. Ugi, M. Almstetter, H. Bock, A. Dömling, B. Ebert, B. Gruber, C. Hanusch, S. Heck, K. Kehagia-Drikos, K. Lorenz, S. Papathoma, R. Raditschnig, T. Schmid, B. Werner, A. Von Zychlinski, *Croat. Chem. Acta* **1998**, *71*, 527; e) I. Ugi, *Proc. Estonian Acad. Sci. Chem*. **1998**, *47*, 107; f) A. Dömling, *Comb. Chem. High Through. Screen*. **1999**, *1*, 1; g) S. L. Dax, J. L. McNally, M. A. Youngman, *Curr. Med. Chem*. **1999**, *6*, 255; h) A. Dömling, *Curr. Opin. Chem. Biol*. **2000**, *4*, 318.

[9] a) M. Tramontoni, L. Angiolini, *Mannich Bases—Chemistry and Uses*, CRC Press, Boca Raton, **1994**; b) H. J. Roth, *Pharm. Unserer Zeit* **1997**, *26*, 299.

[10] M. Arend, B. Westermann, N. Risch, *Angew. Chem*. **1998**, *110*, 1096; *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 1044.

[11] A. Strecker, *Liebigs Ann. Chem*. **1850**, *75*, 27.

[12] A, Laurent, C. F. Gerhardt, *Ann. Chimie Phys.* **1838**, *66*, 181.

[13] R. Robinson, *J. Chem. Soc. (London)* **1917**, *111*, 876.

[14] a) C. Schöpf, *Angew. Chem*. **1937**, *50*, 779; b) C. Schöpf, *Angew. Chem*. **1937**, *50*, 797.

[15] A. Hantzsch, *Justus Liebigs Ann. Chem*. **1882**, *215*, 1.

[16] I. Gatterman, T. Wieland, *Die Praxis der Organischen Chemie*, 43th ed., Walter De Gruyter, Berlin, **1982**.

[17] a) F. Bossert, W. Vater, *Naturwissenschaften* **1971**, *58*, 578; b) F. Bossert, H. Meyer, R. Wehinger, *Angew. Chem.* **1981**, *93*, 755; *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 762.

[18] a) M. Passerini, *Gazz. Chim. Ital*. **1921**, *51*, 126; b) M. Passerini, *Gazz. Chim. Ital*. **1921**, *51*, 181.

[19] a) M. Passerini, *Gazz. Chim. Ital*. **1922**, *52*, 432; b) M. I. S. Dewar, *Electronic Theory of Organic Chemistry*, Clarendon, Oxford, **1949**,

p. 116; c) R. H. Baker, D. Stanonis, *J. Am. Chem. Soc*. **1951**, *73*, 699; d) I. Hagedorn, U. Eberholz, H. D. Winkelmann, *Angew. Chem.* **1994**, *76*, 583; *Angew. Chem. Int. Ed. Engl.* **1964**, *3*, 647; e) T. Carfiglio, P. G. Cozzi, C. Floriani, A. Chiesi-Villa, C. Rizzoli, *Organometallics* **1993**, *12*, 2726; f) D. Seebach, G. Adam, T. Gees, M. Schiess, W. Weigand, *Chem. Ber*. **1988**, *121*, 507.

[20] a) H. Bergs, DE-B 566,094, **1929**; b) T. Bucherer, H. Barsch, *J. Prakt. Chem*. **1934**, *140*, 151.

[21] a) B. Radziszewski, *Ber. Dtsch. Chem. Ges*. **1882**, *15*, 1499; b) B. Radziszewski, *Ber. Dtsch. Chem. Ges*. **1882**, *15*, 2706.

[22] A. Hantzsch, *Ber. Dtsch. Chem. Ges*. **1890**, *23*, 1474.

[23] a) P. Biginelli, *Ber. Dtsch. Chem. Ges*. **1891**, *24*, 1317, 2962; b) P. Biginelli, *Ber. Dtsch. Chem. Ges*. **1893**, *26*, 447.

[24] P. Biginelli, *Ber. Dtsch. Chem. Ges*. **1893**, *26*, 447.

[25] C. Mannich, W. Kröschl, *Arch. Pharm*. **1912**, *250*, 647.

[26] S. Kubik, R. S. Meissner, J. Rebek, *Tetrahedron Lett*. **1994**, 36, 6635.

[27] Carbon monoxide, which is isolobal with isocyanides, also contains a formally divalent carbon. The carbon atom in carbenes is divalent, too. However, most carbenes are extremely short-lived compounds.

[28] J. U. Nef, *Justus Liebigs Ann. Chem*. **1892**, *270*, 267; J. U. Nef, *Justus Liebigs Ann. Chem.* **1899**, *309*, 126.

[29] Reviews: a) P. J. Scheuer, *Acc. Chem. Res.* **1992**, *25*, 433 – 439; b) M. S. Edenborough, R. B. Herbert, *Nat. Prod. Rep*. **1988**, *5*, 229 – 245.

[30] a) I. Ugi, U. Fetzer, W. Unterstenhöfer, P. E., Behrenz, P. E. Frohberger, H. Schinpflug, G. Unterstenhöfer (Bayer AG), DE-B 1,209,798, **1962/1966**; b) U. Fetzer, I. Ugi, G. Unterstenhöfer (Bayer AG), DE-B 1,235,298, **1964/1967**; c) U. Eholzer, U. Fetzer, I. Ugi, I. Hammann, G. Unterstenhöfer (Bayer AG), DE-B 1,215,141, **1964/1966**; d) H. L. Yale (E.R. Squibb and Son, Inc.), US-A 1970.000098106, **1970**.

[31] The diisocyanide xanthocillin was commercially available as a topic antibiotic (Arzneimittelwerk Dresden).

[32] N. Fusetani, *Curr. Org. Chem*. **1997**, *1*,127.

[33] W. Lieke, *Justus Liebigs Ann. Chem*. **1859**, *112*, 316.

[34] A. Gautier, *Ann. Chim. (Paris)* **1869**, *17*, 218.

[35] A. Demhardter, C. Fleck, personal communication.

[36] Values of $LD_{50} = 1 - 5$ g per kg of body weight(mouse) upon subcutaneous and/or oral application are no exception. 1,4-Diisocyanobutane, however, is extremely toxic according to tests carried out by the Bayer AG ($LD_{50} < 10\ mg\,kg^{-1}$!).

[37] A. Gautier, *Justus Liebigs Ann. Chem*. **1869**, *146*, 119.

[38] Reviews of isocyanides: a) C. Grundman, *Methoden Org. Chem. (Houben-Weyl) 4th ed. 1952 –*, Vol. E5, **1985**, p. 1611; b) I. A. O'Neil in *Comprehensive Organic Functional Group Transformations*, *Vol. 3* (Eds.: A. R. Katritzky, D. Meth-Cohn, C. W. Rees), Pergamon, Oxford, **1995**, p. 963; c) review of fluorinated isocyanides: D. Lentz, *Angew. Chem*. **1994**, *106*, 1377; *Angew. Chem. Int. Ed. Engl*. **1994**, *33*, 1315; d) P. Hoffmann, G. Gokel, D. Marquarding, I. Ugi in *Isonitrile Chemistry* (Ed.: I. Ugi), Academic Press, New York, **1971**, p. 9.

[39] a) G. Skorna, I. Ugi, *Angew. Chem*. **1977**, *89*, 267; *Angew. Chem. Int. Ed. Engl*. **1977**, *16*, 259; b) H. Eckert, B. Forster, *Angew. Chem*. **1987**, *99*, 927; *Angew. Chem. Int. Ed. Engl*. **1987**, *26*, 1221.

[40] R. Obrecht, R. Herrmann, I. Ugi, *Synthesis* **1985**, 400.

[41] G. Giesemann, E. von Hinrichs, I. Ugi, *J. Chem. Res (S)* **1982**, 79.

[42] A. Gautier, *Ann. Chem. (Paris)* **1869**, *17*, 193; A. Gautier, *Ann. Chem. (Paris)* **1869**, *17*, 203.

[43] Work with volatile and malodorous isocyanides should always be conducted under well-working exhaust hoods, and all items of equipment that come into contact with the isocyanides should be placed into a bath of dilute mineral acid ($RNC + H_3O^+ \rightarrow RNH\text{-}RNHCHO$).

[44] R. Karl, P. Lemmen, I. Ugi, *Synthesis* **1989**, 718.

[45] a) G. Skorna, I. Ugi, *Chem. Ber*. **1978**, *111*, 3965; b) R. Ashady, I. Ugi, *Z. Naturforsch. B* **1981**, *36*, 1202; c) R. Ashady, I. Ugi, *Angew. Chem*. **1982**, *94*, 367; *Angew. Chem. Int. Ed. Engl*. **1982**, *21*, 374; d) *Angew. Chem. Suppl*. **1982**, 761; e) R. Ashady, I. Ugi, *Talanta* **1984**, *31*, 842; f) review: R. Ashady, I. Ugi, *Polymer* **1990**, *31*, 1164.

[46] a) E. Meyer, *J. Prakt. Chem*. **1866**, 147; b) P. Boullanger, G. Descotes, *Tetrahedron Lett*. **1976**, *38*, 4327.

[47] a) A. Gautier, *Justus Liebigs Ann. Chem*. **1867**, *142*, 289; b) an improvement of the silver cyanide method with dicyanoargentates was described: L. B. Engemyr, A. Martinsen, J. Songstad, *Acta Chem. Scand. Ser. A* **1974**, *28*, 255.

[48] A. W. Hofmann, *Justus Liebigs Ann. Chem*. **1867**, *144*, 114.

[49] A. W. Hofmann, *Ber. Dtsch. Chem. Ges*. **1870**, *3*, 766.

[50] a) I. Ugi, R. Meyr, *Angew. Chem*. **1958**, *70*, 702; b) I. Ugi, R. Meyr, *Chem. Ber*. **1960**, *93*, 239.

[51] a) W. P. Weber, G. W. Gokel, I. K. Ugi, *Angew. Chem*. **1972**, *84*, 587; *Angew. Chem. Int. Ed. Engl*. **1972**, *11*, 530; b) G. W. Gokel, R. P. Widera, W. P. Weber, *Org. Synth*. **1976**, *55*, 96.

[52] R. Appel, R. Kleistück, K. D. Ziehn, *Angew. Chem*. **1971**, *83*, 143; *Angew. Chem. Int. Ed. Engl*. **1971**, *10*, 132.

[53] U.Schöllkopf, *Angew. Chem*. **1977**, *89*, 351; *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 339.

[54] D. H. R. Barton, T. Bowles, S. Husinec, J. E. Forbes, A. Llobera, A. E. A. Porter, S. Z. Zard, *Tetrahedron Lett*. **1988**, *29*, 3343.

[55] a) P. G. Gassman, T. L. Guggenheim, *J. Am. Chem. Soc*. **1982**, *104*, 5849; b) γ-hydroxy isocyanides are obtained from oxetanes in an analogous way: P. G. Gassman, *Tetrahedron Lett*. **1985**, *26*, 4971.

[56] I. A. O'Neil, J. Baldwin, *Synlett* **1990**, 603.

[57] Y. Kitano, K. Chiba, M. Tada, *Tetrahedron Lett*. **1998**, *39*, 1911.

[58] H. Bienaymé, *Tetrahedron Lett*. **1998**, *39*, 4255.

[59] R. Bossio, S. Marcaccini, R. Pepino, *Liebigs Ann. Chem*. **1990**, 935.

[60] P. A. Tempest, S. D. Brown, R. W. Armstrong, *Angew. Chem.* **1996**, *108*, 689; *Angew. Chem. Int. Ed. Engl*. **1996**, *35*, 640.

[61] Y. Kobayashi, T. Fukuyama, *J. Heterocycl. Chem*. **1998**, *35*, 1043.

[62] H. Josien, S.-B. Ko, D. Bom, D. P. Curran, *Chem. Eur. J.* **1998**, *4*, 67.

[63] D.Hoppe, *Angew. Chem*. **1974**, *86*, 878; *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 789.

[64] A. J. M. van Beijnen, *Macromolecules* **1983**, *16*, 1679.

[65] D. Hoppe, U. Schöllkopf, *Liebigs Ann. Chem*. **1972**, *763*, 1.

[66] A. M. van Leusen, *Synthesis* **1991**, 531.

[67] A. M. van Leusen, H. Siderius, B. E. Hoogenboom, D. van Leusen, *Tetrahedron Lett*. **1972**, *13*, 5337.

[68] A. M. van Leusen, J. Wildeman, O. H. Oldenziel, *J. Org. Chem*. **1977**, *42*, 1153.

[69] R. Schröder, U. Schöllkopf, E. Blume, I. Hoppe, *Ann*. **1975**, 533.

[70] U. Schöllkopf, P. H. Porsch, E. Blume, *Ann*. **1976**, 7122.

[71] a) M. Sawamura, Y. Ito, T. Hayashi, *Tetrahedron Lett*. **1989**, *30*, 2247; b) Y. Ito, M. Sawamura, H. Hamashima, T. Hayashi, *Tetrahedron Lett*. **1989**, *30*, 4681; c) S. D. Pastor, R. Kesselring, A. Togni, *J. Organomet. Chem*. **1992**, *429*, 415.

[72] S. Marcaccini, T. Torroba, *Org. Prep. Proced. Int*. **1993**, *25*, 141.

[73] a) I. Ugi, R. Meyr, *Chem. Ber*. **1961**, *94*, 2229; b) I. Hagedorn, U. Eholzer, *Chem. Ber*. **1965**, *98*, 936.

[74] I. Ugi, R. Meyr, *Angew. Chem*. **1962**, *74*, 9; *Angew. Chem. Int. Ed. Engl*. **1962**, *1*, 8.

[75] H. Bock, I. Ugi, *J. Prakt. Chem*. **1997**, *339*, 385.

[76] a) When partly fluorinated parent compounds are used in the P-3CR, the products often are liquid and highly volatile: A. Dömling, J. Achatz, unpublished results ; b) K. Burger, K. Mütze, W. Hollweck, B. Koksch, *Tetrahedron* **1998**, *54*, 5915.

[77] R. H. Baker, A. H. Schlesinger, *J. Am. Chem. Soc*. **1945**, *67*, 1499.

[78] E. Müller, B. Zech, *Liebigs Ann. Chem*. **1966**, *696*, 72.

[79] G. L. Grunewald, W. J. Brouillette, J. A. Finney, *Tetrahedron Lett*. **1980**, *21*, 1219.

[80] B. Zech, E. Müller, *Liebigs Ann. Chem*. **1968**, *715*, 47.

[81] a) U. Fetzer, I. Ugi, *Justus Liebigs Ann. Chem*. **1962**, *659*, 184; b) J. Rachon, *Chimia* **1983**, *37*, 299.

[82] a) M. Passerini, *Gazz. Chim. Ital*. **1924**, *54*, 529; b) E. Müller, B. Zeeh, *Justus Liebigs Ann. Chem*. **1966**, *696*, 72; c) B. Zeeh, E. Müller, *Justus Liebigs Ann. Chem*. **1968**, *715*, 47.

[83] J. W. McFarland, *J. Org. Chem*. **1963**, *28*, 2179.

[84] a) M. Passerini, *Gazz. Chim. Ital*. **1922**, *52*, 432; b) M. Passerini, *Gazz. Chim. Ital*. **1926**, *56*, 826; c) N. Kreuzkamp, K. Lämmerhirt, *Angew. Chem*. **1968**, *80*, 2179; *Angew. Chem. Int. Ed. Engl*. **1968**, *7*, 372.

[85] R. Neidlein, *Z. Naturforsch. B* **1964**, *19*, 1159.

[86] T. El Gomati, J. Firl, I. Ugi, *Chem. Ber*. **1977**, *110*, 1603.

[87] R. Neidlein, *Arch. Pharm*. **1966**, *299*, 603.

[88] W. C. Lumma, *J. Org. Chem*. **1981**, *46*, 3668.

[89] S. W. Kim, S. M. Bauer, R. W. Armstrong, *Tetrahedron Lett*. **1998**, *39*, 7031.

[90] T. Ziegler, R. Schlömer, C. Koch, *Tetrahedron Lett*. **1998**, *39*, 5057.
[91] S. König, R. Klösel, R. Karl, I. Ugi, *Z. Naturforsch. B* **1994**, *49*, 1586.
[92] M. Passerini, G. Ragni, *Gazz. Chim. Ital*. **1931**, *61*, 826.
[93] E. Oliveri-Mandala, B. Alagna, *Gazz. Chim. Ital*. **1910**, *40*, 441.
[94] I. Ugi, F. K. Rosendahl, *Chem. Ber*. **1961**, *94*, 2233.
[95] M. Passerini, *Gazz. Chim. Ital*. **1923**, *53*, 331.
[96] S. Sebti, A. Foucaud, *Synthesis* **1983**, 546.
[97] R. Bossio, C. F. Marcos, S. Marcaccini, R. Pepino, *Tetrahedron Lett*. **1997**, *38*, 2519.
[98] R. Bossio, S. Marcaccini, R. Pepino, *Liebigs Ann. Chem*. **1991**, 1107.
[99] R. Bossio, S. Marcaccini, R. Pepino, T. Torroba, *Synthesis* **1993**, 783.
[100] K. Kobayashi, T. Matoba, I. Susumu, M. Takashi, O. Morikawa, H. Konishi, *Chem. Lett*. **1998**, 551.
[101] R. Bossio, S. Marcaccini, R. Pepino, T. Torroba, *J. Chem. Soc. Perkin Trans. 1* **1996**, 229.
[102] a) I. Ugi, R. Meyr, U. Fetzer, C. Steinbrückner, *Angew. Chem*. **1959**, *71*, 386; b) I. Ugi, C. Steinbrückner, *Angew. Chem*. **1960**, *72*, 267.
[103] I. Ugi, F. K. Rosendahl, F. Bodesheim, *Liebigs Ann. Chem*. **1963**, *666*, 54.
[104] N-isocyanides also react in the U-4CR, albeit with more modest yields: G. Zinner, D. Moderhack, W. Kliegel, *Chem. Ber*. **1969**, *102*, 2536.
[105] R. Kaufhold, I. Ugi, *Liebigs Ann. Chem*. **1967**, *709*, 11.
[106] a) O. Mumm, *Ber. Dtsch. Chem. Ges*. **1910**, *43*, 887; b) O. Mumm, H. Hesse, H. Volquartz, *Ber. Dtsch. Chem. Ges*. **1915**, *48*, 379.
[107] a) I. Ugi, H. Aigner, M. L. V. Arnaez, G. Glahsl, P. Lemmen, R. Stöcklein-Schneiderwind, M. Balla-Tamasi in *Vorträge anlässlich der Königsteiner Chromatographie-Tage* (Ed.: H. Aigner), Waters, Eschborn, **1984**, p. 1; b) H. Aigner, Dissertation, Technische Universität München, **1984**.
[108] H. Quast, S. Aldenkortt, *Eur. Chem. J*. **1996**, *2*, 462.
[109] G. Neyer, J. Achatz, B. Danzer, I. Ugi, *Heterocycles* **1990**, *30*, 863.
[110] A. M. L. Hoel, J. Nielsen, *Tetrahedron Lett*. **1999**, *40*, 3941.
[111] I. Ugi, D. Marquarding, R. Urban in *Chemistry and Biochemisty of Amino Acids, Peptides, and Proteins* (Ed.: B. Weinstein), Marcel Dekker, New York, **1982**, p. 246 – 289.
[112] a) R. Urban, I. Ugi, *Angew. Chem*. **1975**, *87*, 67; *Angew. Chem. Int. Ed. Engl*. **1975**, *14*, 61; b) W. Pfrengle, H. Kunz, *J. Am. Chem. Soc*. **1988**, *110*, 651; c) M. Goebel, I. Ugi, *Synthesis* **1991**, 1095; d) H. Kunz, W. Pfrengle, K. Rück, W. Sager, *Synthesis* **1991**, 1039; e) I. Ugi, M. Goebel, N. Bachmeyer, A. Demharter, C. Fleck, R. Gleixner, S. Lehnhoff, *Chem. Pept. Proteins* **1993**, *5 – 6*, 59 – 72; f) S. Lehnhoff, M. Goebel, R. M. Karl, R. Klösel, I. Ugi, *Angew. Chem*. **1995**, *107*, 1208; *Angew. Chem. Int. Ed. Engl*. **1995**, *34*, 1104.
[113] H. R. Divanfard, Z. Lysenko, P. C. Wang, M. M. Joullié, *Synth. Commun*. **1978**, *8*, 269.
[114] a) P. M. Hardy, I. N. Lingham, *Int. J. Protein Res*. **1983**, *21*, 406; b) T. Yamada, N. Motoyama, T. Taniguchi, T. Kazuta, T. Miyazawa, S. Kuwata, K. Matsumoto, *Chem. Lett*. **1987**, 723; c) T. Yamada, Y. Nakamura, T. Miyazawa, T. Kuwata, K. Matsumoto, *Jpn. Chem. Express* **1993**, *8*, 161.
[115] K. Matsumoto, T. Uchida in *Organic Synthesis at High Pressure* (Eds.: K. Matsumoto, R. M. Acheson), Wiley, New York, **1991**, p. 164.
[116] T. Yamada, Y. Omote, Y. Yamanaka, T. Miyazawa, S. Kuwata, *Synthesis* **1998**, 991.
[117] A. Failli, H. Immer, M. Götz, *Can. J. Chem*. **1979**, *57*, 3257.
[118] T. A. Keating, R. W. Armstrong, *J. Am. Chem. Soc*. **1996**, *118*, 2574.
[119] A. M. Strocker, T. A. Keating, P. A. Tempest, R. W. Armstrong, *Tetrahedron Lett*. **1996**, *37*, 1149.
[120] A. M. M. Mjalli, S. Sarshar, T. J. Baiga, *Tetrahedron Lett*. **1996**, *37*, 2943.
[121] H. Hatanaka, I. Ishimura, *Tetrahedron Lett*. **1983**, *24*, 4837.
[122] a) H. P. Isenring, W. Hofheinz, *Synthesis* **1981**, 385; b) H. P. Isenring, W. Hofheinz, *Tetrahedron* **1983**, *39*, 2591.
[123] J. Geller, I. Ugi, *Chem. Scr*. **1983**, *22*, 85.
[124] C. F. Hoyng, A. D. Pateöl, *Tetrahedron Lett*. **1980**, *21*, 4795.
[125] I. Ugi, K. Offermann, *Chem. Ber*. **1964**, *97*, 2996.
[126] I. Ugi, A. Arora, H. Burghard, G. Eberle, H. Eckert, G. George, G. Gokel, H. Herlinger, E. von Hinrichs, P. Hoffmann, H. Klusacek, H. L. Lam, D. Marquarding, H. S. Nah, K. Offeremann, D. Rehn, S. Stüber, M. Tamasi, R. Urban, L. Wackerle, S. Zahr, H. v. Zychlinsky in *Peptides 1974* (Ed.: Y. Wolman), Wiley, New York, **1975**, p. 71.
[127] M. Waki, Y. Minematsu, J. Meienhofer, N. Izumiya, *Chem. Lett*. **1979**, 823.
[128] M. Waki, J. Meienhofer, *J. Am. Chem. Soc*. **1977**, *99*, 6075.
[129] T. Lindhorst, H. Bock, I. Ugi, *Tetrahedron* **1999**, *55*, 7411.
[130] R. J. Linderman, S. Binet, S. R. Petrich, *J. Org. Chem*. **1999**, *64*, 336.
[131] H. Gröger, M. Hatam, J. Kintscher, J. Martens, *Synth. Commun*. **1996**, *26*, 3383.
[132] P. Bukall, I. Ugi, *Heterocycles* **1981**, *15*, 381.
[133] K. Tsuchida, K. Ikeda, Y. Mizuno, *Chem. Pharm. Bull*. **1980**, *28*, 2748.
[134] F. K. Rosendahl, I. Ugi, *Liebigs Ann. Chem*. **1963**, *666*, 65.
[135] R. Huisgen, H. Gotthardt, H. O. Bayer, F. C. Schäfer, *Angew. Chem.*, **1964**, *76*, 185; *Angew. Chem. Int. Ed. Engl*. **1964**, *3*, 136.
[136] T. A. Keating, R. W. Armstrong, *J. Am. Chem. Soc*. **1995**, *117*, 7842.
[137] S. W. Kim, Y. S. Shin, S. Ro, *Bioorg. Med. Chem. Lett*. **1998**, *8*, 1665.
[138] A. Dömling, I. Ugi, *Tetrahedron* **1993**, *49*, 9495.
[139] H. Gröger, M. Hatam, J. Martens, *Tetrahedron* **1995**, *51*, 7173.
[140] J. Kintscher, J. Martens, *Synthesis* **1992**, 837.
[141] A. Dömling, *Nucleotides Nucleosides* **1998**, *17*, 1667.
[142] A. Dömling, K.-Z. Chi, M. Barrere, *Bioorg. Med. Chem. Lett*. **1999**, *9*, 2871.
[143] W. Maison, I. Schlemminger, O. Westerhoff, J. Martens, *Bioorg. Med. Chem. Lett*. **1999**, *9*, 581.
[144] G. Gokel, G. Lüdke, I. Ugi in *Isonitrile Chemistry* (Ed.: I. Ugi), Academic Press, New York, **1971**, p. 159.
[145] R. Bossio, S. Marcaccini, P. Paoli, R. Pepino, *Synthesis* **1994**, 672.
[146] T. Ziegler, H. J. Kaisers, R. Schlömer, C. Koch, *Tetrahedron* **1999**, *55*, 8397.
[147] a) O. Lockhoff, *Angew. Chem*. **1998**, *110*, 3634; *Angew. Chem. Int. Ed. Engl*. **1998**, *37*, 3436; b) O. Lockhoff (Bayer AG), DE-A 19636538, **1996**.
[148] A. Dömling, W. Richter (Morphochem AG), WO-A 98102860, **1996**.
[149] W. K. C. Park, M. Auer, H. Jaschke, C. H. Wong, *J. Am. Chem. Soc*. **1996**, *118*, 10150.
[150] a) A. Studer, P. Jeger, P. Wipf, D. P. Curran, *J. Org. Chem*. **1997**, *62*, 2917; b) A. Studer, S. Hadida, R. Ferritto, S.-Y. Kim, P. Jeger, P. Wipf, D. P. Curran, *Science* **1997**, *275*, 823.
[151] A. J. Polyakov, N. N. Aseeva, V. G. Bezrukova, *Izv. Akad. Nauk SSSR Ser. Khim*. **1974**, *7*, 1597.
[152] D. P. Sutherlin, T. M. Stark, R. Hughes, R. W. Armstrong, *J. Org. Chem*. **1996**, *61*, 8350.
[153] D. Obrecht, C. Abrecht, A. Grieder, J. M. Villalgordo, *Helv. Chim. Acta* **1997**, *80*, 65.
[154] X. Cao, E. J. Moran, D. Siev, A. Lio, C. Ohashi, A. M. M. Mjalli, *Bioorg. Med. Chem. Lett*. **1995**, *5*, 2953.
[155] E. J. Moran, S. Shashar, J. F. Cargill, M. M. Shahbaz, A. Lio, A. M. M. Mjalli, R. W. Armstrong, *J. Am. Chem. Soc*. **1995**, *117*, 10787.
[156] Z. Li, S. L. Yeo, C. J. Pallen, A. Ganesan, *Bioorg. Med. Chem. Lett*. **1998**, *8*, 2443.
[157] S. W. Kim, S. M. Bauer, R. W. Armstrong, *Tetrahedron Lett*. **1998**, *39*, 6993.
[158] a) C. D. Floyd, M. Whittaker (British Biotech), WO-A 96/26918, **1996**; b) C. D. Floyd, L. A. Harnett, A. Miller, S. Patel, L. Saroglou, M. Whittaker, *Synlett* **1998**, 637; c) S. Patel, L. Saroglou, C. D. Floyd, A. Miller, M. Whittaker, *Tetrahedron Lett*. **1998**, *39*, 8333.
[159] R. H. Schlessinger, G. R. Bebernitz, P. Lin, H. Poss, *J. Am. Chem. Soc*. **1985**, *107*, 1777.
[160] G. Opitz, W. Merz, *Justus Liebigs Ann. Chem.*, **1962**, *652*, 163.
[161] a) I. Ugi, F. Bodesheim, *Liebigs Ann. Chem*. **1963**, *666*, 61; b) G. Zinner, W. Kliegel, *Arch. Pharm*. **1966**, *299*, 746; c) G. Zinner, W. Bock, *Arch. Pharm*. **1973**, *306*, 94.
[162] A. Failli, V. Nelson, H. Immer, M. Götz, *Can. J. Chem*. **1973**, *51*, 2769.
[163] T. Yamada, Y. Nakamura, T. Miyazawa, S. Kuwata, K. Matsumoto, *Chem. Express*, **1993**, *8*, 161.
[164] Hydroxamic acids form complexes with Zn^{2+} in matrix metalloproteases (MMP); MMP inhibitors are interesting in the fields of tumor angiogenesis, restenosis, rheumatoid arthritis, neurodegenerative disease, and healing of wounds, among other things.
[165] a) D. Moderhack, *Liebigs Ann. Chem*. **1973**, 359; b) G. Zinner, D. Moderhack, O. Hantelmann, W. Bock, *Chem. Ber.* **1974**, *107*, 2947;

c) G. Zinner, D. Moderhack, W. Heuer, *Z. Chem*. **1975**, *15*, 55; d) G. Zinner, O. Hantelmann, *Arch. Pharm*. **1975**, *308*, 321; e) D. Moderhack, M. Lorke, *Chem. Ztg*. **1979**, *103*, 268.
[166] I. Ugi, E. Böttner, *Liebigs Ann. Chem*. **1963**, *670*, 74.
[167] S. Zychlinski, I. Ugi, *Heterocycles* **1998**, *49*, 29.
[168] N. Kreutzkamp, K. Lämmerhirt, *Angew. Chem*. **1968**, *80*, 394; *Angew. Chem. Int. Ed. Engl*. **1968**, *7*, 372.
[169] D. S. Matteson, Bailey, *Chem. Ind.* **1967**, 191.
[170] E. Haslinger, *Monatsh. Chem*. **1978**, *109*, 747.
[171] H. Groß, J. Gloede, I. Keitel, D. Kunath, *J. Prakt. Chem*. **1968**, *37*, 192.
[172] T. A. Keating, R. W. Armstrong, *J. Org. Chem*. **1998**, *63*, 867.
[173] L. Weber, *Drug Disc. Today* **1998**, *3*, 378.
[174] L. Weber, S. Waltbaum, C. Broger, K. Gubernator, *Angew. Chem*. **1995**, *107*, 2452; *Angew. Chem. Int. Ed. Engl*. **1995**, *34*, 2280.
[175] K. M. Short, B. W. Ching, A. M. M. Mjalli, *Tetrahedron Lett*. **1996**, *37*, 7489.
[176] a) G. Opitz, A. Griesinger, H. W. Schubert, *Justus Lieb. Ann. Chem*. **1963**, *665*, 91; b) G. Opitz, W. Merz, *Justus Lieb. Ann. Chem*. **1963**, *652*, 158; c) R. Neidlein, *Arch. Pharm*. **1965**, *298*, 491; d) R. Neidlein, *Arch. Pharm*. **1964**, *297*, 589; e) R. Neidlein, *Angew. Chem*. **1964**, *76*, 440, *Angew. Chem. Int. Ed. Engl*. **1964**, *3*, 382.
[177] H. Bienaymé, K. Bouzid, *Tetrahedron Lett*. **1998**, *39*, 2735.
[178] K. M. Short, B. W. Ching, A. M. M. Mjalli, *Tetrahedron* **1997**, *53*, 6653.
[179] G. Gokel, G. Lüdke, I. Ugi in *Isonitrile Chemistry* (Ed.: I. Ugi), Academic Press, New York, **1971**, p. 158.
[180] A. Demharter, Dissertation, Technische Universität München, **1995**.
[181] A. Demharter, W. Hörl, E. Herdtweck, I. Ugi, *Angew. Chem*. **1996**, *108*, 185; *Angew. Chem. Int. Ed. Engl*. **1996**, *35*, 173.
[182] I. Ugi, A. Demharter, A. Hörl, T. Schmid, *Tetrahedron* **1996**, *52*, 11 657.
[183] S. J. Park, G. Keum, S. B. Kang, H. Y. Hoh, Y. Kim, *Tetrahedron Lett*. **1998**, *39*, 7109.
[184] A. Dömling, W. Richter, I. Ugi, *Nucleotides Nuc*leosides **1997**, *16*, 1753.
[185] I. Ugi, A. Dömling, B. Gruber, M. Heilingbrunner, C. Heiß, W. Hörl in *Software-Entwicklung in der Chemie* (Ed.: R. Moll), GDCh, Frankfurt, **1995**, p. 113.
[186] I. Ugi, M. Goebel, B. Gruber, H. Heilingbrunner, C. Heiß, H. Hörl, O. Kern, M. Starnecker, A. Dömling, *Res. Chem. Intermed*. **1996**, *22*, 625.
[187] T. Yamada, N. Motoyama, T. Taniguchi, Y. Kazuta, T. Miyazawa, S. Kuwata, K. Matsumoto, M. Sugiura, *Chem. Lett*. **1987**, 723.
[188] B. M. Ebert, I. Ugi, M. Grosche, E. Herdtweck, W. A. Herrmann, *Tetrahedron* **1998**, *54*, 11 887.
[189] I. A. Natchev, *Tetrahedron* **1988**, *44*, 1511.
[190] I. Ugi, W. Hörl, C. Hanusch, T. Schmid, E. Herdtweck, *Heterocycles* **1998**, *47*, 985.
[191] I. Ugi, T. Schmid, *J. Prakt. Chem*. **1997**, *339*, 652.
[192] I. Ugi, R Obrecht, S. Tourré, *Heterocycles* **1984**, *21*, 271.
[193] I. Ugi, *Angew. Chem*. **1982**, *94*, 826; *Angew. Chem. Int. Ed. Engl*. **1982**, *21*, 810.
[194] a) I. Ugi, E. Wischhöfer, *Chem. Ber*. **1961**, *95*, 136; b) M. Hatanaka, H. Yamamoto, H. Nitta, T. Ishimaru, *Tetrahedron*, *Lett*. **1981**, *22*, 3883; c) A. Schutz, I. Ugi, *J. Chem. Res. (S)* **1978**, 157; 2064; d) K. Sjöberg, habilitation thesis, Stockholm University, **1970**.
[195] H. Martin, R. Herrmann, I. Ugi, *Z. Naturforsch. B* **1987**, *42*, 1588.
[196] G. Neyer, I. Ugi, *Synthesis* **1991**, 743.
[197] A. Schutz, I. Ugi, H.-J. Kabbe, *Z. Naturforsch. B* **1979**, *34*, 1303.
[198] H. Nitta, M. Hatanaka, T. Ishimura, *J. Chem. Soc. Chem. Commun*. **1987**, 51.
[199] K. Kehagia, I. Ugi, *Tetrahedron* **1995**, *51*, 9523.
[200] A. Dömling, M. Starnecker, I. Ugi, *Angew. Chem.* **1995**, *107*, 2465; *Angew. Chem. Int. Ed. Engl*. **1995**, *34*, 2238.
[201] A. Dömling, K. Kehagia, I. Ugi, *Tetrahedron* **1995**, *51*, 9523.
[202] J. Pitlik, C. A. Townsend, *Bioorg. Med. Chem. Lett*. **1997**, *7*,3129.
[203] C. Yoakim, *Antiviral Chem. Chemother.* **1998**, *9*, 379.
[204] T. A. Keating, R. W. Armstrong, *J. Org. Chem.* **1996**, *61*, 8935.
[205] J. Szardenings, presented at the International Symposium Combinatorial Chemistry: New Developments and Applications in Drug Discovery, Schliersee, **1996**.
[206] A. Chucholowski, D. Heinrich, B. Mathys, C. Müller, *Abstr. Pap. Am. Chem. Soc*. **1997**, *214*, 287.
[207] C. Hulme, J. Peng, G. Morton, J. M. Salvino, T. Herpin, R. Labaudiniere, *Tetrahedron Lett*. **1998**, *39*, 7227.
[208] L. Grehn, K. Gunnarsson, U. Ragnarrson, *Acta Chem. Scand. Ser. B.* **1986**, *40*, 745.
[209] C. Hulme, M. M. Morrissette, F. A. Volz, C. J. Burns, *Tetrahedron Lett*. **1998**, *38*, 1113.
[210] C. Hulme, J. Peng, B. Louridas, P. Menard, P. Krolikowski, N. V. Kumar, *Tetrahedron Lett*. **1998**, *39*, 8047.
[211] A. K. Szardenings, T. S. Burkoth, H. H. Lu, D. W. Tien, D. A. Campbell, *Tetrahedron* **1997**, *53*, 6573.
[212] A. K. Szardenings, V. Antonenko, D. A. Campbell, N. DeFrancisco, S. Ida, L. Shi, N. Sharkov, N. Tien, Y. Wang, M. Navre, *J. Med. Chem*. **1999**, *42*, 1384.
[213] C. Hulme, M.-P. Cherrier, *Tetrahedron Lett*. **1999**, *40*, 5295.
[214] a) K. M. Short, B. W. Ching, A. M. M. Mjalli, *Tetrahedron* **1997**, *53*, 6653; b) K. M. Short, A. M. M. Mjalli, *Tetrahedron Lett*. **1997**, *38*, 359.
[215] G. C. B. Harriman, *Tetrahedron Lett*. **1997**, *38*, 5591.
[216] J. Zhang, A. Jacobson, J. R. Rusche, W. Herlihy, *J. Org. Chem*. **1999**, *64*, 1074.
[217] K. Rossen, J. Sager, L. M. DiMichele, *Tetrahedron Lett*. **1997**, *38*, 3183.
[218] K. Rossen, P. J. Pye, L. M. DiMichele, R. P. Voante, P. J. Reider, *Tetrahedron Lett*. **1998**, *39*, 6823.
[219] D. Askin, K. K. Eng, K. Rossen, R. M. Purick, K. M. Wells, R. P. Volante, P. J. Reider, *Tetrahedron Lett*. **1994**, *35*, 673.
[220] R. Bossio, S. Marcaccini, P. Paoli, R. Pepino, C. Polo, *Synthesis* **1991**, 999.
[221] J. A. Deyrup, M. M. Vestling, W. V. Hagen, *Tetrahedron* **1969**, *25*, 1462.
[222] M. Murakami, N. Hasegawa, T. Nagatomi, Y. Ito, *Heterocycles* **1998**, *47*, 85.
[223] a) B. Ebert, Dissertation, Technische Universität München, **1998**; b) I. Ugi, B. Ebert, *Chemosphere* **2000**, in press.
[224] K. Paulvannan, *Tetrahedron Lett*. **1999**, *40*, 1851.
[225] L. Weber, presented at the International Symposium Combinatorial Chemistry: New Developments and Applications in Drug Discovery, Schliersee, **1996**.
[226] Such heterocyclic compounds have antiviral properties, for example: A. Gueiffer, S. Mavel, M. Lhassani, A. Elhakmaoui, R. Snoeck, G. Andrei, O. Chavignon, J.-C. Teulade, M. Witvrouw, J. Balzarini, E. De Clercq, J.-P. Chapat, *J. Med. Chem*. **1998**, *41*, 5108.
[227] a) K. Groebke, L. Weber, F. Mehlin, *Synlett* **1998**, 661; b) C. Blackburn, B. Guan, K. Shiosaki, S. Tsai, *Tetrahedron Lett*. **1998**, *39*, 3635; c) C. Blackburn, *Tetrahedron Lett*. **1998**, *39*, 5469; d) C. Blackburn, *Tetrahedron Lett*. **1998**, *39*, 5469; e) H. Bienaymé, K. Bouzid, *Angew. Chem*. **1998**, *110*, 2349; *Angew. Chem. Int. Ed.* **1998**, *39*, 2234.
[228] C. Hanusch, I. Ugi, *ARKIVOC* **2000**, in press.
[229] K. Ley, R. Nast, *Angew. Chem*. **1965**, *77*, 544; *Angew. Chem. Int. Ed. Engl*. **1965**, *4*, 519.
[230] R. Bossio, R. Marcaccini, R. Pepino, *Liebigs Ann. Chem*. **1993**, 1229.
[231] R. Bossio, S. Marcaccini, P. Paoli, P. Papaleo, R. Pepino, C. Polo, *Liebigs Ann. Chem.* **1991**, 843.
[232] R. Bossio, S. Marcaccini, S. Papaleo, R. Pepino, *J. Heterocycl. Chem*. **1994**, *31*, 397.
[233] R. Bossio, C. F. Marcos, S. Marcaccini, R. Pepino, *Synthesis* **1997**, 1389.
[234] R. Bossio, C. F. Marcos, S. Marcaccini, R. Pepino, *Heterocycles* **1997**, *45*, 1589.
[235] C. Zhang, E. J. Moran, T. F. Woiwode, K. M. Short, A. M. M. Mjalli, *Tetrahedron Lett*. **1996**, *37*, 751.
[236] A. M. M. Mjalli, C. Zhang (Ontogen Corp.), US-A 5840721, **1997**.
[237] I. J. McAlpine, R. W. Armstrong, *J. Org. Chem*. **1996**, *61*, 5674.
[238] A. D. Piscopio, J. F. Miller, K. Koch, *Tetrahedron* **1999**, 55, 8189.
[239] I. Ugi, W. Betz, K. Offermann, *Chem. Ber*. **1964**, *97*, 3008.
[240] R. Bossio, S. Marcaccini, R. Pepino, *Tetrahedron Lett*. **1995**, *36*, 2325.
[241] R. Bossio, S. Marcaccini, R. Pepino, *J. Org. Chem*. **1996**, *61*, 2202.
[242] J. T. Lai, *J.Org. Chem*. **1980**, *45*, 3671.

[243] Primary amines afford isocyanides under the basic phase-transfer conditions (Hoffman method) and could react in a normal U-4CR.
[244] J. R. Falck, S. Manna, *Tetrahedron Lett*. **1981**, *22*, 619.
[245] M. Nagi, K. Ogawa, Y. Muraoka, H. Naganawa, T. Aoyagi, T. Takeuchi, *J. Antibiot.* **1991**, *44*, 956.
[246] U. Schmidt, S. Weinbrenner, *J. Chem. Soc. Chem. Commun*. **1994**, 1003.
[247] M. M. Bowers, P. Carroli, M. M. Joullié, *J. Chem. Soc. Perkin Trans. 1* **1989**, 857.
[248] T. Fukujama, B. D. Robins, A. Sachleben, *Tetrahedron Lett*. **1981**, *22*, 4155.
[249] S. E. de Laszlo, P. G. Williard, *J. Am. Chem. Soc*. **1985**, *107*, 199.
[250] K. Tsuchida, Y. Mizuno, K. Ikeda, *Heterocycles* **1981**, *15*, 883.
[251] J. C. Boehm, D. Kingsbury, *J. Org. Chem*. **1986**, *51*, 2307.
[252] K. Tsuchida, Y. Mizuno, K. Ikeda, *Nucleic Acid Res.* **1980**, s49.
[253] H. Immer, V. Nelson, W. Robinson, M. Götz, *Liebigs Ann. Chem*. **1973**, 1789.
[254] J. E. Semple, P. C. Wang, Z. Lysenko, M. M. Joullié, *J. Am. Chem. Soc*. **1980**, *102*, 7505.
[255] S. M. Bauer, R. W. Armstrong, *J. Am. Chem. Soc*. **1999**, *121*, 6355.
[256] D. S. Tan, M. A. Foley, M. D. Shair, S. L. Schreiber, *J. Am. Chem. Soc*. **1998**, *120*, 8565.
[257] a) A. Dömling, I. Ugi, *Angew. Chem*. **1993**, *105*, 634; *Angew. Chem. Int. Ed. Engl*. **1993**, *32*, 563; b) A. Dömling, I. Ugi, E. Herdtweck, *Acta Chem. Scand*. **1998**, *52*, 107.
[258] Semantics of the union concept: $\cap$ means "combined with", $\equiv$ means "results in the combined reaction"; for example: A-4CR $\cap$ U-5CR $\equiv$ AU-7CR: the union of the Asinger four-component reaction with the Ugi five-component reaction results in the Asinger–Ugi seven-component reaction.
[259] I. Ugi, W. Hörl, B. Ebert, unpublished results .
[260] A. Dömling, K.-C. Chi, unpublished results .
[261] L. Weber, K. Illgen, M. Almstetter, *Synlett* **1999**, 366.
[262] S. Heck, A. Dömling, *Synlett* **2000**, 424.
[263] O. Lack, L. Weber, *Chimia* **1996**, *50*, 445.
[264] S. P. Raillard, G. Ji, A. D. Mann, T. A. Baer, *Org. Proc. Res. Develop*. **1999**, *3*, 177–183.
[265] M. Bergemann, R. Neidlein, *Helv. Chim. Acta* **1999**, *909*, 909–918.
[266] L. Williams, *Third International Electronic Conference on Synthetic Organic Chemistry (ECSOC-3),* **1999**; http://reprints.net/ecsoc-3/b001/b0001.htm.
[267] P. Dumestre, L. El Kaim, A. Gregoire, *Chem. Commun*. **1999**, 775–776.
[268] J. S. Mason, I. Morize, P. R. Menard, D. L. Cheney, C. Hulme, R. F. Labaudiniere, *J. Med. Chem.* **1999**, *42*, 3251–3264.
[269] V. Atlan, C. Buron, L. El Kaim, *Synlett* **2000**, *4*, 489–490.
[270] J. Sisko, A. J. Kassick, M. Mellinger, J. J. Filan, A. Allen, M. A. Olsen, *J. Org. Chem*. **2000**, *65*, 1516.
[271] C. Hulme, L. Ma, M. P., Cherrier, J. J. Romano, G. Morton, C., Duquenne, J. Salvino, R. Labaudiniere, *Tetrahedron Lett*. **2000**, *41*, 1883–1887.
[272] K. Oertel, G. Zech, H. Kunz, *Angew. Chem.* **2000**, *112*, 1489–1491; *Angew. Chem. Int. Ed.* **2000**, *39*, 1431–1433.
[273] C. Hulme, L. Ma, J. J. Romano, G. Morton, S.-Y. Tang, M. P., Cherrier, S. Choi, J. Salvino, R. Labaudiniere, *Tetrahedron Lett*. **2000**, *41*, 1889–1893.
[274] C. Blackburn, B. Guan, *Tetrahedron Lett*. **2000**, *41*, 1495–1500.
[275] D. Lee, J. K. Sello, S. L. Schreiber, *Org. Lett*. **2000**, *2*, 709–712.
[276] S. L. Schreiber, *Science* **2000**, *287*, 1964–1969.
[277] R. Leardini, D. Nanni, G. Zanardi, *J. Org. Chem*. **2000**, *65*, 2763–2772.
[278] G. R. Bebernitz, T. D. Aicher, J. L. Stanton, J. Gao, S. S. Shetty, D. C. Knorr, R. J. Strohschein, J. Tan, L. J. Brand, C. Liu, W. H. Wang, C. C. Vinluan, E. L. Kaplan, C. J. Dragland, D. DelGrande, A. Islam, R. J. Lozito, X. Liu, W. M. Maniara, W. R. Mann, *J. Med. Chem*. **2000**, *43*, 2048–2257.
[279] L. Weber, *Curr. Opin. Chem. Biol*. **2000**, *4*, 295–302.
[280] A. Dömling, *Curr. Opin. Chem. Biol*. **2000**, *4*, 318–323.
[281] K. Illgen, T. Enderle, C. Broger, L. Weber, *Chem. Biol.* **2000**, *7*, 433–441.
[282] A. Chucholowski, M. Nettekoven, *Chim. Oggi* **2000**, 50–53.