Recent Developments in Isocyanide Based Multicomponent Reactions in Applied Chemistry†

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1. Introduction

Multicomponent reactions (MCRs) are generally defined as reactions where more than two staring materials react to form a product, incorporating essentially all of the atoms of the educts. Generally, there are different classification schemes of MCRs possible, e.g. according to the reaction mechanisms, the components involved, or their intrinsic variability.[1]

For example, recently Sonoda et al. described a three-component reaction (3-CR) of epoxides **1**, elemental sulfur

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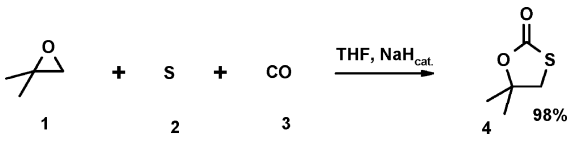
Dr. Alexander Dömling studied Chemistry and Biology at the Technical University Munich (TUM) and performed his Ph.D. research on the theme "The seven component reaction" under the supervision of Prof. Ivar Ugi. After gaining a prestigious Feodor Lynen fellowship of the Humboldt Society, he spent his postdoctoral year (1995) in Prof. Barry Sharpless's lab at Scripps in La Jolla. After returning from the U.S., in 1996 he cofounded the drug discovery company Morphochem, where he served as VP Chemistry and built up the chemistry department to 40 chemists. In 2004 he cofounded R&D Biopharmaceuticals and recently ABC Pharma. In 1996 he received the Friedrich-Weygand award of the Max Bergman Society for his "outstanding contributions to combinatorial chemistry". In 2003 he finished his Habilitation at the TUM, gaining the "Lehrerlaubnis für Chemie". Dr. Dömling serves as independent consultant to several Biotech and Pharma companies. In addition he offers 1–2 day courses on MCR chemistry to the Pharma industry and academia. He is author of more than 70 scientific papers, reviews, and book contributions and holder of more than 30 patent applications. His main research interests are multicomponent reactions (MCRs) and their applications to drug discovery, especially the use of small molecule protein–protein interaction antagonists to treat cancer.

Scheme 1. Sonoda's 3-CR of Epoxides 1, Sulfur 2, and Carbon Monoxide 3, Yielding 1,3-Oxathiolan-2-ones 4



2, and carbonmonoxide **3**, yielding, under basic conditions, 1,3-oxathiolan-2-ones **4** (Scheme 1).[2] From the viewpoint of simple operation, mild reaction conditions, and good yields, the present reaction provides a useful method for synthesis of 1,3-oxathiolan-2-ones. However, this reaction is not very useful to prepare large combinatorial libraries of compounds, since there is only one variable starting material, the epoxide, whereas the other two starting materials are fixed in all reactions. This 3-CR constitutes a MCR of low variability.

On the other hand, a recent publication introduces the union of two highly variable MCRs, the Petasis and Ugi reaction.[3] Both reactions use starting materials which are commercially available in very large quantities. Theoretically, this combination of MCRs spans a chemical space of greater than $1000 \times 200 \times 500 \times 1000 \times 1000 = 10^{14}$ small molecules.[4] This constitutes a combination of MCRs of very high variability, covering a large chemical space.

The *very large chemical space* which is amenable is a major characteristic of MCRs (Figure 1). "Space is big. You just won't believe how vastly, hugely, mind-bogglingly big it is" is a famous sentence out of Douglas Adams *The Hitchhiker's Guide to the Galaxy*. The total number of possible small organic molecules that populate "chemical space" has been estimated to exceed 10^{60}.[5] Thus, it is not surprising that the exploration of chemical space has been extremely limited so far. MCRs, on the other hand, only cover a rather small portion of this huge chemical space. However, as compared to chemical spaces, which are theoretically amenable by linear multistep syntheses, MCRs provide the great advantage of being short *one-pot* syntheses, thus allowing a *fast* probe of a chemical hypothesis.

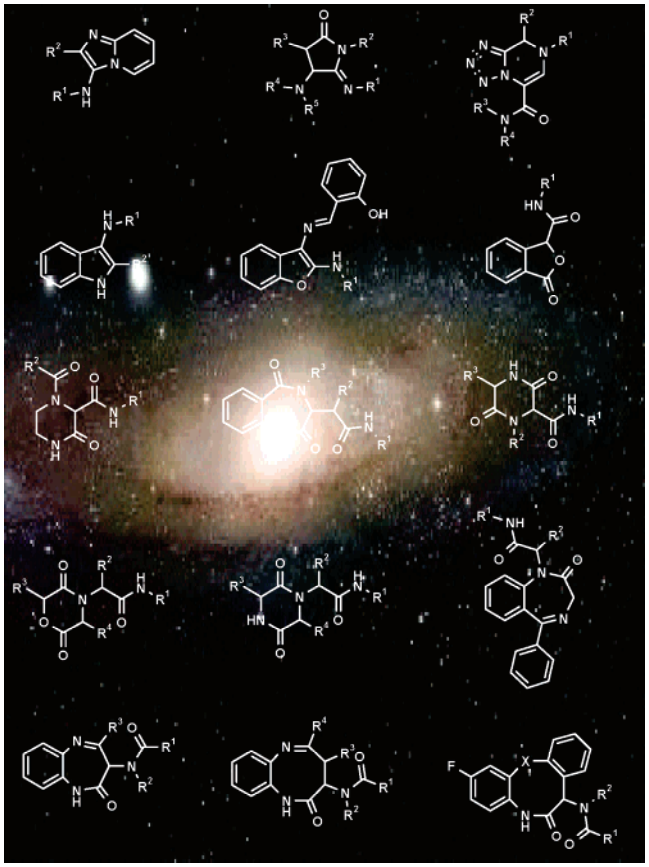
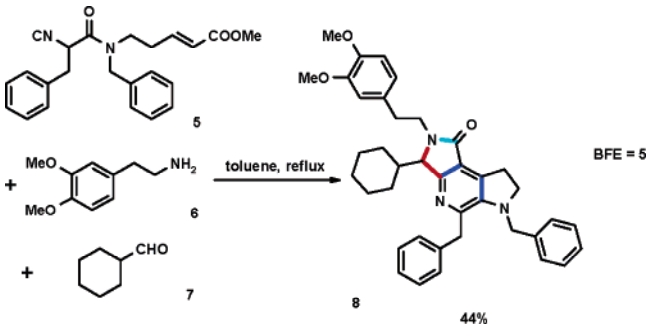


Figure 1. In analogy to the cosmological universe, one can view the chemical space in terms of vastness, with chemical compounds or scaffolds populating space instead of stars or galaxies, respectively. Here a subspace of a IMCR comprising 15 different and highly versatile scaffolds is depicted.

Multicomponent processes are at a premium for the achievement of high levels of *brevity* and *diversity*, as they allow more than two simple and flexible building blocks to be combined in practical, time-saving one-pot operations. Due to their inherent *simple experimental procedures* and their one-pot character, they are perfectly suited for *automated synthesis*. Thus, MCRs have attracted considerable interest owing to their exceptional synthetic efficiency. The structure of the reaction product can easily be diversified by systematic variation of each input. Moreover, the starting materials are either commercially available or easy to prepare. The *bond forming efficiency*, that is the number of bonds that are formed in one process, is an important measure introduced by Tietze to determine the quality of a multicomponent reaction (Scheme 2).[6] Zhu, for example, recently described a MCR of isocyanoacetamide **5**, primary amines **6**, and aldehyde **7** to yield a tricyclic and highly substituted pyridine **8**, a reaction of high bond forming efficiency.[7] During this reaction, three C−C bonds and two C−N bonds are formed.

Unlike the usual stepwise formation of individual bonds in the target molecule, the utmost attribute of MCRs is the

Scheme 2. An MCR of High Bond Forming Efficiency[a]



[a] During this multicomponent reaction, the isocyanoacetamide reacted four times in a highly ordered manner creating three heterocylic rings with the concomitant formation of five chemical bonds and a minimal loss of molecular weight. The red bonds are formed during the initial 3-CR, the blue bond is formed during the subsequent Diels−Alder reaction, and the cyan bond is formed during the final cyclization.

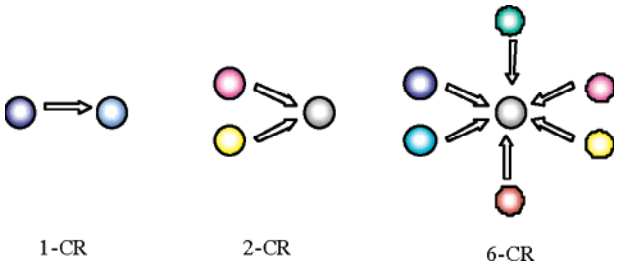


Figure 2. Schematic presentation of a divergent one component reaction, a two component reaction, and a highly convergent six component reaction.

inherent formation of several bonds in one operation, ideally without isolating the intermediates, changing the reaction conditions, or adding further reagents. It is obvious that the adoption of such strategies allows minimization of both waste production and expenditure of human labor. Just pooling their collections of corresponding starting materials forms the products.

In a MCR, several starting materials assemble to form complex products. Thus, one can call MCRs *convergent* reactions, in analogy to a convergent synthesis and in contrast to a divergent multistep synthesis (Figure 2).[8] Similar advantages apply for MCRs as compared to convergent multistep syntheses. Ideal multicomponent synthesis allows the simultaneous addition of all reactants, reagents, and catalysts at the onset of the reaction, which requires that all reactants combine in a uniquely ordered manner under the same reaction conditions. Thus, a MCR is a sequence of mono- and bimolecular events that proceeds sequentially until an irreversible final step traps the product. All these processes are highly efficient, for they create molecular *complexity* by generating more than two chemical bonds per operation.

Hundreds of MCRs have been described over the years.[9] Probably the earliest MCR described is Hantzsch's dihydropyrimidine synthesis dated more than 150 years ago. However, the discovery of novel MCRs is rather a theme of the past decade. With the emergence of high-throughput screening in the pharmaceutical industry over a decade ago, synthetic chemists were faced with the challenge of preparing large collections of molecules to satisfy the demand for new screening compounds. By virtue of its inherent high exploratory power, research on MCRs has naturally become a rapidly evolving field and since 1995 has attracted attention from both academic and industrial researchers. It is therefore not surprising that many efforts are currently being devoted to this new area of research.

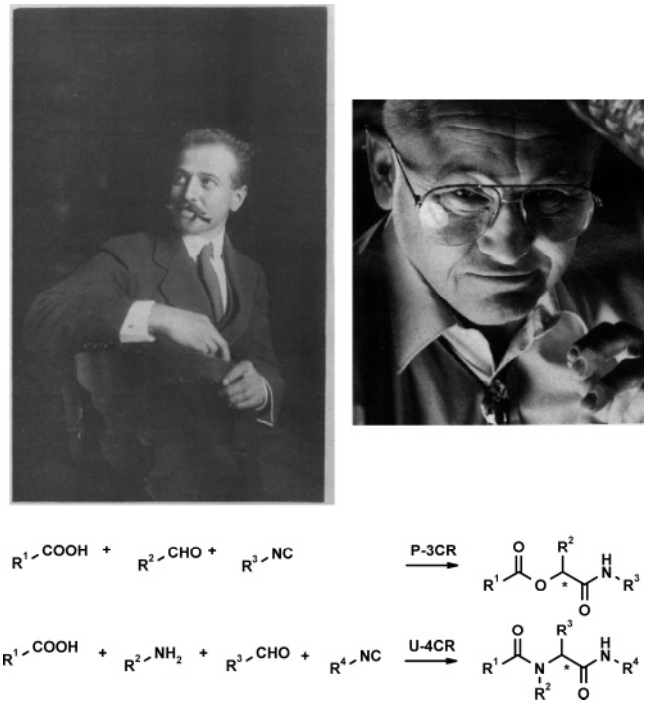


Figure 3. Mario Passerini (1881−1962) and Ivar Karl Ugi (1930−2005), the inventors of the most significant isocyanide based MCRs and the corresponding basic reaction formulas. (The photographs of Passerini and Ugi are reprinted with the permission of Stefano Marcaccini and Ian Ugi, respectively.)

Special subclasses are isocyanide based MCRs (IMCRs). They are particularly interesting because they are more versatile and diverse than the remaining MCRs. The great potential of isocyanides for the development of multicomponent reactions lies in the diversity of bond forming processes available, their functional group tolerance, and the high levels of chemo-, regio-, and stereoselectivity often observed. The outstanding position of IMCRs can be traced back to the exceptional reactivity of the functional group of the isocyanide. No other functional group reacts with nucleophiles and electrophiles at the same atom, leading to the so-called α-adduct.[10] Other functional groups typically react at different atoms with nucleophiles and electrophiles. Moreover, there is virtually no restriction on the nature of the nucleophiles and electrophiles in IMCRs. Other major primary reaction pathways of isocyanides are radical reactions, α-acidity, and an intrinsic high affinity toward metallorganic reagents and their subsequent reactions. Also, IMCRs among MCRs are at the minority overall, at the moment; nevertheless, they provide the largest chemical space.

Today most MCR chemistry performed with isocyanides relates to the classical reactions of Passerini and Ugi (Figure 3). Indeed, the large number of different scaffolds now available mostly builds on these two MCRs and their combination with other types of reactions.

Passerini reactions involve an oxo component, an isocyanide, and a nucleophile. Ugi reactions are defined as the reaction of a Schiff base or an enamine with a nucleophile and an isocyanide, followed by a (Mumm) rearrangement reaction. Interestingly, Ugi as compared to Passerini reactions are much more versatile not only in terms of library size but also in terms of scaffolds. This can be attributed to the

Table 1. Survey of Some Functional Groups and Their Commercial Availability According to the ACD[a]

functional group		availability
isothiocyanate	R−NCS	854
isocyanate	R−NCO	508
isocyanide	R−NC	380
sulfonyl chloride	RSO_2Cl	793
α-amino acid	$H_2NCHRCOOH$	2480
β-amino acid	$H_2NCHRCHRCOOH$	1004
boronic acid	$R-B(OH)_2$	1000
α-ketoaldehyde	R−COCHO	43

[a] The Molecular Weight of the Corresponding Compounds Was Limited to below 500 Dalton

many different acid components or nucleophiles and amine components that have been described to-date for the Ugi reaction.

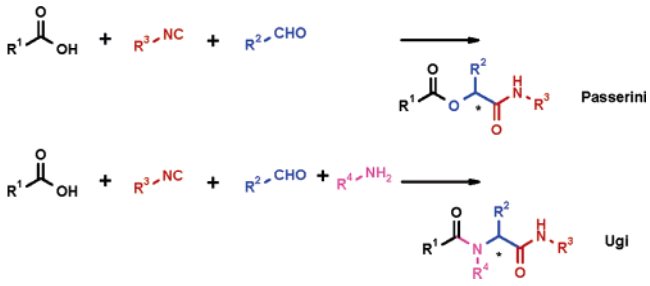
Isocyanides are considered as highly "unpleasant" compounds, due to their intensive odor. Unfortunately, this is true for most commercially available isocyanides. However, higher molecular weight isocyanides are often solid and odorless. Moreover, according to a common prejudice, only a few isocyanides are commercially available. However, a recent search on their commercial availability in the available chemical database (ACD) reveals ca. 380 isocyanides. This is quite comparable with the availability of other functional groups (Table 1). Moreover, isocyanides mostly can be easily prepared in one or two steps from their primary amine precursors, which are among the most abundant commercial chemical compounds.

MCRs are easy and straightforward to perform; every undergraduate student will enjoy running these reactions.[11] On the other hand, their design poses a significant intellectual challenge. The advantages of MCRs render this reaction class very *en vogue*. Besides rapidly growing numbers of publications on the application in drug discovery, examples in material sciences, biocompatible materials, preparation of chiral stationary phases, and preparation of isotopically labeled compounds have appeared. Not surprisingly, several reviews covering special aspects of MCRs and a monograph have appeared recently.[1,12−34] Reviews covering MCRs in general and IMCRs specifically have appeared in the last couple of years. However, on the basis of the rapid growing number of important communications in the area of IMCRs, it is appropriate to review the time since 2000, when the last comprehensive review appeared.[35] Here, I summarize current progress in IMCR chemsitry, I summarize its applications in a variety of areas in science and technology, and I mention the potential targets that are emerging.

2. Stereocontrol in MCRs

Stereochemically pure compounds are of uttermost importance during the development and marketing of drugs. The issue of stereocontrol in IMCRs has only been partially solved in the past. During the Ugi (U) and Passerini (P) reactions, typically a new stereocenter is formed, resulting in racemic products in the absence of stereoinduction (Scheme 3). A major difficulty to induce stereoinformation into isocyanide based MCRs is that they run under different reaction conditions, e.g. solvent, temperature, and highly diverse starting materials, and consequently follow sometimes different mechanisms. Certainly there will be no general solution toward this problem, but rather islands of solutions will be found to solve specific problems.

Scheme 3. Formation of a New Stereocenter during P-3CR and U-4CR

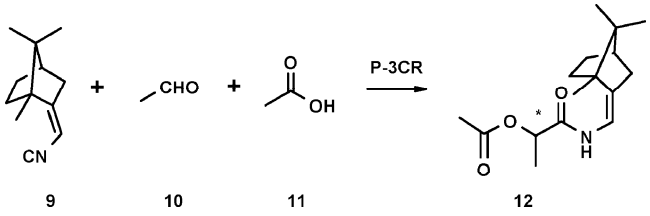


The traditional approach to induce stereoselection in IMCRs, proposed very early on by Ivar Ugi, was the use of chiral starting materials. Thus, he found, by theoretical considerations and experiments, that in the Ugi reaction induction of the new stereocenter could be best achieved by using a chiral amine, whereas other starting materials gave poor or no induction.

2.1. Chiral Isocyanides

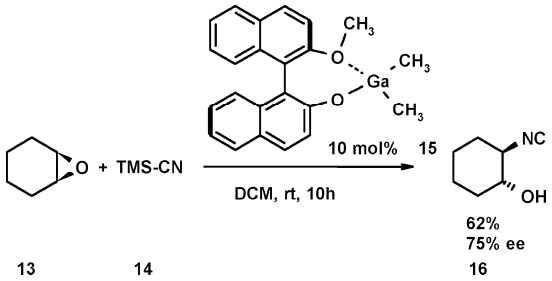
In contrast, high diastereoselectivity in **12** could be obtained in the case of the P-3CR with rigid and chiral isocyanide **11**.[36] In contrast, no induction at all is obtained in a U-4CR. This result also reflects the fundamentally different reaction mechanisms of the U- and P-MCRs (Scheme 4).

Scheme 4. A Highly Diastereoselective P-3CR Using a Conformationally Stiff Isocyanide



Enantiomerically pure isocyanides are important starting materials for stereoselecive IMCRs. The diastereoselective epoxide ring opening with TMS-CN in the presence of the soft Lewis acid ZnI_2 is a powerful process to prepare bifunctional β-hydroxyethylisocyanides.[37] Zhu et al. published an enantioselective variation of Gassmann's isocyanide synthesis.[38] Reacting chiral BINOL derivative with trimethyl gallium or indium, the active catalyst species **15** is formed, which converts meso epoxide **13** into bifunctional, versatile, and chiral isocyanide **16** (Scheme 5).

Scheme 5. Synthesis of a Chiral Isocyanide from a Prochiral Epoxide Using Catalytical Amounts of a Chiral Lewis Acid



Despite the often encountered prejudice that α-amino acid derived isocyanides are not stereochemically stable, there are reports of producing enantiomerically pure isocyanides.[39]

2.2. Chiral Amines

A plethora of work was published on the search for and investigation of the "perfect" chiral amine, giving high de's and high chemical yields, being universally applicable with all other starting materials, and being easy to cleave-off under mild conditions to yield amino acid or peptide derivatives. Three classes of compounds appear to fit the above requirements (Figure 4): 1-phenylethylamines **17**,[40] α-aminoferrocenylamines **18**,[41] and glycosylamines **19**.[42] Induction of up to 100% de could be observed, and more or less mild conditions for the cleavage of the chiral auxiliary could be developed. However, often the cleavage conditions were not compatible with the fragile functional groups present at another position of the molecule. Ugi et al. recently presented a highly improved sugar derived auxiliary, a xylopyranose derived peracylated thiosugar **20** containing the amine function in the anomeric position.[43] Herein, de's of ≫90% could be observed in all cases. Moreover, the auxiliary could be cleaved-off under very mild conditions with a soft electrophile, $HgCl_2$, at room temperature.

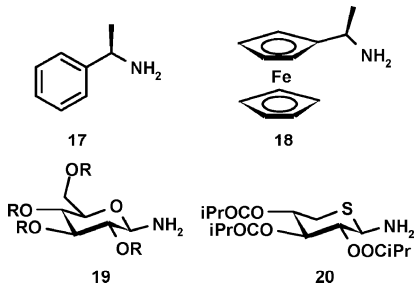


Figure 4. Different chiral amines for stereoselective U-4CRs.

Kunz et al. recently introduced their chiral carbohydrate based auxiliaries successfully onto a solid phase.[44] Synthesis of a polymer-bound galactosylamine **21** and its application as an immobilized chiral auxiliary in stereoselective syntheses of amino acid derivatives, e.g. **24** via a U-4CR, are described (Scheme 6). Generally, yields, as well as the observed diasteriomeric ratios, are good. Moreover, the same group described a stereoselective combinatorial U-4CR on a solid phase.[45]

Ugi et al. recently investigated the use of unprotected anomeric aminosugars in the U-4CR.[46] According to the Kochetkov methodology, the unprotected aminosugars **25**−**27** are obtained stereoselectively and in good yield by simply reacting the sugar with ammonium hydrogencarbonate. These were screened with several aldehydes, isocyanides, and carboxylic acids and different Lewis acids for diastereoselectivity in the U-4CR. Thus, **28** could be formed in 99% de and 95% chemical yield without any addition of Lewis acid at −38 °C. However, **29** could be formed in 99% chemical yield and 99% de using 0.1 equiv of $CeCl_3 \cdot 7H_2O$. The chiral auxiliary could be mildly removed by treatment with 1 M HCl at 40 °C for 19 h (Figure 5).

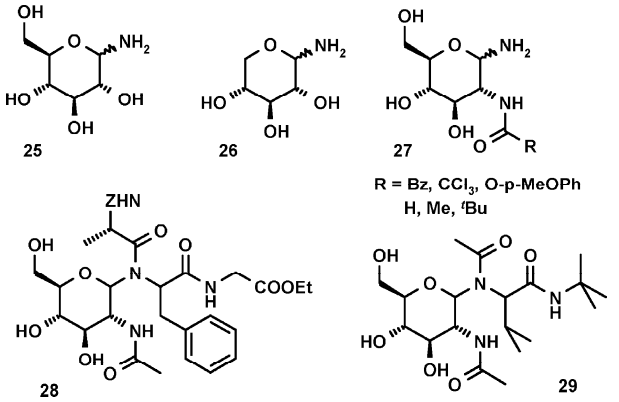
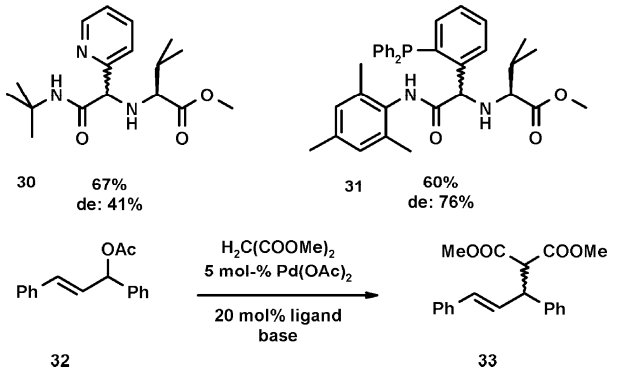


Figure 5. Novel glycosylamines used in diastereoselective U-4CRs.

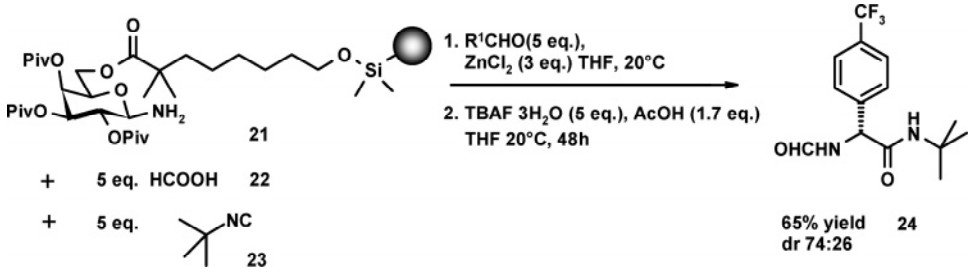
In addition to the exploitation of stereoselective MCRs, one can leverage the diversity and large possible number of MCR products as ligands or chiral auxilliaries for the stereoselection in other reactions. Dyker et al. synthesized small libraries of chiral ligands via U-5C-4CR of α-amino acids and screened them in a Pd catalyzed allylic substitution reaction of allylic acetate functionality by malonate (Scheme 7).[47] Incorporating a phosphine or pyridine functionality

Scheme 7. Use of a Diastereoselective U-5C-4CR To Prepare Arrays of Chiral Ligands for an Enantioselective Allylic Alkylation



yielded novel *P*,*N*-ligands, e.g. **30** and **31**, which were successfully tested in the Pd catalyzed allylic substitution reaction **32** → **33**. Thus, promising ee's of up to 75% and chemical yields of >90% could be observed. A major advantage of this approach is the immediate utilization of amino acids as a source of stereochemical information. Since the Ugi reaction is excellently suited to the synthesis of compound libraries by application of combinatorial prin-

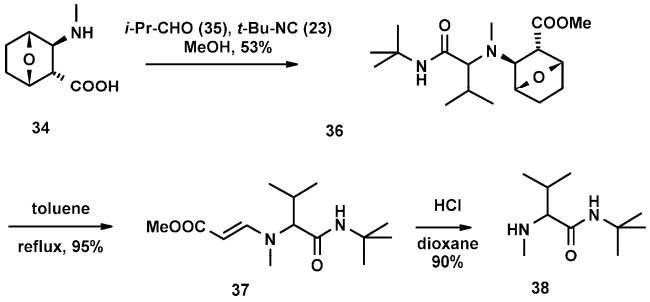
Scheme 6. Kunz's Auxilliary Made Available on Solid Phase and Its Use To Prepare α-Amino Acid Derivatives in a Highly Enantioselective Manner



ciples, further optimization of the ligand structure could be driven forward in a systematic manner by screening of ligand libraries.

Intramolecular Ugi reactions with bicyclic β-amino acids have been performed, and the effects of the configuration and *N*-alkylation have been studied.[48,49] The preferential ring contraction or nucleophilic attack by the solvent depends not only on the presence of *N*-alkylation but also on the relative disposition of the carboxyl group and the amine. Excellent results in terms of stereoselectivity have been obtained in the case of *N*-alkyl-3-*exo*-amino-7-oxabicyclo[2.2.1]-2-*endo*-carboxylic acids, e.g. **34**. For example, the sole diastereoisomer obtained, **36**, was subjected to retro Diels−Alder reaction, yielding **37** and enamine hydrolysis to give the *N*-methyl amino acid derivative **38**. These results prove that certain bicyclic β-amino acids, in their optically active form, could be efficiently used as chiral auxiliaries in the stereoselective synthesis of α-amino amides via U-MCRs (Scheme 8).

Scheme 8. Synthesis of Chiral *N*-Alkylated α-Aminoamides Using a Process Involving a U-5C-4CR of a Chiral β-Amino Acid and Subsequent Retro-Diels−Alder and Acid Hydrolysis

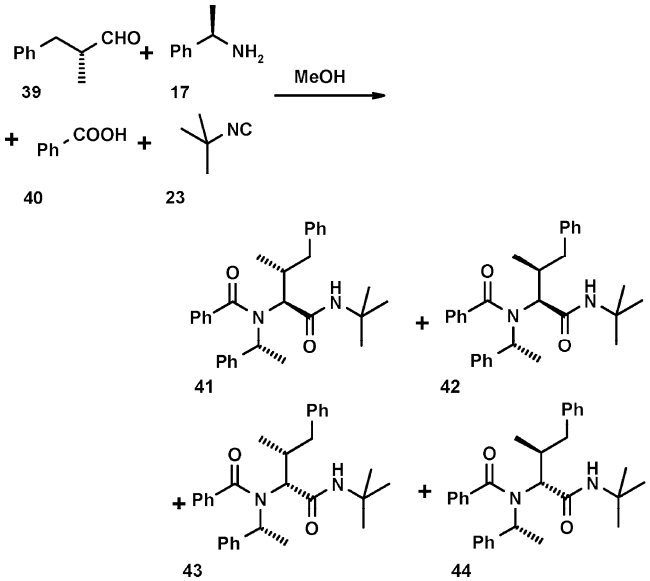


34 36 37 38

2.3. Chiral Oxo Components

Generally speaking, the oxo component does not have great influence on the stereoselectivity in U- or P-MCRs. However, an interesting investigation on the natural stereoinduction of the Ugi reaction was performed by Kelly et al., showing the epimerization of an aldehyde, **39**, possessing a hydrocarbon substituent α to the carbonyl occurs in the U-4CR, yielding all four possible diastereomers, **41**−**44**, whereas, with either benzyl or TBDMS ether at C-2 of the aldehyde, the stereochemical integrity is maintained.[50] A deuterium isotope effect is observed, and by carrying out the reaction in methanol-OD, deuterium can be introduced efficiently into C-3 of the condensation products (Scheme 9).

Scheme 9. Potential Racemization of Certain Aldehydes with a Stereocenter in the α-Position during the U-4CR



39 17 40 23 41 42 43 44

2.4. Chiral Acids

Attempts to induce diastereoselectivity in the Ugi reaction with chiral carboxylic acids normally fail. However, Syngenta workers disclosed a very elegant approach toward enantiomerically pure α-hydroxyacyl amides.[51] By using peracylated D-galacturonic acids **45** in the P-3CR, they observed high diastereomeric induction in the products. After saponification, several mandelamides could be obtained in good to excellent chemical yield and ee's (Scheme 10). For example, **48** can be obtained in an enantiomeric ratio of 98:2. Interestingly, the corresponding diacetonides of the D-galacturonic acids did not give notable stereochemical inductions. This interesting finding points to the importance of a hydrogen bonding network in the course of the Passerini reaction. This diastereoselective Passerini reaction uses a commercially available auxiliary and is amenable to upscaling. Thus, the medicinally important backbone of mandelamides can be easily and enantioselectively prepared in the future by an IMCR.

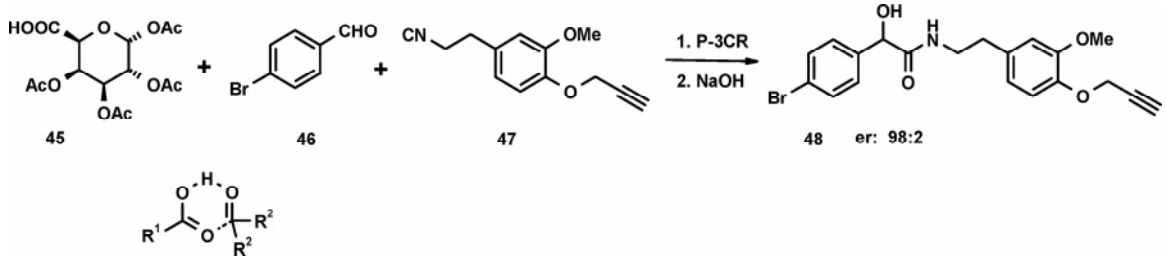
2.5. Chiral Catalysts/Auxiliaries

Denmark et al. described the first asymmetric Lewis base catalyzed enantioselective Passerini-type reaction (Scheme 11).[52] Using bidentate binaphthyl derived ligands together with tetrachlorosilane, the catalytically active species is formed. Generally, the yields were good to excellent and the ee's ranged from 70/30 to 99/1, e.g., **50** with an enantiomeric ratio of 96:4. However, this variation of the Passerini reaction constitutes a pseudo-3-CR, where water is acting as the acid component, thus giving access only to limited library variations.

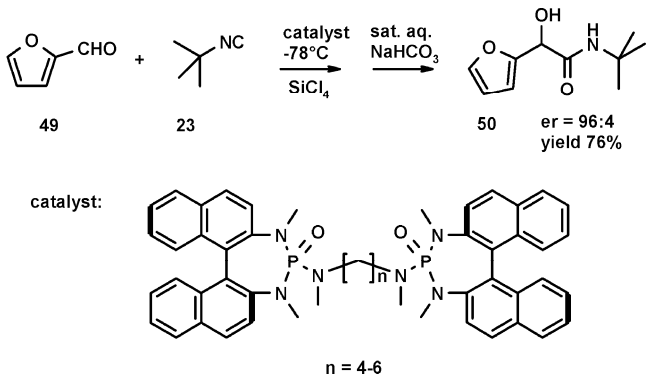
Dömling et al. screened several hundreds of combinations of 12 Lewis acids with 12 chiral ligands to discover additives for enantioselective P-3CRs (Scheme 12).[53] Of these combinations, $Ti(O^iPr)_4$ and TADDOL turned out to give the best ee's. However, the observed ee's ranged only from 32 to 44%, e.g., **52** with 46% ee. In most other combinations it was observed that the P-3CR is very sluggish, giving a plethora of byproducts. The absolute stereochemical induction could be uncovered by a combination of X-ray structure analysis of a diastereomeric product and its degradation to the corresponding mandelamide. This work constitutes the first successful enantioselective P-3CR using a chiral auxiliary and could be the starting point for future improvements.

Recently, Schreiber and co-workers described the use of catalytic amounts of pybox Cu(II) complex to perform P-3CRs.[54] Sixteen examples were described between 60 and 98% ee and 75−98% chemical yield. Thus, **54** is formed in 83% yield and 78% ee involving the heteroaromatic furfural **49**. However, poor or no enantioselectivity at all was observed with aldehydes lacking a second chelating heteroatom, e.g., benzaldehyde (Scheme 13). Tricyclic **56** thus can be produced in good de and yield form a stereoselective P-3CR product undergoing in situ an intramolecular Diels−Alder reaction.

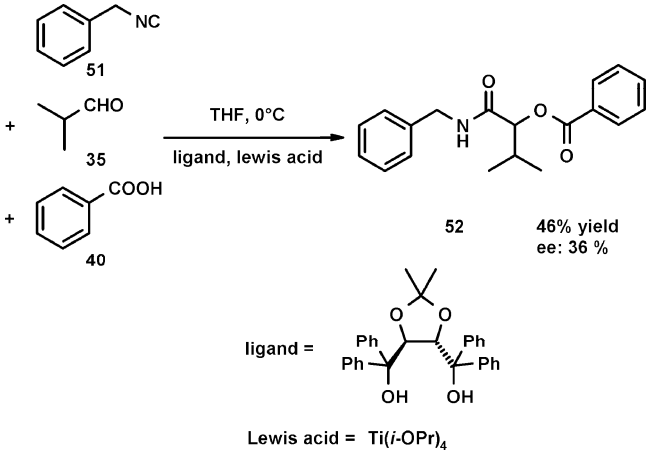
Scheme 10. Syngenta's Process for the Highly Stereoselective Synthesis of Chiral Mandelamides Involving Galacturonic Acid Derivatives



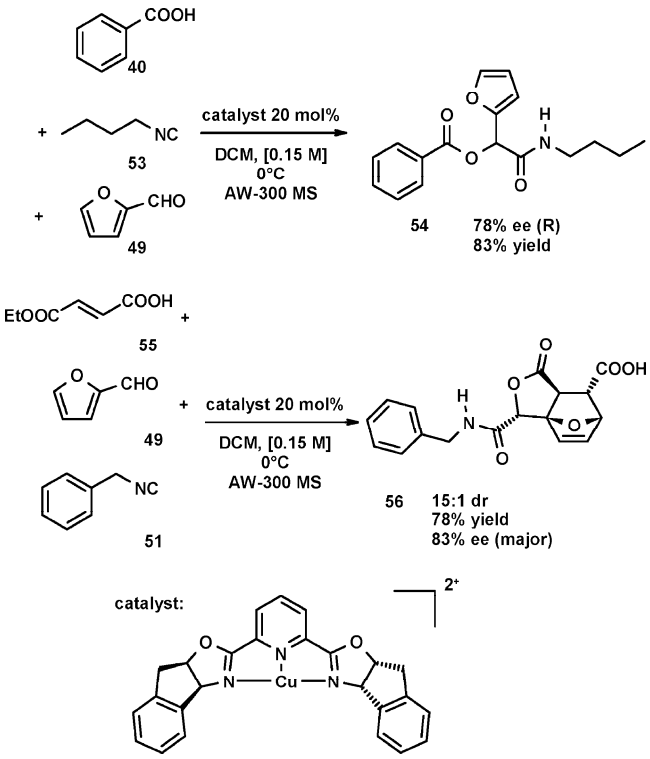
Scheme 11. Denmark's Highly Enantioselective P-2CR of Mandelamides



Scheme 12. The First Enantioselective P-3CR Making Use of a Chiral Lewis Acid



Scheme 13. Use of Catalytical Amounts of a Chiral Cu-pybox Lewis Acid Affords Highly Enantioselective P-3CR Products Only if Chelating Heteroatom Aldehydes Are Used



3. Novel IMCRs

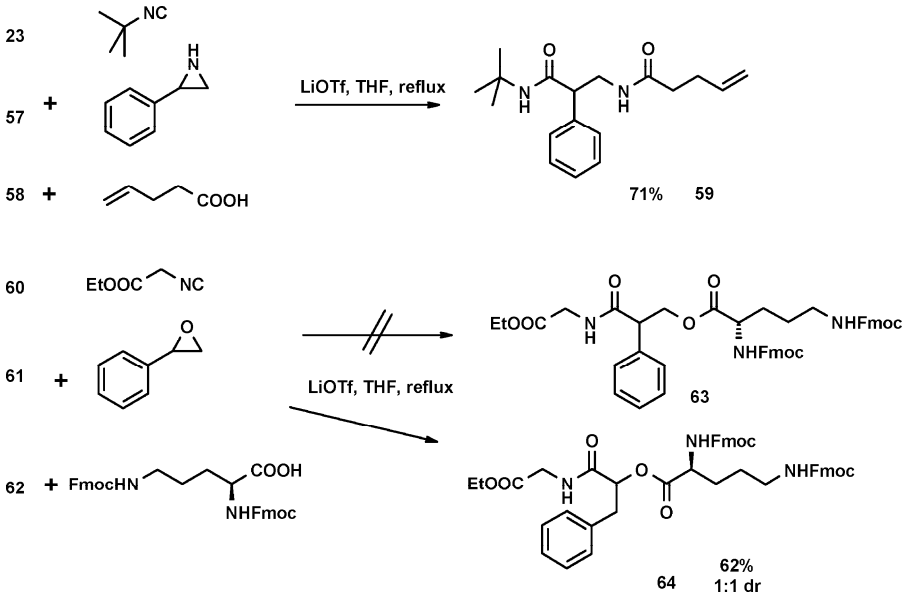
Novel IMCRs refer to novel applications of known transformations as well as transformations involving innovative and unprecedented aspects of reagents, starting materials, and obtained scaffolds. Regarding the wealth of recently published papers involving IMCRs, it is difficult to organize the literature critically. The following sections are ordered according to Ugi and Passerini-like chemistry (sections 3.1−3.27), as defined in section 1, and other types of IMCRs (sections 3.28−3.31).

3.1. Homo U-4CR

A new MCR of isocyanides, carboxylic acids, and epoxides was proposed by Motherwell et al. yielding β-hydroxyacylamides, e.g., **63** (Scheme 14).[55] However, recent structural assignments of the products revealed that the proposals in their original communication are incorrect.[56] The correct structures for the overall reactions arise as a consequence of S_N1-like ring opening of the epoxide followed by hydride migration and subsequent Passerini-type reaction of the resulting carbonyl compound, yielding a classical Passerini product, **64**.

Analogously, it was proposed that aziridines reacted to give β-aminoacylamides. This scaffold contains two carbons between the ester and amide functionalities or the amide and amide functionalities, respectively, and thus is termed here the homo-Ugi product. The reaction is assumed to proceed via a low energy S_N1 reaction generated carbocation and its addition toward the isocyanide, yielding an intermediate imminium ion, followed by the addition of the nucleophile and a subsequent rearrangement. Thus, interesting β-amino acids incorporating compound **59** can easily be obtained in good yields. Given the wealth of functionalized isocyanides and aziridines, which are prepared from readily available starting materials, the present reaction may therefore offer considerable potential for the construction of low molecular weight libraries.

Scheme 14. Aziridines and Epoxides Respectively Yield Homo-Ugi but Normal Passerini Products

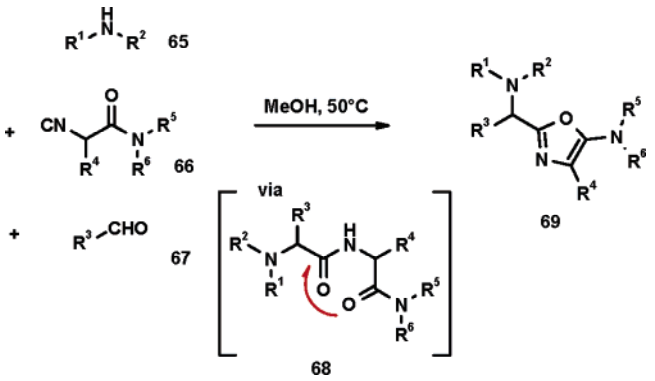


3.2. U-3CR of Isocyanoacetamides

Zhu et al. discovered the dual reactivity of substituted isocyanoacetic amides, undergoing α-addition followed by an intramolecular cyclization toward 5-aminooxazoles.[57] The reactivity of 5-aminooxazoles, electron-rich azadienes that are susceptible to reaction with electron-poor dienophiles, has been widely described in the literature[58] and was subsequently exploited by Zhu to prepare a net of interesting scaffolds taking advantage of the initial U-3CR, **68**.

Thus, simply heating a methanol solution of amine **65**, α-isocyanoacetamide **66** and aldehyde **67** provided the 5-aminooxazole of general structure **69** in good to excellent yield (Scheme 15). The condensation is performed with

Scheme 15. Isocyanoacetic Amides, Aldehydes, and Primary or Secondary Amines React in the Usual Way in a U-3CR[a]

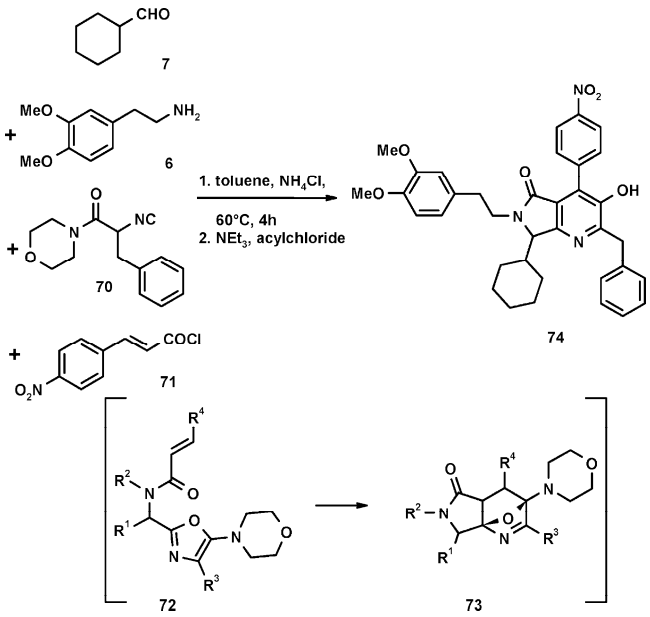


[a] The intermediate α-aminoamide cyclizes to form 5-aminooxazole.

equimolar quantities of three components, simplifying the purification step. Use of α-isocyanoacetamide rather than α-isocyanoacetate is essential to channel the reaction sequence toward oxazole formation.

Another example of the exceptional reactivity of α-isocyanoacetamide is a novel four-component synthesis of pyrrolo[3,4-*b*]pyridin-5-ones **74** (Scheme 16).[59] A toluene solution of an aldehyde **7**, an amine **6**, and an isocyanide **70** in the presence of 1.5 equiv of ammonium chloride is stirred at 60 °C. Once the oxazole formation is complete, an appropriate α,*β*-unsaturated acyl chloride **71** and triethyl-

Scheme 16. Formation of Pyrrolopyridines by a Novel IMCR Involving a Sequence of Complex Reactions[a]

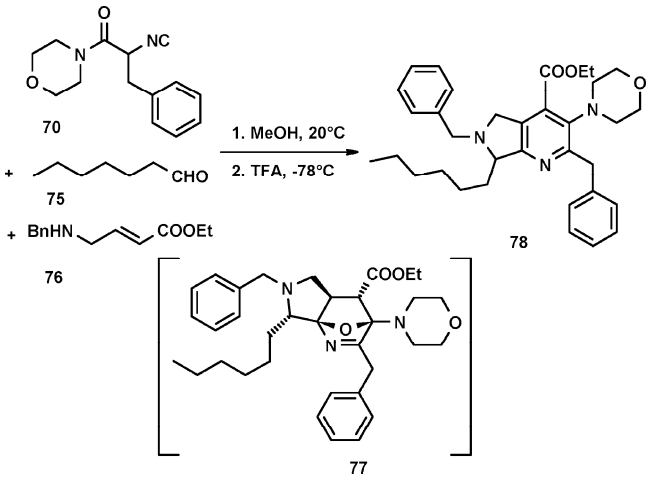


[a] This is another excellent example of BFE, since three C−C bonds and two N−C bonds and a pyrdine ring and a pyrrole ring are concomitantly formed.

amine are added at 0 °C. Heating to reflux produced pyrrolo-[3,4-*b*]pyridin-5-ones **74** in good yield through a domino process involving a three-component condensation, an intermolecular acylation to **72**, an intramolecular Diels−Alder cycloaddition to **73**, and a retro-Michael cycloreversion to **74**.

An alternative pyrrolo[3,4-*b*]pyridine synthesis was described tethering an amine and a dienophile into a single component.[60] The reaction between aminocrotonate **76**, aldehyde **75**, and α-isocyanoacetamide **70** in methanol at room temperature provided oxa-bridged tricycle **77** as a single diastereoisomer in 92% yield (Scheme 17). It is worth noting that one C−N bond, one C−O bond, and three C−C bonds were formed with concomitant creation of five stereocenters in this one-pot multicomponent process. In a

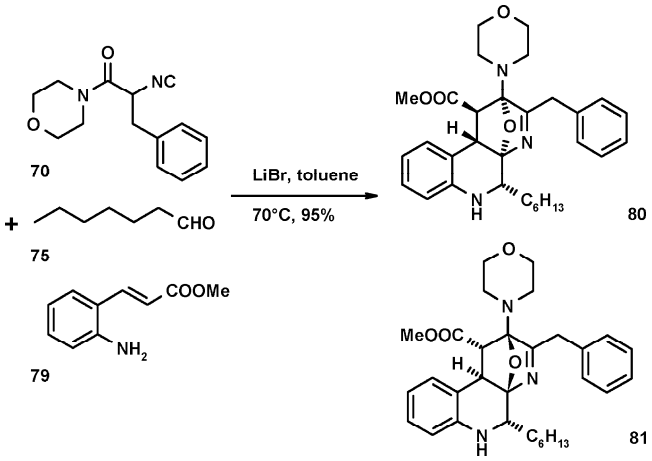
Scheme 17. Alternative Pyrrolopyrdine MCR Synthesis



second step the intermediate can be fragmented to the pyrrolopyridine **78** upon reaction with TFA at −78 °C.

A three-component synthesis of tetracyclic tetrahydroquinolines by condensation of aldehyde **75**, *o*-aminocinnamate **79**, and α-isocyanoacetamide **70** is shown in Scheme 18.[61] The best conditions consisted of use of toluene as

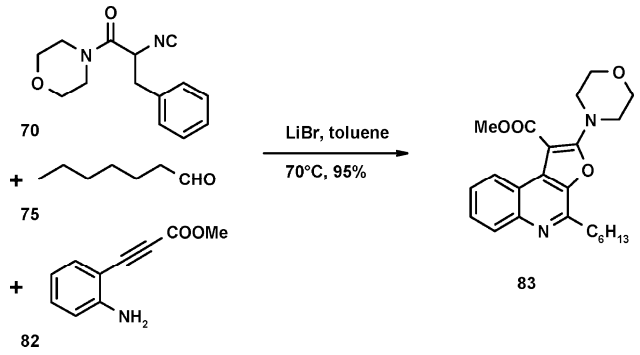
Scheme 18. Highly Complex Tetrahydroquinolines by an IMCR



solvent in the presence of a stoichiometric amount of lithium bromide as a promoter. Under these conditions, two pairs of diastereomers were produced, out of 16 possible isomers **80** and **81**, in a combined 95% yield.

A three-component reaction to give furoquinolines **83** in 75% yield simply by heating a toluene solution of methyl 3-(2-aminophenyl)prop-2-ynoate **82**, heptanal **75**, and isocyanoacetamide **70** at reflux in the presence of ammonium chloride was described in Scheme 19.[62] At least six distinct reactions, including condensation between aldehyde and amine, nucleophilic addition of isocyanide to imine, ring−chain tautomerization of the nitrilium intermediate, intramolecular Diels−Alder cycloaddition of oxazole, retro-Diels−Alder reaction, and oxidation, occurred in this one-pot process. Anilines bearing both electronically poor and neutral acetylene units participated in the reaction. For aldehyde input, aliphatic (including sterically hindered isobutyraldehyde) and aromatic aldehydes bearing electron-donating or -withdrawing groups all took part in this reaction. Incorporation of various substituted amino functions was easily attainable simply by varying the isocyanoacetamide input.

Scheme 19. Furoquinolines Are Assembled by a Complex 3-CR, Involving a U-3CR, Intramolecular Diels−Alder Reaction, Retro-Diels−Alder Reaction, and Subsequent Oxidation



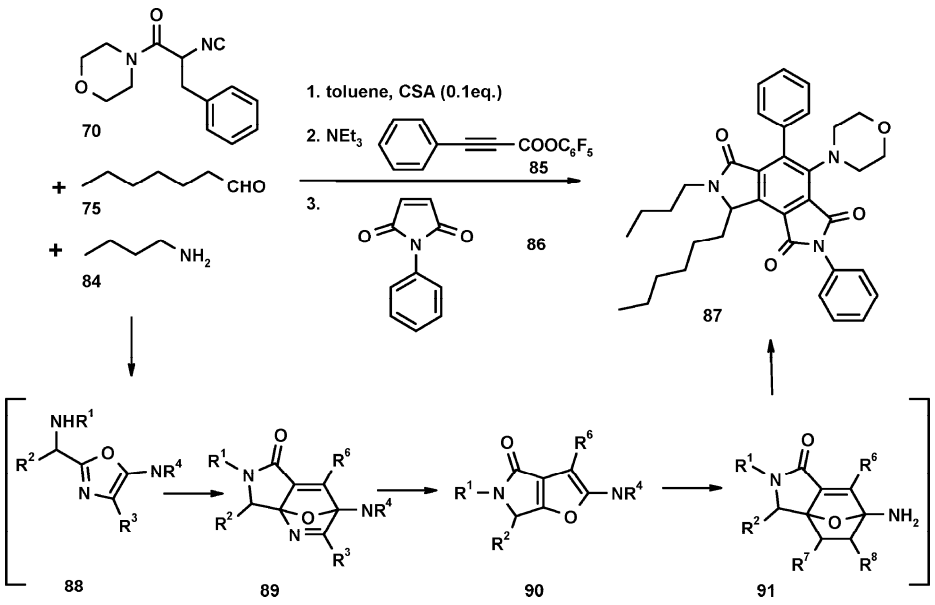
The synthesis of independently hexasubstituted benzene is a major challenge in organic chemistry. A five-component synthesis of polyheterocycles with hexasubstituted benzene cores **87** was described by Zhu (Scheme 20).[63] Three-component condensation of isocyanoacetamide **70**, aldehyde **75**, and amine **84** provided the usual 5-aminooxazole **88**. Reaction between the 5-aminooxazole **88** and pentafluorophenyl 3-arylprop-2-ynoates **85** delivered a pyrrolofuran **90** by a sequence consisting of acylation, intramolecular Diels−Alder cycloaddition, and retro-Diels−Alder cycloreversion. The subsequent cycloaddition between the furan unit of **90** and the dienophile **86** (*N*-phenylmaleimide, quinone, etc.) followed by fragmentation of the oxa-bridged amino ether **91** would then provide the observed product **87**. In this one-pot transformation, seven functional groups reacted with one another in a highly ordered fashion, resulting in the creation of seven chemical bonds and a polyheterocyclic scaffold with a hexasubstituted benzene core. Not fewer than nine reactions were involved in this experimentally simple MCR!

Using bifunctional diamines and diisocyanides, reactions that deliver at least three elements of diversity into the final 18-membered macrocycles **94** have been described by Zhu et al. (Scheme 21).[64] The overall process leads to the creation of six chemical bonds with the concomitant formation of two oxazole groups as part of a new macrocycle, and thus, it involves a large increase in molecular complexity. The synthesis is ecologically benign and atom economic, since only two molecules of water are lost in this rather complex bond forming process. Screening five different Lewis acids and two solvents yielded optimal reaction conditions.

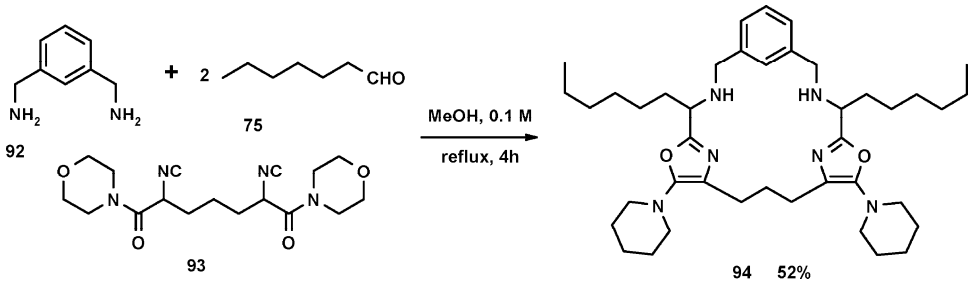
A resin-capture−release methodology to macrocyclization via intramolecular Suzuki−Miyaura coupling was developed and described by Bienaymé et al.[65] Here arylboronic acid aldehyde **95**, morpholine **96**, and isocyanoacetamide **97** first give the expected oxazole **98**, which upon Pd catalyzed coupling affords a 14-membered biphenyl containing macrocycle **100** (Scheme 22). The intermediate boronic acid **98** could be sequestered out of the reaction mixture using an amine resin to give **99**, which upon ring closure released the final product **100**. Note that boronic acids in their unprotected form are compatible with the reaction conditions used. This finding opens up the way to a potential plethora of secondary reactions useful to gain new scaffolds.

Conditions have been developed by Zhu et al.[66] for the multicomponent synthesis of di- and tetrapeptides based on the unique reactivity of isocyano acetic acid (**101** and its α-substituted derivatives) in a Ugi four component, five-

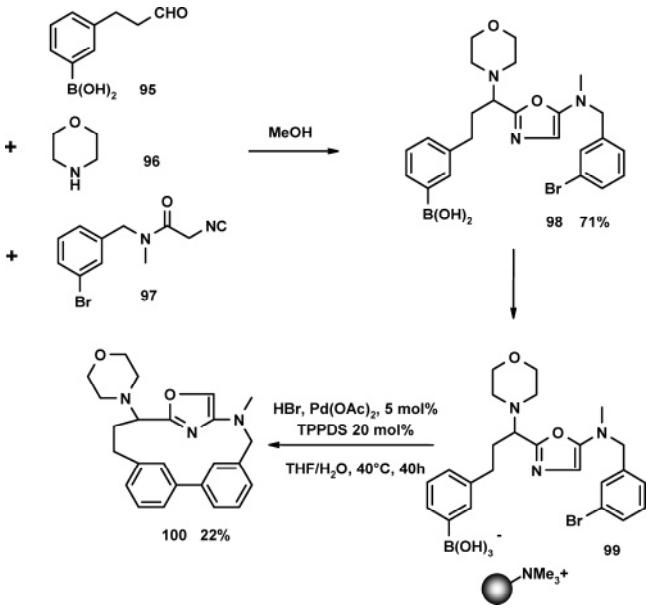
Scheme 20. Independently Hexasubstituted Benzenes Are Elegantly Accessible by This Short Sequential Synthesis Involving an Initial IMCR



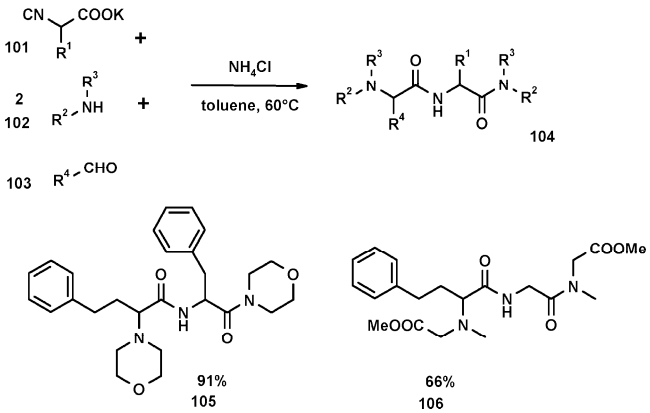
Scheme 21. Macrocycles Are Achievable by a Symmetrical Reaction with Two Starting Materials Containing Two Functional Groups Each, Thus Involving Four Components and Six Functional Groups



Scheme 22. 14-Membered Biphenyl Containing Macrocycles Are Synthesized by a U-3CR Followed by a Susuki Coupling of Boronic Acids



Scheme 23. Complex Bisamides Are Amenable by This Novel 4-CR Involving Five Functional Groups



center reaction (U-4CR-5C) (Scheme 23). Simply mixing **101**, secondary amine **102**, and carbonyl compound (aldehyde or ketone) **103** in toluene in the presence of 1.5 equiv of ammonium chloride afforded the desired product in good to excellent yield as a mixture of two diastereomers, e.g., **105** and **106**. This reaction involves a U-3CR followed by an amide formation with a second equivalent of primary or secondary amine.

3.3. IMCRs of 3,3-(Dimethylamino)-1-isocyanoacrylates

The highly functionalized 3-(dimethylamino)-2-isocyanoacrylic acid methyl ester **107** is a versatile starting material for the diversity generating synthesis of multiple

scaffolds and their libraries, e.g., imidazoles, thiazoles, ketopiperazines, and bicyclic tetrazolopiperazines. A recent review provides the reader detailed insight into this multiarmed "octopus chemistry" (Figure 6).[67]

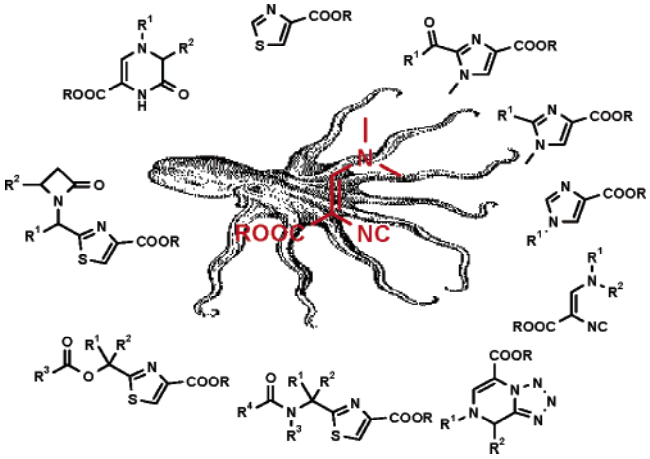
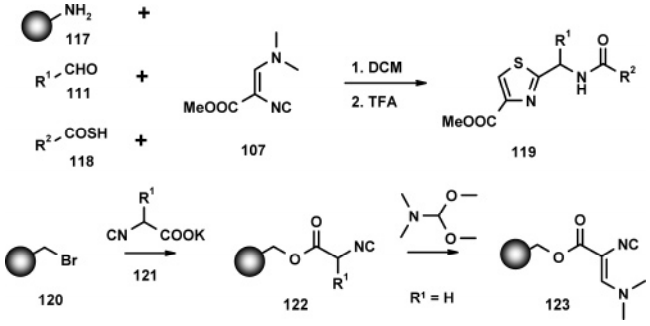


Figure 6. Octopus chemistry of the multiarmed and versatile 3-(dimethylamino)-2-isocyanoacrylic acid methyl ester affording a plethora of possible scaffolds: thiazole-4-carboxylic acid esters, 1-methyl-2-carboxylimidazole-4-carboxylic acid esters, 1-methyl-2-alkylimidazole-4-carboxylic acid esters, 1-*N*-alkyl- or 1-*N*-arylimidazole-4-carboxylic acid esters, 3-alkylamino-2-isocyanoacrylic acid esters, bicyclic tetrazolopiperazines, 2-aminoacylmethylthiazole-4-carboxylic acid esters, 2-oxoacylmethylthiazole-4-carboxylic acid esters, thiazolo-β-lactames, and piperazines. (Reprinted with permission from ref 67. Copyright 2005 Thieme.)

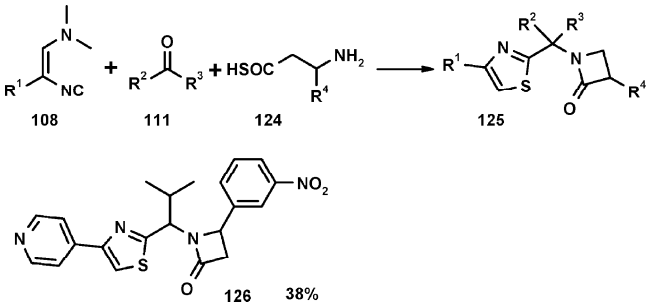
A detailed investigation of the scope and limitations of the recently discovered thiazol-forming MCR was published.[68] Herein primary 3-*N*,*N*-(dimethylamino)-2-isocyanoacrylic acid derivatives **108**, aldehydes or ketones **109**, amines **110**, and thiocarboxylic acids **111** smoothly react to form 2,5-disubstituted thiazoles **112**, e.g., **113**−**116**. This reaction is useful for the preparation of large arrays (10K) of compounds (Scheme 24). The reaction is based upon the rich functional isocyanide, bearing an isocyano functionality, a Michael acceptor, and a dimethylamino leaving group. The reaction was also described on solid phase, with Rink amine and with the resin bond functional isocyanide, respectively.[69,70] In the latter approach, the isocyano derivatized resin **122** was prepared form Wang resin **120** simply by reacting a 2-fold excess of the potassium salt of isocyanocarboxylic acid with (4-bromomethylphenoxy)methyl polystyrene in DMF. Thereafter, the intermediate so obtained was treated with dimethylformamide diethyl acetal in a mixture of ethanol and THF (Scheme 25), giving **123**.

Scheme 25. A Variety of Novel 4-C Syntheses of Highly Substituted Thiazoles on Solid Phase and the Corresponding Synthesis of a Solid-Phase Isocyanide



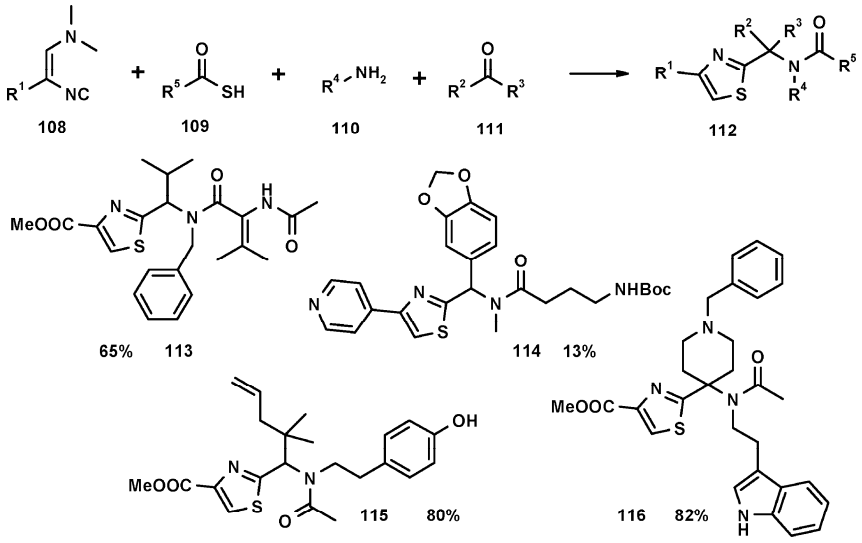
The simultaneous assembly of the β-lactam and the thiazole moiety by a new multicomponent reaction was described by Dömling et al.[71] A novel multicomponent reaction of 3-(dimethylamino)-2-isocyanoacylate **108**, aldehydes **111**, and β-aminothiocarboxylic acid **124** is described (Scheme 26). During the course of these reactions, two

Scheme 26. Under Mild Conditions a β-Lactam and a Thiazole Ring Are Formed in a One-Pot Synthesis



heterocyclic moieties, a thiazole and a β-lactam ring, e.g. **126,** are formed simultaneously and under mild conditions. The increase in molecular complexity here is dramatic, as 2

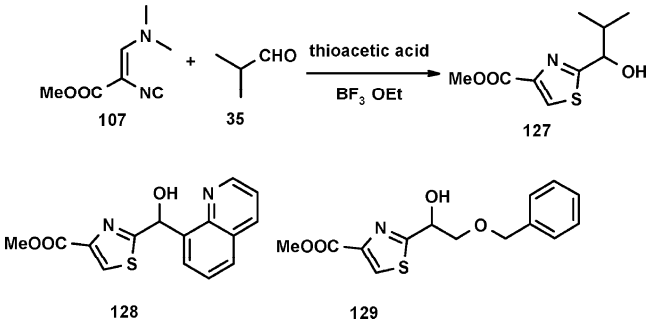
Scheme 24. A Multicomponent Thiazole Synthesis Useful in Library Synthesis



C−N, 2 C−S, and 1 C−C bonds are formed in a new "one-pot" multicomponent reaction. This constitutes another example of high bond forming efficiency (BFE).

The corresponding Passerini variation of the thiazole MCR has also been described.[72] Herein, 3-(dimethylamino)-2-isocyanoacylate **107** reacts with aldehydes or ketones and thioacetic acid to form 2-hydroxymethylthiazole-5-carboxylates **128**−**129**. However, the reaction only yields products upon the addition of 1 equiv of BF_3OEt_2 as a Lewis acid (Scheme 27).

Scheme 27. A Passerini Variation of the Thiazole Synthesis



Illgen et al. from Morphochem discovered a three-component reaction of 3-(dimethylamino)-2-isocyanoacrylic acid methyl ester **107** with primary amines **110** and aldehydes or ketones **111** yielding 6-oxo-1,4,5,6-tetrahydropyrazine-2-carboxylic acid methyl esters **130** (Figure 7).[73] The reaction works with quite a range of educts and is compatible with many functional groups. This reaction can be described as a U-3CR during the course of which a secondary amine is formed, displacing the dimethylamino leaving group, thus forming the six-membered ring system. In a variation of this theme, unprotected α-amino acids react to give iminodicarboxylic acid methyl ester intermediates (see below, section 3.11) bearing a secondary amine, which analogously cyclize to give **131**. This reaction has been studied under array conditions. It is noteworthy that optimal yields can be obtained by the addition of 1 equiv of $Yb(OTf)_3$ or BF_3-OEt_2 (Scheme 7). A general feature of MCRs is their frequent compatibility with unprotected functional groups; for example, the medicinal-chemically important amidine functionality serving as an arginine or sometimes lysine side chain mimetic, which otherwise is introduced at the end of a multistep synthesis (Pinner reaction), can be used here directly in its unprotected form to yield the expected product **132** without interfering with the reaction mechanism. The reaction can be used to easily prepare libraries of the size 10K.

3.4. U-4CR toward Hydroxamic Acids

Hydroxamic acids are important pharmacophors used in medicinal chemistry to inhibit, e.g., metalloproteases. It is well-known that hydroxylamine reacts in U-4CRs as the amine component, yielding inner hydroxamic acids. The Genua group around Banfi and Guanti developed an improved method for the synthesis of hydroxamic acids (Scheme 28).[74] Thus, they used *O*-benzylhydroxylamine **133** in the U-4CR, obtaining the Ugi intermediate in good to excellent yields. Reductive debenzylation with $H_2/BaSO_4$ yields the inner hydroxamic acid. Whereas aliphatic alde-

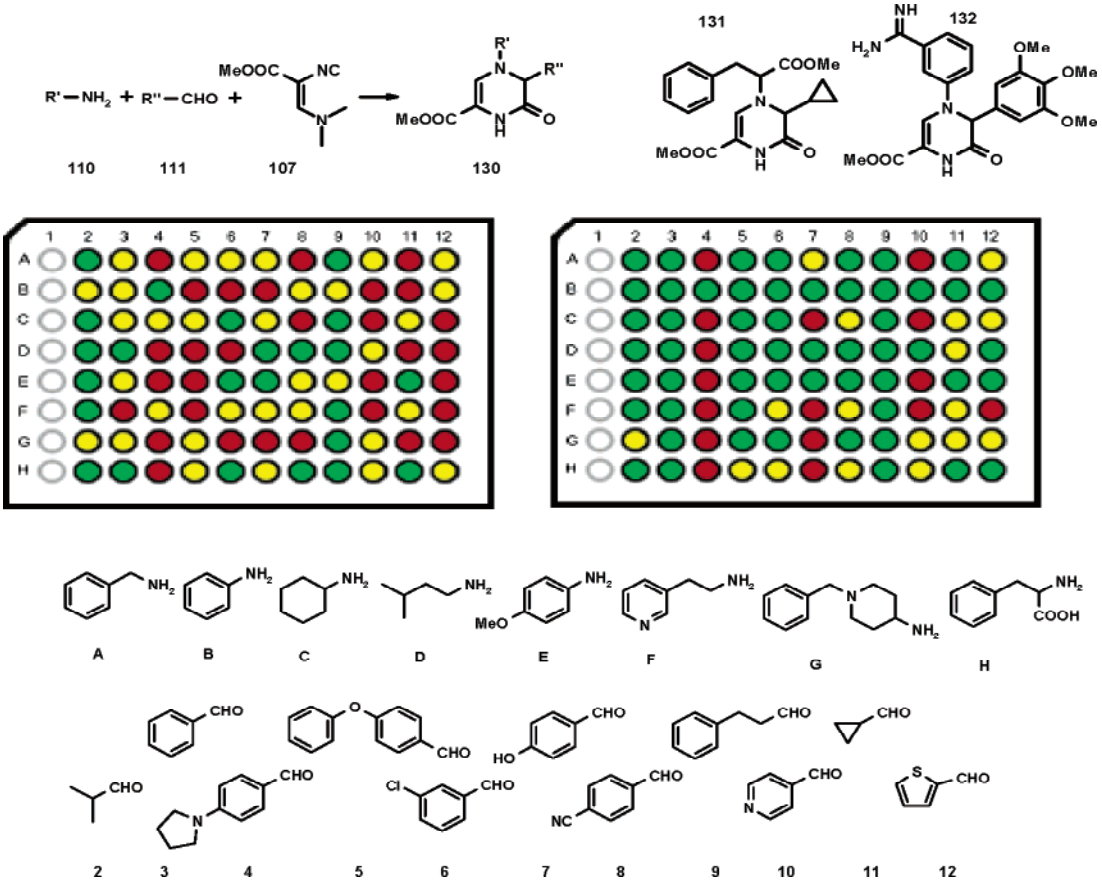
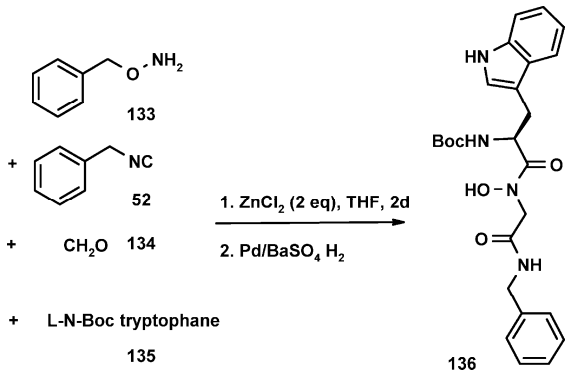


Figure 7. 3-CR of aldehydes and primary amines. In the middle are shown two explorer plates as analyzed by fast HPLC-MS: (left) no additive; (right) $Sc(OTf)_3$ added as Lewis acid. The color code depicts the quality of the reaction as determined by HPLC-MS: green product is major, yellow product is minor, and red indicates no product.

Scheme 28. Inner Hydroxamic Acids Are Not Easily Amenable by Conventional Chemistries but Are Obtained in Two Steps and Good Yields by an IMCR and a Subsequent Deprotection

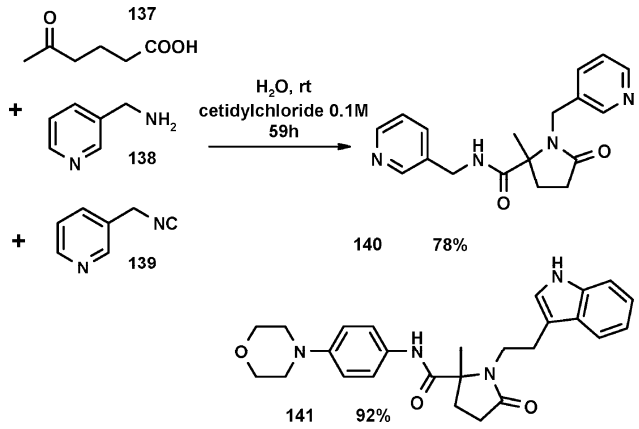


hydes work quite well, aromatic aldehydes do not work at all. This is an excellent access to this otherwise not easy to synthesize compound class of inner hydroxamic acids, yielding, e.g., **136**.

3.5. IMCRs in Water

IMCRs of Ugi type are mostly perfomed in protic alcoholic solvents. Two groups concurrently reported IMCRs in water. Mironov noted the advantage of performing MCRs in water with the addition of small amounts of phase transfer catalysts (PTCs) (Scheme 29).[75] Thus, the reaction of levulinic acid

Scheme 29. U-MCRs of Lactams Performed in Water Are Reported To Give High Yields and Very Pure Products

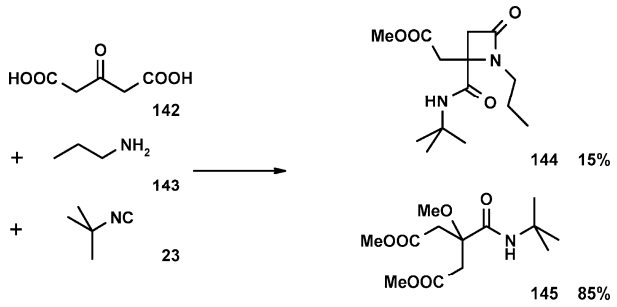


137, isocyanides **139**, and primary amines **138** nicely gives the corresponding γ-lactames **140** or similarily **141** in good yield. Cetylpyridinium chloride (0.1 M) or bovine serum albumin was used as PTC. Advantageously, mostly the pure products precipitated during the reaction. Thus, simple filtering of the solutions afforded products of very pure quality and in good yields.

Pirrung et al. performed an in depth evaluation of the kinetics of different Passerini and Ugi variants in water and classical protic solvents.[76] Surprisingly, they found a profound rate accelerating effect of aqueous solutions compared to organic solvents on Ugi and Passerini reactions. The broadly known acceleration of some organic reactions in water has been attributed to many factors, including the hydrophobic effect, enhanced hydrogen bonding in the transition state, and the high cohesive energy density of water. Other factors that can affect rates of reactions conducted in aqueous solutions are ionic (LiCl) or nonionic (glucose) solutes, which increase the hydrophobic (salting out) effect.

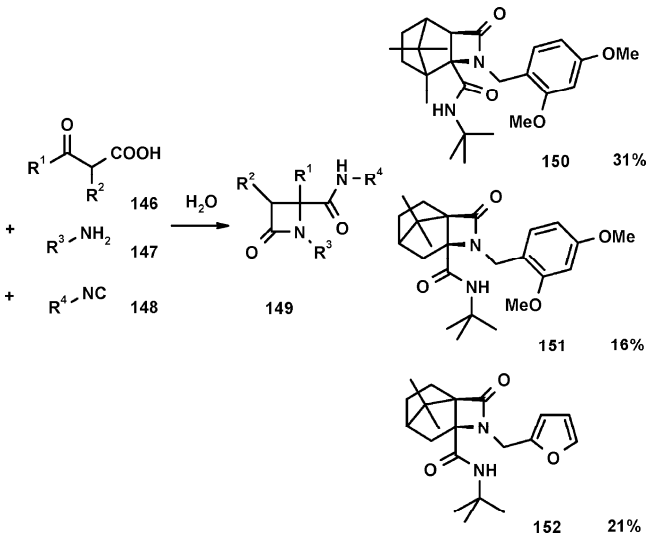
Moreover, the Pirrung group found an almost novel variation of the Ugi reaction mentioned only once in precedent literature (Scheme 30).[77,78]

Scheme 30. The Reaction between Acetonedicarboxylic Acid, Propyl Amine, and *tert*-Butyl Isocyanide To Yield the Corresponding β-Lactam in 15% Yield Together with the Major Product, a Passerini-Type Reaction



The reaction of β-ketoacids **146** with primary amines **147** and isocyanides **148** in a 1 M glucose solution in water affords a novel type of β-lactams **149** in MCRs (Scheme 31). Generally, yields were best with the acyclic compound

Scheme 31. Novel IMCR of β-Ketoacids and Primary Amines and Isocyanides in Water Yielding β-Lactams



acetoacetic acid. With ring fusion, which introduces additional strain into the product β-lactams, yields decrease and reaction times increase. The yields of the highly strained products **150**−**152** were quite modest in glucose solutions, but no conversion at all was observed when reactions to produce these compounds were attempted in pure water. The authors noted that shaking these reactions on a wrist-action shaker in conventional peptide synthesis vessels provides the fastest reaction rate, one that is significantly faster than that when magnetic stirring is used. The reaction conditions described here uniquely enable the production of β-lactams, a class of compounds of high interest for their biological properties, by an efficient IMCR that is amenable to the production of molecular libraries.

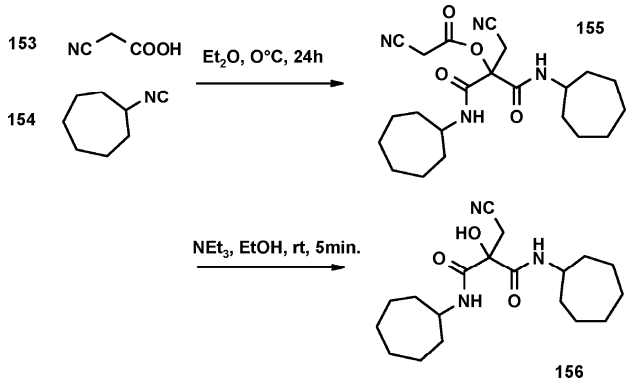
3.6. Novel Scaffolds Based on U- and P-MCRs

Several conceptually different approaches to the discovery and design of new MCRs have been described recently:

discovery by serpendipity, rational design, and combinatorial reaction finding.[79]

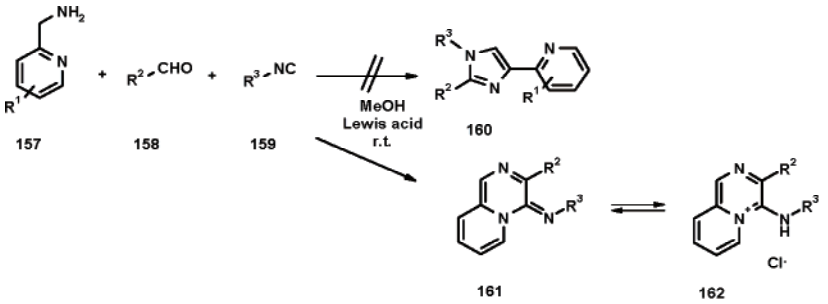
Marcaccini et al. reported the reaction between cyanoacetic acid **153** and isocyanides **154** afforded the unexpected *N*,*N*′-disubstituted 2-cyanoacetoxy-2-cyanomethylmalondiamides **155,** which were easily cleaved in very mild conditions to the corresponding 2-hydroxy derivatives **156** (Scheme 32).[80]

Scheme 32. α-Hydroxy-*β*-cyano Amides Formed by a P-3CR



The authors assume a key intermediate to be cyanoketene, formed through deacylation of the adduct cyanacetic acid and isocyanide. Further addition of the isocyanide and another equivalent of cyanacetic acid affords, after rearrangement, the corresponding Passerini product.

A novel three-component one-pot synthesis of 1*H*-imidazol-4-ylpyridines **160** was proposed by Illgen et al. from Morphochem.[81] In a typical procedure, equimolar amounts of the three starting materials 2-picolylamine **157**, aldehyde **158**, and isocyanide **159** and 50 mol % $InCl_3$ are mixed together in MeOH and react at room temperature overnight. Gratifyingly, the reaction was found to tolerate a range of R groups with different steric and electronic demands, including aliphatic groups and aromatic rings involving electronic donating and electron withdrawing groups (Figure 8). Only bulky isocyanides such as *tert*-butylisocyanide (row D) show some limitations, as do heterocyclic aldehydes, e.g. 2-thiazolylcarbaldehyde (column 8). In most cases, the 1*H*-imidazol-4-ylpyridines were formed (Figure 6). However, recently this reaction turned out to be a second case of wrong structure assignment, since another group from Lilly revised the outcome and mechanism.[82] These authors propose, based upon NOE studies and 1*H*-imidazol-4-ylpyridines synthesized by an alternative route, the formation of pyrido[1,2-*a*]pyrazines **161** and **162**. Their mechanistic proposal involves Schiff base formation, its and the 2-picolyl nitrogen addition onto the isocyanide carbon (α-addition), subsequent oxidation, and H-rearrangement.



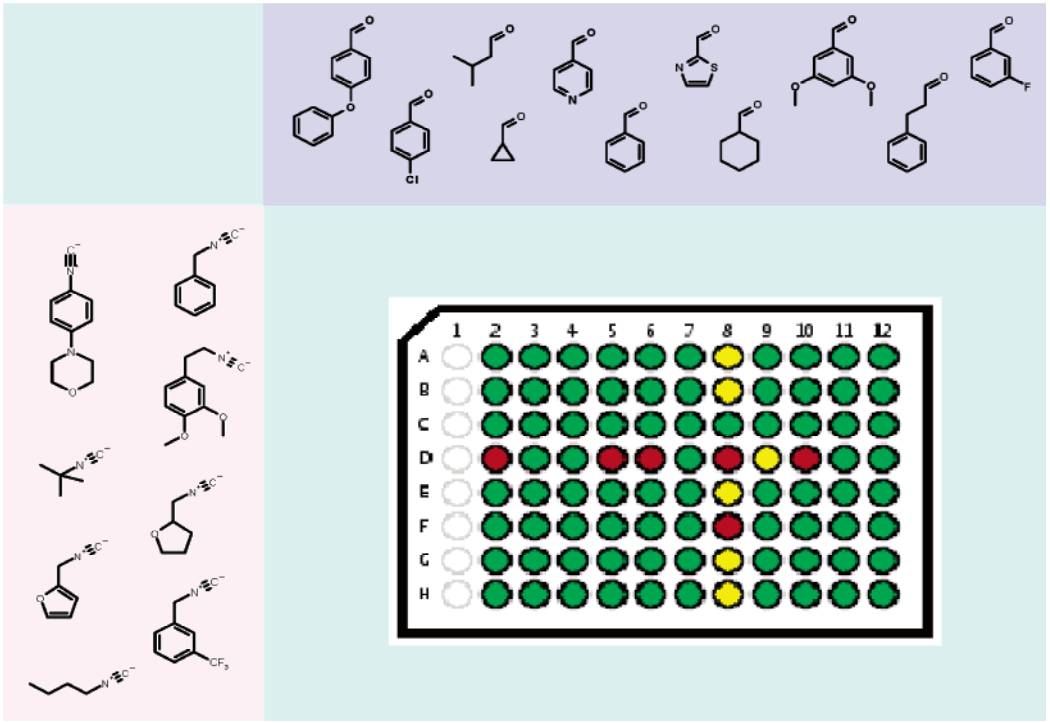


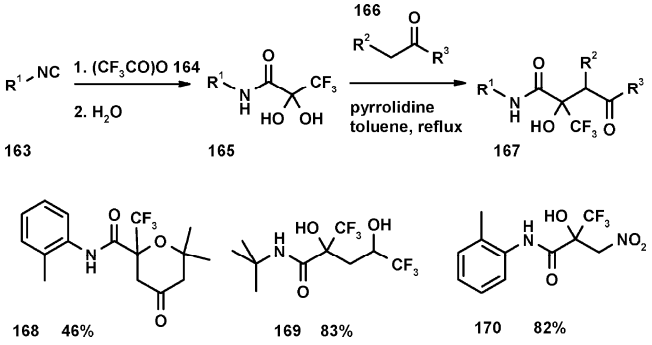
Figure 8. Explorer plate of a newly discovered IMCR of 2-picolylamine, aldehydes, and isocyanides. According to fast HPLC-MS analysis, most reactions took place nicely (green) on this plate in the presence of $InCl_3$ as a Lewis acid promoter.

3.7. α-Hydroxy- and α-Ketoamides by MCRs

El Kaïm et al. reported the reaction of isocyanides **163**, trifluoroacetic acid anhydride **164**, and water, forming trifluoropyramides as their hydrates **165**.[83] Under catalysis with secondary amines, these hydrates were successfully reacted with various methyl ketones **166** to form fluorinated aldol-type compounds **167**−**169**. Moreover, they could perform Henry-type addition to the trifluoropyramides **170** in high yield in nitromethane as solvent under DBU catalysis.

Alternatively, Shabaani et al. described the P-3CR of alkyl isocyanides with 1,1,1,5,5,5-hexafluoropentane-2,4-dione in the presence of water, leading to highly fluorinated γ-dihydroxy-α-hydroxy amide and γ-keto-α-hydroxy amide compounds, e.g. **169** (Scheme 33).[84]

Scheme 33. Fluorinated α-Hydroxyamides Assembled by a P-3CR or by the Reaction of Isocyanides with TFAA and Subsequent Hydrolysis



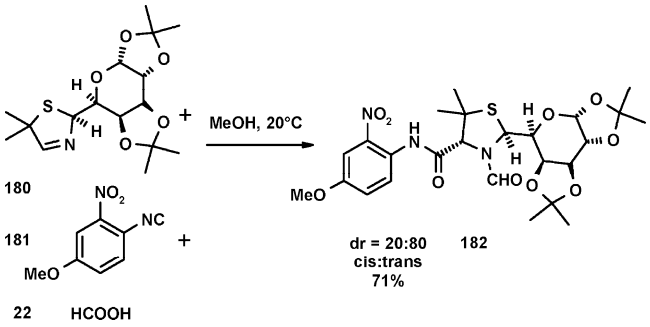
Similarily, trichloroacetic acid anhydride **172** reacts with isocyanides **171** to form stable hydrates of trichloropyruvamides **173** (Scheme 34).[85] These compounds are valuable intermediates for obtaining oxamides **175** by reaction with $TMSCl/NEt_3$ followed by addition of an amine. Refluxing of intermediate **173** in basic toluene afforded selectively oxalic acid monoamide **174**.

α-Ketoamides are of potential medicinal interest, e.g. as reversible cysteine protease inhibitors. They can be synthesized by a Passerini reaction and subsequent oxidation of the hydroxy functionality. Moreover, they can be synthesized by a U-4CR using α-ketoacids as the carboxylic acid input. In an Ugi protocol from 1960, an acyl chloride couples with an isonitrile to form a α-ketoimidoyl chloride intermediate, which is then converted to a α-ketoamide upon hydrolysis.[86] Chen et al. from Procter & Gamble Pharmaceuticals reported a rapid synthesis of α-ketoamides, e.g. **179**, using a microwave irradiation−simultaneous cooling method (Scheme 35).[87] Microwave-assisted acyl chloride−isonitrile condensation and $CaCO_3$-mediated hydrolysis constitute a one-pot, 2-min process to prepare divers α-ketoamides.

3.8. Asinger/Ugi Combination

The combination of Asinger's and Ugi's MCRs is an intensive field of research, yielding cis-constrained cyclic compounds, proline analogues. Thus, Martens et al. have presented a practical approach to enantiomerically pure 3-thiazolines **180** using a galactose-derived carbohydrate as a chiral auxiliary.[88] Subsequent Ugi reaction with a cleavable isocyanide **181** and formic acid **22** proceeded in good yield and diastereomeric ratio to give **182** (Scheme 36).

Scheme 36. Enantioselective Synthesis of a Thiazolidine by a U-4CR of an A-4CR Imine Intermediate

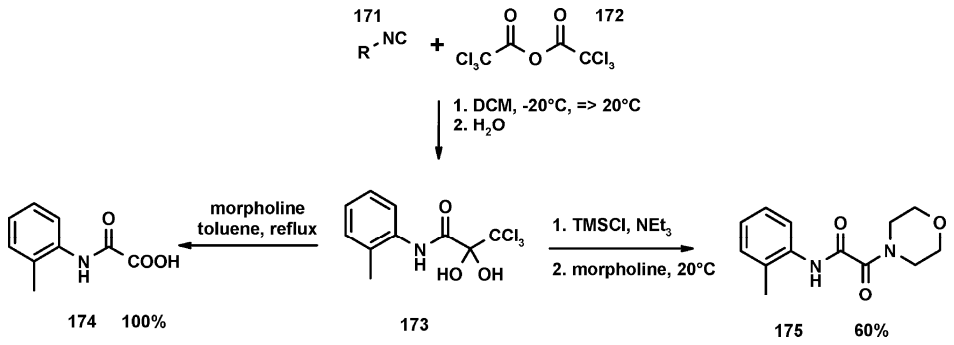


3.9. β-Lactams

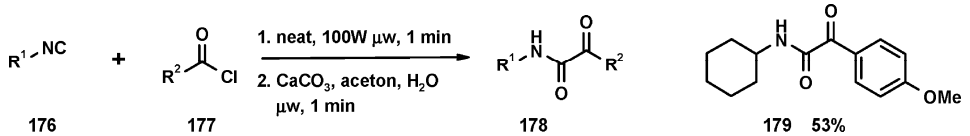
A conceptually novel MCR assembling β-lactams is described in section 3.5. Here Pirrung et al. used β-ketoacids in conjunction with primary amines and isocyanides to yield 1-*N*-substituted 3-aminocarboxymethyl-β-lactams.[100]

β-Lactams play an important role not only in a major class of antibiotics but also as inhibitors of serine proteases, elastase, cysteine protease, and papain. It has been early recognized that β-amino acids yield β-lactams in the Ugi reaction. Fueloep et al. described the liquid- and solid-phase

Scheme 34. MCR Chemistry of Isocyanides, Trichloroacetic Acid Anhydride, and Water and Subsequent Transformations



Scheme 35. Microwave Assisted α-Ketoamide Synthesis from Isocyanides and Acyl Chlorides



combinatorial synthesis of alicyclic β-lactams, e.g. **183**−**185**, via U-4CRs (Figure 9).[89,90] SASRIN (Super Acid

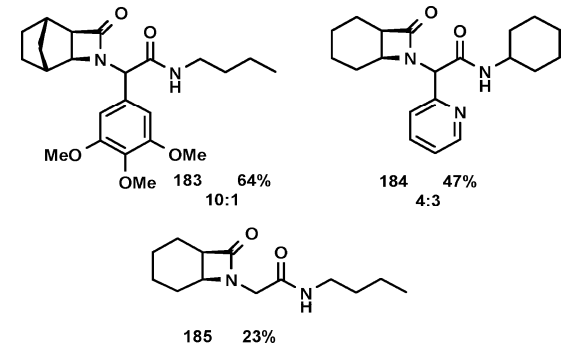


Figure 9. Bicyclic β-lactams from cyclic β-amino acids.

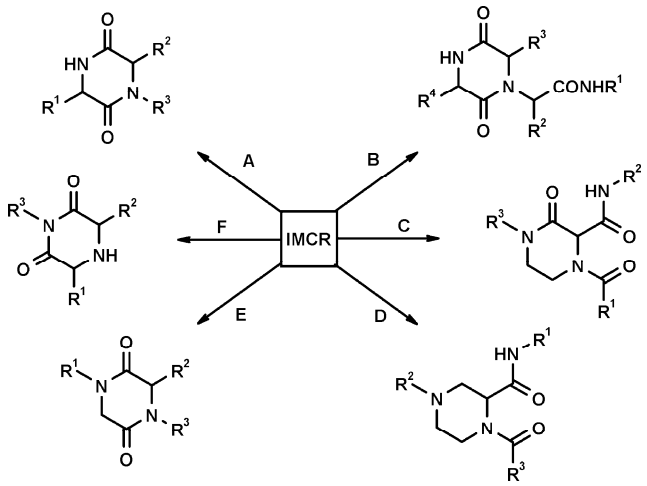
Sensitive Resin) was used for the solid-phase synthesis of bicyclic *cis*-2-azetidinone derivatives from cyclic β-amino acids. 2-, 3-, or 4-Formylbenzoic acid was immobilized on the resin through its carboxy function. The U-4C-3CR was also carried out in solution, making use of scavenger resins for purification. The formation of some of these bicyclic β-lactams is remarkable due to their high steric crowding.

A mixture based solution-phase Rubik's Cube-like library comprising 128 bicyclic β-lactams, synthesized as five mixture based sublibraries, was subsequently described (Figure 10).[91] All compounds were formed, as monitored by ESI-MS. The library was purified by column chromatography and screened against Hela cell proliferation, elastase, and plasma membrane glycoprotein.

3.10. Piperazines

Interestingly, many scaffolds amenable by IMCRs can be thus obtained in several different complementary ways. According to a recent review, there are many pathways to ketopiperazines.[92] However, multicomponent reactions (MCRs) seem to be particularly well suited to assemble piperazines, since six different methods have been published so far (Scheme 37). A three-step diketopiperazine synthesis using a U-4CR and a convertible isocyanide, diphenylmethyl isocyanide, was reported by Boehm and Kingsbury in their polyoxin antibiotic synthesis, strategy A.[93] A similar approach has also been recently used in the total synthesis of Ecteinascidin 742 by Fukuyama et al. using convertible *p*-methoxyphenyl isocyanide.[94] As part of the so-called UDC (Ugi reaction/deprotection/cyclization) strategy, Hulme et al. described several new scaffolds which can be easily built-up by using a Boc-protected bifunctional starting material; for example, Boc-protected α-amino acids and convertible cyclohexenyl isocyanide yield highly substituted diketopiperazines in one step using again strategy A.[95] Another one-pot diketopiperazine synthesis using a MCR was introduced

Scheme 37. Complementary Piperazine Synthesis by MCRs[a]



[a] A: (1) cyclohexenyl isocyanide, $HOOCCHR^1NHBoc$, R^2CHO, R^3NH_2; (2) TFA, DCM; (3) NEt_3. B: (1) H_2NCHR^3COOR, R^1NC, R^2CHO, $BocHNCHR^4COOH$; (2) TFA, DCM; (3) toluene, EtOH, reflux. C: $OHCCOOEt$, $H_2NCH_2CH_2NR^3H$, R^1COOH, R^2NC. D: (1) chloroacetic aldehyde, R^1NC, $R^2HNCH_2CH_2NH_2$, R^3COOH; (2) base. E: (1) chloroacetic acid, R^1NC, R^2CHO, R^3NH_2; (2) KOH, EtOH, sonicate. F: (1) $HOOCCHR^2NH_2$, R^1CHO, R^3NC, MeOH; (2) ^{t}BuOK, THF, Δ.

by Szardenings et al. reacting an α-aminoester, a *N*-protected α-amino acid, an aldehyde, or a ketone and an isocyanide, yielding after the primary U-4CR and the secondary deprotection and cyclization the desired diketopiperazine according to strategy B.[96] The use of glyoxylic acid esters, in conjunction with isocyanides, ethylenediamine, and acids according to Ugi et al.[97] (strategy C) or with mono-Boc-protected ethylendiamines, carboxylic acids, and isocyanides according to Hulme et al., also yields ketopiperazines.[98] Rossen et al. from Merck reacted mono-Boc-protected ethylendiamines, carboxylic acids, isocyanides, and chloroacetaldehyde smoothly to give piperazines (strategy D).[99] This reaction has been advantageously used in the synthesis of the HIV protease inhibitor Crixivan. Marcaccini et al. introduced a rapid route toward 2,5-diketopiperazines utilizing chloroacetic acid in the MCR and closing the ring through a substitution reaction (strategy E; see below).[100] Ugi et al. used unprotected α-amino acids, isocyanides, and aldehydes in methanol and a subsequent base induced cyclization to yield 2,6-diketopiperazines (strategy F).[101]

Note that the overall six different described ways to assemble the (mono/diketo)piperazine moiety utilize a MCR and a subsequent cyclization strategy, but their outcomes are quite different, in terms of molecular connectivity and starting materials! This is potentially useful in fully exploiting a chemical space; for example, many starting materials are only available as certain functional elements.

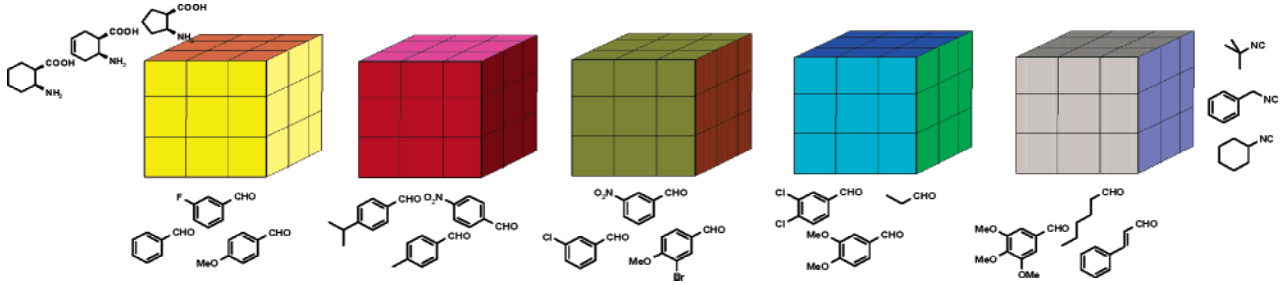
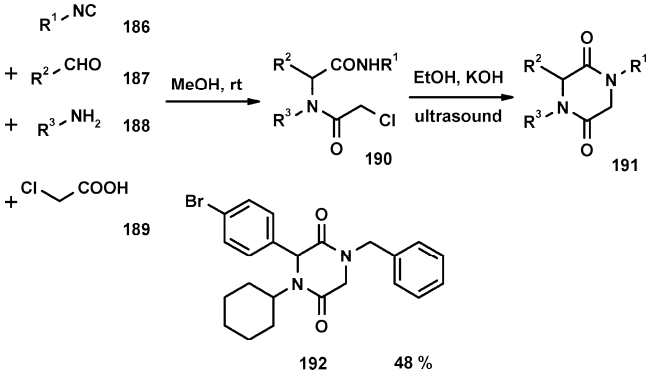


Figure 10. 3D array of bicyclic β-lactams yielding five Rubik's Cube-like sublibraries.

Recently, Maccacini et al. described another complementary approach toward diketopiperazines.[102] The U-4CR between isocyanides **186,** aldehydes **187**, amines **188**, and chloroacetic acid **189** and afforded the expected adducts **190**, which were cyclized to the title compounds upon treatment with ethanolic KOH under ultrasonication (Scheme 38).

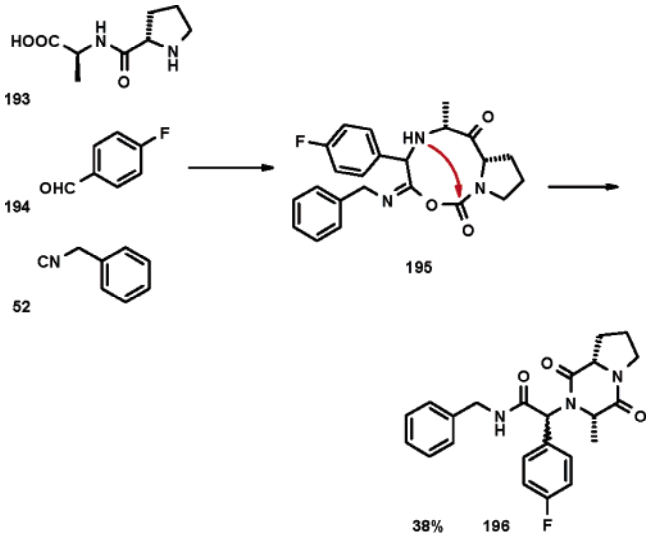
Scheme 38. Maccacini's Diketopiperazine Synthesis Based upon a U-4CR of Chloroacetic Acid and a Subsequent Intramolecular Substitution Reaction under Basic Ultrasound Conditions



Although the Ugi four-component condensation was successfully performed by employing aliphatic aldehydes as starting materials, attempts to cyclize the resulting products gave complex reaction mixtures. Cyclizations performed by employing KOD in EtOD showed that epimerization at the stereogenic center took place to a large extent. Even though this method suffers from limitations due to the nature of the aldehyde, the authors made the point that a wide variety in the substitution pattern of the Ugi intermediate, and subsequently in the diketopiperazines, can be easily achieved by changing the components in the Ugi reaction. Thus, **192** can be synthesized in 48% yield over the two steps in a straightforward manner.

On top of these, another new approach toward diketopiperazines was published using dipeptides, aldehydes, and isocyanides.[103] For example, bifunctional L-Ala-L-Pro **193** react with 4-fluorobenzaldehyde **194** and benzyl isocyanide **52** to form **196** in 38% yield in a dr of 3:2 (Scheme 39). The intramolecular reaction is assumed to proceed via the

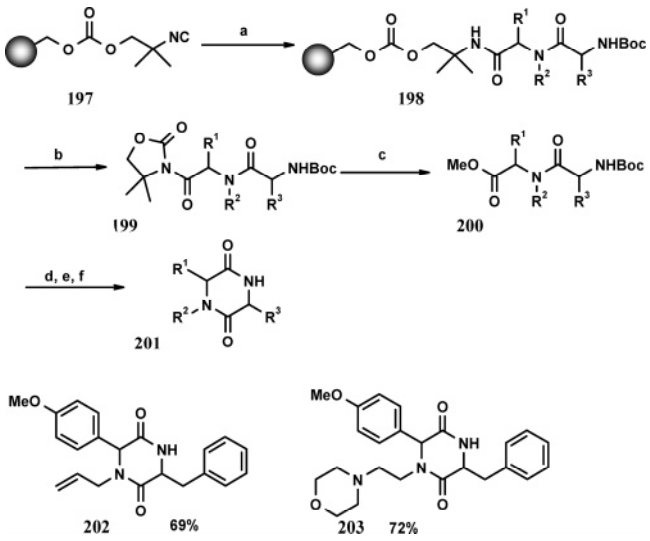
Scheme 39. A Korean Group Described the Stereoselective IMCR To Give Diketopiperazines from Dipeptides



nine-membered intermediate α-adduct **195**, which collapses to the six-membered diketopiperazine, by an intramolecular transacylation.

Arrays of 4000 diketopiperazines have been described using a convertible solid-phase bound carbonate isocyanide according to Scheme 40.[104] For a 2,5-diketopiperazine

Scheme 40. Array Biopharmaceuticals Described a Large Array of Diketopiperazines on Solid Phase[a]



[a] (a) 10 equiv of R^1CHO, R^2NH_2, D,L-*N*-Boc-amino acid, TFE, 4A molecular sieves, DCM, 20 °C, 3 d; (b) KO^{t}Bu (2 equiv, 1 M in THF), THF, 20 °C, 16 h; (c) NaOMe (1.3 equiv, 0.65 M in MeOH), THF, 20 °C, 48 h; (d) 70/30 hexafluoroisopropanol, TFA, 20 °C, 48 h; (e) silicycle-carbonate, THF, 6 h; (f) silicycle isocyanate-3, THF, 16 h.

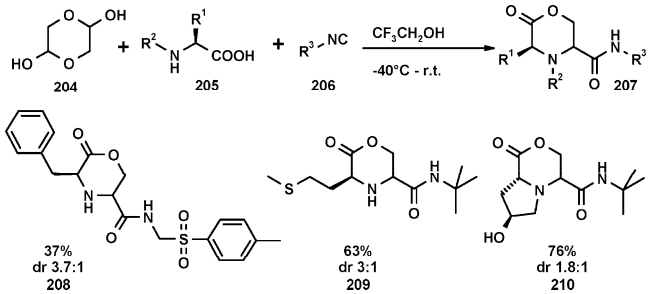
showcase plate, where 80 compounds were made in parallel format, the average mass recovery was 83%. Compounds **202** and **203** for example were formed in good yields.

3.11. U-5C-4CR of Amino Acids

The U-5C-4CR involves four components (4C) and five functional groups (5C). It is based upon the reaction of unprotected α-amino acids, isocyanides, and oxo compounds and an internal or external nucleophile. The reaction has been used to prepare imino dicarboxylic acid monoamides, aziridines, butenolides, and ϵ- or δ-lactames.

On the basis of the U-5C-4CR, Kim et al. described a novel stereoselective morpholin-2-one synthesis.[105] By using commercially available glycolaldehyde dimer **204** incorporating an aldehyde and an alcohol functional group in one component, *S*-amino acids **205**, and isocyanides **206** in a U-5C-3CR, unique morpholine structures were prepared, e.g. **208** and **209** (Scheme 41). To direct the reaction into an intramolecular channel, it has to be performed in the less nucleophilic solvent trifluoroethanol. If the reaction is

Scheme 41. Kim's 2-Oxomorpholine U-5C-4CR



performed in methanol, mostly the methyl ester is formed as a product. These new structures broaden the scaffolds that are accessible through the Ugi reactions of α-amino acids. When the cyclic amino acids, e.g., proline derivatives, were used, other unique heterobicyclic compounds were produced in moderate to good yields, e.g. **210**.

A highly diastereoselective one-pot synthesis of the α,α-iminodiacetic acid analogues **211**−**213** was accomplished by the U-4CR-5C of an isocyanide, an aldehyde, and an L-amino acid in methanol (Figure 11).[106] The diastereo-

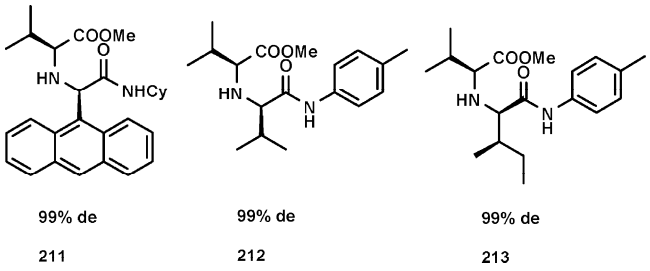
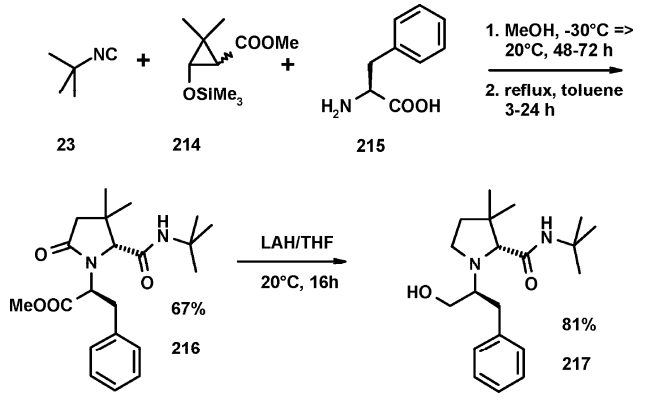


Figure 11. Compounds of high stereochemical purity can be obtained by U-5C-4CRs.

selectivity of the reaction is very sensitive to the substituent size of both the aldehyde and the enantiomerically pure amino acid. Thus, 9-anthranyl aldehyde affords generally excellent de **211**. Isobutyric aldehyde and 2-*S*-methylpropionic aldehyde also afford excellent de products, e.g. **212** and **213**, in combination with bulky amino acids such as valine.

Reissig et al. described the use of siloxycyclopropanes as γ-ketocarboxylate equivalents in the U-5C-4CR.[107] Reacting unprotected tyrosine **215**, isocyanide **23**, and siloxycyclopropane **214** in methanol afforded imino dicarboxylic acid derivatives in good yields and diastereoselectivities. The Ugi product can be cyclized in refluxing toluene to yield the pyrrolidones **216** in good to excellent yields. Reduction of pyrrolidinones **216** with lithium aluminum hydride chemoselectively furnished proline related amino alcohols **217** in good yield (Scheme 42). If executed in a one-pot sequence,

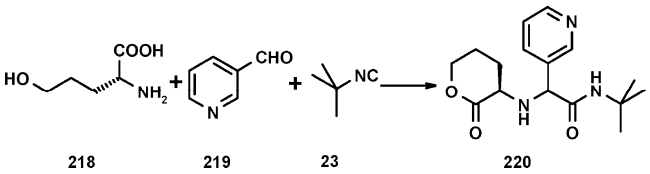
Scheme 42. Use of Siloxycyclopropanes as γ-Ketocarboxylate Equivalents in a U-5C-4CR



the overall process may be classified as a six-center four-component reaction. Since precursor cyclopropanes **214** are easily available in many structural variations, this new modification of the Ugi reaction as presented here should allow preparation of highly diverse libraries of compounds **216** or **217** as well as of other related products.

An efficient synthesis of chiral α-amino-δ-valerolactones by the Ugi five-center three-component reaction was described by a Korean group (Scheme 43).[108] L-Pentahomoserine **218** was shown to react with 32 different aldehydes or ketones and three different isocyanides in methanol to give, e.g., **220**. This clearly constitutes a novel variation of the U-5C-3CR of bifunctional and bireactive α-amino acids in Ugi-type MCRs.

Scheme 43. Pentahomoserine Affords α-Amino-δ-valerolactones in the U-5C-4CR



Ciufolini et al. reported on the $TiCl_4$ catalyzed U-5C-4CR of α-amino acids and aromatic aldehydes (Scheme 44).[109] They found that the $TiCl_4$ catalyzed reaction affords better yield than the uncatalyzed one. Moreover, the preferred diastereoselectivity was found to be (*S*,*S*)-**223**. Aromatic, cinnamic, and heteroaromatic aldehydes reacted with glutamic acid monomethyl ester **222** and isocyanides in 10 examples to give between 75 and 91% yields and dr's ranging from 1.5 to 10. Other amino acids gave similar good results. The authors were interested in preparing pyroglutamate derivatives; thus, they described the further transformation of the U-5C-4CR product to form pyroglutamic acid derivatives **224**−**225**. Depending on the reaction conditions, different cyclized products were observed. Thus, refluxing in acetic acid afforded the pyroglutamic acid derivative **225**, whereas refluxing in TFA gave a further diketopiperazine cyclization to give **224**. Interestingly, the attempted Passerini reaction of pyrroglutamic acid in protic alcoholic solvents afforded unexpected products, **228** and **229**. Reaction to **229** constitutes a Passerini-type reaction, whereas formation of **228** is explained by the authors by a complex mechanism involving an oligocyclic *O*,*N*-diacyl *N*,*N*-diamino ketal intermediate.

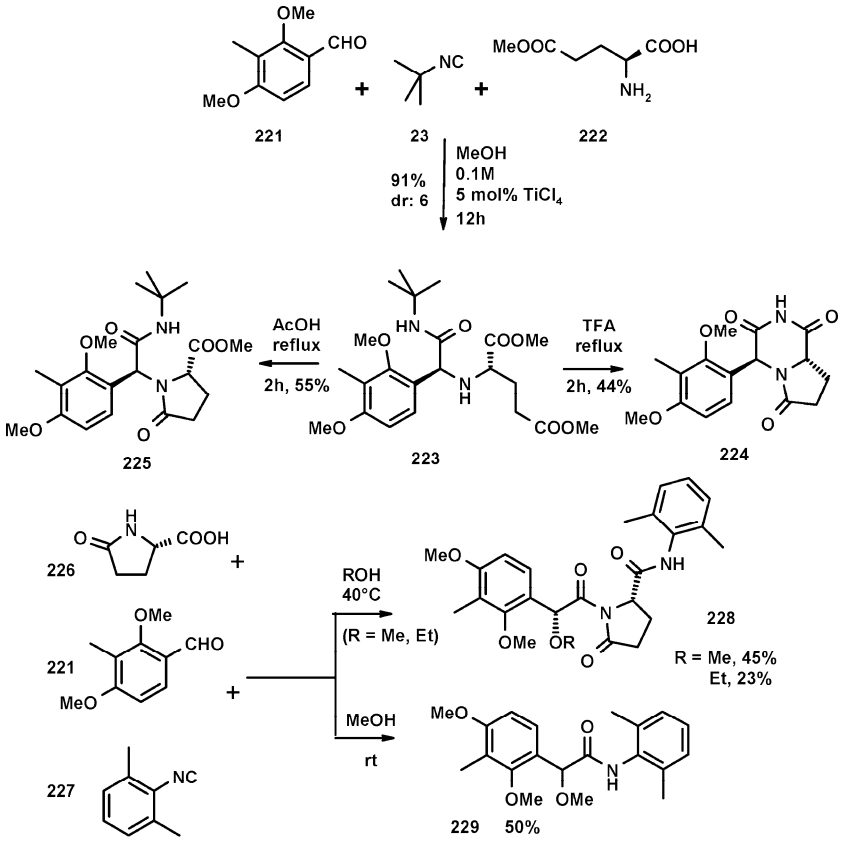
3.12. IMCR/Cyclic Condensations

o-Aminobenzophenone **230** reacting in a U-4CR with electron deficient substituted acetic acids, e.g. **231**, can be ring-closed either spontaneously or in a second step with the aid of sodium methanolate in a Knoevenagel condensation to form substituted quinoline-2(*1H*)-ones in a one-pot fashion in often excellent yields (Scheme 45).[110] The acetic acids with reactive methylene groups used were cyano acetic acid, malonic monomethyl ester, and tosylacetic acid. Thus, **234** is formed in 58% overall yield. This tandem Ugi−Knoevenagel chemistry seems to be useful for high-throughput chemistry and spans an interesting large chemical space, since all starting materials are broadly commercially available.

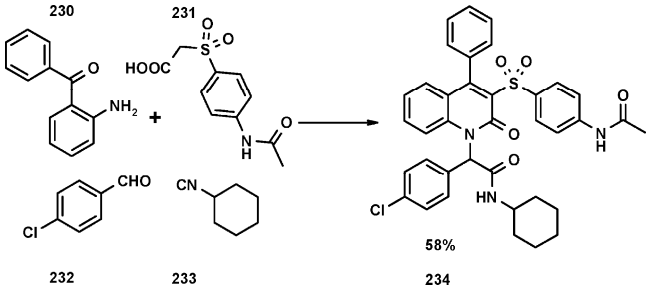
An efficient synthesis of Δ^5-2-oxopiperazines in solution phase and on solid support has been established via a U-4CR followed by *N*-acyliminium ion cyclization between the acetal functionality and the newly formed amide bond (Scheme 46).[111] The use of amino acetaldehyde dieethylacetal **235** as amine component is the crucial input to afford the subsequent condensation−cyclization. The desired oxopiperazines, e.g. **238**, are obtained in excellent yields and purity.

A facile synthesis of 1,6-dihydro-6-oxopyrazine-2-carboxylic acid derivatives **243** via Ugi four-component condensation was described by Marcaccini et al.[112] Reaction of

Scheme 44. IMCR of Pyrroglutamic Acid



Scheme 45. U-4CR and Knoevenagel Condensation Yielding Substituted Quinoline-2(1*H*)-ones

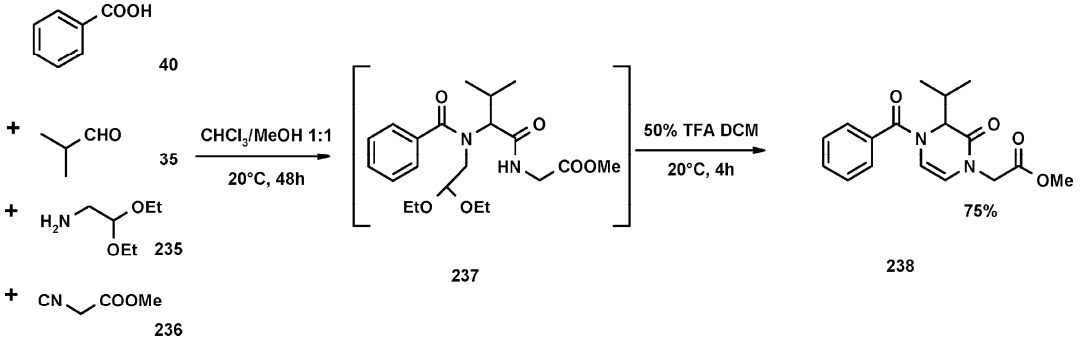


phenylglyoxals **239** with amines provides the Schiff base **240**, which undergoes a U-4CR with α-ketocarboxylic acids **241** and isocyanides **242** (Scheme 47). Subsequent condensation of ammonia in refluxing acetic acid affords the pyrazine scaffold, e.g. **244** and **245**, in moderate to good yields.

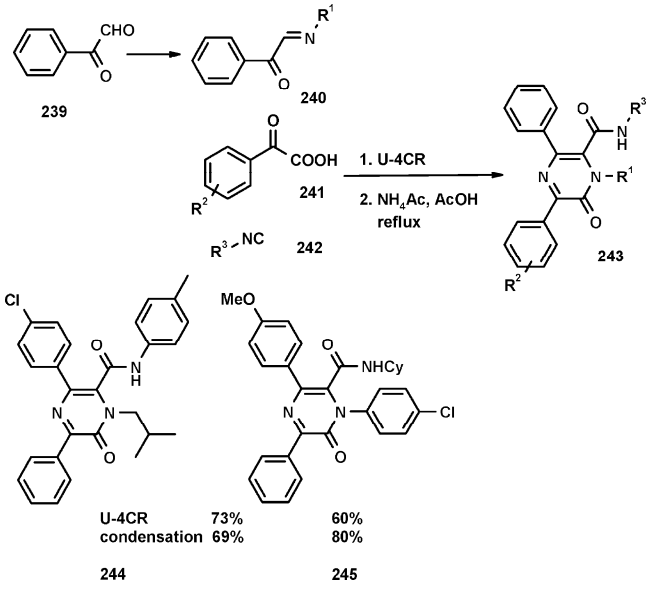
Functionalized pyridazinones can be synthesized by a U-4CR of diarylglyoxal monohydrazones.[113] During this transformation, diarylglyoxal monohydrazones **246**, isocyanides, aldehyde, and methylene active acids, e.g. **248,** afforded a series of 3(2*H*)-pyridazinones, e.g. **249,** in a very simple manner (Scheme 48). The intermediate Ugi four-component condensation products were usually not observed, because of their tendency to cyclize. When the less reactive cyclopentanone **247** is used instead of aldehydes, satisfactory yields of 3(2*H*)-pyridazinone **249** were obtained by employing the preformed azine **246**.

A facile synthesis of 4-phenyl-1-(*2H*)phthalazinone-2-alkanoic acid amides was described by Marcaccini et al. (Scheme 49).[114] The reaction between azine **251**, 2-benzoylbenzoic acid **252**, and cyclohexyl isocyanide **233** spontaneously afforded 2-(1,2-dihydro-1-oxo-4-phenylphthalazin-2-yl)propionamide **253** upon loss of 1 equiv of aldehyde or ketone from the intermediate U-4CR adduct. Under the

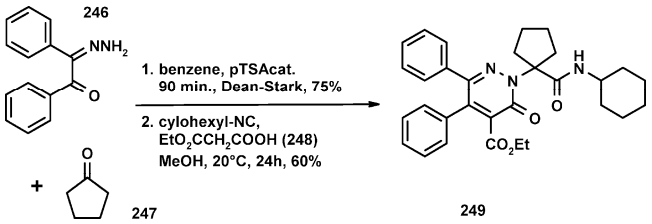
Scheme 46. U-4CR of Amino Acetaldehyde Dieethylacetal and Subsequent Acid Catalyzed Condensation−Cyclization as Described by Chugai Pharma Chemists



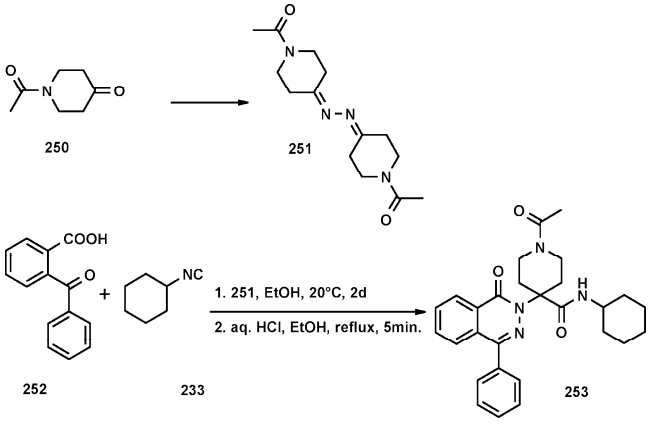
Scheme 47. U-4CR of Arylgloxales and Arylketocarboxylic Acids Yields Diketo Ugi Intermediates Which Condense with Ammonia To Afford the Corresponding 1,6-Dihydro-6-oxopyrazines



Scheme 48. Diarylglyoxales, α-Acidic Acetic Acids, and Hydrazine React in the U-4CR, and Subsequent Condensation−Cyclization Affords Pyridazinones



Scheme 49. Phthalazine Derivatives by U-4CR of Hydrazones, Diphenyl Ketone-1-carboxylic Acid and Subsequent Deprotection and Condensation−Cyclization

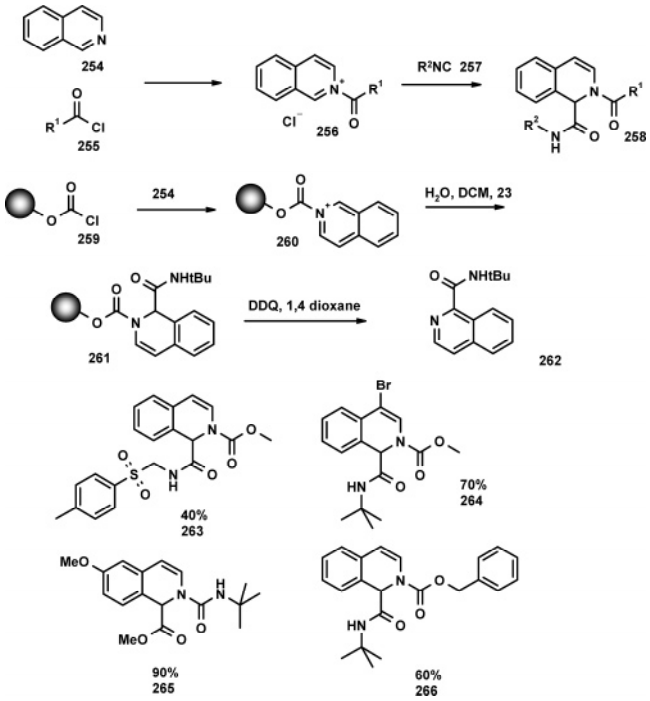


almost neutral Ugi conditions, the intermediate did not spontaneously cyclize, but only in acidic medium.

3.13. MCRs of Isoquinolines

Already in 1960, Ugi could show that *N*-alkyl isoquinoline salts and carboxylic acids undergo α-addition to isocyanides and subsequent hydrolysis, yielding the corresponding *N*-alkyl-3-acyl-4-hydroquinoline-4-carboxamides **258**.[115] Lavilla and co-workers introduced a valuable extension showing that the corresponding *N*-acyl isoquinoline salts equally undergo Ugi-type processes.[116] *N*-Acyl azinium salts **256** can be prepared form isoquinoline **254** and acyl chlorides **255**, chloroformates, or sulfonyl halides. Typical examples of products of this reaction are **263**−**266** (Scheme 50). Considering the availability of acylating agents, this procedure dramatically improves the accessibility of these important classes of scaffolds. The most popular *N*-protecting groups such as Boc, Alloc, and Z- can easily be introduced by this MCR process. The authors also archived a solid-phase variant using chloroformate resin **259**. After Ugi reaction with isocyanide in water/DCM, the product can be oxidatively cleaved off from resin, thus leading to the corresponding isoquinoline-1-carboxamide **262**.

Scheme 50. Lavilla's *N*-Acylazinium Salts in U-MCRs

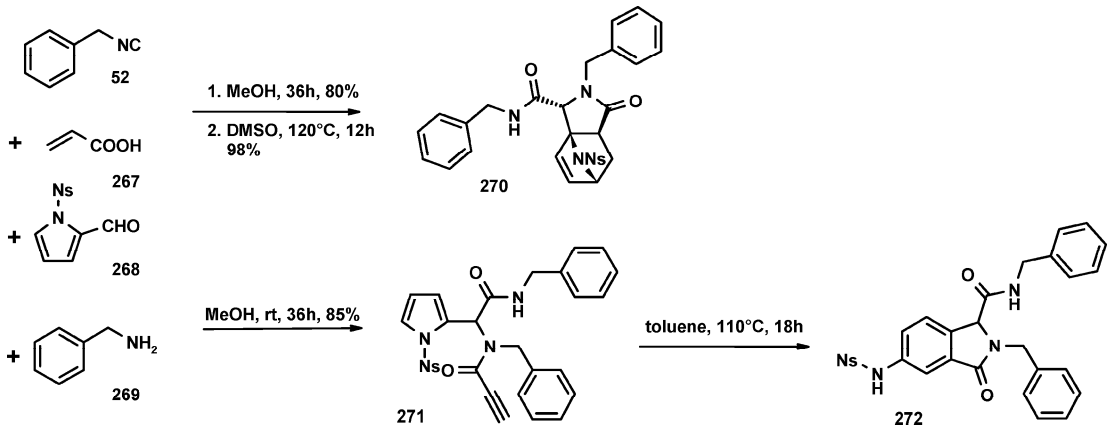


3.14. IMCRs Followed by a Cycloaddition

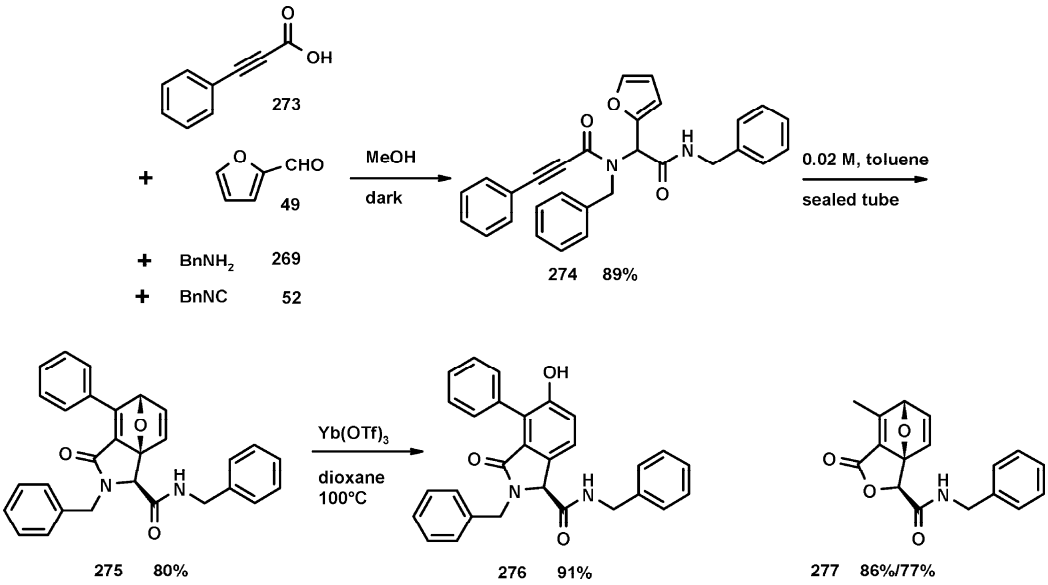
Combining the Ugi and Passerini reactions with a subsequent Diels−Alder reaction is a popular theme in IMCR based diversity generation. Affymax chemist Paulvannan investigated *en detail* the combination of Ugi reactions with intramolecular Diels−Alder reactions yielding rigid tricyclic scaffolds **270** (Scheme 51).[117] The key to the success of the Ugi/IMDA cycloaddition strategy is the selection of *N*-protected pyrrole aldehyde **268** and activated dienophile acid **267** as the aldehyde and acid components, respectively. The attractive feature of this approach is the stereocontrolled generation of five stereocenters, including a quaternary center, and two rings in a single chemical transformation from readily available achiral starting materials. When using propargylic acid instead of acrylic acids, the intermediately formed Diels−Alder adduct is rearranged and aromatisized to the corresponding isoindolone **272**.

Wright et al. also investigated the sequential IMCR/Diels−Alder cycloaddition reaction.[118] The nature of the heteroatom in the tether of the MCR intermediate was determined to play a critical role. Whereas the U-4CR **274** underwent the DA reaction **275**, the P-3CR product failed to yield the oxabicyclo derivatives under thermal conditions (Scheme 52).

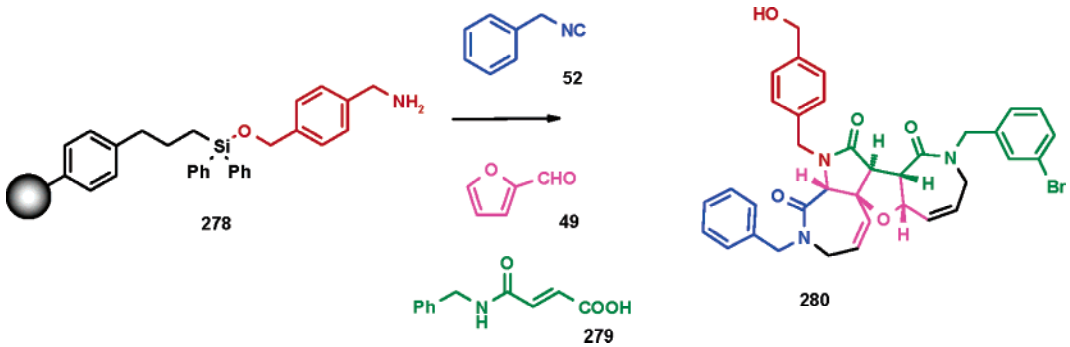
Scheme 51. The Combination of Ugi and Diels−Alder Reactions Afforded Complex Tricyclic Scaffolds or Isoindones Dependent on the Reaction Conditions



Scheme 52. Intramolecular Diels−Alder Reaction Involving Furan (IMDAF) of P-3CR and U-4CR Products



Scheme 53. During This Sequence of Four Reactions Involving an Initial U-4CR, DA, Perallylation, and ROCM, Highly Complex Tetracyclic Products, e.g. 280, Are Formed[a]

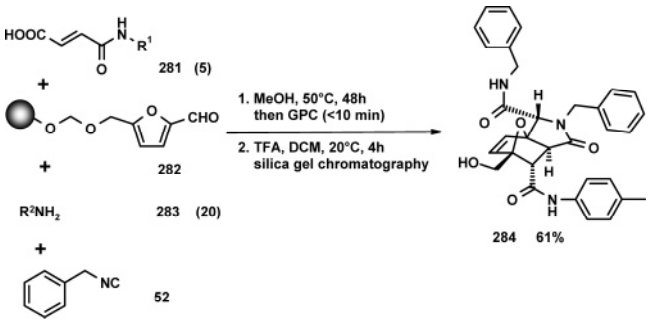


[a] Noteworthy is the fact that the molecular integrity of the furan input is lost in the product.

This striking difference in reactivity is quite interesting considering the small change from nitrogen to oxygen in the tether. This difference in reactivity may reflect the difference in conformation between an ester and amide side chain or in the stability of the cycloadducts. Yb(III) induced a rearrangement of the oxabicycle **275** to yield the corresponding phenol **276**. The P-3CR product could be converted into **277** by a cycloaddition catalyzed with the Lewis acid Me_2-AlCl. Moreover, it was observed that the DA products from the Passerini reaction were much less stable than those derived from the Ugi reactions. The lactones quickly undergo retro Diels−Alder reaction at elevated temperatures, while the lactams are completely stable.

Schreiber et al. used a four-step sequence to prepare highly complex tetracyclic structures starting from available and structurally simple starting materials (Scheme 53).[119] The sequence consists of four reactions, a first U-4CR, a Diels−Alder reaction, a double allylation of the intermediate two secondary amide nitrogens, and finally a ring opening−closing metathesis reaction. During this short sequence, as

Scheme 54. Solid-Phase Sequence of U-4CR/DA Reactions



many as four new rings and 15 new bonds are formed, ecce BFE. This is noteworthy, since in a typical sequential synthesis using two component reactions, typically only one bond or ring is formed per step. Obviously, not all four reactions contribute similarly to the diversity and the complexity of the backbone structure and the final product library. The diversity of the resulting compounds arises from the starting materials of the first Ugi reaction and to a much smaller degree from subsequent steps such as the allylation. The Ugi reaction determines most of the diversity via four independently introduced substituents. It also greatly contributes to complexity, since during the reaction five new bonds are formed. The Diels−Alder reaction contributes to complexity through the formation of two C−C bonds and the formation of three ring systems, but only one of them is retained in the final product. The allylation introduces new fragments (two new N−C bonds) and paves the way for the most dramatic molecular rearrangement in the overall sequence by the last reaction, the ring opening−closing metathesis. During this reaction, a five-membered ring is opened and two seven member rings are formed through four new C−C bonds. Overall, the Ugi and, to a much lesser extent, the allylation reactions contribute to the diversity in this scaffold. The Ugi, Diels−Alder, and metathesis reactions are responsible for the augmentation of complexity in this sequence as counted by bond formation and newly formed rings. Therefore, combining complexity and diversity generating MCRs together with other complexity generating reactions provides a powerful tool toward the parallel synthesis of molecular libraries with impressive chemical structures. A detailed analysis of this reaction is given in the literature.[120]

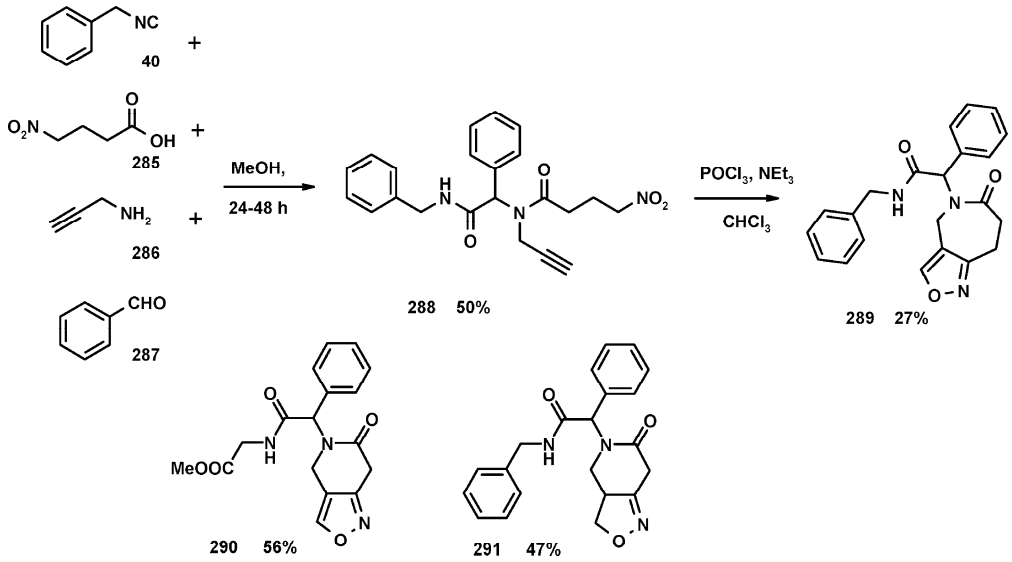
A series of parallel reactions were carried out for the tandem Ugi/Diels−Alder reaction on a MPEG−O−CH_2-platform (Scheme 54).[121] Ninety-six out of 100 entries were successful to give complex heterotricycles, e.g. **284**. The amount of benzylisocyanide, **52**, was kept constant. The stereoselectivity was found not to be influenced by the building blocks used for amine and carboxylic acid components. The reaction was also performed on solid phase, by which a larger library is potentially realized by employing the split-pool method.

Abbott and co-workers performed Ugi reactions employing nitro propionic or butyric acids **285** and propargylamine **286**, followed by an intramolecular nitrile oxide cyclization (Ugi/INOC), thus entering the classes of fused isoxazoles and isoxazoline ring systems (Scheme 55).[122] The intermediate Ugi product **288** undergoes a [2+3]-cycloaddition, thus yielding fused six- and seven-membered lactames **289**−**291**.

The same group reported the combination of an Ugi reaction with an azide/alkyne cycloaddition yielding diverse fused triazolo derivatives **292**−**296** (Figure 12).[123] Both azides and alkynes do not interfere with Passerini or Ugi reactions and can thus be introduced and used for a secondary reaction. The cycloaddition takes place in refluxing benzene or copper catalyzed at room temperature. The needed functionalized starting materials are either commercially available or easy to synthesize form the corresponding precursors. Overall highly functionalized heterocyclic ring systems are accessible by a two-step synthesis in excellent overall yields.

Orru et al. discovered a novel multicomponent reaction for the combinatorial synthesis of 2-imidazolines (Scheme 56).[124] The three-component condensation between an amine, an aldehyde, and an α-acidic isocyanide, i.e. **298** or **299**, efficiently provides substituted 2-imidazolines, i.e. **299** and **300**, respectively, in a one-pot reaction under mild conditions and can be formally described as [2+3] cycloaddition. Thus, the combination of glycine derived isocyano esters with functionalized aliphatic, aromatic, or benzylic amines and aliphatic, (hetero)aromatic, or α,β-unsaturated aldehydes provides a range of imidazolines **302** and **303**. Except for the reaction with sterically demanding benzhydrylamine, all

Scheme 55. Sequence U-4CR/Nitrile Oxide Cyclization−Cycloaddition Yielding Fused Lactam Isoxazoles



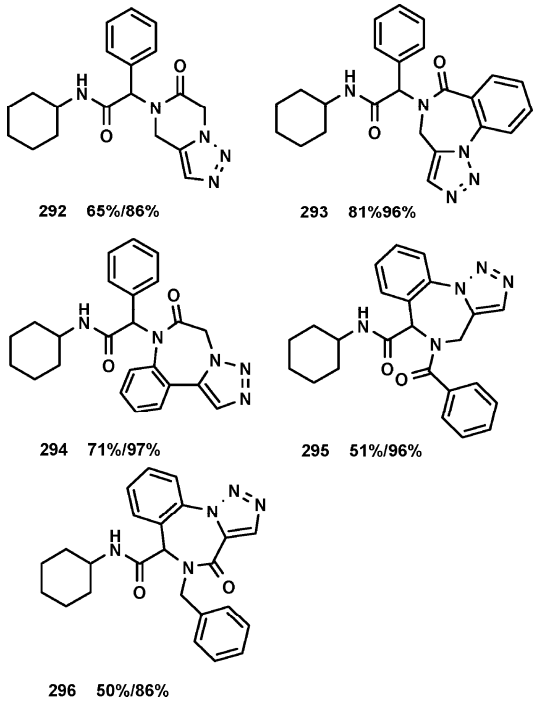
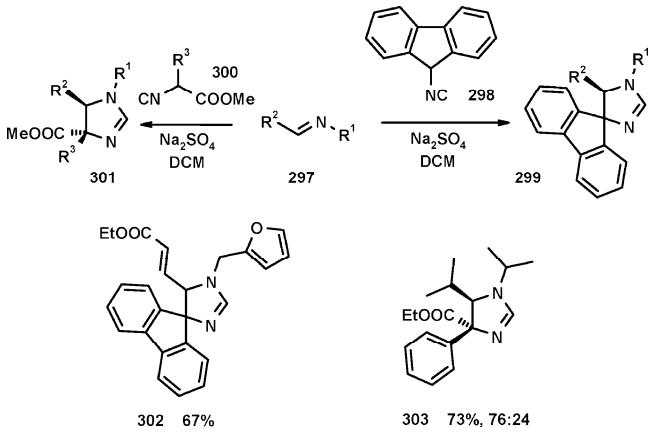


Figure 12. U-4CR/azide acetylene cycloaddition yielding diverse fused triazolo lactames. Yields of the U-MCR and cycloaddition are given.

Scheme 56. Formal [3+2] Cycloaddition of α-Acidic α-Aminoester Derived Isocyanids or Fluorene Isocyanide and Schiff Bases Yields Stereoselectively Three-fold Substituted Imidazolines

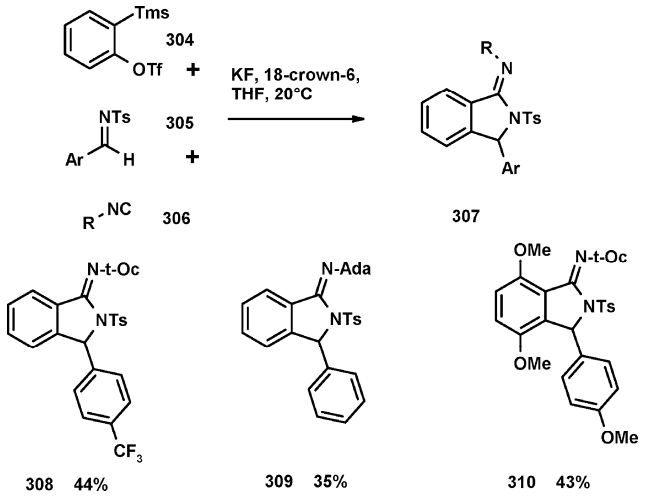


reactions went smoothly and the products were obtained in fair to good yields (47−91%). The reaction of α-amino acid derived isocyano esters is stereoselective, favoring the anti product.

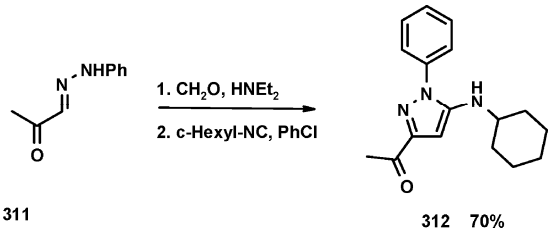
A three-component coupling reaction of arynes, isocyanides, and *N*-tosylaldimines has been developed to offer modest to high yields of diverse 2-iminoisoindolines **307** in one step (formally [2+2+1] cycloaddition), e.g. **308**−**310** (Scheme 57).[125] Benzynes were prepared from *o*-trimethylsilylphenyl triflate **304** with KF/crown ether, and reaction thereof with *N*-tosylbenzaldimine **305** and isocyanides **306** in THF at room temperature affords the three-component coupling product in moderate to good yields. The intermediacy of arynes in the coupling has been verified by the reaction of unsymmetrical arynes.

El Kaïm described the formation of aminopyrazoles by a formal 4-CR, a scaffold of major medicinal importance (Scheme 58).[126] Here they reacted hydrazone **311** in refluxing

Scheme 57. 2-Iminoisoindolines Are Widely Accessable by the MCR of Isocyanides, *N*-Tosylaldimines, and the Aryne Precursor *O*-Trimethylsilylphenyl Triflate



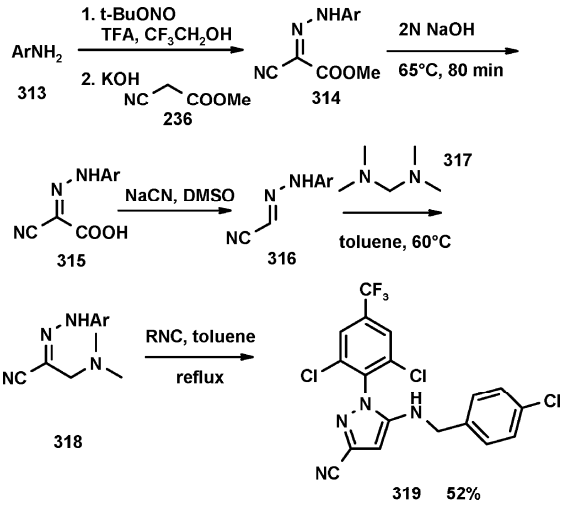
Scheme 58. A General MCR toward 3-Aminopyrazoles



diethylamine with formaldehyde to form the intermediate Mannich adduct, which was transformed smoothly with an isocyanide to give 3-aminopyrrazole **312** in 70% yield.

Analogously, the Mannich reaction of hydrazones coupled with a [4+1] cycloaddition with isocyanides has been used for the synthesis of aminopyrazole analogues **319** of the insecticide Fipronil (Scheme 59).[127] The starting cyanohydrazone was prepared with new experimental conditions for efficient diazonium coupling in fluorinated solvents followed by a new sodium cyanide catalyzed decarboxylation. The [4+1] cycloaddition of the isocyanide and the intermediate azoalkene affords the 1-aminopyrazole in good yields.

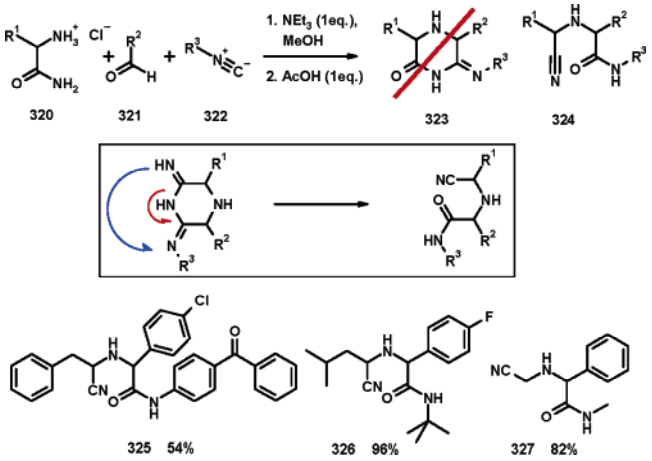
Scheme 59. Sequential Synthesis of an Insecticidal 3-Aminopyrazole by a Mannich Reaction and a Cycloaddition Involving an Isocyanide



3.15. Novel U- and P-MCR Variations

An interesting new MCR was discovered by Behnke et al. from Morphochem.[128] They reacted α-aminoamides as bifunctional educts with aldehydes and isocyanides expecting the formation of 2-keto-5-imino piperazines **323** (Scheme 60). Herein addition of the Schiff base and the primary amide

Scheme 60. α-Cyano-α′-carboxamide Amines Are Formed Instead of Keto-imino Piperazine during the Reaction of α-Aminoamides, Aldehydes, and Isocyanides

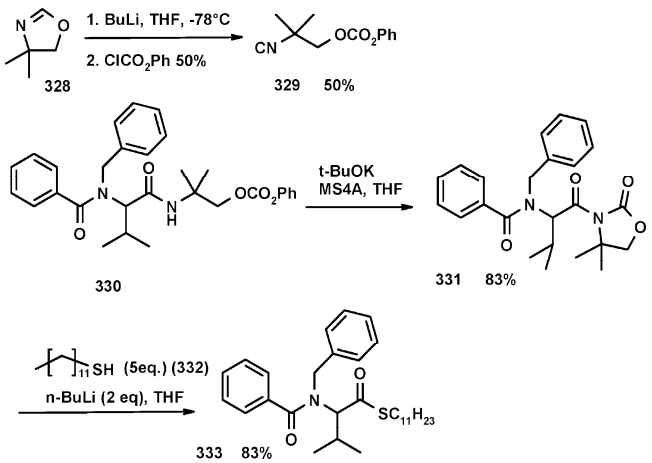


onto the isocyanide carbon should not allow for any further rearrangement. The reaction was assumed to stop at the stage of the piperazine.

Careful inspection of the NMR spectrum and the preparation of an X-ray structure analysis, however, revealed the formation of α-cyano-α′-carboxamide amines **324**, instead. By chance, the molecular weights of both scaffolds are the same. It is assumed that the harder atom O attacks the isocyanide to form the α-adduct. Then, migration of the O- and H-atoms and N−C bond cleavage forms a cyano group out of the former primary amine and an amide bond onto the former isocyanide. This Ugi reaction is worth mentioning, since the amide−O bond formed is not derived from the solvent, as mostly is the case in U-3CR-type reactions. The scaffold is of potential medicinal interest and can be varied within wide boundaries, e.g. **325**−**327**.

Ugi et al. first described isocyanocarbonic acid esters as convertible isocyanides.[129] Now Fukuyama et al. reported the U-4CR with the carbonate-type isonitrile **329** proceeding

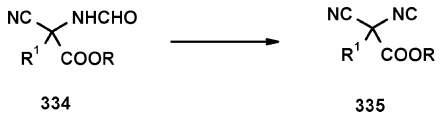
Scheme 61. Variation of Ugi's Cleavable Carbonate Isocyanide and a Base Induced Conversion Thereafter



smoothly, and subsequent base treatment of the Ugi products **330** provided the *N*-acyloxazolidinones **331** in high yield (Scheme 61).[130] The *N*-acyloxazolidinone derivatives can be reacted with several heteronucleophiles; namely, reaction of **331** with thiolate **332** gave thiol ester derivative **333** efficiently. Thus, this isocyanide provides an alternative to the so-called Armstrong "cleavable" isocyanide−cyclohexenyl isocyanide.

Neidlein et al. explored the use of 2-cyano-2-isocyanoalkanoates in the Passerini and the Ugi reactions (Scheme 62).[131] These reactions are limited to aliphatic aldehydes, to

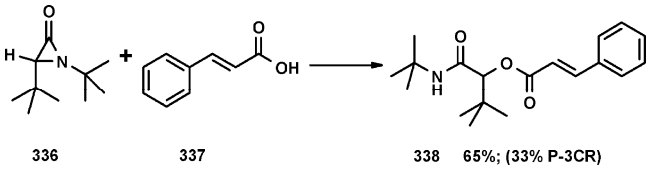
Scheme 62. 2-Cyano-2-isocyanoalkanoates Are Multifunctional Starting Materials for IMCRs



halogenated acetic acid derivatives, and, in the U-4CR, to primary nonaromatic amines. The products of the Ugi-4CC were transformed to the free acids, which decarboxylated immediately under the experimental conditions used.

α-Lactams (aziridinones) can function to replace two of the three reactants, the oxo compound and the isonitrile, in the Passerini reaction (Scheme 63).[132] α-Lactams, e.g. **336**,

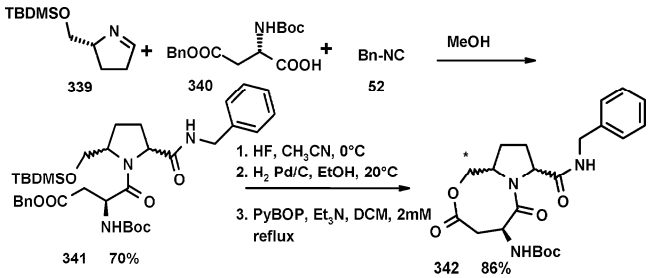
Scheme 63. A P-3CR Product Formed from an α-Lactam and a Carboxylic Acid



were reacted with mono- and dicarboxylic acids **337** to give 2-acyloxycarboxamides and bis-2-acyloxycarboxamide products **338**. The same compounds were also prepared via the Passerini reaction. It was found that acids with a negative pK_a decarbonylate α-lactams to give immonium salts. The main path of the reaction thus depends on the pK_a of the acid component, the reactivity of the α-lactam, and the reaction conditions.

Banfi et al. developed a new enantio- and diastereoselective synthesis of 2,5-disubstituted pyrrolidines through a multicomponent approach, using highly reactive pyrrolines **339** as preformed cyclic imines (Scheme 64).[133] The pyrro-

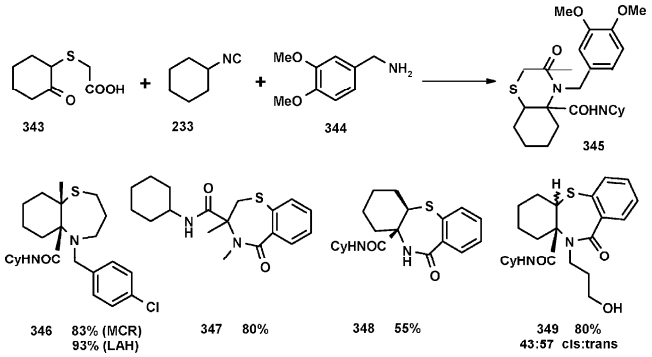
Scheme 64. Reverse Turn Inducers Synthesized by a Small Sequence Involving U-4CR and Ring Closing Esterification



lidines obtained using protected aspartic acid as acid component in the Ugi condensation have been transformed into epimeric bicyclic lactone **342**, which may find an application as an external reverse turn inducer.

Marcaccini et al. investigated the formation of 1,4-benzothioxepin orthoamides and thiomorpholins **346**, 1,4-thiazepines **347**, and 1,4-benzothiazepin-5-ones **348** via multicomponent reactions of isocyanides (Scheme 65).[134,135]

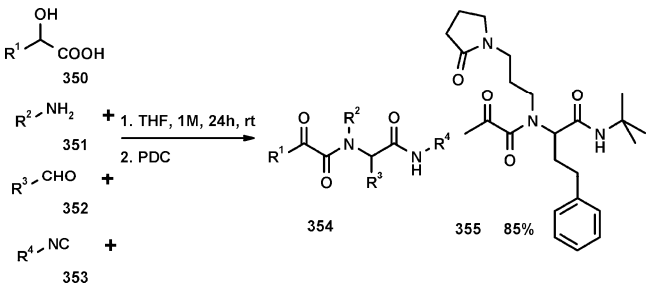
Scheme 65. Sulfur Containing Cyclic Amides Derived from the U-4CR of the Corresponding Ketoacids



They reacted the bifunctional and bireactive 5-oxo-3-thiocarboxylic acids **343** in a Ugi manner with primary amines and isocyanides to give smoothly 5-oxothiomorpholine-3-carboxamides **345** and their larger cyclic homologues in mostly good to excellent yields. The three components were refluxed in a 1 M methanol solution for 3 h. The observed de's were between 0 and 70% favoring the *cis* over the *trans* isomere. The corresponding bifunctional oxo carboxylic acids can be easily and versatily obtained from mercaptoacetic acid and α-halo ketones. The secondary amide group resulting from the isocyanide unit remains stable upon reduction with LAH/$AlCl_3$, thus selectively yielding **346**.

A common motif in many cysteine protease inhibitors is the α-ketoamide moiety, which reversibly reacts with the cysteine SH to form hemi thioketals. Co-workers form Senju Pharmaceuticals prepared a 100 member solution-phase library of α-ketoamides by Ugi reaction of hydroxycarboxylic acids and subsequent oxidation of the secondary hydroxy group (Scheme 66).[136] The two reactions were performed in

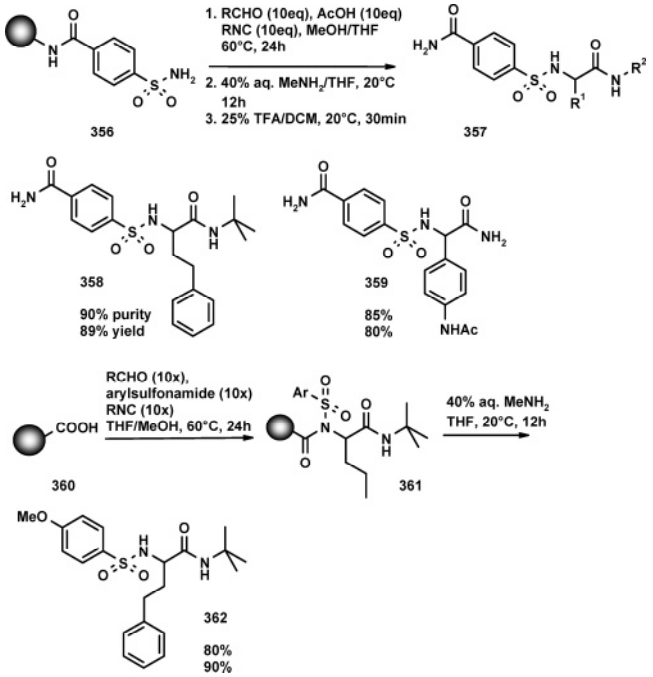
Scheme 66. α-Ketoamides by One-Pot U-4CR/Oxidation



a one-pot fashion. Due to the incompatibility of the PDC oxidation with MeOH, THF was used for both steps. The purities of the final compounds, e.g. **355**, were determined to be 80% on average. Alternatively, one could imagine the preparation of an Ugi α-ketoamide library by directly using available α-ketocarboxylic acids and carefully precondensed Schiff bases.

A method for solid-phase synthesis of α-sulfonylamino amides has been developed, which relies on a new U-4CR involving arylsulfonamides as amine input followed by removal of the acid moiety under basic conditions (Scheme 67).[137] Either polymer-bound sulfonamides **356** or carboxylic

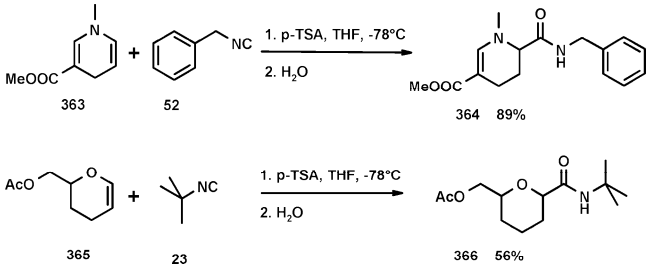
Scheme 67. α-Aminosulfonylamides by a U-4CR of Schiff Bases Formed from Arylsulfonamides



acids **360** can be used in this reaction to afford structurally diverse products **358, 359**, and **362** with good purity and in moderate to excellent yield.

The scope of the Ugi and Passerini reactions was enlarged by the recent introduction of cyclic dihydropyridines and enol ethers as substrates (Scheme 68).[138] The reaction runs in the

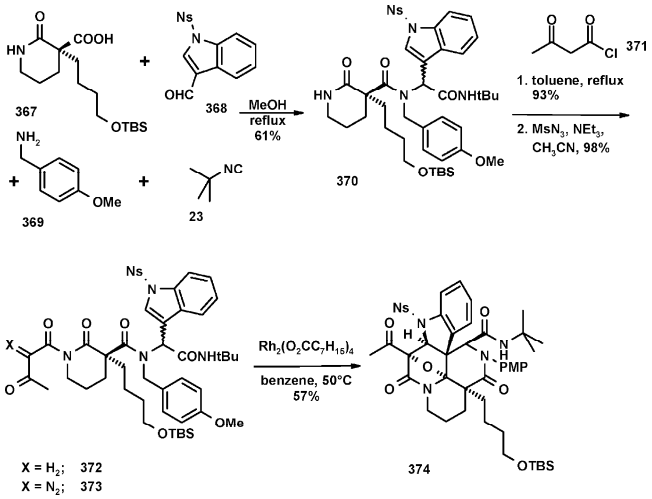
Scheme 68. Ugi and Passerini Reactions of Cyclic Enamines and Enolethers, Respectively



presence of a variety of Lewis and Brønsted acids. Under optimal conditions, THF is used as solvent and p-TSA as acid catalyst.

Schreiber et al. developed a folding pathway for the synthesis of indole alkaloid-like skeletons using first a stereocontrolled tandem reaction that can be used with elaborate substrates and second a versatile scaffold that allows for multiple modes of intramolecular reactions in a systematic fashion (Scheme 69).[139] The pathway is expected to provide an approach to diverse indole alkaloid-like compounds in only four steps, involving a pair of diversity- and complexity-generating processes, a U-4CR, and an Rh catalyzed tandem reaction. Inspired by the skeletal diversity of naturally occurring indole alkaloids and the rich potential of Rh catalyzed diazo-cyclization chemistry, they conceived a pathway entailing six modes of intramolecular reactions leading to indole alkaloid-like skeletons. In this context, an efficient reaction pathway involving three of the modes has been developed that affords densely functionalized polycyclic compounds **374** in a stereocontrolled manner.

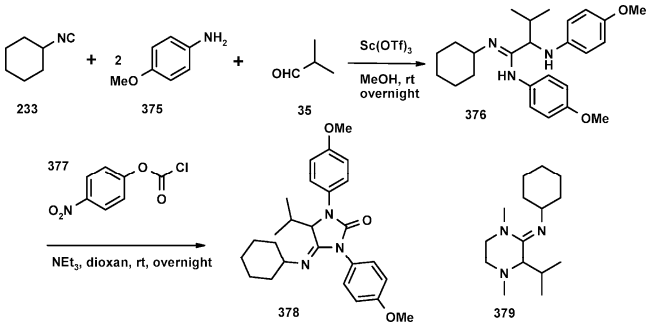
Scheme 69. Natural Product Indole Alkaloid-like Scaffolds of High Complexity Can Be Stereoselectively Generated in Only Four Steps Involving U-4CR



3.16. *N*-Acids in MCRs

α-Aminoamidines can now be reliably synthesized by a method published by chemists from Senomix.[140] This constitutes a major improvement over the work of McFarland.[141] Scanning several Lewis acids, scandium(III) triflate turned out to be the most reactive and optimal. Thus, the reaction of an isocyanide **233** and an aldehyde **35** with 2 equiv of a secondary amine or aniline **375** gives the target compounds, e.g. **376**, in good yields and purities (Scheme 70). When anilines are used, the corresponding product can

Scheme 70. α-Aminoamidines by a U-4CR Involving 2 equiv of Primary Amine



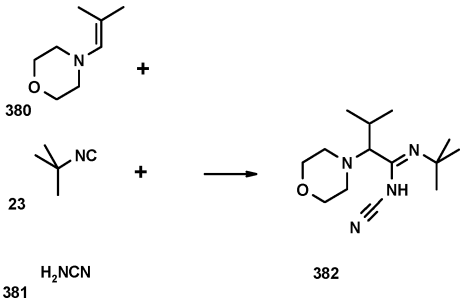
be cyclized with *p*-nitrochloroformate **377** to the corresponding hydantoine **378**. Diamines yield the corresponding imidopyrazine **379**. This chemistry is highly robust and can be easily performed with standard Tecan dispensing systems in polypropylene 96-deep well plates, by simply sealing and shaking.

α-Amino-*N*-cyanoamidines **382** have been recently reporteded to be accessible by reaction of cyanamide **381**, enamines **380**, and isocyanides **23** (Scheme 71).[142] This class of compounds is of interest as potential antidiabetic drugs. Moreover, it is the first report on the use of cyanamide as acid or nucleophilic component in Ugi-type reactions.

3.17. Fluorinated IMCRs

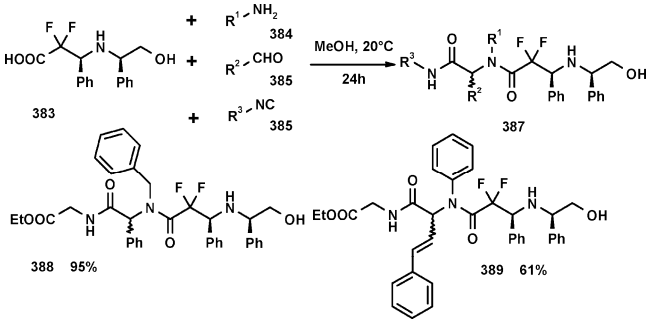
Fluoro compounds have raised a great deal of interest, e.g. as transition-state-type inhibitors, for modifications to the physiological activity of bioactive compounds or the generation of new derivatives. In particular, *gem*-difluoroamino

Scheme 71. Novel Formal U-MCR Involving Cyanamide and an Acid Component Yielding *N*-Cyano-α-amino Amidines



acids and derivatives have been the subject of an important area of research, as the CH_2/CF_2 transposition has been recognized as a valuable tool in the blockage of metabolic processes. Quirion et al. prepared a small library of difluorinated pseudopeptides, e.g. **388** and **389**, using chiral α,α-difluoro-*β*-amino acids in the Ugi reaction (Scheme 72).[143]

Scheme 72. U-MCRs Involving α,α-Difluoro-*β*-amino Acids



Mostly products were produced in excellent to good yields and the diastereomers could be easily separated by column chromatography. Moreover, the (*R*)-phenylglycinol unit could be easily removed by selective hydrogenation.

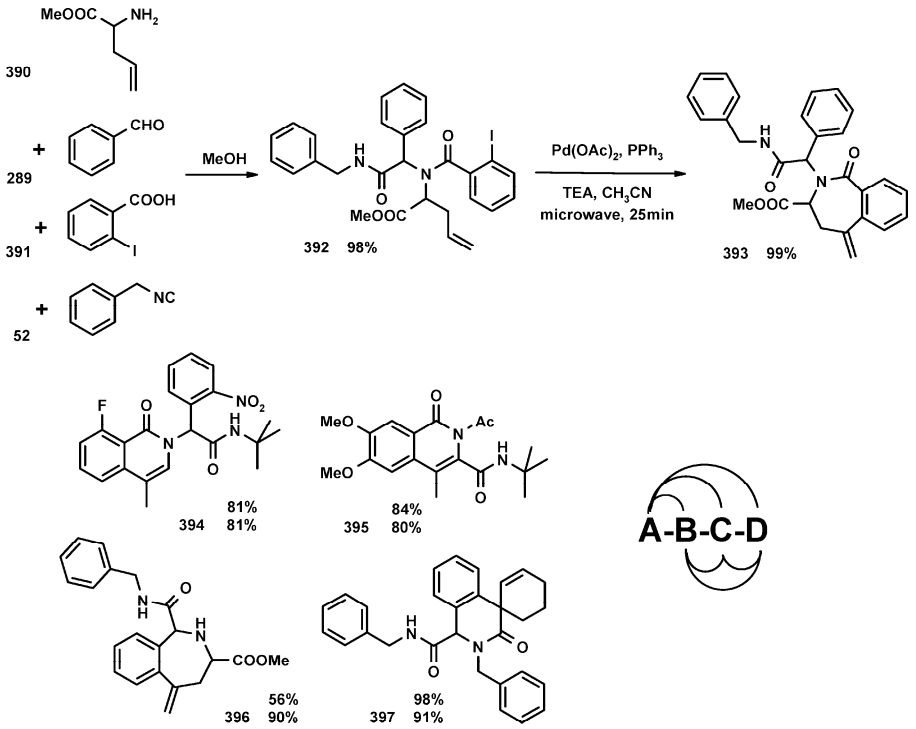
3.18. IMCR/Heck Reaction

The compatibility of halogen substituted starting materials with those containing C−C double bonds makes MCR chemistry ideal for subsequent metallorganic reactions. In principle, six different connection modes are possible, since each of the educts can contribute either a C−C double bond or an aromatic halide. Moreover, multiplying these with the plethora of backbones amenable by U- or P-MCR variants, very many scaffolds can be envisioned. Thus, the combination of Ugi and Heck reactions providing a plethora of heterocyclic ring systems **393**−**397** was investigated and published at the same time by two groups from Abbott and VivoQuest (Scheme 73).[144,145] The benzo-fused seven-membered lactam **393** can be synthesized from allylglycine methyl ester **390** as the amine component, benzyl isocyanide **52**, and *o*-iodobenzoic acid **391** in only two steps involving Ugi/Heck reaction in overall excellent yields. Moreover, this methodology has been extended to solid-phase systems. Here an allylglycine loaded Wang resin served as an amine component, yielding **393** in 44% in three steps.

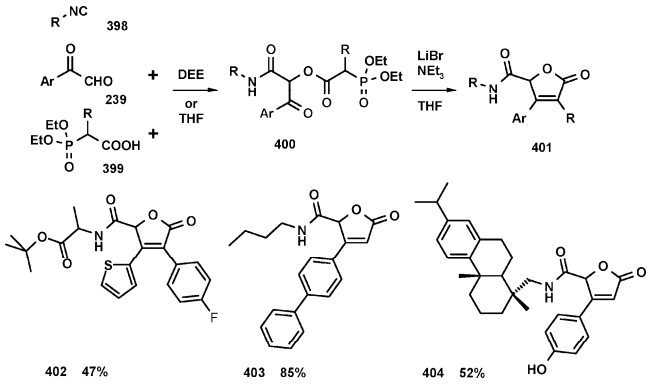
3.19. IMCR/Wittig Reaction

Morphochem scientists combined the P-3CR of arylglyoxales, isocyanides, and α-substituted phosphonoacetic acid esters with a subsequent Wittig ring closure yielding di- or trisubstituted butenolides **402**−**404** (Scheme 74).[146] Both the

Scheme 73. A Diversity of Fused Heterocyclic Scaffolds Are Available by the Combination of U-MCRs and Subsequent Heck Reactions



Scheme 74. The Combination of P-3CRs and Subsequent Wittig Reactions Affords Highly Substituted Butenolides



Passerini and the Wittig reactions are performed in the same solvent, THF. Thus, this one-pot sequence is quite useful for the synthesis of arrays of butenolides. Butenolides are of considerable interest as substantial parts of synthetic bioactive compounds as well as in many natural products.

In an extension of the Wittig approach, the same group performed Ugi reactions of arylglyoxales and β-ketoaldehydes or their salts to obtain the trisubstituted pyrrolinones and the piperidinones **405**−**408**, respectively (Figure 13).[147] The yields reported were only moderate to good, but the reaction was easy to perform and yielded mostly very pure products. This was due to a simple silica gel plug filtration with ethyl acetate and subsequent precipitation.

3.20. IMCR/RCM

Bicyclic lactams **411**, **414**, and **415**, suitable for incorporation into conformationally restricted peptide mimics, can be synthesized by using olefinic starting materials **410**, **412**, and **413** for the Ugi multicomponent reaction, setting up an olefin metathesis reaction that is easily carried out with the Grubbs catalyst (Scheme 75).[148] The influence of the different starting materials is evaluated. In addition, the utilization of chiral, nonracemic amines is described.

A straightforward entry into unsaturated nine-membered lactams of potential use as external reverse turn inducers was developed.[149] Again, it is based on a U-4CR using two unsaturated substrates, followed by highly stereoselective ring-closing metathesis (RCM). In this study, 5-hexen-2-one was used as in situ source of the imine (Scheme 76). In the course of the experiments it was found that, by simply mixing this ketone with an amine, various acids, and ethyl or *tert*-

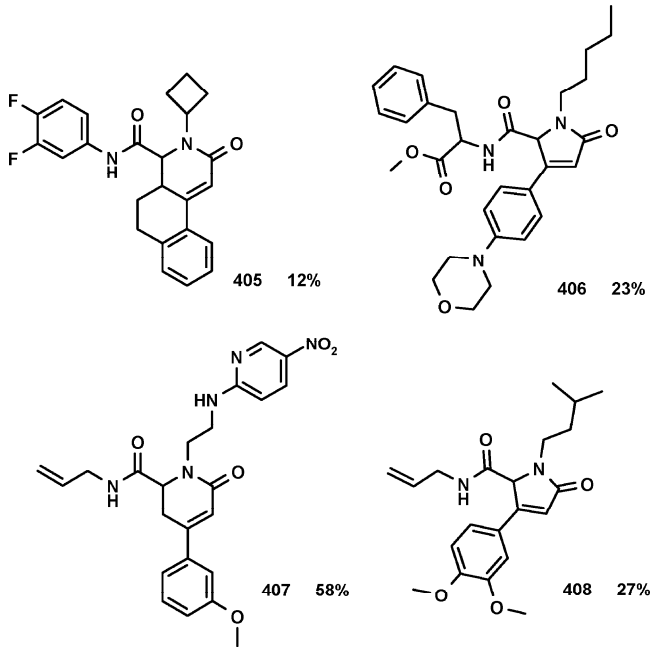
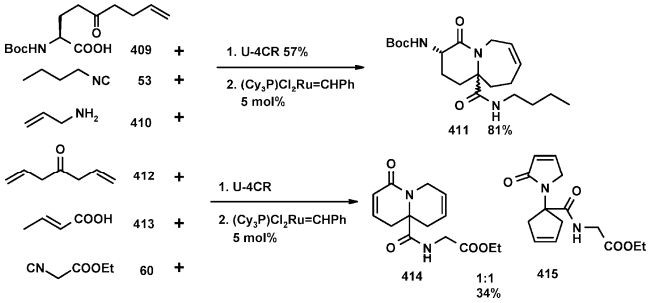
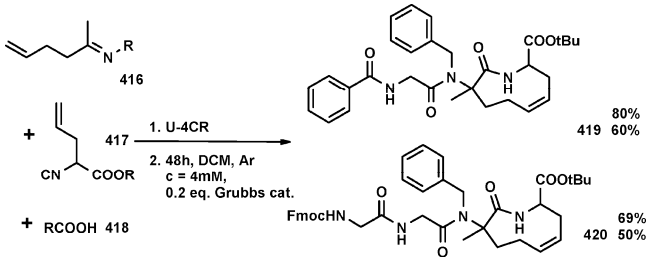


Figure 13. Reactions of arylglyoxales and β-ketoaldehydes in the sequence U-4CR/Wittig reaction yield substituted five- and six-membered lactames.

Scheme 75. A Bifunctional Diallylketone in Conjunction with a Second Alkene Containing Starting Material in the Sequence U-4CR/RCM Yields Bicyclic Lactones of Variable Ring Size



Scheme 76. Medium Sized Nine-Membered Lactams Are Accessible in Overall Good Yields from α-Amino Acid Derived Alkene Isocyanide and an Unsaturated Ketone Imine by U-4CR/RCM



butyl isocyanoacetate, the desired Ugi reaction took place, but with very long reaction times and in some cases in unsatisfactory yields. On the other hand, the analogous reactions employing preformed imines were complete in 1−2 days, affording excellent yields. The synthesis of a nine-membered secondary lactam **419** and **420** by RCM is reported for the first time.

Macrocyclic natural products as opposed to a hypothetical linear structure display a specific three-dimensional binding pattern that is responsible for their biological activity. Moreover, the conformational space of bioactive macrocyclic natural products differs substantially from that of small synthetic drugs. The latter are often small heterocyclic molecules with quite rigid ligands, thus allowing only for minute degrees of conformational freedom. The solution and target-bound conformations are identical to a first approximation.

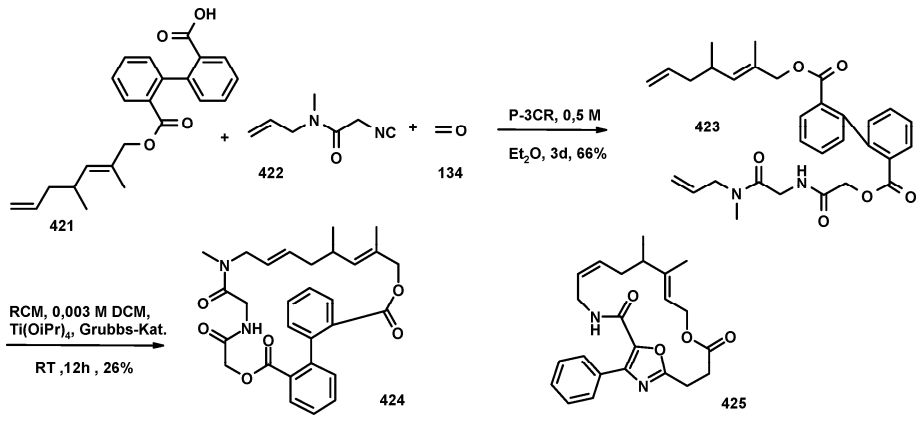
Morphochem chemists described a general strategy for the short and diverse access toward complex natural-product-like macrocycles using multicomponent reaction (MCR) chemistry, e.g. Passerini and Ugi variants and ring closing metathesis (RCM) (Scheme 77).[150] The corresponding bifunctional starting materials bearing a terminal olefin as well as a functional group of need in MCR chemistry, e.g. isocyanide **422** or carboxylic acid **421**, are easy to prepare in one step from the corresponding commercially available starting materials. Advantageously, this strategy allows fast access to a diverse conformational space of natural-product-like macrocycles and could thus be of interest in the discovery of novel bioactive agents. The novel concept MCR/RCM is exemplified by several described syntheses of the corresponding starting materials, as well as by different MCRs and their final ring closure.

3.21. U-MCR/Pt-3CR

Combining several high-diversity MCRs in a sequence provides access to especially large chemical spaces. Thus, researchers from Procter & Gamble Pharmaceuticals combined the Petasis-3CR (Pt-3CR) with the U-4CR in a one-pot manner (PtU-5CR) (Scheme 78). The reaction sequence was performed using solid-phase chemistry, either on Rink amine resin or isocyanide based resin. In each case the products, e.g. **434**, obtained after cleavage from the resin were purified by column chromatography and the yields were moderate, ranging from 22 to 50%. The method is practical, and as described in the general procedures, the intermediate Petasis amino acid can be used without purification. Given the large number of commercially available secondary amines, arylboronic acids, aldehydes, ketones, primary amines, and isocyanides, virtually billions of compounds are accessible via this method.

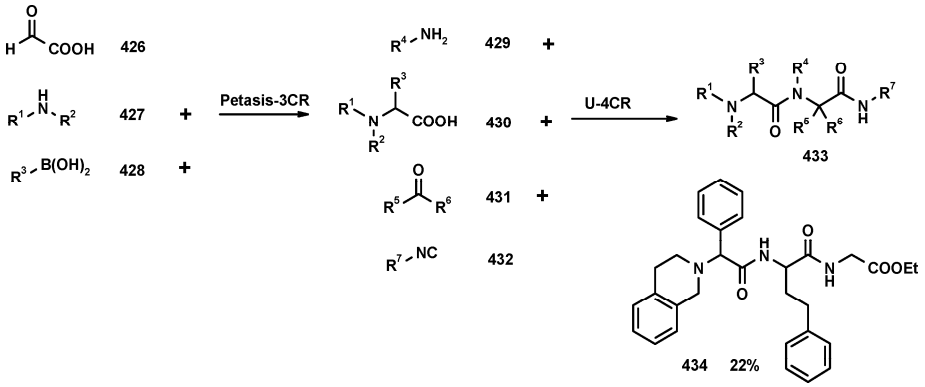
In another variation, the synthetic utility of a PtU-5CR has been employed to efficiently prepare two- to four-dimensional libraries of aza-β-lactams.[151] Pt-3CR of glyoxylic acid, *N*-Boc-protected hydrazines, and boronic acid yields after deprotection the intermediate α-hydrazino acid (Scheme 79). This can be converted to aza-β-lactams using isocyanides and aldehydes in analogy to Ugi's β-lactam synthesis. It is noteworthy that the reactions proceed from the Boc-protected hydrazine, glyoxylic acid, aryl boronic acid, aldehyde, and isocyanide all in one pot without purification until the final products **437** and **438** are isolated. Although the yields are only moderate, the methods provide rapid entry into this interesting structural class of molecules.

Scheme 77. The General Strategy P-3CR/RCM Employed with Two Bifunctional Terminal Alkene Containing Starting Materials Affords Natural Product-like 22-Membered Macrocycle 424[a]

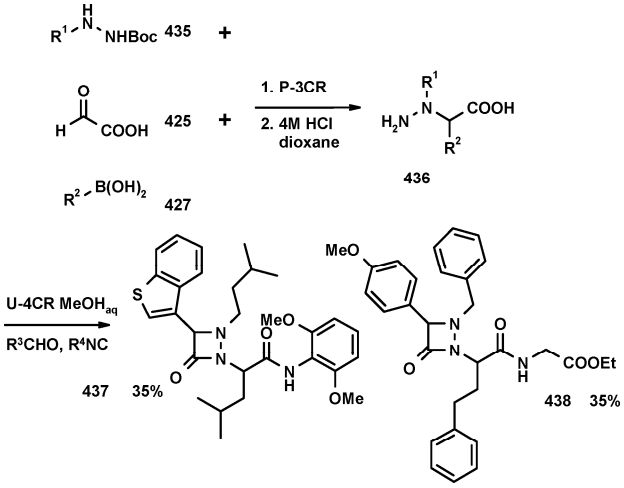


[a] In the latter case, a P-3CR and a subsequent oxazole ring closure, followed by a RCM, affords 17-membered **425**.

Scheme 78. A Pt-3CR Yields Substituted α-Amino Acids, Which Form the Educt for the Subsequent U-4CR—Overall a Union of MCRs, PtU-6CR, Involving Six Classes of Starting Materials



Scheme 79. Pt-3CR of Monosubstituted, Boc-Protected Hydrazines Yields α-Hydrozinoacids, and after Boc-Deprotection, a Subsequent U-3CR Assembles Highly Substituted Aza-*β*-lactams



3.22. Ugi/Passerini and Ugi/Ugi

Unions of MCRs, i.e., combination of MCRs, theoretically provide the largest chemical space in this area. They were first introduced in 1993 by Dömling and Ugi.[152] Recently, Ugi published repetitive Ugi reactions as an example of combining IMCRs in one pot (Figure 14).[153,154] Thus, **439** is formed by a U-4CR with Boc-protected glycin, subsequent

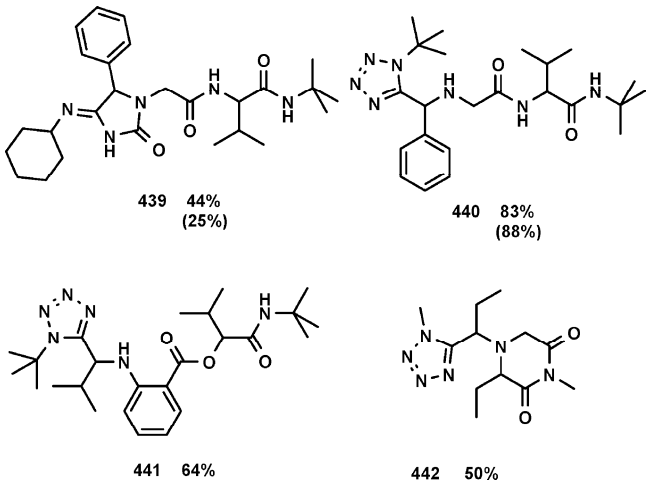


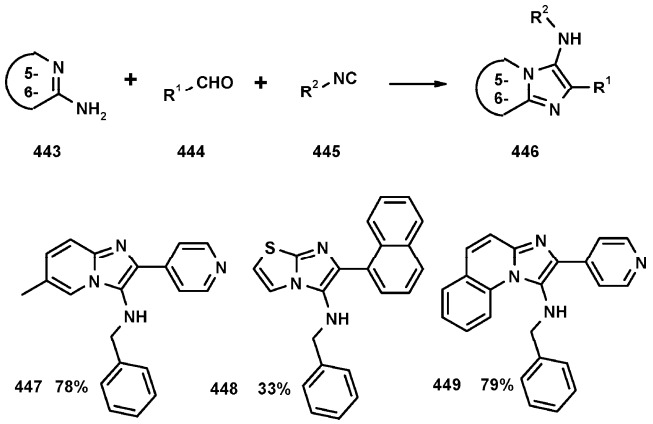
Figure 14. Unions of U- and P-MCRs yielding diverse heterocyclic scaffolds.

Boc-deprotection, and a U-4CR with cyanate yielding substituted hydantoines, whereas **440** is formed by a secondary tetrazole U-4CR. **441** proceeds via a P-3CR combined with a U-4CR using bifunctional anthranilic acid. Finally, glycine reacts as a bifunctional educt in the presence of acidic Dowex resin in a double U-4CR, involving the tetrazole variant and a U-5C-4CR and a subsequent condensation—cyclization to form a molecule, **442**, containing a tetrazole and a 1,6-diketopiperazine moiety.

3.23. Groebcke Reaction

Substantial effort has been put into the reaction of aromatic heterocyclic 2-aminoazines, aldehydes, and isocyanides in the presence of a variety of Lewis acids or Brønsted acids, yielding fused 3-aminoimidazoles, after the first description of the Groebcke reaction (Scheme 80).[155] The industrial

Scheme 80. Fused 3-Aminoimidazoles Are Broadly Accessible by U-3CR of Isocyanides, Aldehydes, and Five- or Six-Membered Imidine Aromatics[a]



[a] The reaction generally occurs under Lewis or Brønsted acid catalysis.

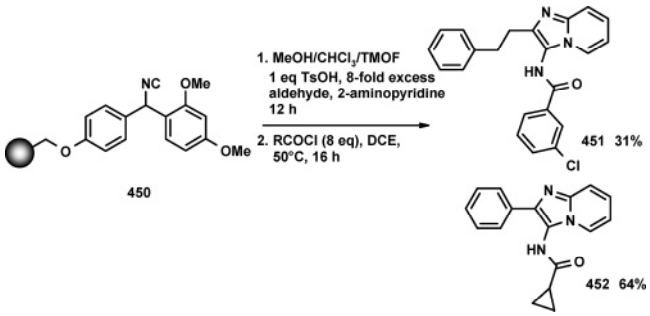
relevance of this powerful 3-CR transformation is significant because imidazo[1,2-*a*]heterocycles of this nature have received a great deal of attention in drug discovery. Imidazopyridines, imdazopyrazines, and imidazopyrimidines, in particular, have been the focus of pharmaceutical investigations across a broad range of therapeutic areas, and these heterocycles are represented by the launched drugs zolimidine, zolpidem, and alpidem.

A variety of fused 3-aminoimidazoles have been synthesized by a microwave assisted U-3CR catalyzed by scandium triflate in methanol as solvent (Scheme 80).[156] Preformation of the imine intermediate was found to be unnecessary, and

immediate addition of the isocyanide followed by microwave irradiation in a sealed 10 mL vial (200 W, 160 °C, 10 min) gave the best results. It is noteworthy that in the absence of scandium triflate only a 25% conversion was achieved after 2 h in the microwave at 160 °C. Yields of 33−93%, e.g. of **447**−**449**, have been achieved after just 10 min of microwave irradiation using a simple one-stage procedure. The methodology described is suitable for the rapid and efficient synthesis of a range of fused heterocycles of pharmacological interest. Varma et al. earlier reported a solvent free microwave procedure of this U-3CR.[157]

Chen et al. from Procter & Gamble Pharmaceuticals reported a traceless synthesis of imidazo[1,2-*a*]pyridines on solid support (Scheme 81).[158] Thus, Rink-type isocyano resin

Scheme 81. *N*-Acylated Imidazo[1,2-*a*]pyridines Synthesized by a Rink Amide Derived Solid-Phase Isocyanide

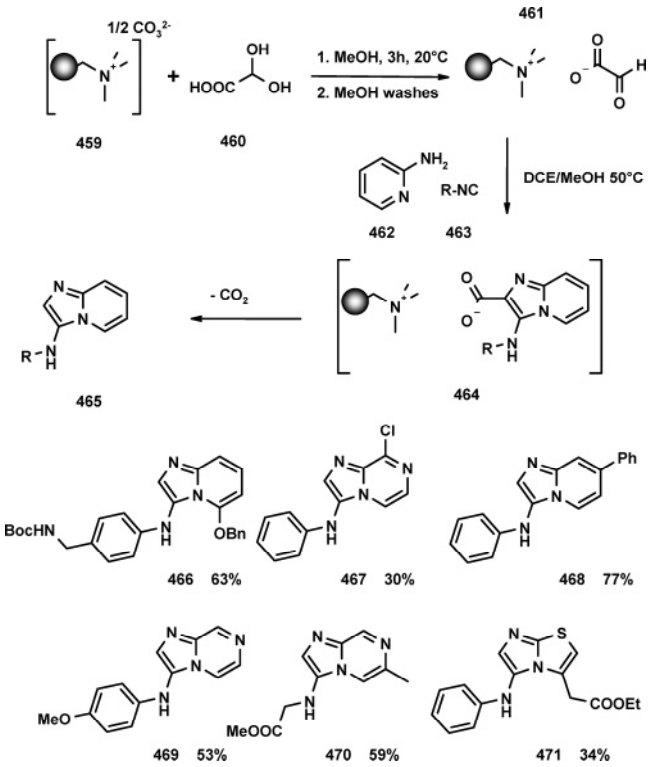


450 was prepared by formylation with HCO_2H/diisopropylcarbodiimide followed by $POCl_3$/diisopropylethylamine dehydration. This polymer-supported isonitrile was then employed in the multicomponent synthesis of imidazo[1,2-*a*]pyridines. The resin-bound imidazo[1,2-*a*]pyridine, e.g. **451** and **452**, was acylated and spontaneously released by acyl chloride treatment in dichloroethane.

Multicomponent reactions between aldehydes, isonitriles, and 2-aminoazines do not always give the expected products. Bradley et al. reevaluated the Groebcke reaction imidazo-[1,2-*a*]pyridine synthesis and found in some cases the concomitant formation of the regioisomeric 2- and 3-aminoimidazo[1,2-a]pyrimidines, e.g. **457** and **458**.[159] Depending on the substrates and the used catalyst, different ratios of the two regioisomers are formed (Scheme 82).

Although the scope of this 3-CR spanning all three substrates is quite impressive, there is, however, no literature precedence for the successful inclusion of formaldehyde as the aldehyde component, thus enabling the synthesis of *2-unsubstituted*-3-aminoimidazoheterocycles. In fact, examples of successful preparations of 2-unsubstituted-3-aminoimidazoheterocycles are scarce, and those reported are low-yielding. Glyoxylic acid **460** has been described to be an efficient formaldehyde equivalent in the Groebcke reaction of aminoazines, aldehydes, and isonitriles (Scheme 83).[160]

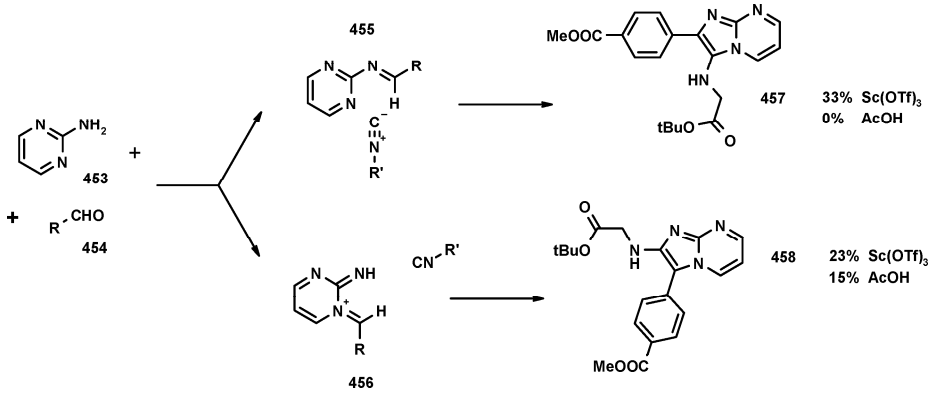
Scheme 83. A Resin Capture Methodology Involving Resin Bound Glyoxal Affords Bicyclic Imidazoles, and Glyoxylic Acid Reacts under Decarboxylation, Replacing Formaldehyde



Glyoxylic acid, either in solution or immobilized on macroporous polystyrene carbonate (MP-glyoxylate), participates in an uncatalyzed 3-CR with 2-aminoazines and isonitriles to afford novel 2-unsubstituted-3-aminoimidazoheterocycles, e.g. **466**−**471**. MP-glyoxylate serves as a particularly efficient and experimentally convenient formaldehyde equivalent and readily liberates products through decarboxylation/self-release from the resin.

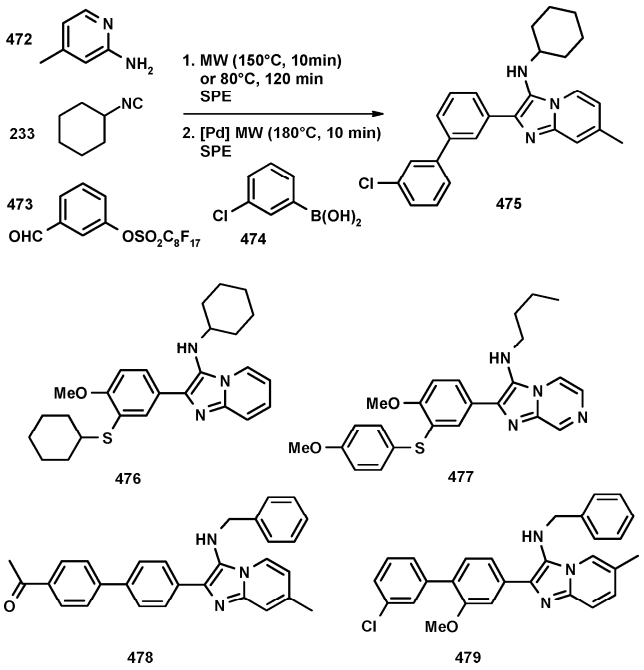
Zhang et al. from Fluorous Technologies employed a combination of microwave and fluorous technologies to prepare libraries of imidazopyridines/pyrazines in the liquid phase.[161] Groebcke U-3CR of perfluorooctanesulfonyl-tagged

Scheme 82. Concomitant Formation of Two Regioisomers during the Reaction of 2-Aminopyrimidine with Aldehydes and Isocyanides



benzaldehyde **473** with 2-aminopyridines or 2-aminopyrazines and isocyanides is followed by Pd catalyzed cross-coupling to form biphenyls or aryl sulfides. The intermediate Groebcke products are purified by fluorous solid-phase extraction (Scheme 84). Yields of 60 MCRs ranged between

Scheme 84. Suzuki Coupling and the Groebcke U-3CR Variation Yield Highly and Divers Substituted Libraries of 3-Amidazopyridine Biphenyls 3-Aminopyridine Thiophenylether[a]



[a] The reactions were purified by fluorous-phase solid-phase extraction.

0 and 100% (45% on average) whereas yields of the subsequent Suzuki reaction were between 8 and 58% (28% on average). Certainly these variable yields reflect also the application of one intermediate reaction condition, which is far from optimal for each individual reaction.

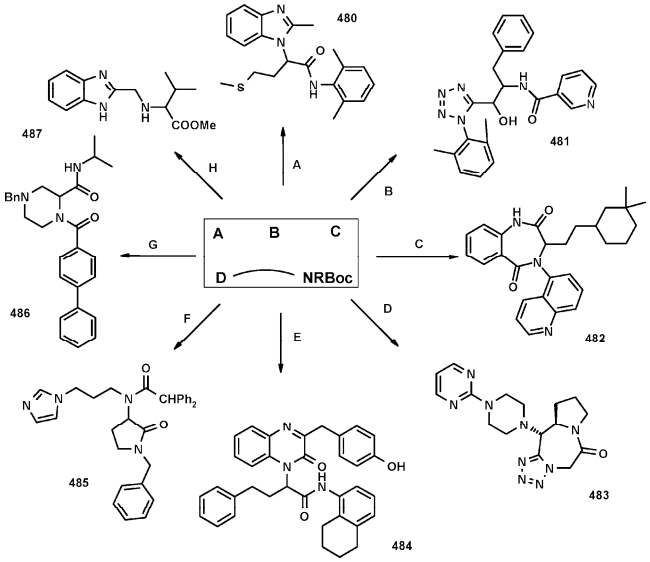
3.24. Ugi Reaction/Deprotection/Condensation (UDC)

The UDC concept was developed by Hulme and co-workers. It involves a Boc-protected bifunctional starting material in a U- or P-type MCR, followed by a Boc-deprotection reaction and a subsequent, mostly spontaneous cyclization. Thus, several different scaffolds of medical relevance are easily accessible, such as benzodiazepines, benzimidazoles, (di)ketopiperazines, morpholines, quinazolines, or γ-lactams (**480**−**487**; Scheme 85).

By using UDC, solution- and solid-phase syntheses of 1,2-disubstituted benzimidazoles were described (Scheme 86).[162,163] The novel solution-phase synthesis of an array of biologically relevant benzimidazoles in a simple two-step procedure is revealed. Transformations are carried out in excellent yield by condensation of mono-Boc-protected *o*-phenylene diamine and supported Ugi reagents. Subsequent acid treatment and evaporation affords benzimidazoles in good to excellent yield. The described protocol represents a highly attractive solution-phase procedure for the rapid generation of benzimidazole libraries. Typical representatives out of a library are **495**−**497**.

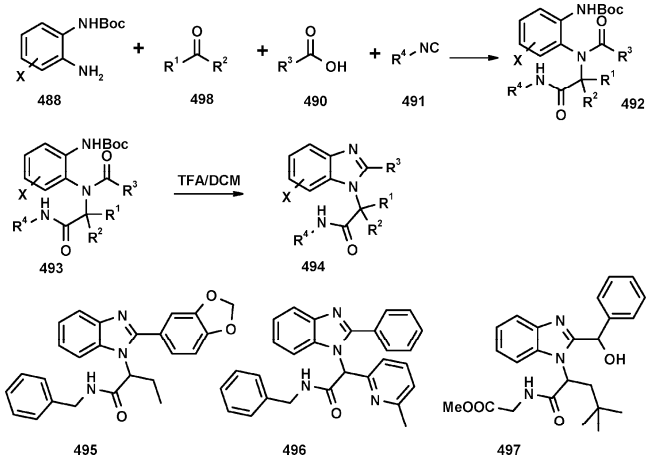
The efficiency of an Ugi reation/deprotection/improved cyclization strategy for construction of quinoxalinones and

Scheme 85. Product Scaffold Variability of UDC Chemistry[a]



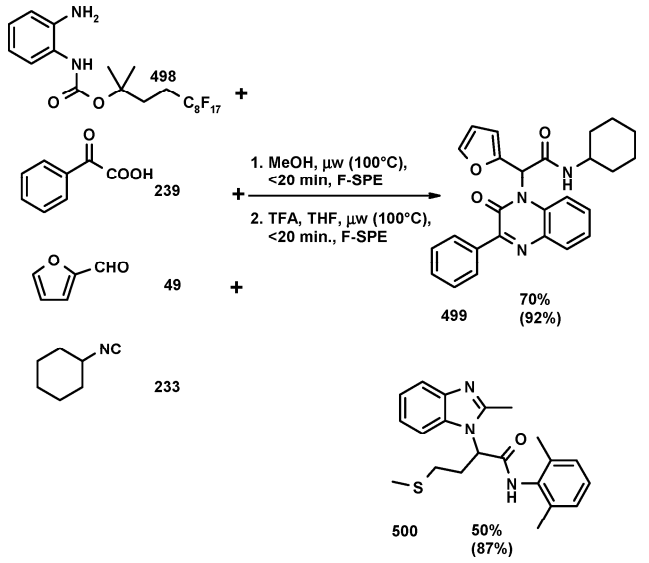
[a] A: (1) mono-Boc-protected 1,2-phenylene diamine, aldehyde, isocyanide, carboxylic acid; (2) TFA, DCM; (3) NEt_3. B: (1) Boc-protected α-aminoaldehyde, HN_3, isocyanide; (2) TFA, DCM; (3) NEt_3. C: (1) Boc-protected anthranilic acid, cyclohexenyl isocyanide, aldehyde, amine; (2) TFA, DCM; (3) NEt_3. D: (1) Boc-protected α-aminoaldehyde, HN_3, isocyanoacetic acid methyl ester; (2) TFA, DCM; (3) NEt_3. E: (1) mono-Boc-protected 1,2-phenylene diamine, isocyanide, aldehyde, α-ketoacid; (2) TFA, DCM. F: (1) *N*-Boc-propionaldehyde, cyclohexenyl isocyanide, amine, carboxylic acid; (2) TFA, DCM. G: (1) Boc-protected ethylenediamine, isocyanide, chloroacetaldehyde, carboxylic acid; (2) TFA, DCM; (3) NEt_3. H: mono-Boc-protected 1,2-phenylene diamine derived isocyanide, aldehyde, glycine; (2) TFA, DCM.

Scheme 86. Novel Synthesis of 1,2-Disubstituted Benzimidazoles Involving UDC



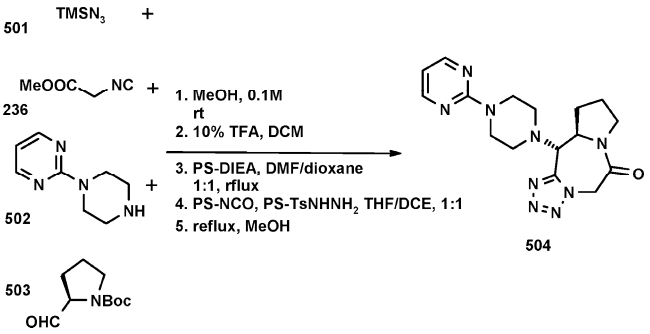
benzimidazoles has been improved through the incorporation of microwave and fluorous technologies.[164] In the synthesis of substituted quinoxalinones **499** and benzimidazoles **500**, a fluorous, Boc-protected phenylendiamine **498** is employed for the Ugi reactions (Scheme 87). Both the Ugi and the postcondensation reactions proceed rapidly under microwave irradiation, and the reaction mixtures are purifed by solid-phase extraction (SPE) over FluoroFlash cartridges. Compared to the original Ugi reaction/deprotection/cyclization procedures, which take 1−2 days, the flourous/microwave approach has more favorable reaction and purification conditions: less than 20 min for each reaction and no need for the double scavenging step. This general strategy can be applied to other MCRs and postcondensation reactions of the UDC type.

Scheme 87. Fluorous Technology Quinoxalinone and Benzimidazole UDC Synthesis



Highly substituted and annealed tetrazoloazepines can be synthesized in large libraries by UDC chemistry (Scheme 88).[165] Herein TMS azid **501**, a safe substitute for HN_3

Scheme 88. Three-fold Substituted Fused Tetrazoloazepines by the UDC Methodology and Subsequent Resin Scavenger Purification



solutions, reacts with Boc-protected amino acid aldehydes, primary or secondary amines, and α-amino acid methyl ester derived isocyanides, forming the expected U-4CR product. Upon acidification, the Boc group is cleaved off and the liberated amine can cyclize to give the bicyclic target compound. The Amgen group described a detailed sequence of a resin scavenging procedure to purify the intermediates and afford the cyclization. Libraries with three points of variation were synthesized in the 10.000 range. The purity investigation of a representative 80 compound library showed that more than 75% of the compounds were between 75 and 100% pure.

Novel substituted quinoxalines were described by Hulme et al. from Amgen using again the UDC strategy (Scheme 89).[166] Mono-Boc-protected phenylene diamines **507**, α-ketocarboxylic acids **505**, isocyanides **508**, and aldehydes **506** react in a classical U-4CR yielding **509**. Excess aldehyde was used to improve the Ugi yields. Boc-deprotection and subsequent cyclization yields disubstituted quinoxalines, e.g. **510**−**513**. Again using a clever sequence of resin scavenging, the yields and purities of representative libraries were good to excellent.

A Rhône-Poulence Rorer group described novel applications of convertible isonitriles for the solid-phase synthesis of mono- and bicyclic γ-lactams via a UDC strategy (Scheme 90).[167] A solid-phase bound convertible cyclohexenyl isocyanide was employed. Use of tethered *N*-Boc aldehydes in the U-4CR, followed by Boc removal and base treatment (a "3-step, 1-pot procedure"), affords γ-lactams, e.g. **516**−**519**, in good yield. The UDC strategy, coupled with a convertible isonitrile, is now feasible from all three substitution sites of the Ugi product.

The β-turn is a common feature in biologically active peptides and is defined as any tetrapeptide sequence with a 10-membered intramolecularly H-bonded ring, in which the CR(i) to CR(i + 3) distance varies from 4 to 7 Å. Model conformers have been developed for linear, short peptides. In natural proteins, turn fragments can adopt an even larger variety of conformations due to stabilization provided by the remaining portion of the molecule. Golebiowski et al. from Procter & Gamble Pharmaceuticals reported on the array synthesis of β-turn mimetics **520** by using Ugi reactions.[168] The U-4CR of R-*N*-Boc-diaminopropionic acid resin ester (an amine input) **521**, optically active *R*-bromoacid **524**, aldehyde **525**, and isocyanide **522** is the key step in the proposed synthetic protocol (Scheme 91).[169] Subsequent Boc-deprotection, *N*-Boc amino acid coupling, and internal nucleophilic substitution reaction affords bicyclic pyridopiperazines **526**−**527**, closely resembling β-turns. Application of cyclitive cleavage as the final step led to the desired products in high purity.

Root-mean-square deviations were calculated for the compounds and ideal β-turns, suggesting that the synthesized structures are likely to adopt a type I β-turn.

3.25. Benzodiazepines

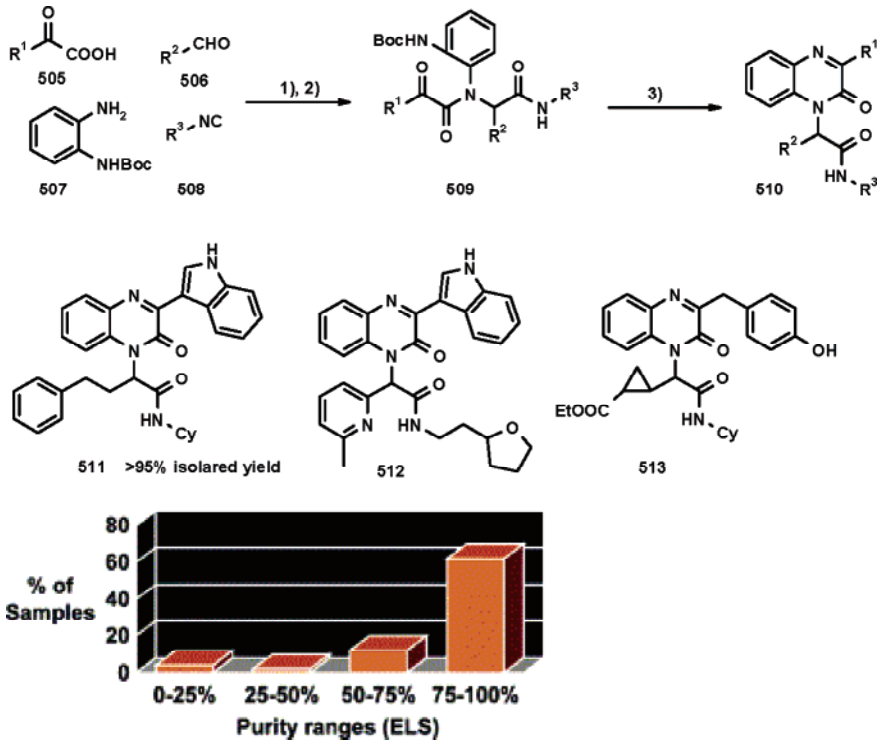
Benzodiazepines are archetypical scaffolds in medicinal chemistry. Because of their regular appearance in diverse screening assays, they have been coined a privileged structure. Important classes of drugs, e.g. the tranquilizer valium, are based on the benzodiazepine scaffold. Thus, there is a plethora of synthetic approaches toward this scaffold known in the literature. Among them, several approaches are via U-MCRs. Recently this MCR arsenal of benzodiazepine syntheses has been completed by several alternatives, shown in Scheme 92.

Marcaccini et al. described a new benzodiazepine synthesis involving a Ugi reaction of *o*-nitrobenzoic acids, α-amino acid esters, isocyanides, and aldehydes or ketones, followed by a reduction of the nitro group and a spontaneous cyclization to 1,4-benzodiazepine-2,5-diones (Scheme 93).[170] This reaction closely resembles the method using *N*-protected anthranilic acid, but it offers the advantage that many more *o*-nitrobenzoic acids are commercially available. Several compounds, for example **537**, were obtained as only one diastereomer.

Benzodiazepines have also been synthesized recently by a U-4CR followed by a Cu mediated *N*-arylation (Goldberg reaction) (Scheme 94).[171] Reacting *o*-iodobenzoic acids with the other Ugi components afford the expected Ugi products, which upon Cu(I) mediated catalysis give the corresponding 1,4-benzodiazepine-2,5-diones. The Ugi reaction as well as the Goldmann *N*-arylation gives generally good to excellent yields. Typical examples are **539**−**541**, showing the versatility of this reaction.

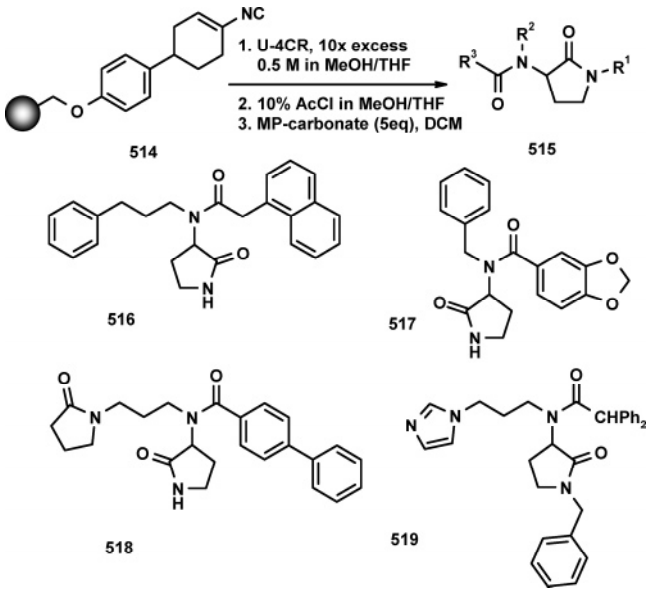
Interestingly, only a small number of derivatives of 4,5-dihydro-*3H*-1,4-benzodiazepin-5-one bearing aryl groups in the 2-position have been reported so far. These benzodi-

Scheme 89. UDC for the Synthesis of Substituted Quinoxalines[a] and (Bottom) Purity Distribution for an Array of 80 Quinoxalinones (Reprinted with permission from ref 166. Copyright 2002 Elsevier.)



[a] (1) Aldehyde, glyoxylic acid, isonitrile, mono-Boc-protected 1,2-phenylene diamine, 20 °C, 36 h; (2) PS-tosylhydrazine (3 equiv), THF/CH_2Cl_2, 1:1, 24 h; (3) 10% TFA/CH_2Cl_2, 18 h.

Scheme 90. γ-Lactams by UDC



azepines, e.g. **547** and **548**, are now broadly available form isocyanides **545**, oxo components **544**, *o*-nitrobenzoic acids **542**, and aminoacetophenone hydrochloride **543**, by a sequence U-4CR and iron mediated reduction and cyclization (Scheme 95).[172]

Kennedy et al. from Array Biopharmaceuticals prepared arrays of benzodiazepines on solid phase using a variant of a convertible isocyanide (Scheme 96).[173] A novel resin-bound carbonate convertible isonitrile **197** (CCI resin) as an extension of a class of convertible isonitriles reported by Ugi et al. was prepared on a 200 g scale with a loading of 0.84mol/g. Base activation of the resin bound multicomponent reaction product cleaves the product to form an *N*-acyloxazolidone intermediate that can be further elaborated to form benzodiazepine. A 1,4-benzodiazepine-2,5-dione plate where 80 compounds were made in parallel format had an average mass recovery of 95%. Sample structures are **553**−**555**.

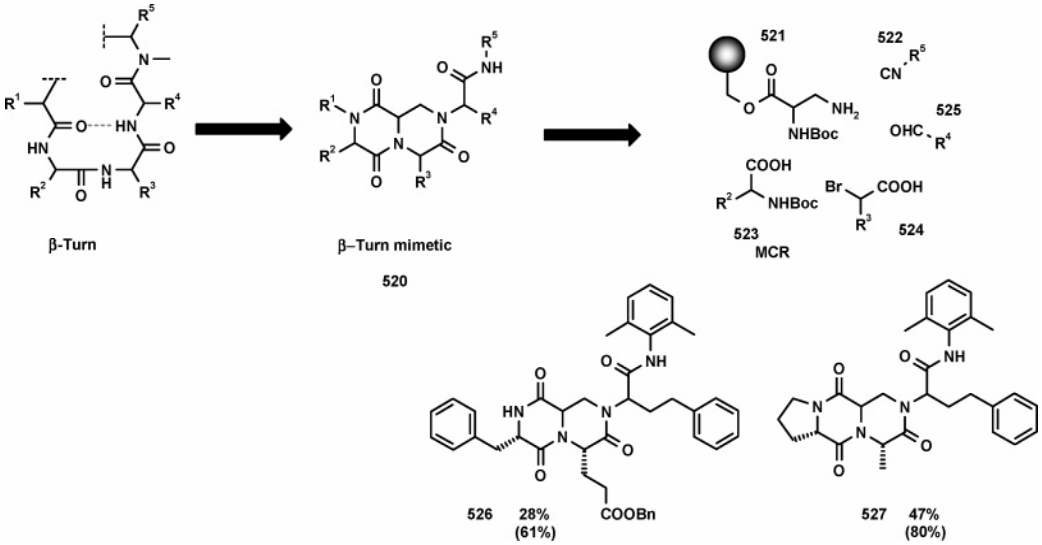
A solution-phase synthesis of arrays of biologically relevant indazolinones **559**, benzazepines **557**, and benzoxazepines **558**, utilizing multicomponent condensation (MCC)/S_NAr methodology is reported (Scheme 97).[174] Reaction of commercially available 2-fluoro-5-nitrobenzoic acid **556** with an aldehyde, isonitrile, and a primary amine tethered to a Boc-protected internal amino or hydroxyl nucleophile affords the Ugi product in good yield. Subsequent acid treatment followed by proton scavenging promotes cyclization of internal amino nucleophiles to a variety of ring sizes. Base treatment alone is sufficient to generate benzoxazepines. This chemistry was used for the synthesis of 10K libraries of diverse scaffolds. Sample structures are **560**−**562**.

Overall there are now 10 complementary MCR routes toward benzodiazepines described in the literature.

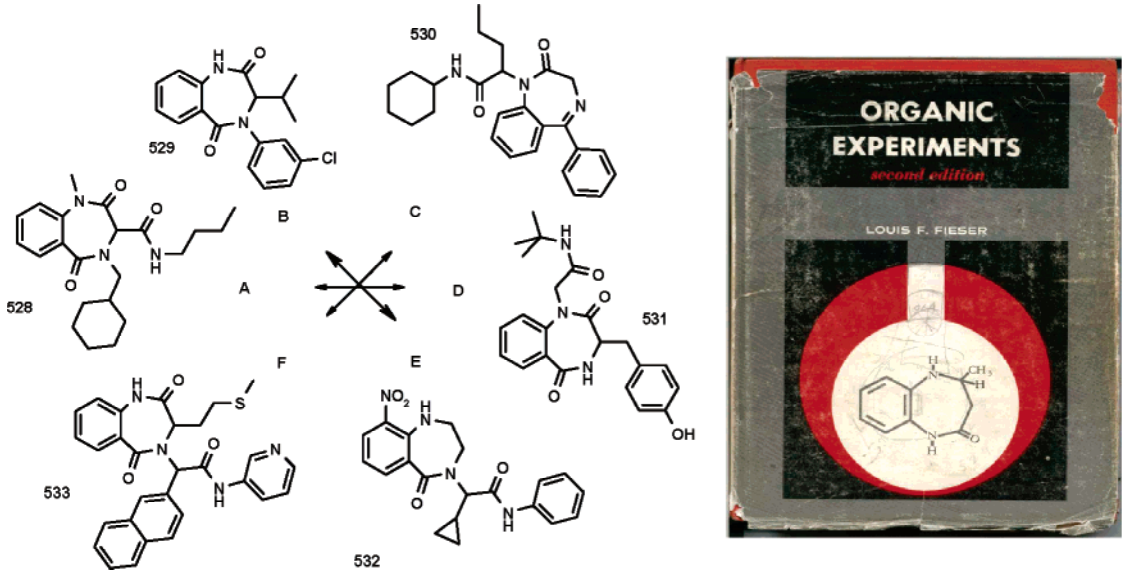
3.26. IMCR/Nucleophilic Substitution Reaction

Chemists from Priaton introduced a novel isocyanide, bearing an internal nucleofuge **565** (Scheme 98).[175] They synthesized the aminoethanol **563** derived 2-isocyanoethyltosylate **565**, which readily undergoes intramolecular nucleophilic substitution reactions. During the classical tetrazol U-4CR, when using a primary amine, a secondary amine appears in the product. In conjunction with the usage of the new isocyanide, a ring closing reaction toward tetrazolopiperazines **567** takes place. Since no extra base is added to the

Scheme 91. *β*-Turn Mimetics as Medicinally Important Scaffolds and Their Preparation via Solid-Phase UDC

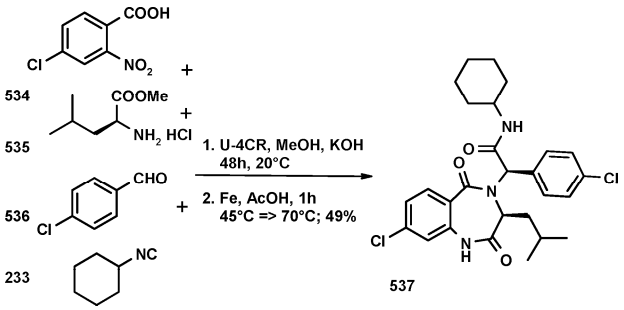


Scheme 92. (Left) Diverse MCR Synthesis of the Benzodiazepine Backbone[a] and (Right) the Cover of Fieser's Famous Textbook, Depicting an Archaetypical Benzodiazepine (Copyright 1968 D.C. Heath and Company. Used by permission of Houghton Mifflin Company.)



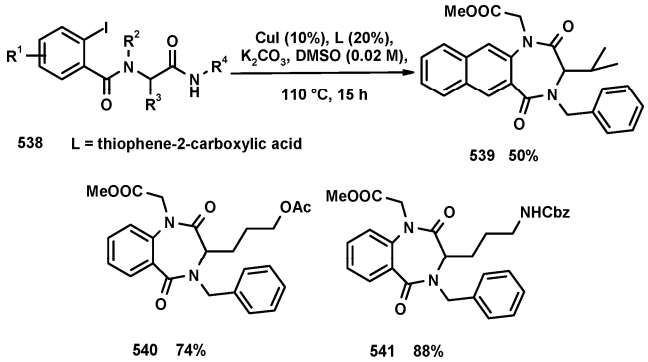
[a] A: (1) Boc-protected anthranilic acid, RNH_2, glyoxal ethyl ester, RNC; (2) TFA/DCM then NEt_3. B: (1) Boc-protected anthranilic acid, RNH_2, aldehyde, cylohexenyl isocyanide; (2) TFA/DCM. C: (1) *o*-aminobenzophenones, α-azido acids, RCHO, RNC; (2) phosphine resin, reflux. D: (1) anthranilic acid ester, *N*-Boc-protected α-amino acid, RNC, RCHO; (2) TFA/DCM then NEt_3. E: (1) 2-fluoro-3-nitrobenzoic acid; monoprotected ethylenediamine, RCHO, RNC; (2) TFA/DCM then DBU. F: (1) Boc-protected anthranilic acid, α-amino acid ester, RNC, RCHO; (2) TFA/DCM then NEt_3

Scheme 93. Diastereoselective Benzodiazepine Synthesis Involving a U-4CR, Nitro Group Reduction, and Spontaneous Ring Closure

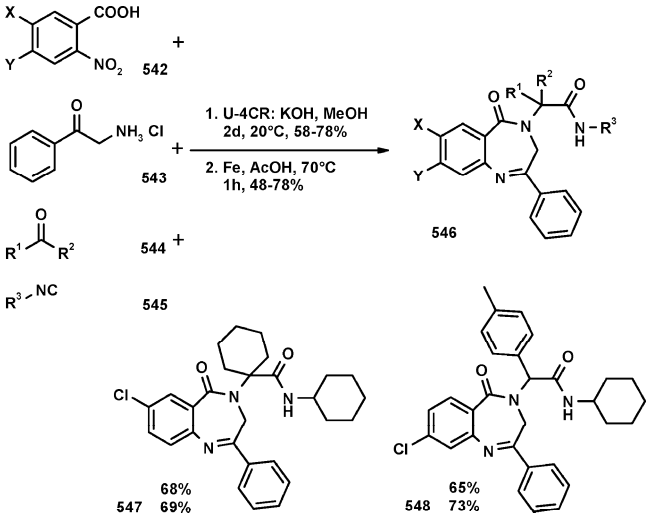


reaction, it can be speculated that the ring closing reaction takes place during basic aqueous work up. This interesting class of bifunctional isocyanides certainly offers many more possibilities to access interesting backbones by inter- and intramolecular substitutions.

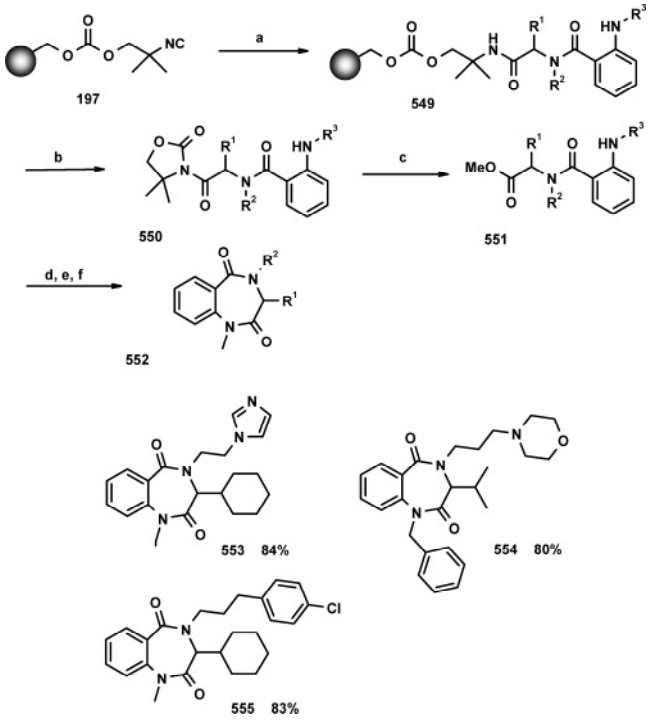
Scheme 94. U-4CR/Goldmann Sequence Yielding Substituted Benzodiazepines



Scheme 95. U-4CR, Reduction, and Cyclization Affording 2-Aryl Substituted 4,5-Dihydro-*3H*-1,4-benzodiazepin-5-ones



Scheme 96. Solid-Phase Array Synthesis of Benzodiazepines Using a Convertible Carbonate Isocyanide Resin[a]



[a] (a) Resin (110 μmol), $R^2CH_2NH_2$ (10 equiv), R^1CHO (10 equiv), Boc-D,L-amino acids (10 equiv), trifluoroethanol, 4 Å molecular sieves, CH_2Cl_2, rt, 3 days; (b) KO^{t}Bu (2 equiv, 1 M solution in THF), THF, rt, 16 h; (c) NaOMe (1.2 equiv, 0.65 M solution in MeOH), THF, rt, 48 h; (d) 70/30 hexafluoroisopropanol, TFA, rt, 48 h; (e) silicycle TMA carbonate, THF, 6 h; (f) silicycle isocyanate-3, THF, 16 h.

3.27. IMCR/S_NAr

From readily accessible starting materials, macrocycles with an *endo* aryl−aryl ether bond are synthesized in only two operations by combination of the Ugi four-component reaction and an intramolecular S_NAr reaction (Scheme 99).[176,177] The phenylalanine derived isocyanide **569**, interestingly, was synthesized from the corresponding benzyl bromide **568** via a formamidodiethyl malonate substitution, subsequent monodecarboxylation, and dehydration. The nitro group serves as an activator for the macrocyclization, e.g. **574**, and provides a handle for the introduction of functional group diversity. An U-4CR promoted by ammonium chloride in aprotic solvent is documented for the first time.

An on-resin Ugi four-component reaction followed by an intramolecular nucleophilic aromatic substitution (S_NAr) has been developed for rapid access to biaryl-ether containing macrocycles.[178]

3.28. IMCRs of DMAD

In 1969 Winterfeld first described the reaction of isocyanides and acetylene compounds.[179] This early finding forms the basis for a large class of new backbones thus accessible. The chemistry is based upon the initial formation of a zwitterionic adduct of the isocyanide with the acetylene compound, which further undergoes cycloaddition-type reactions (Scheme 100).

Cyclopentanetrione, DMAD, and an isocyanide allowed the preparation in good yields of a series of bicyclic enaminine esters **579** as a single diastereomer.[180]

The 1:1 intermediate generated by the additon of cyclohexyl isocyanide to dimethyl acetylenedicarboxylate (DMAD) is trapped by aldehydes to yield 2-aminofuran derivatives, e.g. **580**, in good yields (Scheme 101).[181] Moreover, it was found that the three-component coupling of aldehyde, DMAD, and cyclohexyl isocyanide proceeds efficiently in $[bmim]BF_4$ ionic medium under comparatively mild conditions to afford the corresponding 2-aminofuran derivatives in high yields.[182] The zwitterionic intermediate formed in situ from DMAD and isocyanide shows enhanced reactivity in ionic liquids, thereby reducing reaction times and improving the yields significantly. Ionic liquid can avoid the use of highly toxic and environmentally unfavorable benzene as solvent for this conversion. The recovered ionic liquid was reused five to six times with consistent activity.

A novel synthesis of 2-aminopyrroles **581** using a three-component reaction of dimethyl acetylenedicarboxylate, *N*-tosylimines, and isocyanides has been described.[183] The reaction is quite general, as several isocyanides and tosylimines could be converted to the desired products in good yields. Mechanistically, the authors propose the reaction may involve the initial generation of a zwitterionic intermediate from isocyanide and DMAD, which adds to the carbon−nitrogen double bond of the tosylimine to yield an intermediate iminolactam. Subsequently, it undergoes a [1,5]-H shift to yield aminopyrroles.

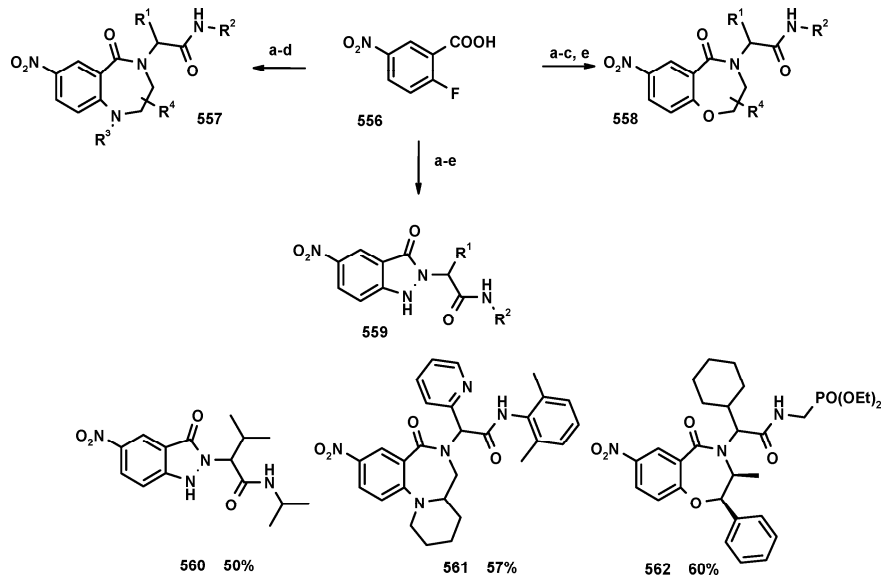
In contrast the reaction of isocyanides, DMAD and quinones yield iminolactones.[184] In this versatile reaction, *o*- and *p*-quinones and acenaphthene quinones react equally well to form a variety of iminolactones **582**. The reaction is performed in refluxing benzene.

Aminoisocyanides, a rarely used but accessible species, allow for a facile synthesis of substituted 3(5*H*)-pyrrolin-2-ones **583** via a Dimroth-type rearrangement.[185] As opposed to the reaction yielding aminofuran **580**, here the isocyanide reacts with aromatic aldehydes and DMAD to form pyrrolines.

The 1:1 zwitterionic intermediate generated from DMAD and isocyanide is intercepted with 2-hydroxy-1,4-naphthoquinone, 4-hydroxycoumarin, 4-hydroxy-1-methylquinolinone, 4-hydroxy-6-methylpyrone, and 1-naphthol in one-pot to give novel pyrane annulated heterocyclic systems **584** in good yields.[186]

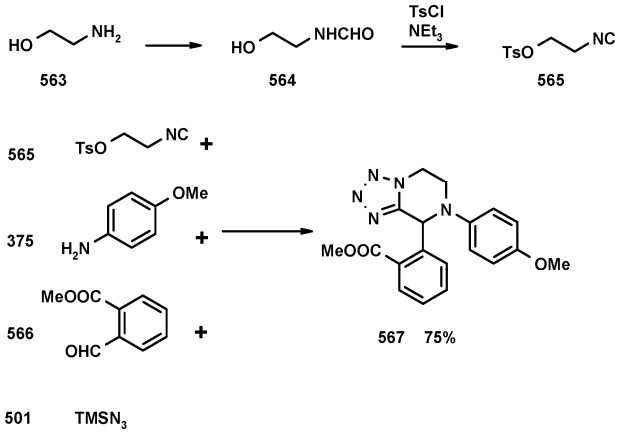
tert-Butyl isocyanide reacts with DMAD in the presence of 2-thenoyltrifluoroacetone to yield 4*H*-pyran derivatives **585** in good yields.[187]

Scheme 97[a]



[a] Reagents and conditions: (a) R^1CHO (0.2 M, 200 μL, MeOH), R^2NC (0.1 M, 200 μL, MeOH), **1** (0.1 M, 200 μL, MeOH), Boc-protected diamine or amino alcohol or $H_2NNHBoc$ (0.1 M, 200 μL, MeOH), rt, 48 h; (b) PS-tosylhydrazine (3 equiv), PS-diisopropylethylamine (3 equiv), THF/CH_2Cl_2 (600 μL, 1:1), 24 h; (c) 20% TFA/CH_2Cl_2 (600 μL), 4 h; (d) PS-morpholine (3 equiv), DMF (600 μL), 36 h; (e) PS-TBD (7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene), DMF (600 μL), rt, 36 h.

Scheme 98. Synthesis of an Isocyanide with a Leaving Group in the β-Position and a U-4CR with a Subsequent Intramolecular S_N2 Reaction



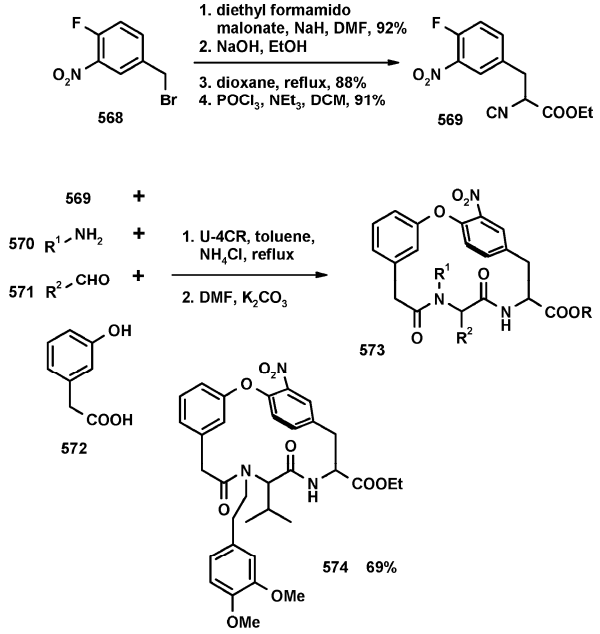
A novel pseudo-four-component reaction of isocyanides and dialkyl acetylenedicarboxylates in the presence of acidic N−H compounds such as maleimide or succinimide is described.[188] Unexpectedly, during the course of this reaction densely functionalized pyrroles **586** are formed.

Reaction of *tert*-butyl isocyanide with DMAD esters in the presence of *N*1-[(*Z*)-1-benzoyl-3-oxo-3-phenyl-1-propenyl]-2-(2-furyl)-2-oxoacetamide leads to dialkyl 5-*tert*-butylamino[2,2]bifuranyl-3,4-dicarboxylates **587** in moderate yields.[189]

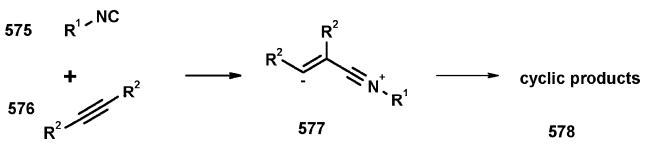
Highly chlorinated benzofused spiro lactone **588** is formed during the reaction of DMAD, an isocyanide, and the corresponding phthalic acid anhydride.[190]

The reactive intermediate generated by the addition of alkyl isocyanides to DMAD was trapped by phenols such as resorcinol, catechol, hydroquinone, pyrogallol, 2,4-dihydroxybenzaldehyde, or 8-hydroxyquinoline to produce highly functionalized 4*H*-chromenes, e.g. **589**, in fairly good yields.[191]

Scheme 99. Macrocyclic Biphenyl Ethers as Central Fragments of Many Natural Products Can Be Synthesized by the Sequence U-4CR and Intramolecular S_NAr



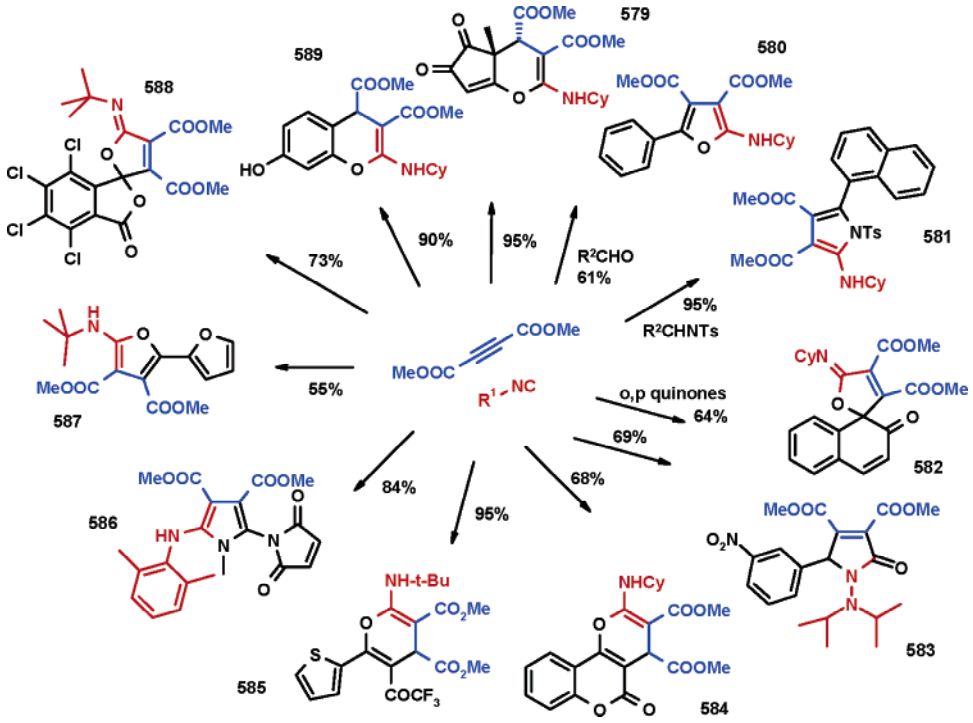
Scheme 100. Acetylenes and Isocyanides Form Zwitterionic Eneimine 577, Which Is Trapped by Dipolarophiles To Form Diverse Cycloadducts



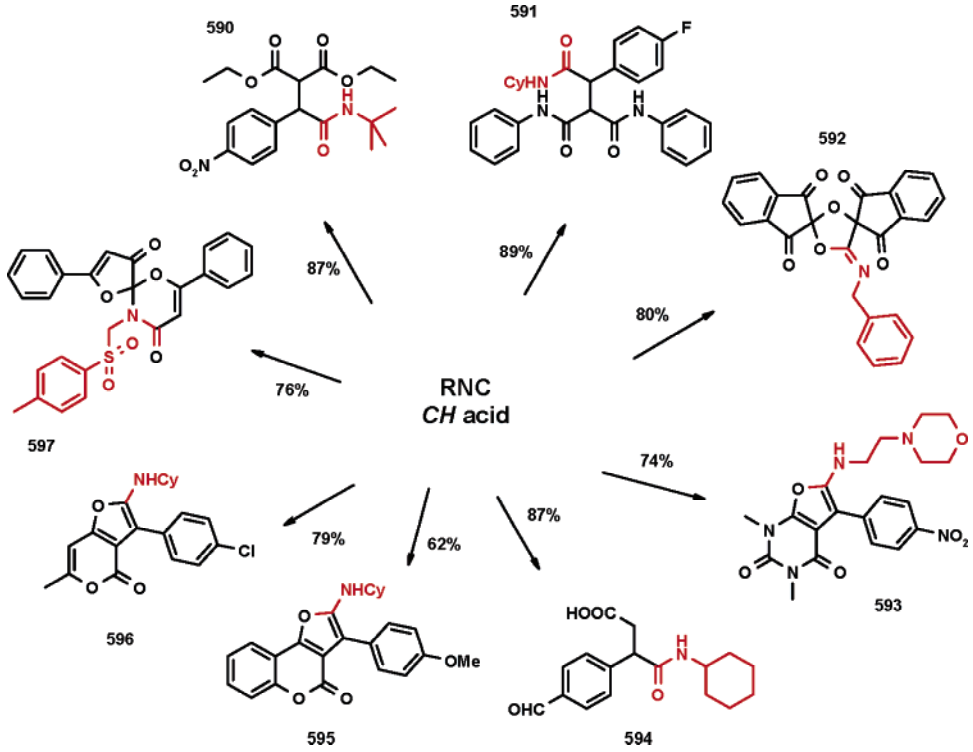
3.29. IMCRs of CH Acids

Shaabani et al. from Iran investigated the reactions of CH acids with isocyanides and other reactants and found a plethora of novel scaffolds, now generally accessible by IMCR (Scheme 102). For example, a novel four-component

Scheme 101. DMAD and Isocyanides with a Third Component Undergo a Variety of Cycloadditions To Form Diverse Heterocyclic Scaffolds



Scheme 102. Isocyanides Undergo a Variety of MCRs Involving CH Acids



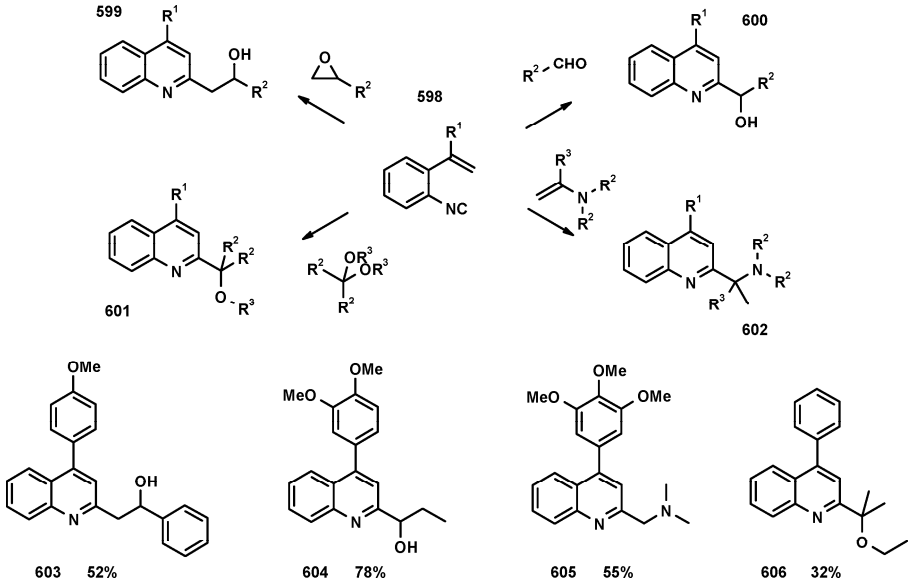
reaction approach to the efficient synthesis of triamide and amidodiester derivatives using amines or alcohols, aldehydes, and alkyl or aryl isocyanides in the presence of Meldrum's acid as a CH acid, instead of carboxylic acid of the Ugi four-component reaction, was studied.[192] Thus, **590** and **591** are formed in 87 and 89% yields, respectively.

The reaction of isocyanides with 2 equiv of ninhydrin gives dispiro iminodioxolanes **592** with C_s symmetry, at refluxing conditions in chloroform in fairly high yields.[193]

The environment-friendly three-component condensation reactions of *N*,*N*-dimethylbarbituric acid, 4-nitrobenzaldehyde, and alkyl or aryl isocyanides to afford the corresponding furo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **593**, in water, in high yields after several minutes are reported.[194]

The reaction between alkyl isocyanides and substituted benzylidene Meldrum's acid derivatives in the presence of water produces 4-(alkylamino)-3-aryl-4-oxobutanoic acids **594** in good yields.[195] The mechanism of the reaction was

Scheme 103. A Diverse Synthesis of Substituted Quinolines Is Accessible from Bifunctional 2-Isocyanostyrenes and a Second Electrophilic Component



not investigated, but the authors propose a [4+1] cycloaddition of the alkyl isocyanide with the electron-deficient heterodiene moiety of the benzylidene Meldrum's acid derivatives. Then, the intermediate iminolactone affords after decarboxylation the 4-(alkylamino)-3-aryl-4-oxobutanoic acids.

The in situ generated quinone methides from reaction of 4-hydroxycoumarin and 4-hydroxy-6-methylpyrone with various aldehydes undergo facile reaction with cyclohexyl isocyanide to produce furocoumarins **595** in good yields.[196] Quinone methides from 4-hydroxy-6-methylpyrone afforded furopyrone **596**. The reaction presumably occurs via a [4+1] cycloaddition followed by a [1,3]-H shift. A microwave accelerated improvement of this one-pot, three-component condensation reaction of 4-hydroxycoumarin or 4-hydroxy-6-methylpyrone, para-substituted benzaldehydes, and alkyl or aryl isocyanides to afford furan annulated heterocycles, in high yields after only 3 min, is reported.[197] Finally, the environment-friendly one-pot, three-component condensation reactions of 4-hydroxycoumarin or 4-hydroxy-6-methylpyrone, para-substituted benzaldehyde, and alkyl or aryl isocyanides to afford furocoumarines or furopyranones in water in good yields after about 1 h at 75 °C are reported.[198]

It was found that reaction of 5-aryl-2,3-dihydro-2,3-furandiones with tosylmethyl isocyanide (TOSMIC) in a 2:1 ratio in refluxing toluene leads to 5′,6-diaryl-3-tosylmethyl-(3,4-dihydro-*2H*-1,3-oxazine-2-spiro-2′-2′,3′-dihydrofuran)-3′,4-diones **597**.[199]

Despite the above-described *C*-nucleophiles in isocyanide based MCRs, CH acids have been sparingly reported in the past.[200]

However, several intramolecular Ugi- and Passerini-type reactions involving a *C*-nucleophile have been recently described by Kobayashi et al. (Scheme 103).[201] Introducing a versatile and new class of isocyanides, 2-isocyanostyrenes **598**, and treatment thereof with aldehydes, epoxides, acetaldehyde diacetal, or iminium salts afforded the 2,4-disubstituted quinolines **603**−**606**. Most reactions involved 0.1 equiv of the Lewis acid $BF_3 \cdot OEt_2$. The ready availability of the starting isocyanides, which were prepared from available *o*-aminoacetophenone, and the ease of operation make the present quinoline synthesis attractive compared to existing ones.

3.30. [2+2+1] Cycloadditions

Mironov et al. disclosed a new method for the combinatorial search of MCRs.[202] Four types of unsaturated compounds (isocyanides, electron poor alkenes, alkynes, and nitriles) have been chosen as having different reactivity, where they do not react irreversibly with each other. A combinatorial reaction scheme was performed. Comparison of educt mixture and product mixture by HPLC analysis revealed a novel reaction. Whereas most chromatograms were similar to those of the control two-component reactions, some combinations (Figure 15) have given a mixture with less than 30% content of the three-component products, and only one experiment has exhibited high selectivity (>80%). Detailed analytical elucidation revealed a process resulting in the formation of substituted 2,3-dihydro-10*H*-pyrrolo[2,1-*a*]isoquinoline-1-one. The reaction between *gem*-diactivated olefins, isoquinolines, and isocyanides turned out to be quite general. Thus, **610**−**612** are formed in good yields after crystalization.

3.31. Metal Catalyzed IMCRs

Yamamoto et al. reported a palladium catalyzed 3-CR of 2-alkynylisocyanobenzene with allyl methyl carbonate and TMS azide leading to *N*-cyanoindoles (Scheme 104).[203] A wide variety of functional groups are tolerated under the reaction conditions, e.g., the azo group in **613**. Twenty-three different aromatic isocyanides were described to undergo the reaction in mostly good to excellent yields. This unusual reaction is thought to involve a π-allylpalladium complex which together with the TMS azide forms the classical isocyanide α-adduct. The α-adduct eliminates nitrogen. A π-allylpalladium carbodiimide complex and its isomerization to a π-allylpalladium cyanamide complex are assumed. In a final step the insertion of the alkyne moiety into the π-allylpalladium intermediate takes place in a trans manner to afford the *N*-cyanoindoles **615**.

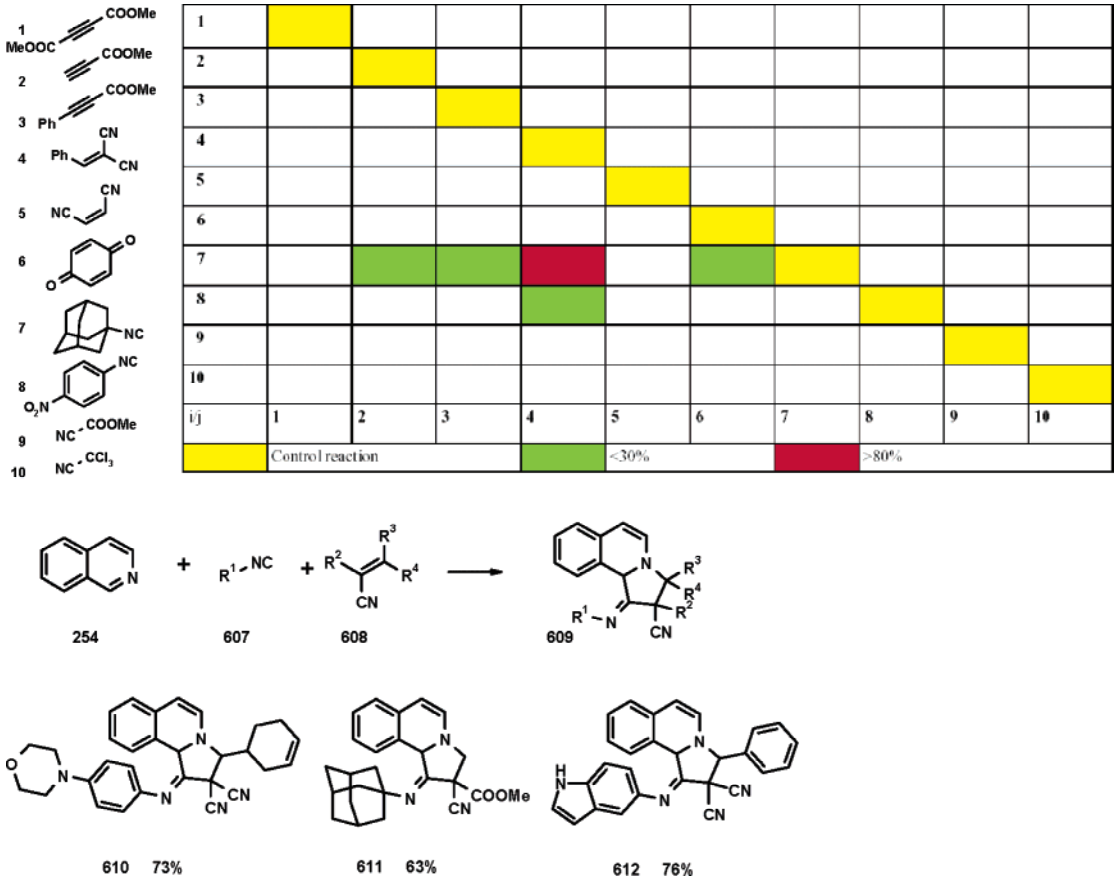
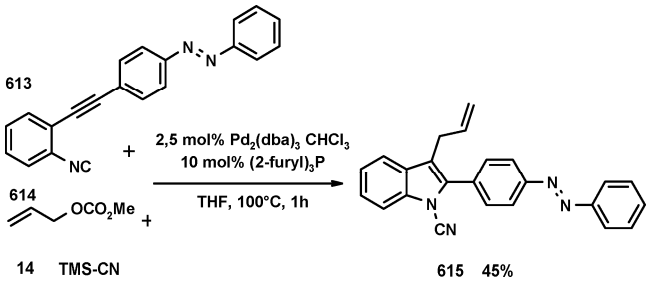


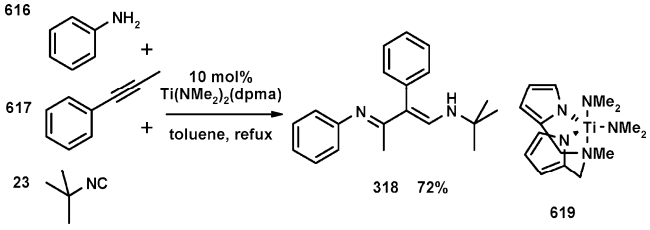
Figure 15. Rational combinatorial MCR discovery. Upon detailed analysis of the HPLC-MS of the reaction plate, a new MCR leading to annulated isoquinolines has occurred. The reaction can be formally described as a [2+2+1] cycloaddition. The different colors indicate different quantities of new reaction products in the HPLC trace. (Reprinted with permission from ref 202. Copyright 2003 Thieme.)

Scheme 104. *N*-Cyanoindoles by a Pd Catalyzed 3-CR



Titan catalyzed synthesis of α,β-unsaturated β-imino-amines **618** from aniline **616**, arylalkine **617**, and isocyanide **23** was discovered by Odom et al. (Scheme 105).[204] The

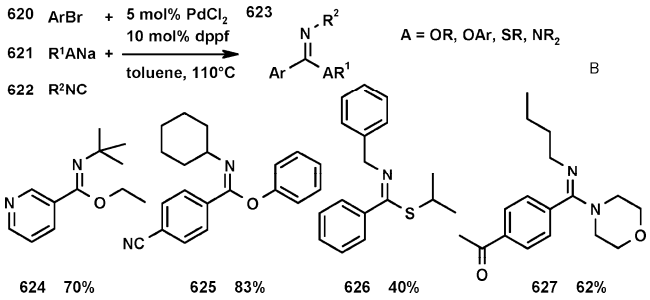
Scheme 105. Reaction Involving the Formation of a Ti-Azacyclobutene and Subsequent Isocyanide Insertion Leading to a Five-Membered Iminoacyl Complex with Subsequent Protonolysis To Yield the Product



catalytic complex **619** is available in almost quantitative yield by treatment of commercially available $Ti(NMe_2)_4$ with H_2-dpma. To avoid isolation of the air-sensitive complex, **619** can be generated in situ with comparable catalytic activity. Catalyst **619** has a relatively broad scope and is applicable for hydroamination of terminal and internal alkynes by alkyl and arylamines.

Whitby et al. show how internal amidines can be elegantly synthesiszed in a 3-CR of arylbromides, secondary amines, and isocyanides under Pd ctalysis (Scheme 106).[205] This

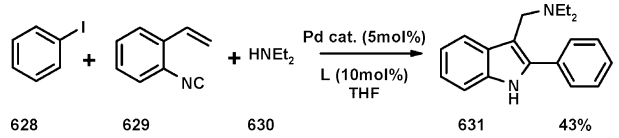
Scheme 106. Pd Catalyzed α-Addition of Arylbromides and Amines, Alkoxydes, or Thiolates



efficient reaction should become of considerable use, regarding the importance of imidines in medicinal chemistry. Using alkoxides, aryloxides, or thioalkoxides instead of secondary amines yields aryl-imidates and -thioimidates in high yield.[206]

Another unrelated three-component coupling reaction of aryl iodide **628**, *o*-alkenylphenyl isocyanide **629**, and amine **630** in the presence of palladium catalysts produced 2,3-substituted indoles **631** in moderate yields (Scheme 107).[207] A phenylpalladium complex is generated by the oxidative addition of aryl iodide to a Pd(0) species which reacts with

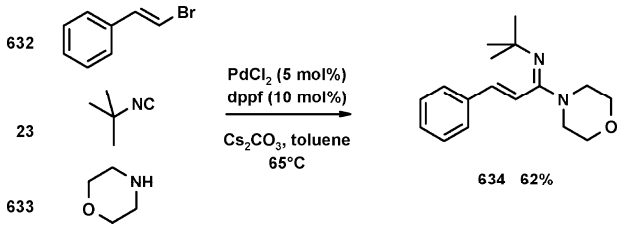
Scheme 107. Reaction of Aryliodides, *o*-Alkenylisocyanides, and Secondary Amines Yielding 2,3-Disubstituted Indoles



styrene isocyanide to induce the successive insertion of the alkenyl and isocyano groups followed by the 1,3-migration of hydrogen to give a (η^3-indolylmethyl)palladium complex. Nucleophilic attack by diethylamine produces 2,3-disubstituted indoles along with a palladium hydride complex, which is converted into Pd(0) species by the reaction with amine.

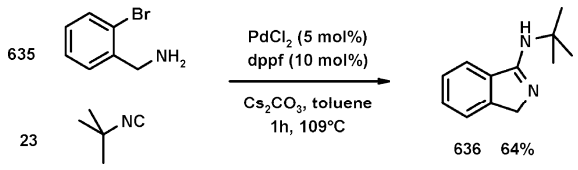
Palladium catalyzed 3-CR of an alkenylbromide **632**, isonitrile **23**, and an amine **633** or alkoxide/phenoxide affords α,β-unsaturated-amidines and -imidates **643** in good yields (Scheme 108).[208]

Scheme 108. Intermolecular 3-CR of a Secondary Amine, Isocyanide, and Alkenyl Bromide Yielding Amidines



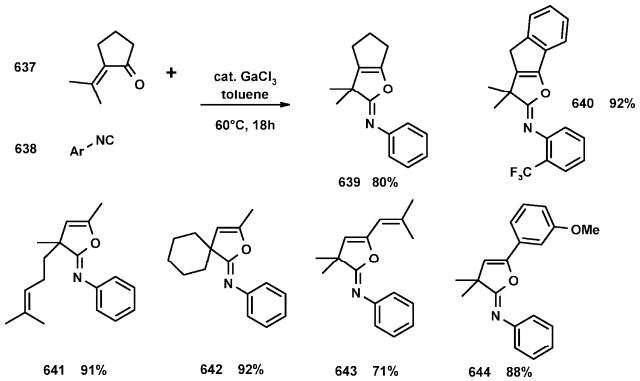
Similarily, Whitby describe the palladium catalyzed insertion of isonitriles into aryl bromides carrying a pendant amine or an alcohol group on the ortho position affording cyclic amidines or imidates in good yield (Scheme 109).[209]

Scheme 109. Intramolecular Reaction of an Isocyanide and *o*-Bromobenzylamine Yielding Benzannulated Amidines



The $GaCl_3$ catalyzed [4+1] cycloaddition reactions of α,β-unsaturated ketones **637** with isocyanides leading to lactone derivatives **639**−**644** are described (Scheme 110).[210] While

Scheme 110. Intramolecular MCR of α,β-Unsaturated Ketones and Aromatic Isocyanides Yielding Imino Lactones



some other Lewis acids also show catalytic activity, $GaCl_3$ was the most efficient catalyst. The reaction is significantly affected by the structures of both the isocyanides and the α,β-unsaturated ketones. Aromatic isocyanides, especially sterically demanding ones and those bearing an electron-withdrawing group, can be used, but aliphatic isocyanides cannot. The bulkiness of substituents at the β-position of acyclic α,β-unsaturated ketones is an important factor for the reaction to proceed efficiently. Interestingly, it was found that the more bulky substituent, the higher the yield. The success of the catalysis was attributed to the low affinity of $GaCl_3$ toward heteroatoms, compared with usual Lewis acids.

4. Applications of MCRs in Drug Discovery

By far, most applications of IMCRs described until today arise from the area of drug discovery. Potentially, the ease of performance, the time-saving aspect, the versatility and diversity of scaffolds, and the very large chemical space will attract chemists in pharmaceutical companies to use IMCRs for their projects. Another interesting aspect of MCRs in the context of drug discovery is the effective assembly of scaffolds out of smaller fragments. This aspect leads smoothly into a novel kind of "fragment based drug discovery", which, as opposed to NMR or X-ray, screens many different MCR scaffolds and incorporates fragment based starting materials, once a suitable fragment is identified. The following overview describes examples taken from recent patent and journal literature in an exemplary fashion (Figure 16).

4.1. Tubulin Inhibitors

Potent, orally available tubulin inhibitors with potential application in cancer therapy were described by Abbott scientists.[211] The imidazole MCR of van Leussen was used in this approach.[212] Herein, α-substituted tosylmethyl isocyanides (TOSMIC) **645** react with primary amines **646** and aldehydes **647** to form 1,4,5-trisubstituted imidazoles (Scheme 111).

These promising tubulin inhibitors nicely fit into the pharmacophor model of colchicine site binders, such as colchicin **650**, combrestatine **651**, and podophylotoxin **652**. Thus, **648** and **649** show IC_{50} values of 170 and 32 nM in the cancer cell line NCI-H460 and oral bioavailabilities of 82 and 36%, respectively. Moreover, mice xenograft models revealed that both have remarkable oral efficacy against the solid murine M5076 reticulum sarcoma cell line.

4.2. Kinase Inhbitors

The GSK p38 inhibitor **653**, previously in phase III clinical trials, is made by a vL-3CR (Scheme 112).[213] Several highly substituted imidazoles have been under investigation at GlaxoSmithKline (GSK) as potential therapies for the treatment of rheumatoid arthritis, which has spawned the need for a general synthetic method for their preparation on a multi-kilogram scale.

The GSK process chemistry group has safely produced in excess of 500 kg of isonitrile **661**. Once isolated, the isonitrile **661** is a stable, crystalline solid that is easily handled. From the work performed, it became clear that these aryl-substituted TosMIC reagents were truly versatile for preparing polysubstituted imidazoles under simple and mild conditions, in high yields, and in a completely regioselective fashion.[214] A particularly attractive feature of this methodology is the variety of fruitful reaction conditions employed and the wide assortment of compatible functional groups. A systematic study was performed to explore and highlight these qualities, and the results are demonstrated in the

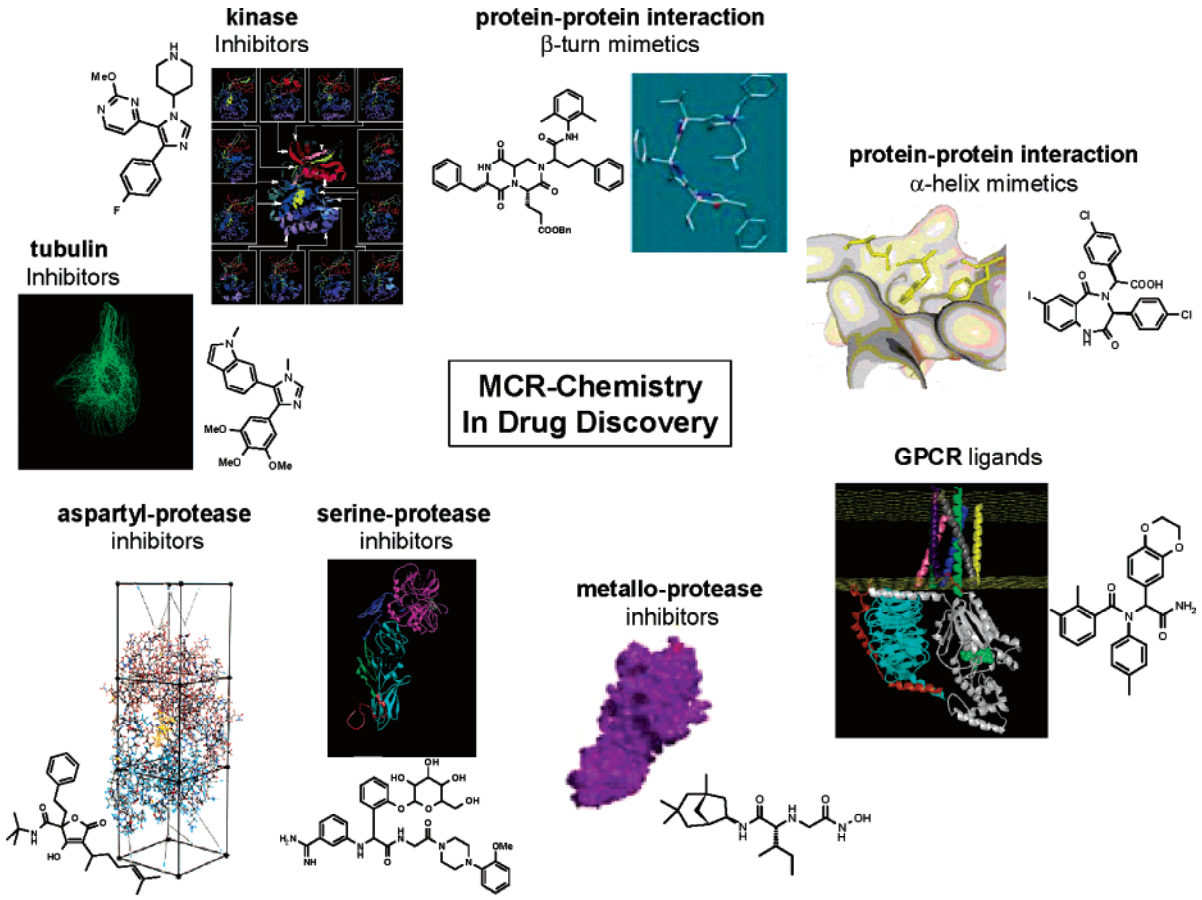
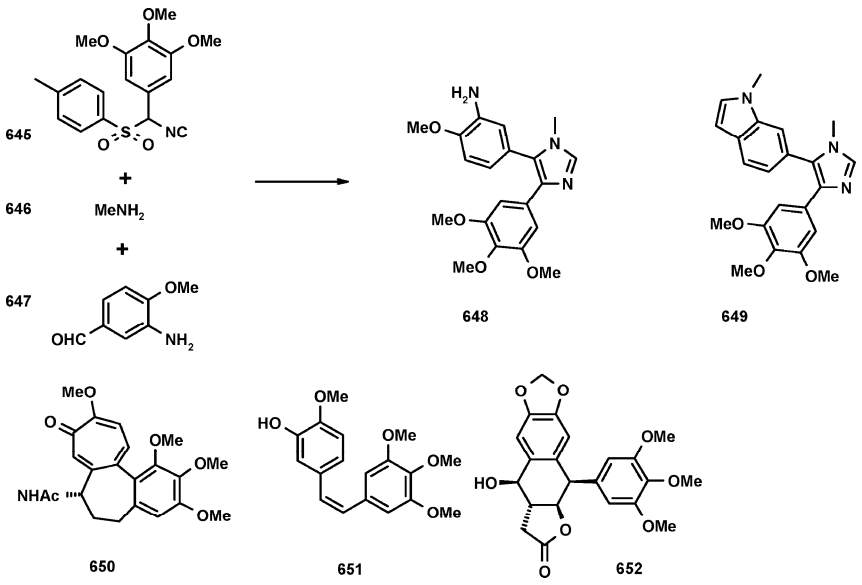


Figure 16. Schematic sketch of IMCR application in drug discovery.

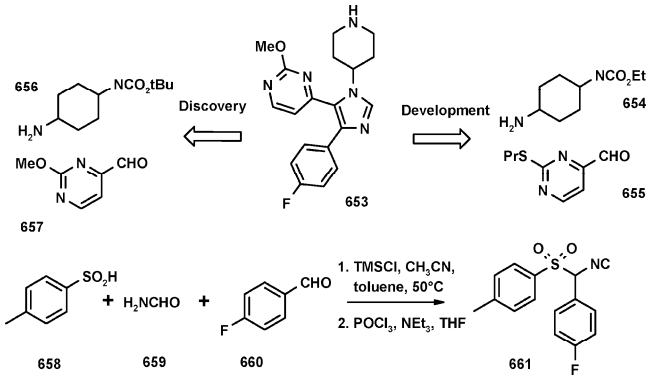
Scheme 111. (Top) VL-3CR Used To Make Potent Tubulin Inhibitors, and (Bottom) the Natural Tubulin Inhibitors Colchicine, Combrestatine, and Podophyllotoxin



examples below. The examples in Figure 17, **662**−**671**, highlight the functional group tolerability without resorting to protecting groups. In addition, it is demonstrated that (hetero)aryl TosMIC reagents can also be readily prepared and employed in a similar manner.[215] Also noteworthy is the fact that chiral amino acids, e.g. **668** and **671**, can be employed in the imine formation with complete preservation of the chirality. Moreover, it was found that employing glyoxylic acid as the aldehyde component in this multicomponent reaction leads to 1,4-disubstituted imidazoles **669** and **671** in high yield. These compounds presumably arise via decarboxylation of the intermediate tosyl imidazoline. Finally, replacing primary amines in this reaction with NH_4-OH leads directly to 4,5-disubstituted imidazoles **670** in good yield.

Pfizer chemists used the oxazol variante of van Leussen TOSMIC chemistry to synthesize p38 kinase inhibitors, e.g. **674** (Scheme 113).[216] Herein, TOSMIC derivative **673** reacts

Scheme 112. (Top) The GSK P38 Inhibitor Was Made in Discovery and Development Employing a VL-3CR but Using Different Starting Materials, and (Bottom) Synthesis of α-Substituted TOSMIC Derivatives by a MCR Followed by Dehydration



with aldehyde **672** under basic conditions to form an oxazol ring. The said compounds had an $IC_{50} < 10\ \mu M$ in the TNFα and MAPKAP in vitro assays, and an $EC_{50} < 50$ mg/kg in the in vivo TNFα assay. These compunds are potentially

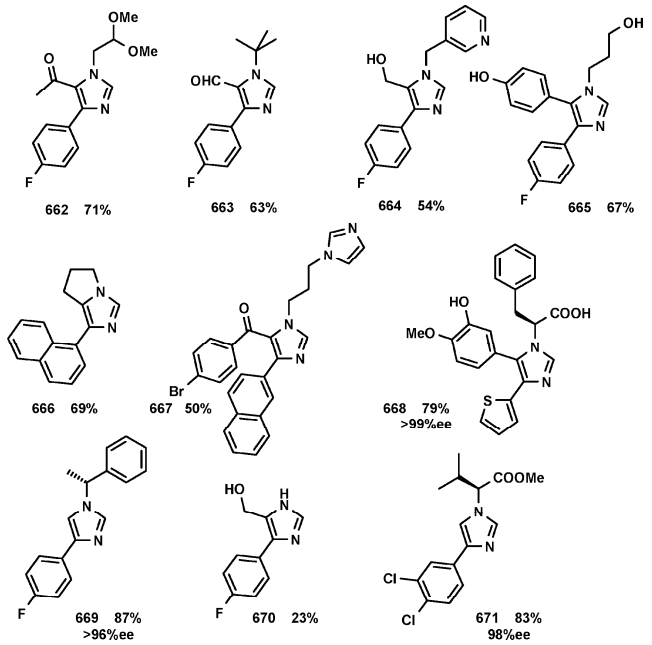
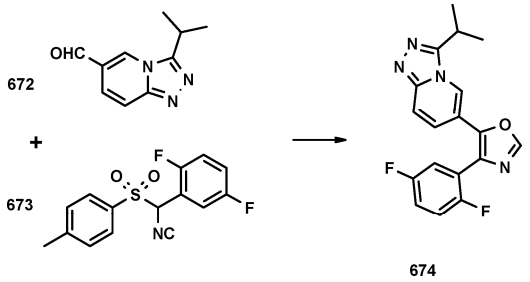


Figure 17. A diversity of functional groups is compatible without protection in the vL-3CR.

useful for treating inflammation, osteoarthritis, rheumatoid arthritis, cancer, reperfusion or ischemia in stroke or heart attack, autoimmune diseases, and other disorders.

Scheme 113. P38 Kinase Inhibitor Synthesized According to Van Leussen's Oxazole Reaction



Again, Pfizer chemists disclosed van Leussen-type trisubstituted imidazoles, e.g. **675**, as MAP kinase inhibitors as anti-inflammatory agents (Figure 18).[217]

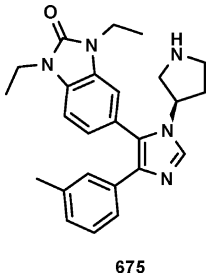


Figure 18. A chiral MAP kinase inhibitor formed by a vL-3CR.

4.3. Phosphatase Inhibitors

Morphochem workers used the Groebcke reaction to prepare a new class of specific PTP1B inhibitors, which may be expected to enhance insulin sensitivity and act as therapeutics for the treatment of Type II diabetes, insulin resistance, and obesity (Figure 19).[218] In a one-pot MCR,

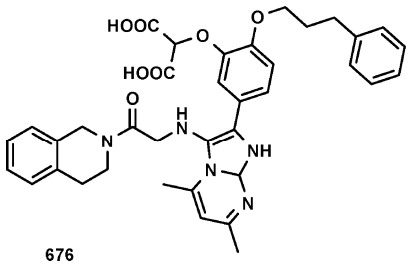


Figure 19. A novel PTP1b inhibitor, **676**, synthesized by a Groebcke MCR.

nonhydrolyzable phosphate mimetics were introduced via the benzaldehyde component. Several inhibitors exhibited low micromolar activity and remarkable selectivity versus similar phophatases such as TCPTP, LAR, and CD45. For example, **676** possessed an IC_{50} (PTP1B) of 700 nM, versus 44 μM (TCPTP), 118 μM (LAR), and 58 μM (CD45). The active compounds, interestingly, were discovered by the application of a drug discovery cycle involving genetic algorithms, MCR chemistry, and biology. A feature of this combined virtual and "wet chemistry" approach is that only relatively few compounds out of a very large chemical space have to be made. Compounds are becoming more and more potent and selective over the synthesis generations.

Glucose-6-phosphate translocase (G6PT) is a multienzyme complex involving a phosphatase activity. The G6Pase system catalyzes the hydrolysis of glucose 6-phosphate into glucose and phosphate as a final step in both glucose-producing pathways in the liver: gluconeogenesis and glycogenolysis. Thus, G6PT is a potential target useful in Type 2 diabetes. Morphochem scientists described the use of a genetic algorithm driven discovery of potent G6PT inhibitors involving vL-3CR and other scaffolds (Figure 20).[219] Thus, one imidazole plate (88 compounds) was synthesized with four acid-substituted aldehydes in combination with 22 amines, which appeared as useful, potent structure elements in the genetic algorithm run, and benzo-(1,3)dioxole-TosMIC as the isonitrile component. Promising activities below IC_{50} 10 μM were found among these imidazoles, most compounds being also selective against

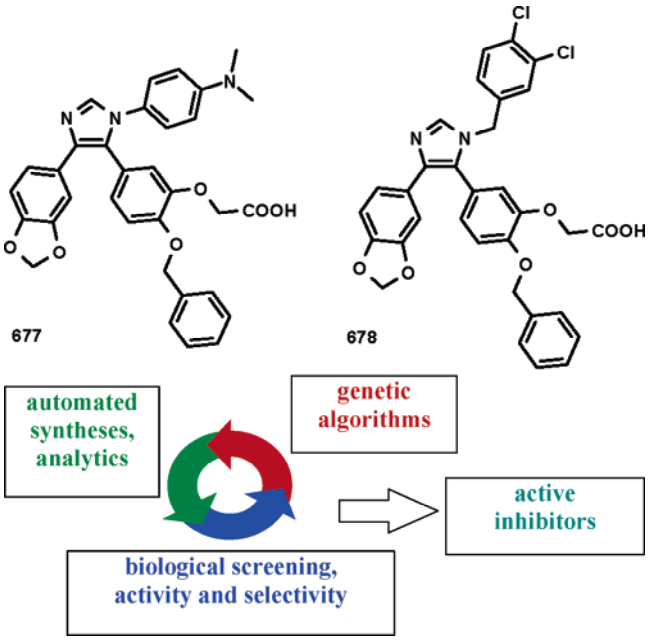


Figure 20. Top: G6P inhibitor found by genetic algorithm driven MCR chemistries. Bottom: Evolutionary drug discovery involving a fast and automated chemistry of mostly MCRs, genetic algorithms, and biological screening of activity and selectivity. (Reprinted with permission from ref 219. Copyright 2005 American Chemical Society.)

disrupted microsomes (IC_{50} disrupted > 200 μM), e.g. **677** and **678**.

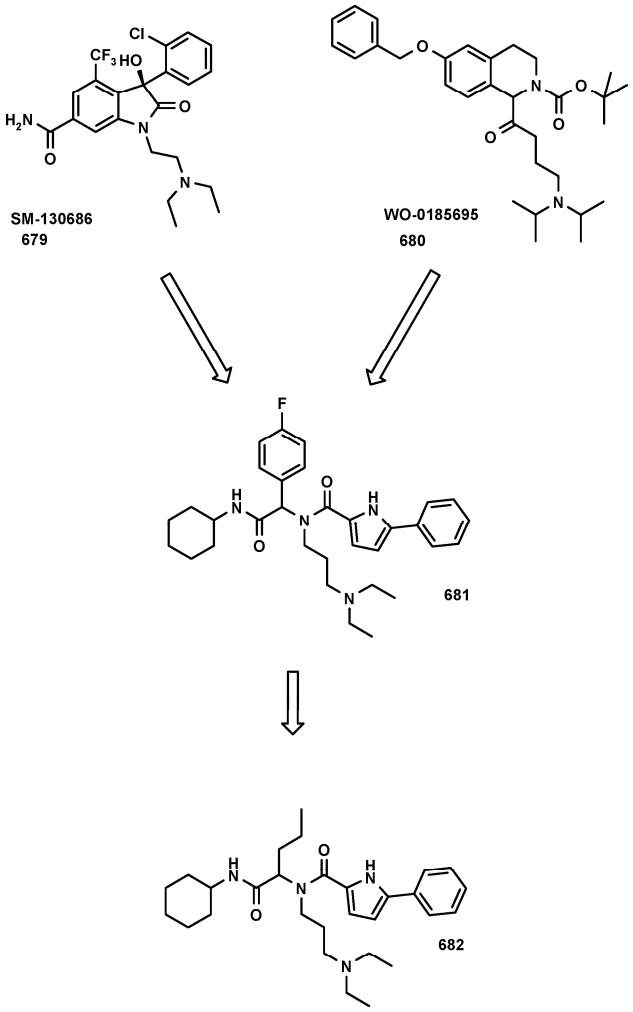
4.4. GPCR Ligands

G-protein coupled receptors are by far the most important drug discovery target of the past, present, and forseeable future. Moreover, detailed analyses have been reported showing that some 200 out of around 500 biomolecules identified as drugable are formed from GPCRs. Because of the rareness of biostructural information in the GPCR field, however, the most common way to initiate chemistry programs is via high-throughput screening (HTS).

A group of Asahi Kasei Pharma choose two molecules with known growth hormone secretagogue (GHS) agonist activity, **679** and **680**, which were used as templates to computationally screen a large in-house library by Tanimoto similarity and cell based partitioning (Scheme 114).[220] A total of 108 candidate compounds were selected out of the corporate library, and five of them were found to be active in the low-micromolar range in both cell based and direct binding assays. Among those, two α-aminoacylamides, e.g. **681**, were present which are easily amenable by Ugi chemistry. These were chosen for rapidly preparing a small, directed library of analogues. Synthesizing only 40 compounds by one-pot U-4CR, an inhibitor with a K_i = 0.22 μM, **682**, could be discovered and an initial SAR could be established. These compounds were structurally diverse and significantly different from known GHS agonists; thus, patentability was given. This approach clearly shows the value of MCR chemistry in fast hit to lead conversion and a ready establishment of a SAR. Moreover, this approach could be nicely translated to use the very large virtual MCR chemistry space to computationally and finally physically discover useful compounds.

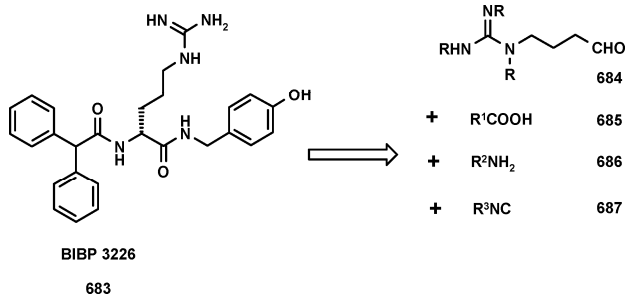
Arginine is involved in specific interactions of endogenous neuropeptides with their specific receptors, such as neuropeptide FF, neuropeptide Y, or neurotensine. Thus, most non-peptidic receptor (ant-)agonists constitute the hydrogen donating network of a guanidine functional group. BIBP 3226, **683**, possesses a good affinity for NPFF receptors. To synthesize rapidly a library of *N*-terminal and *C*-terminal arginine derivatives, Guery et al. needed a more convergent method than those usually used in conventional peptide synthesis, and they choose a U-4CR (Scheme 115).[221] Thus, they prepared a fully protected guanidylated aldehyde **684**

Scheme 114. Computational Approach To Search Large Physical or Virtual Libraries for Similarity to Prior Art Compounds[a]



[a] Here growth hormone secretagogue agonists could be identified which are amenable by U-4CR. Fast and directed library synthesis yielded a 220 μM lead starting from a weak micromolar hit.

Scheme 115. A Library of Neuropeptide FF Receptor Antagonists Was Prepared Using U-4CR of a Specially Synthesized, Fully Protected Guanidine Moiety Containing Aldehydes, Thus Mimicking Arginine



and introduced it in solid- and liquid-phase syntheses of U-4CR libraries in mostly good yields and purities.

GSK scientists discovered highly affine compounds binding to the 7-transmembrane receptor EP_1, whose natural ligand is prostaglandin PGE_2.[222] A series of compounds, e.g. **688**, have been synthesized by the vL3-CR of TOSMIC, 3-aminobenzoic acids, and 2-*O*-benzyl anilines (Figure 21).

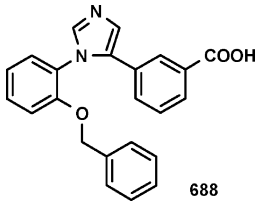


Figure 21. Example of a EP_1 receptor antagonist prepared by vL-3CR of protected *m*-formylbenzoic acid esters and subsequent saponification.

The exemplified compounds had an antagonist pIC_{50} value of between 7.0 and 9.5 at EP_1 receptors and an pIC_{50} value of <6.0 at EP_3 receptors. The EP_1 receptor is associated with smooth muscle contraction, pain, inflammation, allergic activities, renal regulation, and gastric or enteric mucus secretion.

Pfizer chemists disclosed oxytocin inhibitors prepared by U-4CR (Scheme 116).[223] Extensively employed U-4CRs lead to inhibitors with low nanomolar activity, e.g. **693** and **694**. Herein, the use of a convertible, stable, and odorless isocyanide, 4-phenylcylohex-1-ene isocyanide **(690),** is described. Whereas cyclohexenyl isocyanide ("Armstrong isocyanide") is know in the literature to be convertible after U-MCRs into a primary amide, an ester, or even the free carboxylic acid, it has the disadvantage of being tedious to prepare, being unstable (storage at −40 °C), and having an incredible malodor. Large arrays of compounds were described ($>^1/_2$K). The resulting racemic mixtures were resolved by chiral chromatography.

Also, a GSK group leveraged U-MCRs in order to prepare diketopiperazines for treating or preventing diseases or conditions mediated through the action of oxytocin (Figure 22).[224] Thus, the piperazinedione **695** was obtained by U-4CR

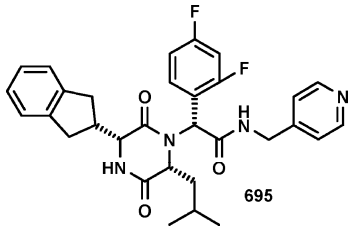
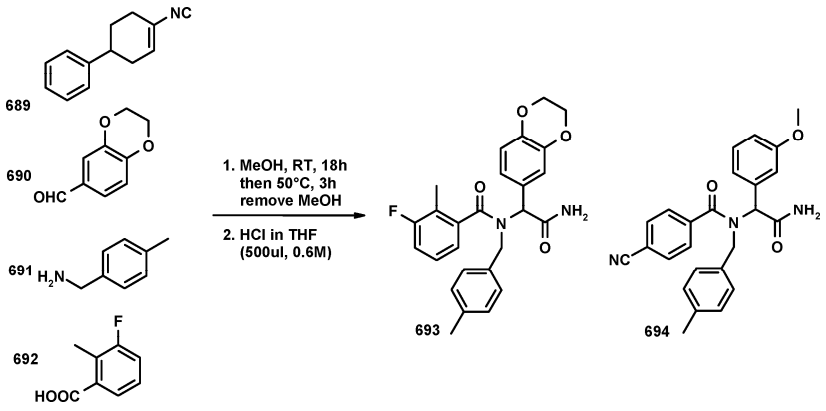


Figure 22. A stereoselective diketopiperazine useful as an oxytocin agonist synthesized by UDC.

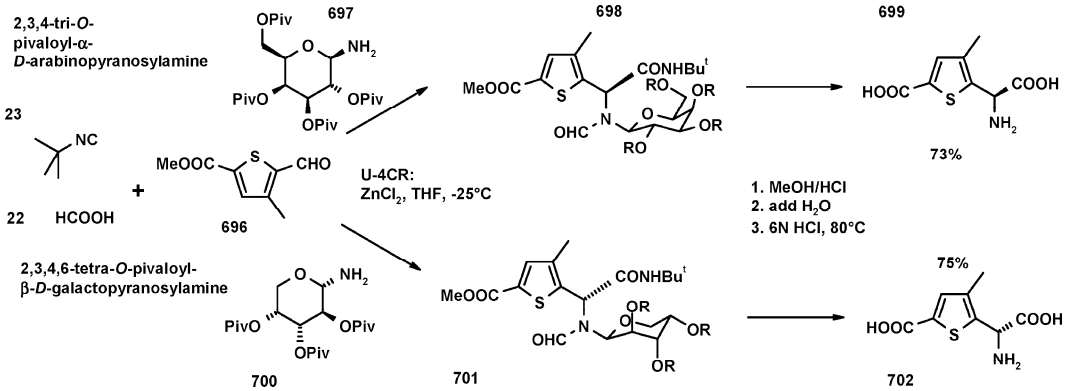
of H-D-Leu-OMe HCl, aldehyde, 4-picolylisocyanide, and *N*-Boc-D-indanylglycine and subsequent Boc deprotection and cyclization (UDC).

Type I GTP-binding metabotropic glutamate receptors (mGluR) are of great medicinal interest because of their involvement in processes leading to excitotoxic neuronal death after ischemia. Stereoselective synthesis and preliminary evaluation of (+)- and (−)-3-methyl-5-carboxythien-2-ylglycine (3-MATIDA), **699** and **702**, and the subsequent identification of (+)-3-MATIDA, **699**, as a novel mGluR1 competitive antagonist were reported by Costantino et al. (Scheme 117).[225] These researchers used chiral sugar based

Scheme 116. Primary α-Aminoacylamide Oxytocin Agonist Prepared by U-4CR and Subsequent Selective *N*-Terminal Hydrolysis



Scheme 117. Enantioselective Preparation of a Carboxythiophene α-Amino Acid as a Novel Type of MGluR1 Antagonist



auxiliaries **697** and **700** to prepare the enantiomerically pure unnatural amino acids using a U-4CR.

Ono chemist used a U-4CR to prepare nitrogen-containing heterocyclic derivatives such as chemokine receptor CCR5 antagonists.[226] *N*-Butyl-*N*-[1-[4-[4-(methylsulfonylamino)-phenoxy]benzyl]piperidin-4-yl]cyclohexanecarboxamide hydrochloride, **703**, inhibited the human RANTES-induced temporary increase in cellular Ca^{2+} ion concentration in CHO cells stably expressing excess human CCR5 with an IC_{50} of 0.077 μM (Figure 23).

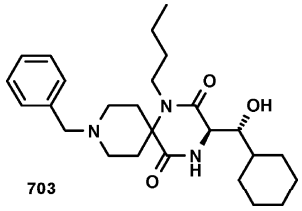


Figure 23. A CCR5 antagonist prepared by a U-4CR.

Gerlach from Gruenenthal discovered imidazopyridineamines and analogues, e.g. **704**, as analgesics (Figure 24).[227]

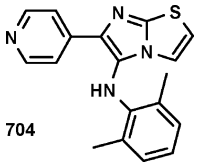
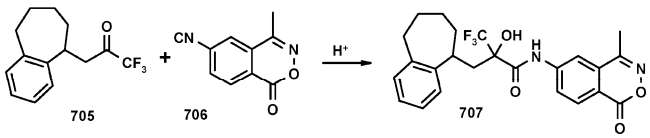


Figure 24. Analgetic Groebcke product.

He used Groebcke chemistry to prepare libraries of bicyclic products, using $HClO_4$ as a catalyst.

Chemists from Glaxo described the synthesis of *N*-benzoxazinylpropanamides, e.g. **707**, as glucocorticoid receptor binders and agonists for the treatment of inflammatory, allergic, and skin diseases.[228] Often these classes of inhibitors contain an α-hydroxy-α-trifluoromethylcarboxamide pharmacophor. This moiety can be advantageously prepared by means of a Passerini reaction (Scheme 118).

Scheme 118. Reaction of a Trifluoromethyl Ketone and Isocyanides in a P-2CR Results in Potent Glucocorticoid Receptor Binders



Amgen scientists reported on the generation of a 10.000 membered Ugi tetrazole lead generation library, from which several sub-micromolar antagonists of the GPCR melanin-concentrating hormone 1 (MCH1), an important obesity target, were discovered.[229] **708**, for example, exhibits an acceptable PK profile (Figure 25). Moreover, a statistically significant reduction in feeding and a clear dose response were observed for those animals treated with the compound. The author emphasized the speed of hit to lead and in vivo data generation ($^1/_2$ year, 2 FTEs), that he ascribed to the efficacy and enabling power of MCRs.

4.5. Antituberculosis Drugs

In principle, a pharmacophore can be introduced into a MCR backbone in two conceptually different ways. Either the pharmacophore element is introduced via one of the staring materials, or it is formed during the course of the MCR through the atom and bond skeletal rearrangement. The former process possesses obvious limitations concerning the number of available starting materials and the "weighting" of the product library. The pharmacophoric structure is only variable at one or a few connection points, whereas the in-situ assembly of the pharmacophore during the MCR allows for many more variations and convenient variations all around the core structure. Moreover, often the change from one scaffold to another scaffold while retaining the biological activity is possible ("scaffold hopping").

An example for the former "ligand-introduced pharmacophore approach" is the discovery of novel 4-aminoquino-

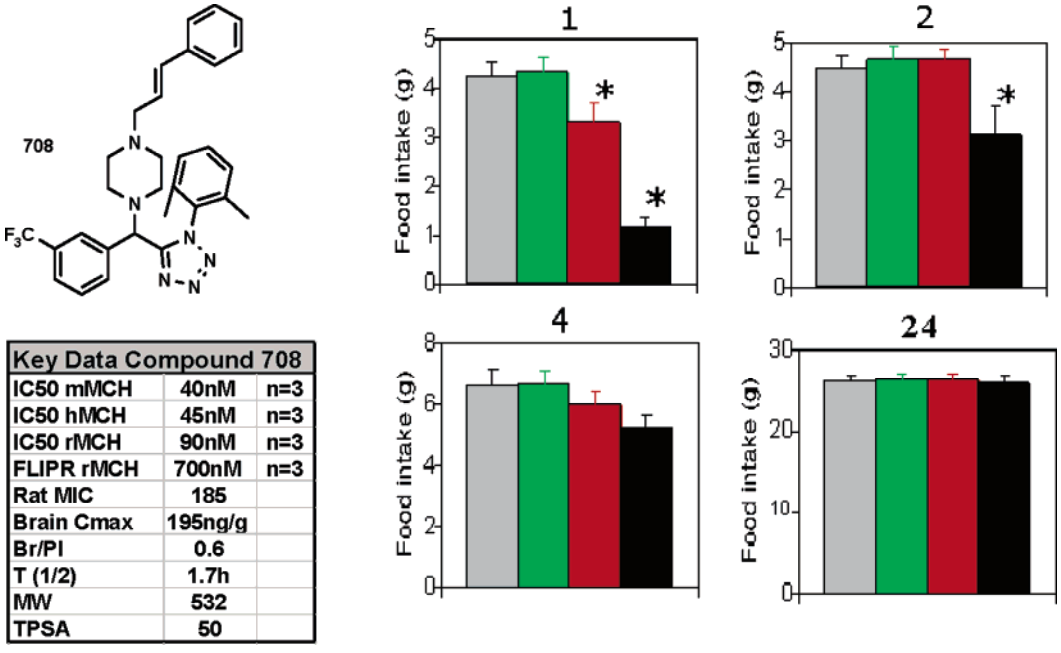
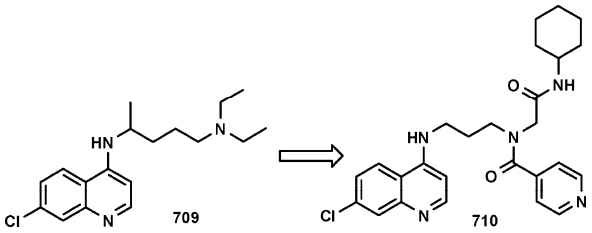


Figure 25. Potent MCH1 receptor antagonists prepared by U-4CR of an isocyanide, HN_3, a secondary amine, and a benzaldehyde. Food uptake measured at different time points and concentrations of **708** using intraperitoneal (ip) dosing. Key pharmacokinetic data of **708**: gray, HPMC/Tween; green, 3 mg/kg; red, 10 mg/kg; black, 30 mg/kg. (diagrams reproduced with kind permission of Dr. C. Hulme.)

line antimalaria drugs by using Ugi chemistry.[230] On the basis of the structure of chloroquine **709**, the authors synthesized an amine building block, 4-(3-aminopropyl)amino chloroquine, and produced a library of antimalaria compounds. Compound **710** was found to be slightly less active than chloroquine in one of the three tested *P. falciparum* strains, but it exhibited a superior resistance index (Scheme 119).

Scheme 119. Discovery of Potent Anti-malaria Drugs by Incorporation of Pharmacophore Motifs of Marketed Drugs into the Starting Materials

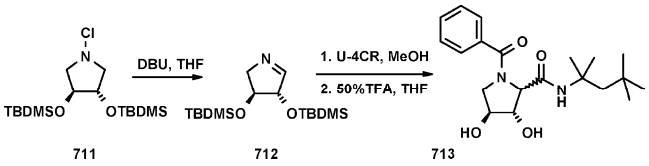


Here, several things are noteworthy. First, the introduction of an already known and validated pharmacophore precludes the need for the synthesis of large and costly libraries. Second, the author mentioned the possibility of combining two different modes-of-action in one molecule made by an MCR. These dual or multiple action molecules could be potentially useful to slow or even overcome the emergence of drug resistance. Thus, this approach would be similar to a combination therapy, but combined in one drug. Finally drugs for diseases prevalent in the third world, such as malaria, must be cheap to produce, which is often true for compounds produced by MCRs.

4.6. Enzyme Inhibitors

Glyco- and peptidomimetics from a U-3CR showed selective antiviral activity; see, for example, **713** in Scheme 120.[231] Chlorination−elimination chemistry coupled with

Scheme 120. Glyco- and Peptidomimetics Synthesized by U-3CR of in Situ Generated Erythritol Imine



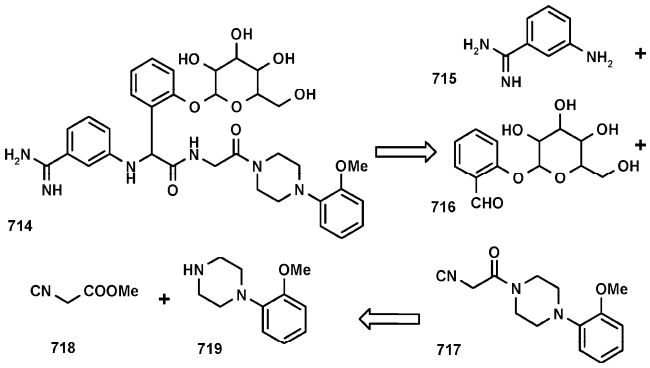
U-3CR and facile deprotection allowed efficient access through parallel synthesis to an array of polyhydroxylated pyrrolidines that may be considered to be a library of imino (aza) sugars and/or dihydroxyprolyl peptides. The utility of generating such a library was illustrated by screening against 15 different targets that revealed potent and selective inhibition of Gaucher's disease glycosyltransferase enzyme glucosylceramide synthase and of the primary pathogen model for human hepatitis C virus (HCV) and bovine diarrhoeal virus (BVDV). An observed selectivity for this HCV model over hepatitis B virus and remarkably low toxicity suggest a novel mode of action.

4.6.1. Serine Protease Inhibitors

IMCR chemistry seems to be particularly well suited for the discovery and synthesis of factor Xa inhibitors, since several companies claim their use for the discovery of highly potent and selective inhibitors. Thus, two groups from Morphochem and Eli Lilly reported pM factor Xa inhibitors, potential anticoagulation drugs.

A group at Morphochem discovered potent, highly selective, and, in several animal models, orally bioavailable factor Xa inhibitors (Scheme 121).[232,233] A corresponding large

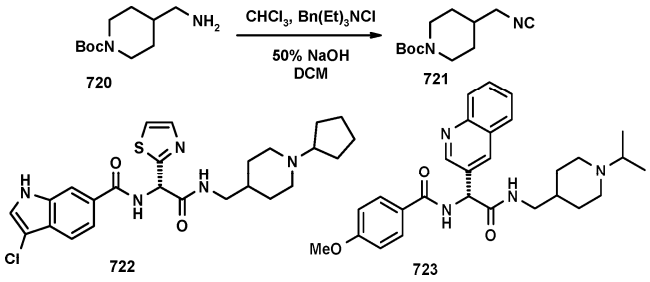
Scheme 121. Highly Selective (against Thrombin and Other Related Proteases) and Active FXa Inhibitor Available in a Two-Step Synthesis on a Multigram Scale from Commercially Available Starting Materials



library of 16.480 compounds were prepared by a U-3CR, using $InCl_3$ as a Lewis acid catalyst. Using chemoinformatic tools, e.g. genetic algortithms, highly active and selective compounds could be discovered. Thus, the depicted complex compound **714** can be stereoselectively prepared from readily available starting materials **715**−**719**.

A Lilly/Tularik group disclosed potent and selective factor Xa inhibitors prepared by a U-4CR (Scheme 122).[234] They

Scheme 122. Hoffman Synthesis of Boc-Protected 4-Isocyanomethyl Piperidine Useful in the Synthesis of FXa Inhbitors



reacted acidic cleavable 2,4-dimethoxybenzylamine as a component, and subsequent reductive amination of the Boc-deprotected piperidine thus yielded **722** and **723** in a three-step sequence. This approach allowed rapid access to a variety of substituents, and heterocyclic replacements for the central aryl unit enabled the chemists to readily scale-up compounds for further evaluation. Central to the activity was an *N*-substituted 4-(aminomethyl)piperidine system addressing the S4 pocket. The corresponding isocyanide, **721**, was rapidly prepared on a 45 g scale from the Boc-protected 4-(aminomethyl)piperidine **720** by the classical Hoffman procedure under phase-transfer conditions. The authors noted that, despite the moderate yield (24%) of the U-4CR reaction to form **722**, they found the Ugi route to be superior to alternate approaches involving the synthesis of 2-thiazolylglycine for multigram preparation of **722**. The racemic mixtures were separated by chiral HPLC. The authors have found that the majority of Xa binding affnity results from

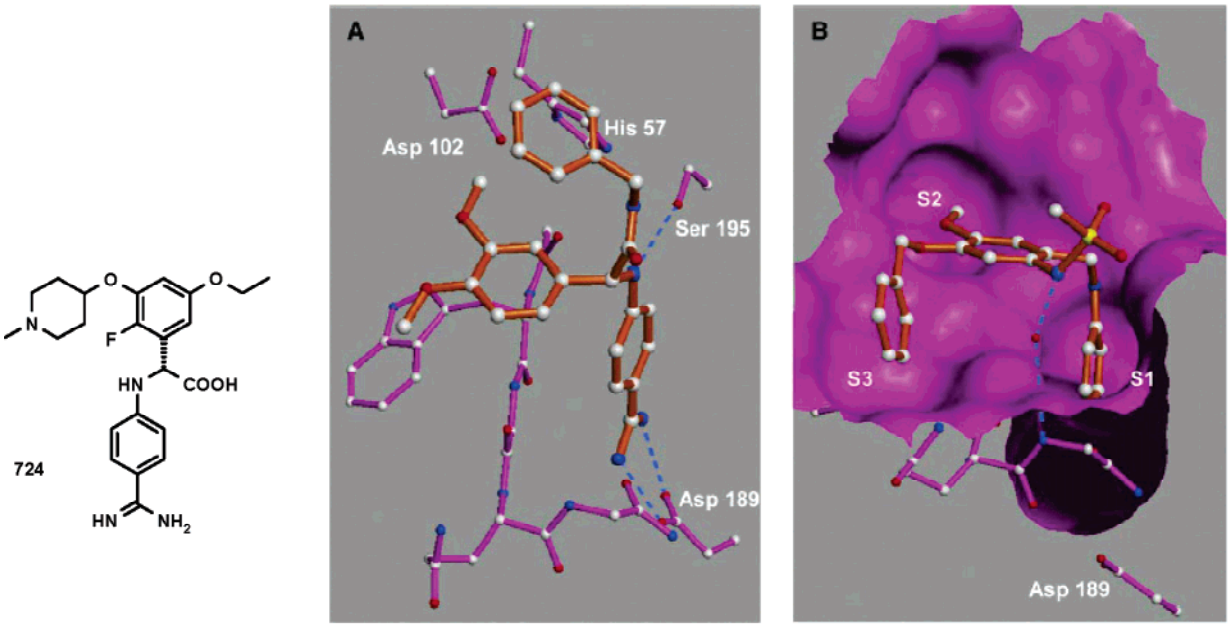


Figure 26. Potent series of fVIIa inhibitors, e.g. **724**, discovered using U-3CR and the binding mode of other representatives as seen in an X-ray structure revealing a hydrogen bonding network and the addressing of the binding pockets by the molecule fragments. (Reprinted with permission from ref 236. Copyright 2005 Elsevier.)

one enantiomer; thus, they tested the U-4CR products as racemates for expedience.

Tissue factor/factor VIIa inhibitors have been shown to exert antithrombotic activity without enhancing bleeding propensity. Starting from lead compounds generated by a biased combinatorial approach, phenylglycine amide tissue factor/factor VIIa inhibitors with low nanomolar affinity and good selectivity against other serine proteases of the coagulation cascade were designed, using the guidance of X-ray structural analysis and molecular modeling (Figure 26).[235,236] The active compounds have been synthesized using U-3CR and subsequent hydrolysis. The compound **724**, for example, was found to double prothrombin time (PT) in human plasma at a concentration of 1.6 μM, and it had a solubility of 5.7 mg/mL in pH 6.5 phosphate buffer.

Sneddon et al. from Genzyme Corp. claimed Passerini and Ugi products, e.g. **726**, as kallikrein and urokinase inhibitors with potential applications in cancer therapy (Figure 27).[237]

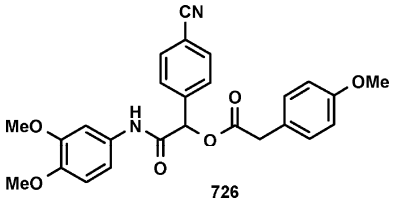
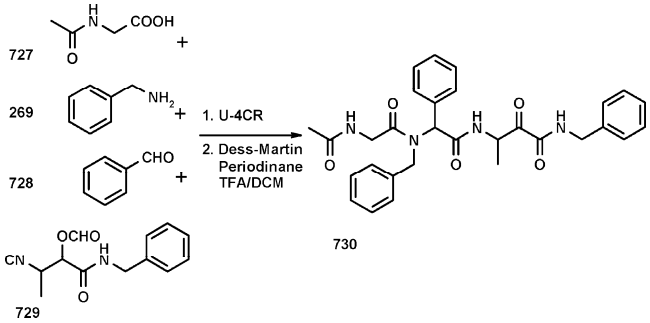


Figure 27. P-3CR of a substituted phenyl isocyanide, benzaldehyde, and phenylacetic acid yields compounds active as kallilrein and urokinase inhibitors.

The synthesis of a peptidomimetic HCMV protease inhibitor library using a U-4CR was described by a Chinese group (Scheme 123).[238] A peptidomimetic skeleton, e.g. **730**, was designed, and a chemical library containing 32 compounds with different substitutions on the skeleton was prepared by the oxidation of a precursor library, which was constructed from four types of building blocks: four carboxylic acids, two amines, two aldehydes, and two isocyanides, based on U-4CR multicomponent condensation following liquid-phase strategies.

Scheme 123. Libraries of Inhibitors of the Human Cytomegalo Virus Synthesized in Liquid Phase Using Isocyanides Incorporating a Protected α-Hydroxyamide Moiety in the U-4CR, Which Was Subsequently Oxidized, Resulting in Substituted α-Ketoamides, e.g. 730

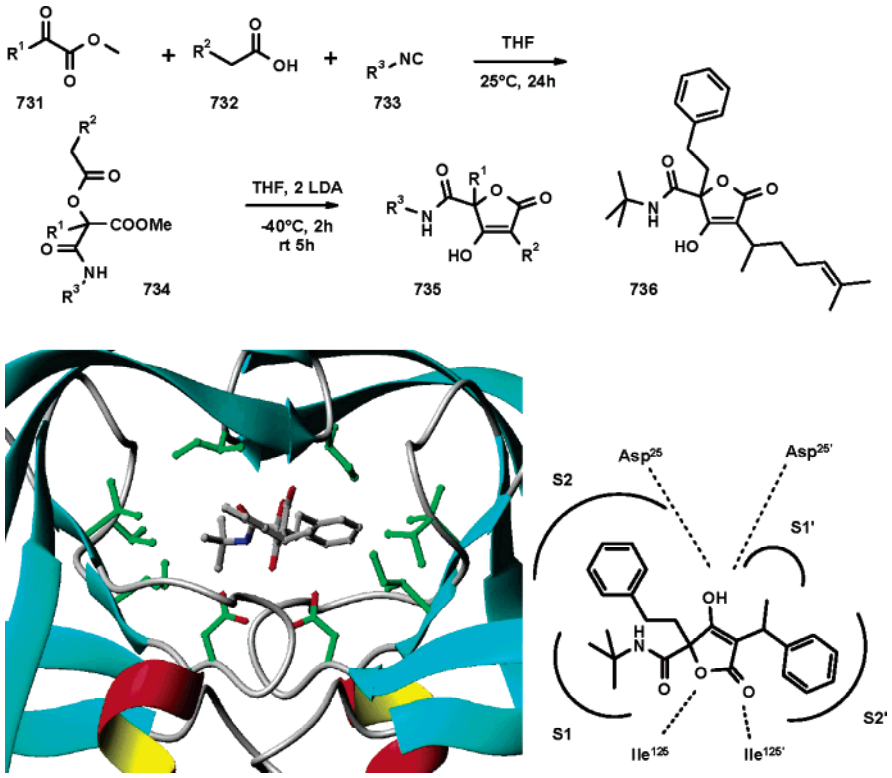


4.6.2. Aspartyl Protease Inhibitors

AIDS is primarily (>95%) a third world disease. Current combination therapies for treating the HIV infection are not affordable by these patients. The cost of goods (COG) of HIV protease inhibitors highly depends on the complexity of the synthesis. Unfortunately, all HIV protease inhibitors are made by very long and costly, sequential syntheses.

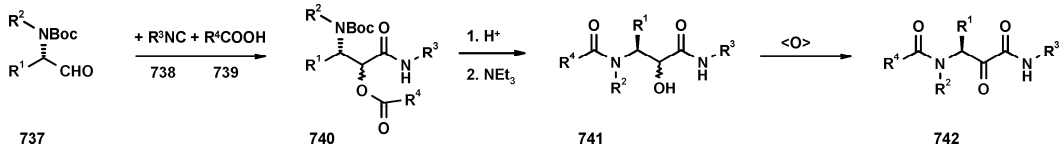
The first HIV protease inhibitors synthesized by IMCR were described in 1995.[239] Later, Merck kilo-lab chemists showed the usefulness of Ugi's 4-CR to rapidly and enantioselectively synthesize a core fragment of Crixivan on a kilogram scale, thus saving several steps in the sequential >20-step synthesis.[240] Recently, we could introduce a novel sequence of a P-3CR of α-ketocarboxylic acid esters, isocyanides, and substituted acetic acids and a subsequent Dieckmann ring closing reaction yielding five-membered *N*,2,4-trisubstituted 3-hydroxy-5-oxo-2,5-dihydrofuran-2-carboxylic acid amides (Scheme 124).[241] The particular chemistry can be performed in a one-pot manner in 96-well plates (PP) by first performing the Passerini reaction in THF at room temperature, then cooling to −40 °C, and then adding 2 equiv of LDA. A small library of four 96-well plates

Scheme 124. An Unprecedented Class of HIV Protease Inhibitors by the P-3CR of α-Ketocarboxylic Acid Esters and Subsequent Base Induced Ring Closing Reaction (Reprinted with permission from ref 241. Copuright 2004 Elsevier.)[a]



[a] Modeling and X-ray structure analysis of representative compounds reveal the expected interaction of the hydroxy groups with the catalytic aspartates and of the lactone unit with the backbone NH of the two isoleucins.

Scheme 125. P-3CR of Protected α-Amino Acid Derived Aldehydes and a Subsequent Deprotection Induced *O,N*-Acyl Migration Opens a Fast and Powerful Entry into Protease-Type Inhibitors, and Subsequent Oxidation Yields a Highly Substituted α-Ketoamide Backbone Useful for the Construction of Reversible Protease Inhibitors



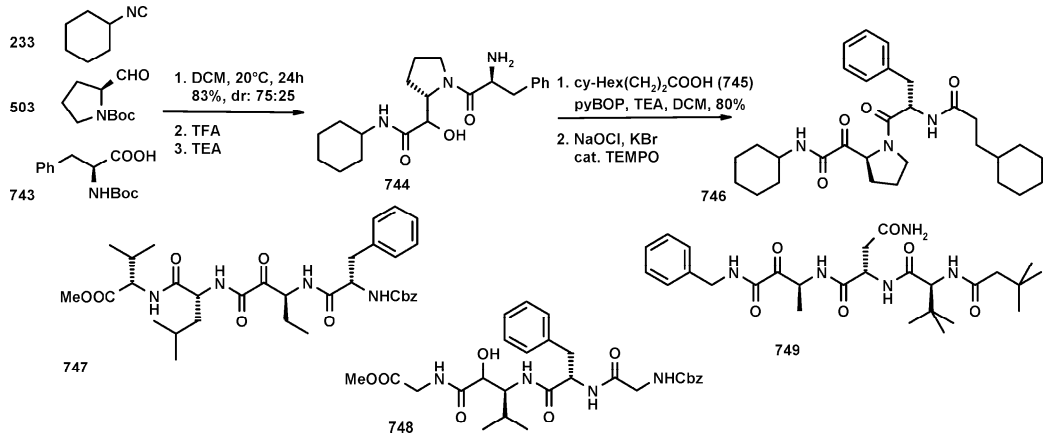
revealed several low micromolar to nanomolar inhibitors. For example, **736** (1 μM) could form a starting point for novel HIV protease inhibitors accessible by a much shorter route. This example nicely presents the advantages of scaffold diversity and convergence of MCR chemistry. Whereas all marketed HIV protease inhibitors are synthesized in a 15 or more step linear synthesis, the herein-described inhibitors are synthesized by a convergent two-step sequence. Moreover, they are unprecedented in the patent literature. This MCR is an example of an assembled pharmacophore, since none of the starting materials contains a pharmacophore element.

Several aspartyl proteases are important human disease targets. These involve β-secretase (Alzheimer and other neurodegenerative diseases), HIV protease (AIDS), cathepsin D (malaria), and renin (cardiovascular diseases). Statins, norstatins, and, in general, secondary hydroxy functions often serve as "needles" in aspartyl protease inhibitors. There are several opportunities to prepare such compounds via IMCR chemistry.

Banfi et al. and Semple simultaneously reported the Passerini reaction of isocyanides, carboxylic acids, and *N*-Boc-protected aldehydes yielding after Boc-deprotection and rearrangement a multitude of norstatine derivatives.[242,243] This general strategy is termed PADAM (Passerini reaction/amine deprotection/acyl migration) (Scheme 125).

To exemplify this powerful PADAM strategy, Banfi et al. recently prepared several protease inhibitors known in the literature (Scheme 126).[244] For example, P-3CR of protected proline carbaldehyde **503** and *N*-protected Phe **743** yields after Boc-deprotection and subsequent acyl migration the intermediate **744** in 83% as a mixture of separable diasteromers, which can be further elaborated in two more steps to yield the target protease inhibitor **746**. A similar strategy was employed in the synthesis of α-oxoamides **747** and **749**, known to be potent inhibitors of two important serine proteases: prolyl endopeptidase and *Cytomegalovirus* protease, respectively. The synthesis of *Cytomegalovirus* protease inhibitor **749** is particularly noteworthy, since in this case a complex structure formed by five fragments joined through four amide bonds was prepared convergently in only three steps and with an overall yield of 35%. Another way to increase the complexity of the α-oxoamides prepared by the PADAM methodology is to employ a dipeptidic isocyanide, for the synthesis of **747**, which is the methyl ester of a known potent inhibitor of prolyl endopeptidase. The target could be prepared in three steps and 35% overall yield. This compound is formed by four different units joined by amide

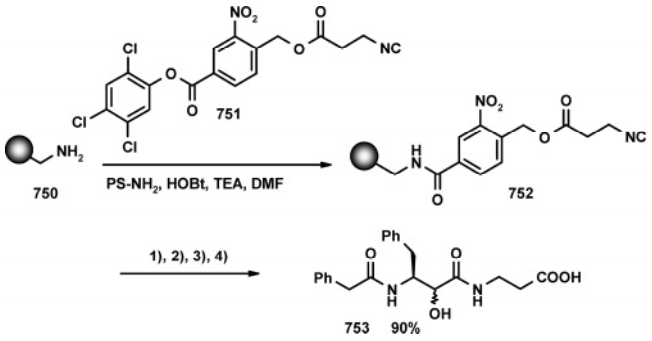
Scheme 126. Several Highly Complex Protease Inhibitors Could Be Assembled in a Highly Convergent and Step Saving Fashion Involving a P-3CR and a Subsequent Transesterfication



bonds. The high convergency of the synthetic pathways shown in this communication definitely compensates for the fact that the yields of Passerini condensations, in some cases, were not as good as those when simple monofunctionalized components were used.

Finally, the Italian group reported on a solid-phase startegy of PADAM (Scheme 127).[245] Thus, a UV light cleavable

Scheme 127. PADAM on Solid Support[a]

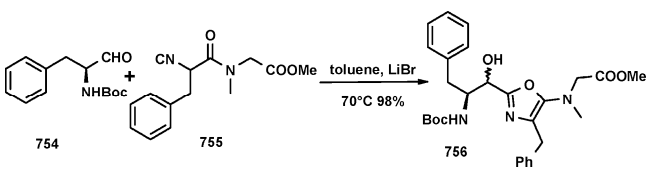


[a] (1) *N*-Boc-L-phenylalaninal, phenylacetic acid, DCM, 24 h; (2) irradiation, 24 h; (3) TFA, DCM, 2 h; (4) TEA, DCM, 18 h.

isocyano resin was developed and libraries of protease inhibitors were produced. Isocyanide with an incorporated leaving group **751** was reacted with aminomethylpolystyrene **750** in the presence of HOBT and triethylamine to afford the light cleavable resin **752**. For example, final compound **753** was obtained in 66% yield over all steps.

Zhu et al. reported that the P-3CR of protected chiral α-amino aldehydes **754** with amides of α-isocyano-*β*-phenylpropionic acid **755** in toluene in the presence of lithium bromide gives 2,4,5-trisubstituted oxazoles as norstatine-containing peptides **756** in good to excellent yield (Scheme 128).[246] Interestingly, the nucleophilic addition

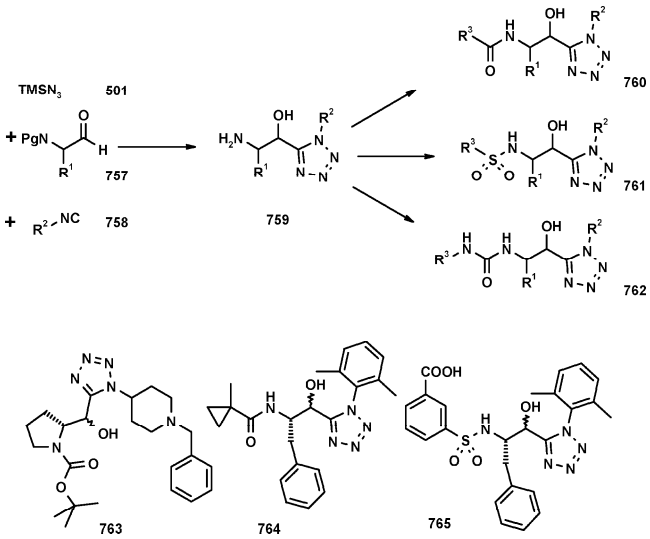
Scheme 128. Heterocyclic Norstatine Building Blocks as Obtained by the Reaction of Isocyanoacetic Acid Amides and α-Amino Aldehydes



of isonitriles to *N*,*N*-dibenzylphenylalanal is found to be stereoselective, leading predominantly to the anti-adduct (dr = 9:1), whereas the reaction between the *N*-Boc-phenylalaninal and isonitrile is nonstereoselective.

Hulme from Amgen described the rapid entry into the class of cis-constrained norstatine analogues using a $TMSN_3$-modified Passerini MCC/N-capping strategy (Scheme 129).[247]

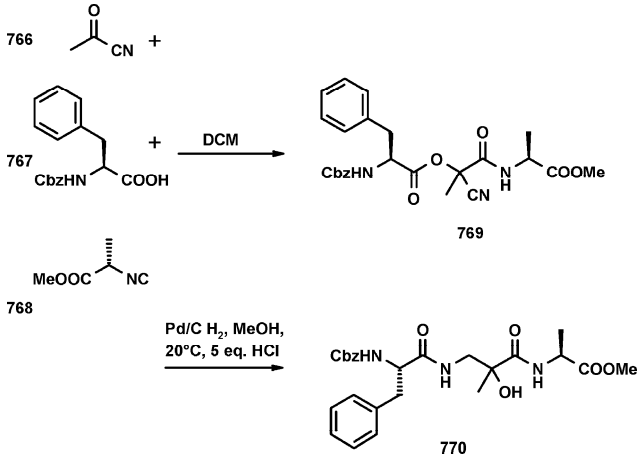
Scheme 129. Diverse Norstatine-like Scaffolds Available by P-3CR of α-Amino Acid Derived Aldehydes, Subsequent Deprotection in the Tetrazole Variation, and Subsequent Deprotection/Acylation of the Resulting Secondary Amines, Resulting in a Two-Step Sequence with Three Points of Diversity



Amino acid derived Boc-protected aldehydes **757** react with $TMSN_3$ **501** and isocyanides **758** to form the Passerini adduct. Upon deprotection, the amine functionality can be further acylated or sulfonylated. This type of chemistry can conveniently be used to prepare large libraries. Exemplary structures are **763**−**765**.

Reacting acylcyanides **766** in the P-3CR has been described in the past (Scheme 130).[248] Oaksmith et al. subsequently reduced the intermediately formed nitrile **769** to the primary amine, which upon spontaneous rearrangement affords *β*-amino acid diamides.[249] These structures are interesting peptidomimetics, which according to modeling studies form intramolecular hydrogen bonds, thus forming a rigid six-membered ring. Compounds such as **770** embody the well-known norstatine peptide isostere found in many

Scheme 130. Another Type of Norstatine Element Accessible by P-3CR and Subsequent Reduction and Acyl Migration

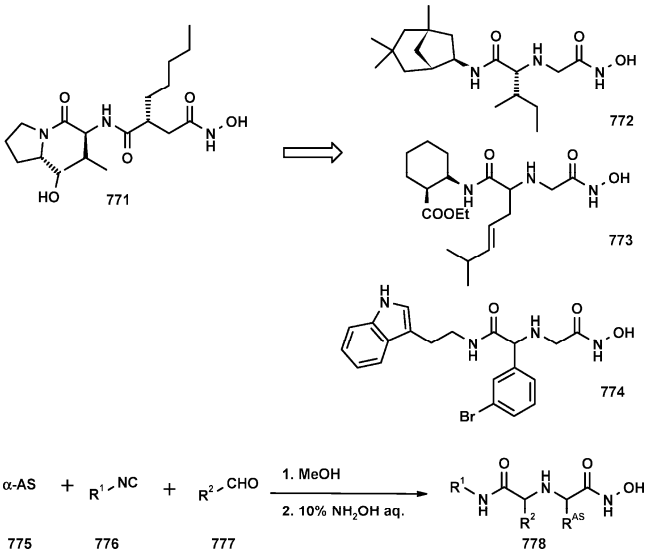


aspartyl protease inhibitors. Twenty-two examples of this versatile sequence are described.

4.6.3. Metalloprotease Inhibitors

In 1996 Whittaker et al. expoited the U-4CR to target matrix metallo-proteases via preparation of hydroxamic acid, a known functional group being a well-recognized zinc-binding motif.[250] Recently, the use of a U-5C-4C reaction of α-amino acids for the preparation of bioisosteres of the natural product actinonin **771** was described (Scheme 131).[251]

Scheme 131. Two-Step Strategy To Build Metallo-protease Inhibitors by U-5-C-4CR and Subsequent Hydroxylamine Hydrolysis



The resulting Ugi product was subsequently hydrolyzed with aqueous hydroxylamine to give terminal hydroxamic acids, **772**−**774**. The compounds are potent peptide deformylase (PDF) inhibitors with a potential application as antibiotics. Moreover, these compounds exhibit good water solubility due to their zwitterionic nature.

4.6.4. Cysteine Protease Inhibitors

Cornea permeable calpain inhibitors as anticataract agents such as **779** were described to be synthesized by a P-3CR involving water as an acid component, followed by oxidation to the α-ketoamide (Figure 28).[252] The compounds showed

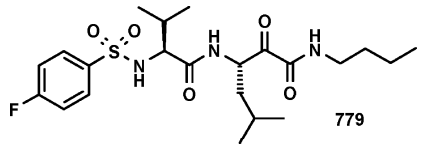


Figure 28. A P-3CR followed by oxidation of the hydroxy group affords α-ketoamides useful as cysteine protease inhibitors.

potent inhibitory activities, high cornea permeation, and excellent efficacy in a rat lense culture cataract model.

4.7. Glycoconjugates

Glycobiology opens a wide field for new therapeutic approaches. However, the complexity and unavailability of various carbohydrate test compounds has often excluded this class of natural products from modern screening systems. Alternatively, glycomimetics are considered to be more druglike candidates for development. Lockhoff from Bayer reported on the array synthesis of glycoconjugate libraries accessed by isocyanide based MCRs.[253] Highly diverse libraries involving IMCRs could easily be prepared in 2-mL 96-well microtiter plates at room temperature and purified by preparative LC-MS out of the same reaction block. By using HPLC on reverse-phase columns, approximately 150 raw products can be chromatographed in 24 h, yielding the pure products in amounts between 20 and 60 mg. Automated fraction collection is managed by using a coupled electrospray ionization mass spectrometer (ESI-MS): only fractions containing the mass of the expected product are collected. Employing this technical equipment, the authors constructed several random glycoconjugate libraries for in-house HTS. Therefore, they synthesized carbohydrate synthons with *O*-, *C*-, and *N*-glycosidically linked functional groups and included biologically relevant sugar configurations. The functional groups were also placed at nonanomeric positions. These building blocks were combined with each other to give Passerini- or Ugi-condensates containing one to four carbohydrate moieties, such as **780** and **781** (Figure 29). The focus

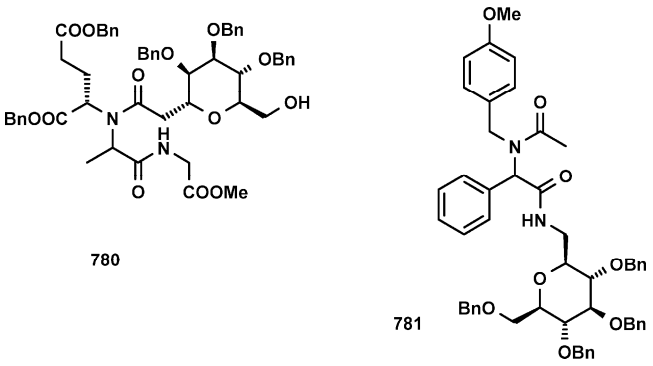


Figure 29. Glycoconjugate libraries of the size 10^5 have been described using IMCRs.

was put on glycoconjugates with only one or two sugar residues, whereby the remaining units were chosen from the wide spectrum of available starting materials. It can be anticipated that IMCRs containing carbohydrate moieties will play an increasing role in glycomimetic chemistry and biology.

Fibroblast growth factors are attractive targets to combat proliferative and angiogenic diseases. Especially the discovery of small molecules able to block the heparin/FGF/FGFR ternary complex is a promising avenue toward antiprolif-

erative drugs. Thus, co-workers from Progen Industries designed Ugi libraries of sulfated glycoconjugates trying to mimic the heparin part binding to FGF/FGFR.[254] These sulfated glucoconjugate libraries were made by U-4CR and subsequent sulfatation of the free hydroxy groups with SO_3NMe_3. **782** showed a K_d of 4.8 mM toward FGF1 vs a 20-fold higher K_d toward FGF2 (Figure 30).

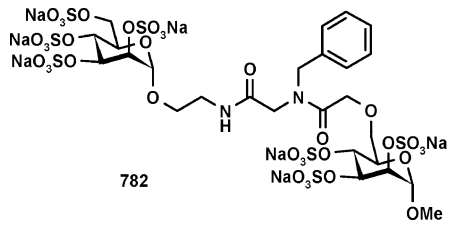
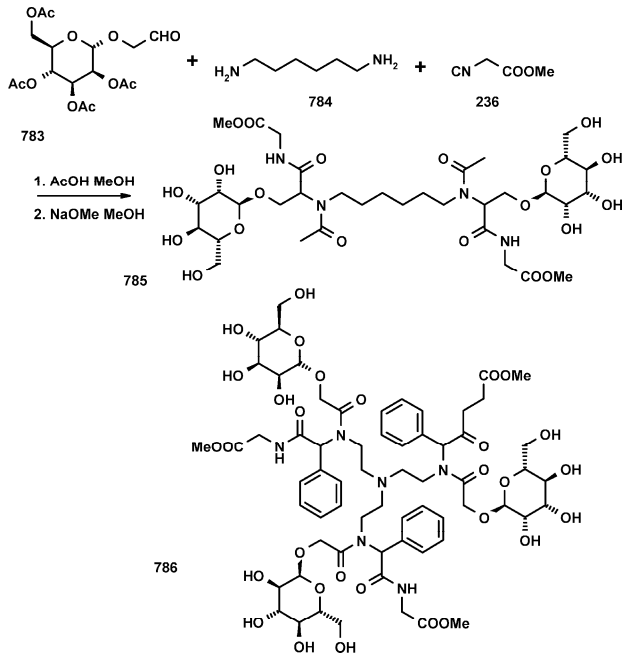


Figure 30. Polysulfated glycol Ugi products as selective FGF1 binders.

Li et al. investigated the binding of glycoclusters prepared by U-4CR to plant lectin concanavaline A (Scheme 132).[255]

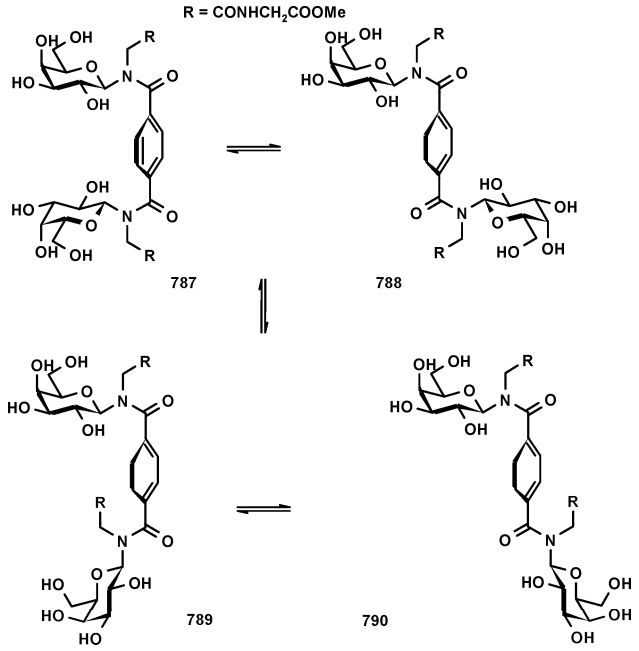
Scheme 132. Di- and Trivalent Glycoclusters by U-4CR Having Affinity for Plant Lectins



Initially, allyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside was prepared as a useful precursor, which reacted with OsO_4/$NaIO_4$ to give glycosyl aldehyde **783**. U-4CR was then utilized to prepare divalent cluster mannosides. The reactions of glycosyl aldehyde **783**, 1,6-hexanediamine **784**, and methyl isocyanoacetate **236** with acetic acid **11**, or other acids, gave the divalent compounds, which upon reaction with NaOMe/MeOH provide smoothly the corresponding target dimers, e.g. **785**. Additional cluster mannosides of diverse structures could also be obtained readily by this method. Using tris(2-aminoethyl)amine, higher valent clusters could be obtained, e.g. **786**. For all cluster mannosides synthesized in this paper, the binding affnities to Con A were much higher than that of methyl α-D-mannopyranoside, even after valency correction. Cluster mannosides containing aromatic residues bound more tightly to Con A in comparison with those without aromatic residues, and some divalent ligands showed higher affinity for Con A than trivalent ligands. The binding affnities of cluster mannosides to Con A, as observed in other cases, did not necessarily increase with an increase in valency. Other factors, such as space orientation of various groups of the glycoclusters, may also have a great effect on the binding affinity.

Application of U-4CR in synthesis of divalent neoglycoconjugates was reported by Murphy et al. (Scheme 133).[256]

Scheme 133. Conformational Space of U-4CR Divalent Neoglycoconjugates



NMR analysis shows that a divalent neoglycoconjugate, where the glycopeptides are bridged by a terephthaloyl group, is a mixture of two conformers. The amide groups of the major isomer have *E-anti* conformations. The spatial relationship and the relative orientation of the sugars are restricted, which may have consequences for the recognition of this and related structures in biological systems. NMR indicates that an 83:17 mixture of *E*/*E* and *Z*/*E* isomers is present at 40 °C in D_2O.

4.8. Protein–Protein Interaction Inhibitors by MCR

The p53 gene has been the subject of intense study, since it was discovered that more than 50% of human cancers have nonfunctional p53 and that abnormalities in this gene are among the most common molecular events correlated with neoplasia. The hdm2 oncogene product suppresses the transcriptional activity of p53 by direct binding to the *N*-terminal transactivation domain of p53. The protein−protein interaction between hdm2 and p53 is mediated by a small piece of a α-helix, as has been recently revealed by an X-ray structure (PDB ID: 1YCR). Evident from the crystal structure and mutational studies are three crutial and hydrophobic pockets occupied by Phe-19, Trp-23, and Leu-26 of the p53 peptide. The discovery and optimization of a series of 1,4-benzodiazepine-2,5-diones (BDPs) that act as potent antagonists of the HDM2-p53 interaction has been reported.[257,258] A library of BDPs was designed using a suite of computational tools that can be used to analyze compound properties as part of the library design process. The library was synthesized utilizing the highly effcient and versatile U-4CR: An anthranilic acid, an amine, an aldehyde, and

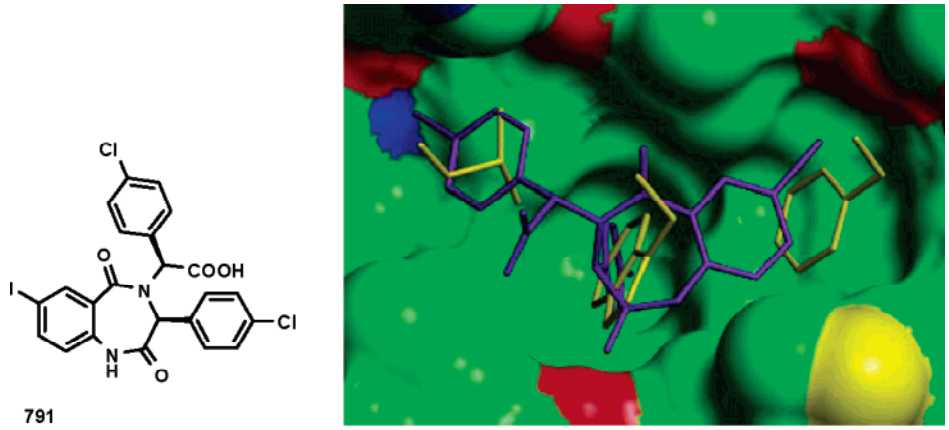
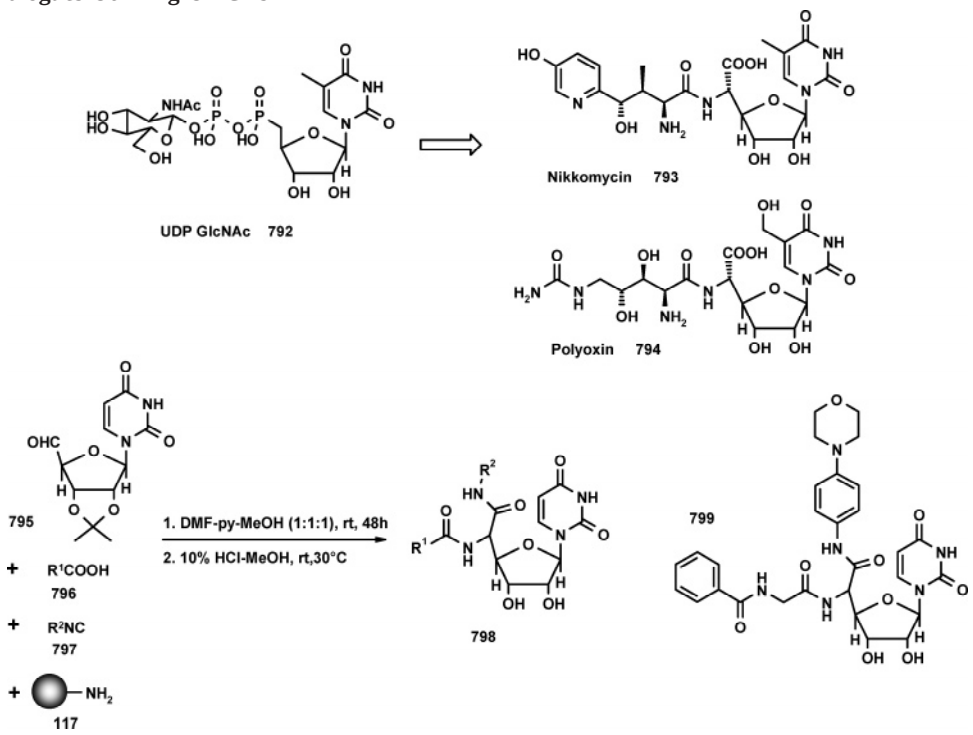


Figure 31. A benzodiazepine p53-hdm2 inhibitor made by a U-4CR in one step and the binding mode as seen by the X-ray structure. In yellow are the side chains of the α-helical amphiphatic p53 peptide in the *i*, *i* + 4, and *i* + 7 positions (F19, W23, L26). In blue is the superimposed benzodiazepine. The green surface represents the acceptor protein mdm2. A nice spatial overlap of the *p*-chlorophenyl and the second *p*-chlorophenyl substituents with Phe and Ile, respectively, and of the *p*-iodophenyl with the indole side chain is observed. (Reprinted with permission from ref 257. Copyright 2005 Elsevier.)

Scheme 134. The Class of UDP GlcNAc Substrate Analogue Antifungals of Nikkomycin and Polyoxin, and a Library Synthesis of Nikkomycin Analogues Utilizing U-4CRs



1-isocyanocyclohexene were combined, followed by acid catalyzed cyclization, producing the desired BDPs in good yield and purity. Twenty-two thousand BDPs were produced in this way and were screened in a fluorescence polarization (FP) peptide displacement assay. Compound **791** showed a potent K_i of 67 nM and potent cell based activity (Figure 31). This is surprising, taking into account the relatively small size of these molecules as compared to the p53 binding peptide.

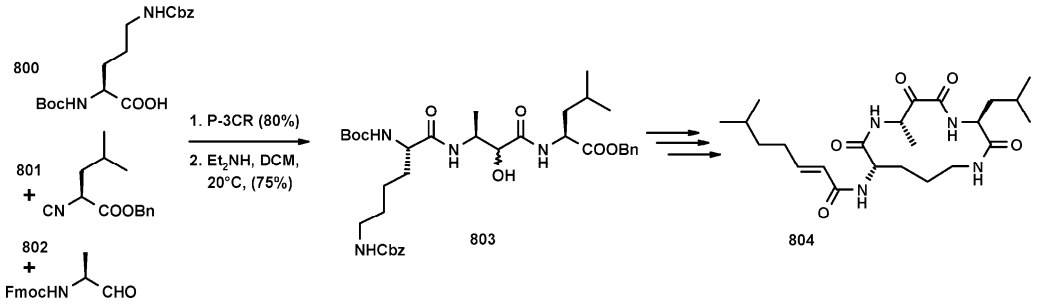
5. MCRs in Natural Product Synthesis

Regarding the almost unlimited possibilities of IMCRs in organic synthesis, it is not surprising to find numerous applications of it in the total synthesis of natural products as well.

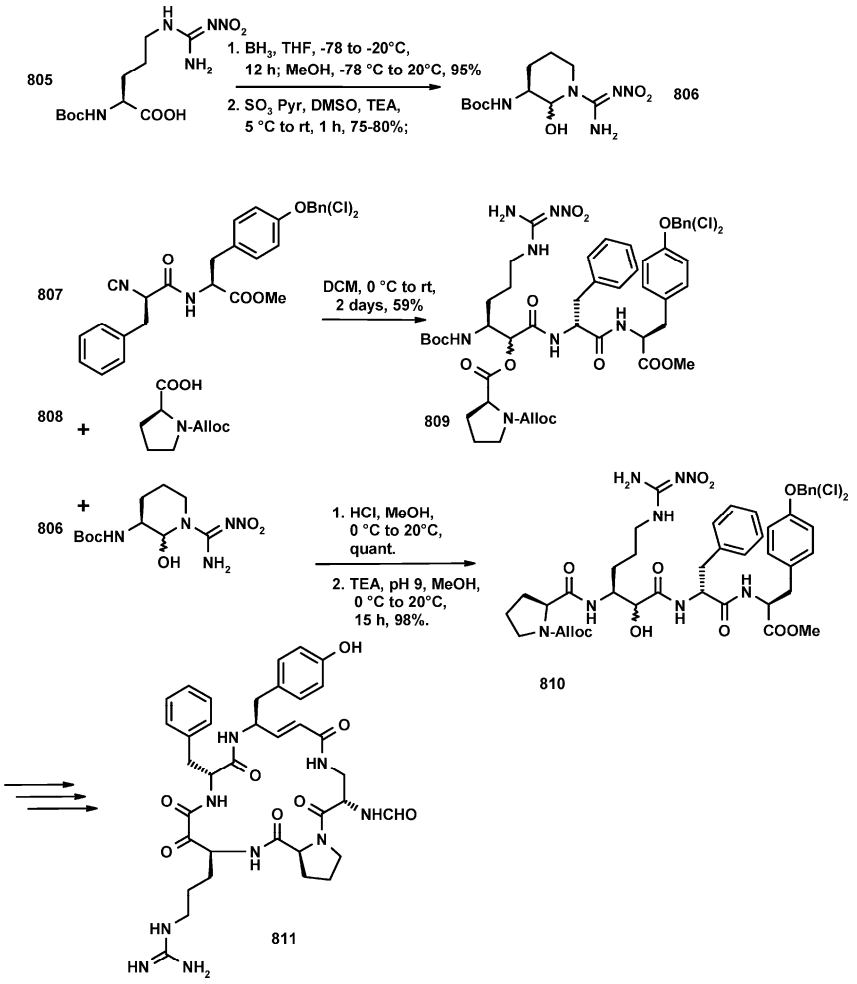
5.1. Nikkomycin

Nikkomycin **793** and polyoxin **794** are naturally occurring peptidyl nucleoside antibiotics targeting fungal chitin cell wall assembly. The structural similarity between these compounds and UDP−*N*-acetylglucosamine **792**, a substrate for chitin synthases, was thought to be responsible for their biological activity. Chemists from Roche prepared libraries of nikkomycin analogues on solid support by U-4CR (Scheme 134).[259] They reacted protected uracil aldehyde building block **795** with an array of isocyanides and carboxylic acids on Rink amide resin **117** and obtained after acidic deprotection and cleavage the screening compounds. In total, 450 different derivatives were prepared. One derivative, **799**, showed comparable activity to nikkomycin.

Scheme 135. The Key Step in Semple's Eurystatine Synthesis Is a PADAM Sequence



Scheme 136. Semple's Cyclotheonamide Synthesis Involving a Key PADAM Sequence



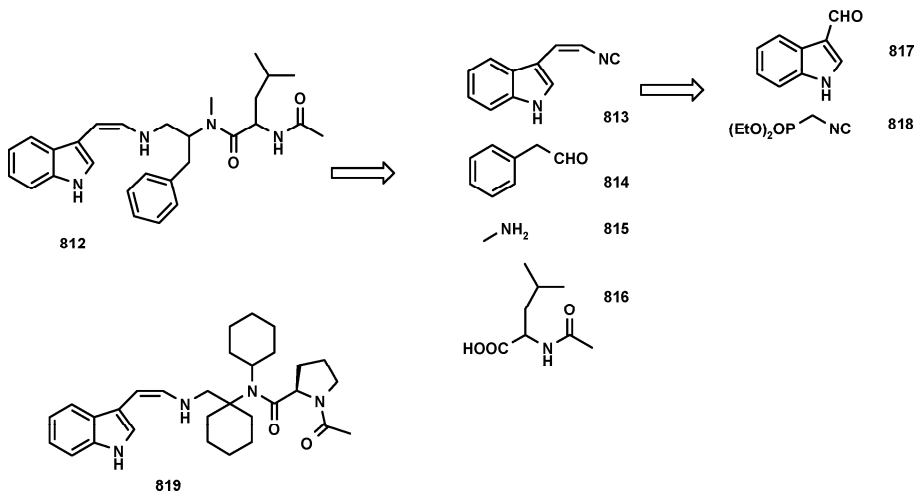
5.2. Eurystatin A and Cyclotheonamide

Eurystatins A and B are 13-membered macrocyclic natural products **804** isolated from *Streptomyces eurythermus* R353-21 featuring leucine, ornithine, and α-ketoalaninamide subunits. They are reported to be potent inhibitors of the serine protease prolyl endopeptidase (PEP). Due to their relative structural simplicity, they serve as attractive targets for the development of new α-hydroxy-*β*-amino amide and α-ketoamide methodologies. Semple performed a concise total synthesis of the peptidase inhibitor eurystatine utilizing the PADAM strategy as a key step (Scheme 135).[260] He reacted orthogonally protected ornithine **800**, chiral Ile derived isocyanide **801**, and chiral Ala derived α-amino-aldehyde **802** in a P-3CR. Base induced Fmoc deprotection and subsequent *O*,*N*-transacylation yielded **803** in 60% over the two steps.

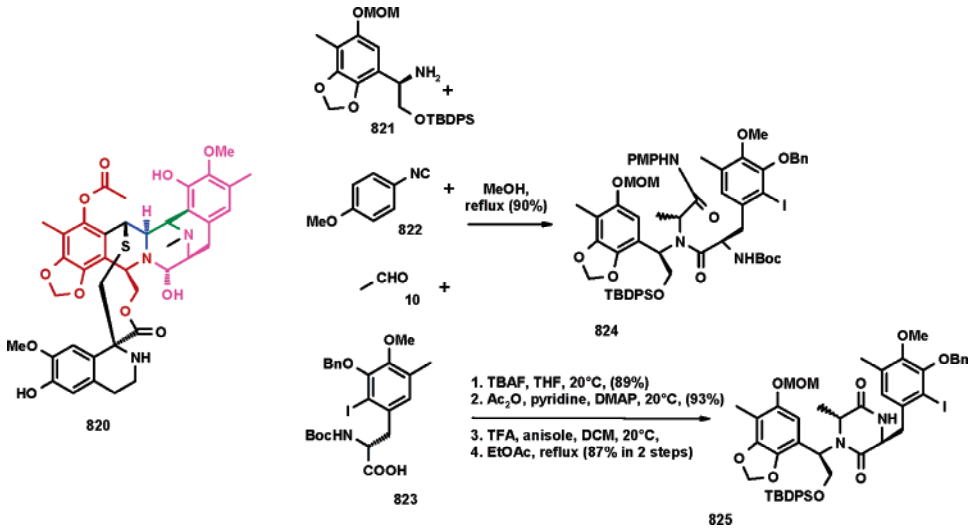
The cyclotheonamides constitute a family of 19-membered macrocyclic pentapeptide derivatives, e.g. **811**, isolated from the marine sponge *Theonella swinhoei.* They are potent, slow-binding inhibitors of several important trypsin-like serine proteases including thrombin (factor IIa), factor Xa, trypsin, plasmin, and tissue plasminogen activator. The potent biological activity is derived from the key pharmacophore, an electrophilic α-ketoarginine amide group, which docks into the S1 pocket of serine proteases and engages the catalytic triad serine hydroxyl group to form a hemiketal (TSA) intermediate, which effectively but reversibly inhibits the enzyme.

Again using PADAM, Semple synthesized an advanced fragment of cyclotheonamide **810** (Scheme 136). P-3CR between suitably protected argininal **806**, dipeptide isonitrile **807**, and proline component **808** afforded adduct **809**.[261]

Scheme 137. The Natural Product Class of Aspergillamides of Intermediate Complexity Can Be Synthesized in Two Steps from Commercially Available Staring Materials—An Example of Rapid Diversification of a Natural Product Motif Using MCR Chemistry



Scheme 138. Fukuyama's Ecteinascidine 743 Total Syntheses Involve as a Key Step a U-4CR—An Example of the Highly Convergent Character of MCRs, Since in One Step >60 atom % of the Total Molecule Is Assembled



Acid catalyzed *N*-Boc cleavage of **809** afforded the corresponding stable vicinal *O*-acyloxyamine hydrochloride salt quantitatively. Dissolution of this salt in methanol and adjustment of the solution pH to ~9 with triethylamine led, via facile *O*- to *N*-acyl migration, to the desired advanced intermediate **810** in practically quantitative overall yield.

5.3. Aspergillamide

Aspergillamides are cytotoxic natural products isolated from *Aspergillus sp*. with unknown mode-of-action. Dömling et al. published the first total synthesis of apergillamide A **812** using a one-pot U-MCR of the corresponding and easily available starting materials (Scheme 137).[8] Synthesis of the α,β-unsaturated indolisocyanide **813** was accomplished by a Wittig condensation from commercially available isocyanomethylphosphonic acid diethyl ester **818** and indole-3-carbaldehyde **817**. The mixture of *E*/*Z* isomers can be separated by chromatography. U-4CR of **813**, phenylacetaldehyde **814**, methylamine **814**, and *N*-acetylleucine **816** affords the target **812** conveniently in one-pot in one step. Moreover, they prepared arrays comprising several hundred derivatives. Several of these derivatives, e.g. **819**, showed similar or better activity in cell based assays.

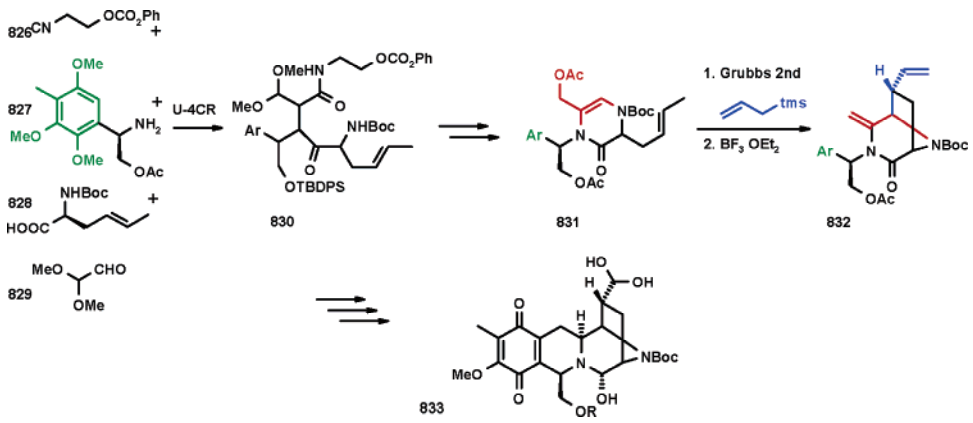
5.4. Ecteinascidine

Fukuyama et al. performed a total synthesis of the antitumor antibiotic ecteinascidine 743, **820**, which is currently undergoing advanced clinical trials.[262] A key reaction in this ambitious total synthesis is the convergent assembly of several parts of this molecule into **824**, which already constitutes 66% of the atoms of the final molecule in a U-4CR (Scheme 138). Using the convertible *p*-methoxyphenylisocyanide **822** allows for the mild conversion into a diketopiperazine **825** in the next steps.

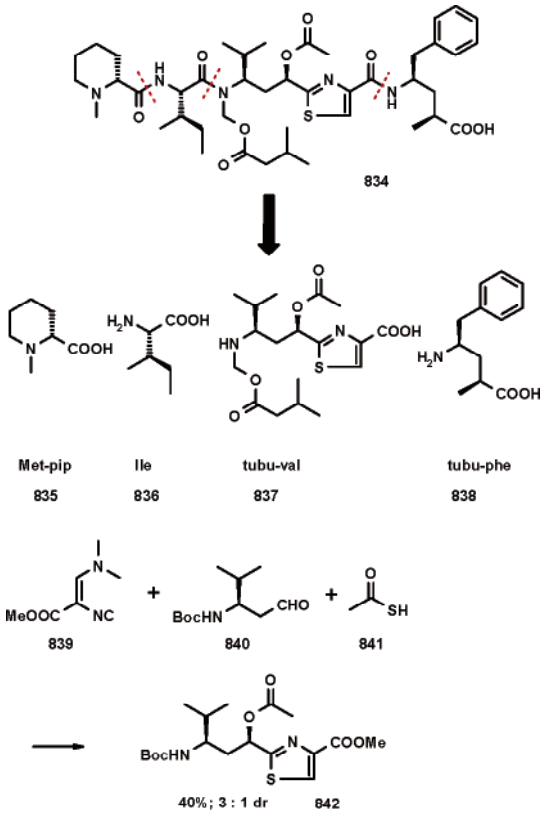
5.5. (–)-Lemonomycin

Similarily, Fukuyama et al. performed synthetic studies toward the class of naphthyridin antibiotics using a U-4CR and a subsequent regioselective diketopiperazine formation.[263] A stereocontrolled construction of the 3,8-diazabicyclo[3.2.1] skeleton, an immanent part of the tetrahydroisoquinoline alkaloid lemonomycin **833**, was recently published (Scheme 139).[264] Once more employing the efficient synthetic strategy for the synthesis of the tetrahydroisoquinoline alkaloids via the U-4CR, **827** was used as

Scheme 139. Stereoselective MCR Assembly of the Natural Product (−)-Lemonomycin



Scheme 140. Stereoselective MCR Synthesis of the Central Part of the Antiangiogenic Natural Product Tubulysin



an amine component and converted to the ketopiperazine **831**. U-4CR of Ugi's convertible carbonate isocyanide **826**, amine **827**, amino acid **828**, and glyoxyaldehyde dimethylacetal **829** in trifluoroethanol was more suitable for an efficient preparation of **830** than using *p*-methoxyphenyl isocyanide. Thus, upon treatment of the amidocarbonate **830** with *t*-BuOK, the oxazolidinone formation proceeded smoothly with release of phenol to provide **831** after reduction and protection. Later cross-metathesis and Lewis acid catalyzed cyclization affords **832**, which can be further elaborated to yield the target natural product.

5.6. Tubulysin

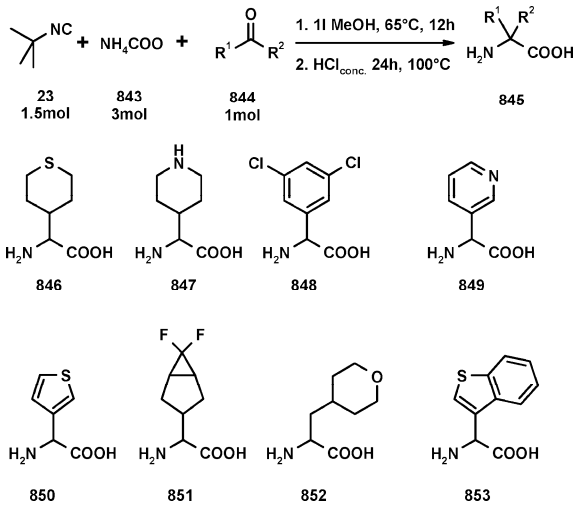
Tubulysin D, **834**, is an extremly potent antiangiogenic tetrapeptide, discovered by Höfle and Reichenbach in a fermentation broth of Myxobacteria. This synthetically challenging molecule is composed of the unnatural amino acids *N*-methylpipecolinic acid **835**, tubuval **837**, tubuphe **838**, and natural Ile, **836**. The synthetically demanding part of tubulysin **837** has been described by a convergent and stereoselective thiazole multicomponent reaction (Scheme 140).[265] The central part of tubulysin is thus amenable in one step in 40% yield from its precursors, protected homo-Val carbaldehyde **840**, thioacetic acid **841**, and multifunctional isocyanide **839** in a dr of 3:1 favoring the desired diastereomer, **842**.

6. Miscellaneous Applications of IMCRs

6.1. Peptides and Aminoacids

Since the very beginning of use of U-MCRs, it has been known that these reactions provide an elegant way to prepare (un-)natural monosubstituted α-amino acids. Chemists from Pharmacore claimed unnatural amino acids as pharmaceuticals in a recent patent application (Scheme 141).[266] Herein,

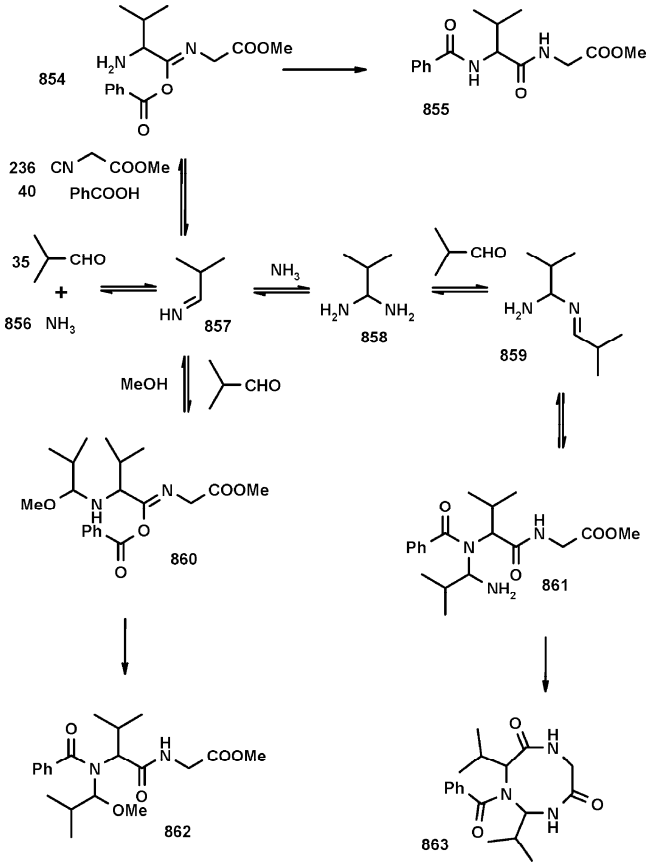
Scheme 141. Large Scale Preparation of Unnatural α-Amino Acids Using U-4CR of Ammonium Formiate and Hydrolysis



mole scale syntheses of amino acids are described involving ammonium formate **843**, *tert*-butyl isocyanide **24**, and aldehydes or ketones **844** and subsequent acidic hydrolysis. Typical examples obtained are **846**−**853**.

If ammonia is used as amine component in Ugi reactions, the desired peptide sometimes is obtained only as the minor

Scheme 142. Side Reactions Using Ammonia as a Strating Material in a U-4CR Yielding Eight-Membered Rings Containing an Aminal Structure and Linear Products Involving 1 equiv of Solvent Methanol and a Second Aldehyde, Overall Comprising a 6-CR



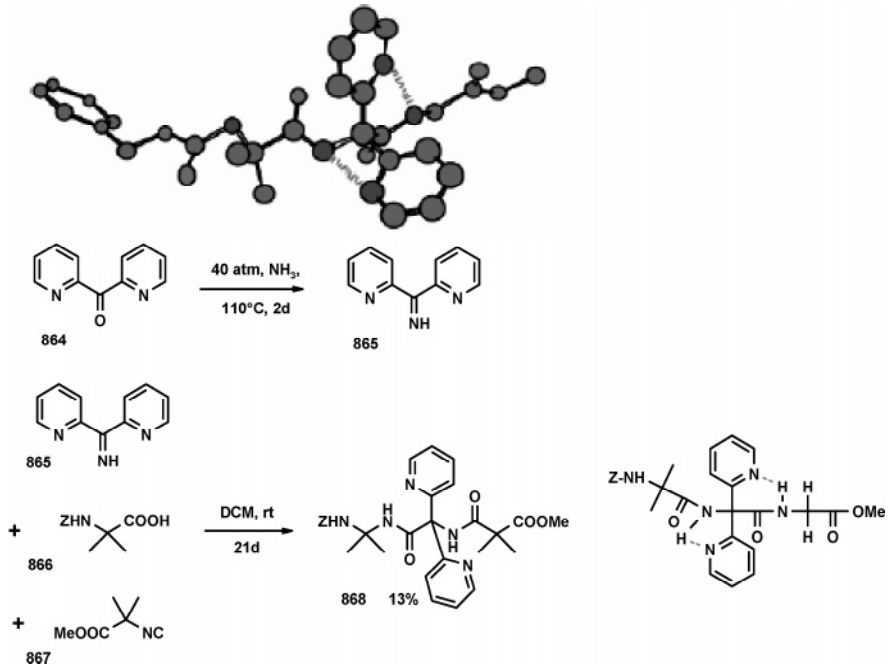
product or in traces (Scheme 142).[267] Side reactions such as six-component couplings, to form **862** and cyclic **863**, have been found to be responsible for this observation. These side reactions can be suppressed by using non-nucleophilic alcohols, such as trifluoroethanol.

α,α-Disubstituted amino acids provide an excellent tool for the construction of conformationally rigid peptides due to the steric hindrance associated with the quaternary α-carbon atom. It may shown that peptides, even small oligopeptides, rich in α,α-disubstituted glycines, adopt a β-turn structure, 3_{10}/α-helical structures, or planar, fully extended conformations. Unfortunately, bulky α,α-disubstituted amino acids and their peptides are not easily accessible. The U-4CR is very useful and potent for the synthesis of sterically hindered peptides containing α,α-disubstituted glycines (Scheme 143). Yamada et al. synthesized α,α-di-(2-pyridyl)glycine containing tripeptides, e.g. **868**, using U-4CR.[268] According to NMR investigations, these peptides adopt an interesting conformation due to intramolecular hydrogen bonding between the pyridine nitrogen and the adjacent backbone NH.

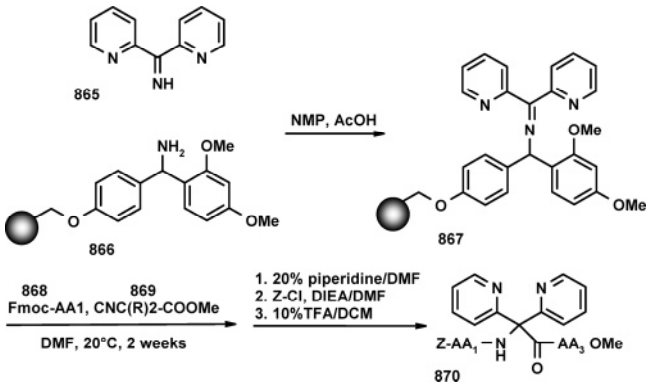
Similarily, tripeptides containing a α,α-disubstituted glycine with two pyridine rings, α,α-di(2-pyridyl)glycine (2Dpy), were synthesized by the solid-phase U-4CR using di(2-pyridyl)methanimine **865** attached directly to a Rink amide resin **866**. Interestingly, yields of the tripeptides, Z-AA1-2Dpy-AA3-OMe (AA1 and AA3 = Gly or Aib), were markedly improved, compared with yields by the solution method.[269] The resin-bound imine component **867** was subjected to the modified Ugi reaction conditions along with Fmoc amino acid and the isocyanide as shown in Scheme 144. Investigation of different solvents such as DMF, DCM, TFE, and NMP and their mixtures yielded NMP-DCM as optimal.

A U-4CR was described to build up novel cyclic somatostatin analogues deriving from sandostatin and from TT-232, **876**.[270] A photolytically cleavable amine derivative of the nitroveratryl type, **871**, is used for the U-4CR (Scheme 145). Because of a racemic build up of the new stereocenter of the diaminoglutaric acid, and racemization of the isonitrile component **874**, four diastereomeric peptides resulted, i.e.

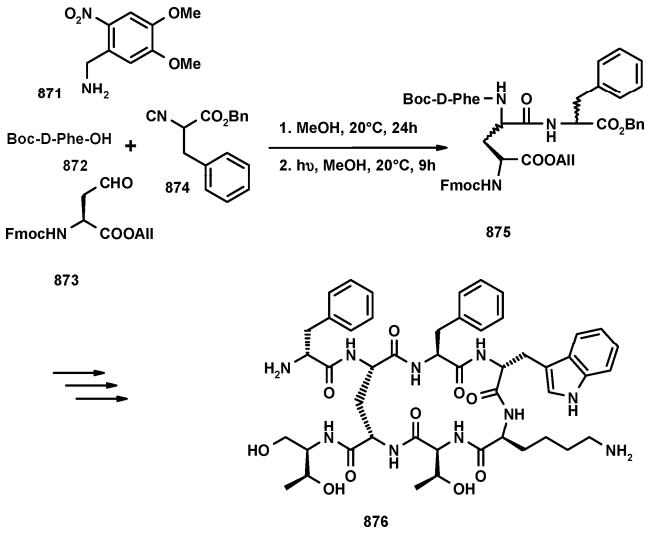
Scheme 143. Synthesis of Small Tripeptides Containing α,α-Disubstituted Glycines by a U-4CR and Their Assumed Respective Intramolecular Hydrogen Bonding (Reprinted with permission from ref 268. Copyright 2004 The Royal Society of Chemistry.)



Scheme 144. Solid-Phase Synthesis of Small Peptides Containing α,α-Disubstituted Glycines Using a Mixed Strategy of U-4CR and Classical Peptide Coupling on a Rink Amide



Scheme 145. Use of a U-4CR in the Synthesis of Modified Somatostatine Derivatives Using a Photoprotecting Group Strategy

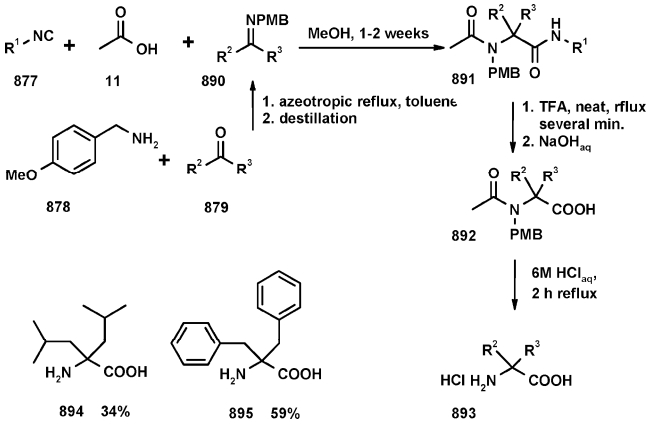


875, which were separated by HPLC. The stereochemistry of the cyclopeptides could be easily and unambiguously assigned by chiral gas chromatography and a reference sample of enantiomerically pure (2*S*,4*S*)-diaminoglutaric acid.

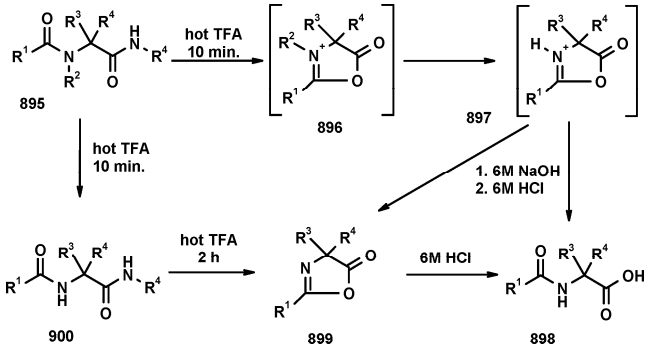
Costa et al. described an improved approach for the synthesis of α,α-dialkyl glycine derivatives **893** by the U-4CR (Scheme 146).[271] The corresponding dialkyl ketone **879** and *p*-methoxybenzylamine **878** derived Schiff bases **890** were formed by azeotropic reflux in toluene and subsequent distillation. The isonitrile required for the reaction can be relatively simple and its selection is based on cost, as the group it generates is easily removed under acidic conditions; in addition, this removal is not visibly affected by the bulkiness of the α-alkyl groups. Being a good leaving group from the *N*-terminal amino group of the amino acid, 4-methoxybenzyl was the choice for the amine component of the reaction. The method is illustrated with the synthesis of a series of acyl derivatives of several α,α-dialkyl glycines in generally overall good yields, e.g. **894** and **895**.

The same group could also show that several symmetric *N*-acyl-*N*,α,α-trialkyl glycine amides can be selectively cleaved with trifuoroacetic acid (Scheme 147).[272] In most investigated cases, it was possible to obtain the corresponding *N*-acyl-*N*,α,α-trialkyl and *N*-acyl-α,α-dialkyl glycines in fair to good yields directly from the reaction adducts. With some

Scheme 146. α,α-Dialkyl Glycine Derivatives by the Ugi Reaction



Scheme 147. Processes Involved in the Acidic Cleavage of the U-4CR Product



of the bulkier compounds, the results show that the selectivity of cleavage is concentration dependent with respect to the acid, which suggests kinetically controlled processes. The isolation of a stable oxazolone **899** as the product of some of the reactions seems to confirm that amide cleavage involves in all cases formation of an oxazolone-type derivative.

A simple approach to several cyclopeptidemimetics containing an *N*-alkylated amino acid, e.g. **901**, was found via a U-4CR followed by a ring-closing metathesis starting from readily available precursors (Figure 32).[273] The author mention that the combinatorial technique has the advantage that different polar, hydrophilic, or hydrophobic moieties can be placed at any position in the cycles and unnatural amino acids can also be incorporated.

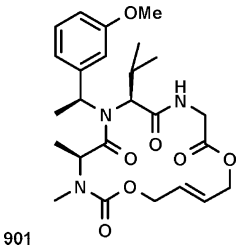
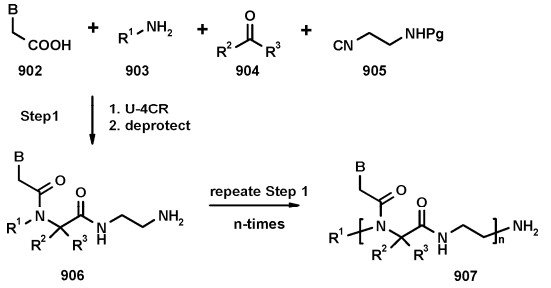


Figure 32. *N*-Alkylated cyclopeptide mimetics by U-4CR and subsequent metathesis.

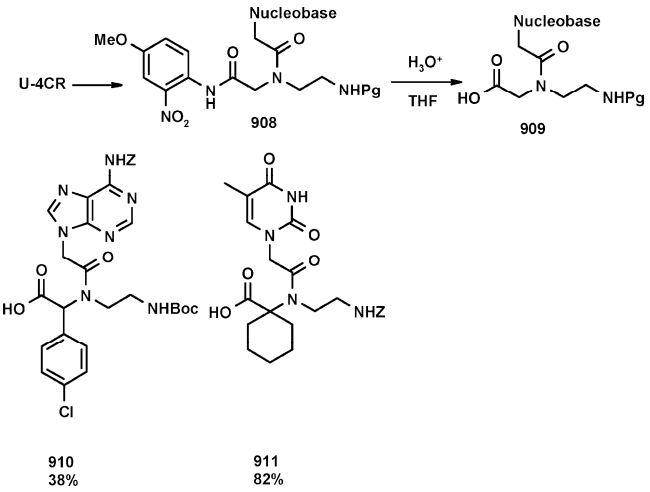
6.2. Peptide Nucleic Acids (PNAs)

Using ethylenediamine derived *N*-monoprotected isocyanides, nucleobase acetic acids, and primary amines and aldehydes and ketones affords an *N*-protected PNA monomer, which upon deprotection affords a novel amine component

Scheme 148. The First Proposal of PNA Synthesis via Repetitive U-4CRs



Scheme 149. Versatile Strategy of PNA Building Blocks with Free Carboxy Termini



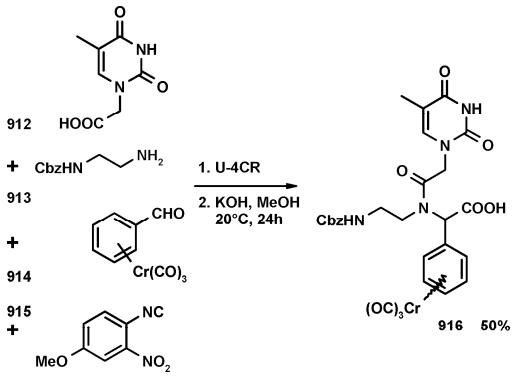
which can repeatedly be extended to PNA oligomers (Scheme 148).[274,275] This constitutes a versatile and potentially efficient alternative toward classical PNA synthesis. Moreover, a couple of ethylenediamine derived monoisocyanides containing different protecting groups, e.g. Boc, Z, Alloc, Fmoc, or photolabile NVOC, allowing different synthetic strategies have been described. Since the first introduction of Ugi's MCRs for the versatile and convenient one-pot synthesis of peptide-nucleic acids, several new applications have appeared.

Martens et al. described a new approach for PNA synthesis, whereby C-terminal unprotected mono- or oligomers result.[276] Cleavable isocyanides, mostly 4-methoxy-2-nitrophenyl isocyanide, react with an appropriate oxo-component, a nucleobase acetic acid, and a suitable monoprotected diamine, yielding the U-4CR product (Scheme 149). Acidic or basic cleavage of these intermediates yields PNA C-terminal unprotected building blocks in overall good yields. Obviously, this versatile synthesis allows for the synthesis of valuable building blocks with variable substitution patterns, e.g. **910** and **911**.

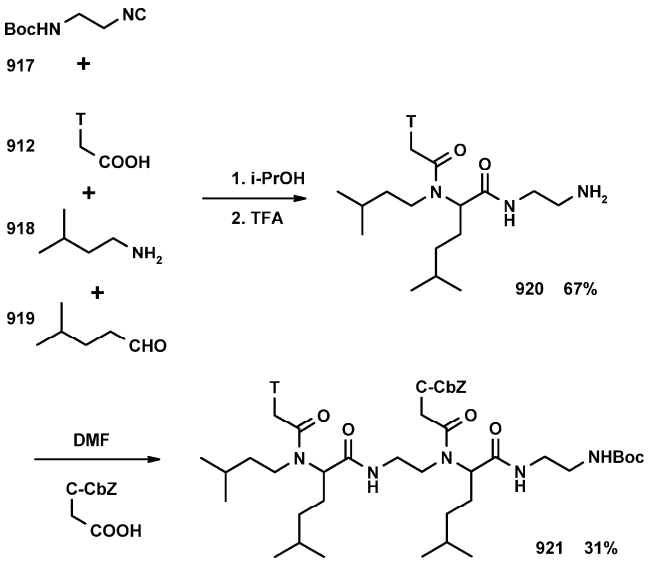
A new PNA monomer was synthesized for use as the isocyanide component in a Ugi condensation in order to produce peptide nucleic acid (PNA) also labeled with $Cr(CO)_3$ (Scheme 150).[277,278] The unique chemical and spectroscopic properties of organometallic complexes can be exploited in PNAs as a means of comparing various biological and diagnostic issues, such as the improvement of lipophilicity and the direct detection of a labeled biomolecule.

On the basis of our initial publications, Xu et al. published the synthesis of PNA dipeptides using two sequential U-4CRs

Scheme 150. Organo Chromium Labeled PNAs by U-4CR



Scheme 151. Repetitive U-4CRs Resulting in a PNA Dimer



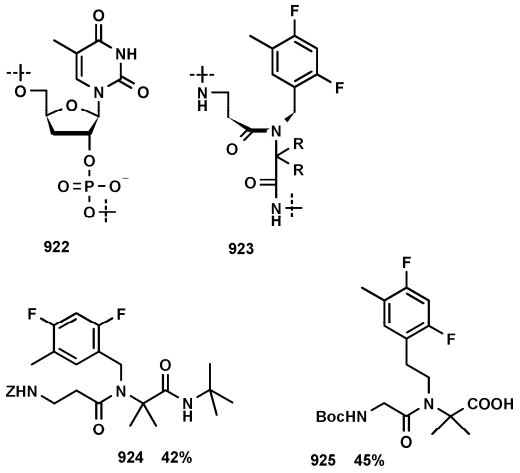
(Scheme 151).[279] The intermediate PNA monomer **920** was Boc-deprotected. Upon addition of pyridine, the primary ammonium salt was deliberated and the second cycle toward the PNA dimer was performed in DMF as a solvent yielding **921**.

Difluorotoluene nucleoside **923** has been developed as a nonpolar shape mimic for natural thymidine **922**, and it has been intensively used as a probe of the biological noncovalent interactions of oligonucleotides. Unexpectedly, the difluorotoluene nucleoside serves as a template for DNA synthesis even though it lacks standard polar hydrogen bonding. Thus, Shibata et al. reported the synthesis of PNA dipeptides **924** and **925** having a difluorotoluene group appended to the nitrogen atom using U-4CR (Scheme 152).[280,281] The preparation of the target compounds undoubtedly could be accomplished by conventional peptide synthesis procedures. However, this would require multistep syntheses as compared to the elegant and short one-pot synthesis from commercially available starting materials.

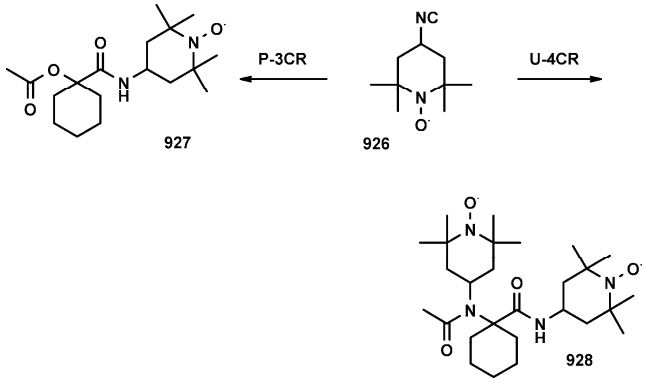
6.3. IMCR To Generate ESR Spin Labels

Zakrzewski et al. synthesized 4-isocyano-2,2,6,6-tetramethylpiperidine-1-oxyl **926** as a valuable precursor for new nitroxides useful for EPR spin-label measurements (Scheme 153).[282] The corresponding isocyanide can be smoothly reacted in Ugi and Passerini reactions, thus yielding **928** and **927**, respectively. This method could potentially become a

Scheme 152. Synthesis of PNA Monomer Building Blocks Containing Unnatural Bases Devoid of Each Hydrogen Donor−Acceptor Function



Scheme 153. U- and P-MCRs Involving a Stable Isocyanide Bearing an NO Radical—Useful in the Investigation of (Bio)Molecules by ESR Spectroscopy



powerful tool for the parallel and fast EPR investigation of molecules in diverse biological environments.

6.4. Polymers

Ugi from 1962 to 1967 was research head of the central laboratory at Bayer in Leverkusen. During this time he studied the industrial applications of isocyanide based MCRs. Besides agricultural and medicinal aspects of MCR research, he was also highly interested in investigating material science aspects.[283] Recent and future usage of IMCRs in the synthesis of polymers will certainly lead to new materials with novel properties.

Polymeric hydrogels belong to a class of materials that can swell largely in water and maintain their three-dimensional network structure in the swollen state. The mechanical, solvent permeability, swelling, and hydrophilic/hydrophobic properties of a hydrogel can be modulated by choice of type of polymer/monomer and method of synthesis. Among biopolymers that can form hydrogels are alginate, collagen, and chitosan. These polymers are biocompatible and attractive in the development of potential materials for drug release systems and tissue engineering.

Crescenzi et al. provided data demonstrating that IMCRs of Ugi and Passerini type are simple and versatile methods for the synthesis of hydrogels based on a variety of carboxylated polysaccharides (Figure 33).[284] In their work, the biopolymers considered are sodium hyaluronate and

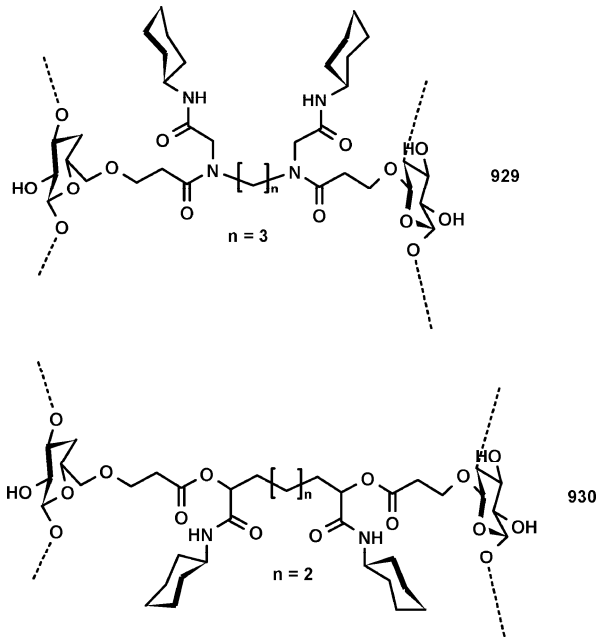


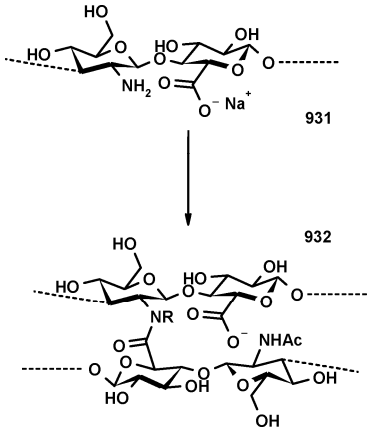
Figure 33. Cross-linking of polysaccharides via U- and P-MCR, respectively.

sodium alginate. Nonnatural carboxylated polysaccharides were commercial, e.g. (carboxymethyl)cellulose, or were obtained by carboxymethylation or selective oxidation of primary alcohol groups of scleroglucan and dextran. Hydrogels prepared via the Passerini reaction were transparent, alkali labile materials whereas the transparency of the Ugi gels depended on the polysaccharide, the cross-linker, and the degree of cross-linking. The Ugi gels were stable for several months at a pH ranging from 1.3 to 11 and up to temperatures over 90 °C. The structure of the networks was studied by means of ^{13}C CP-MAS and ^{15}N CP-MAS NMR spectroscopy. A quantitative NMR analysis and elemental analysis of the dry gels allowed for the estimation of the efficiency of the reactions, i.e., the actual degree of cross-linking, which appeared to be about 80% of theoretical. The influence of added salt and pH on the swelling of several Ugi gels with different degrees of cross-linking was studied in a qualitative manner.

Partially deacylated hyaloronic acid (deHA) chains are well suited for chemical gel formation by means of U-4CR processes inasmuch as they exhibit a sufficient degree of polymerization and two out of four functional groups necessary for such rapid and high yield reticulations.[285] Chemical gels have been prepared with different degrees of cross-linking by means of a U-4CR involving aqueous deHA, formaldehyde, and cyclohexylisocyanide: the gels are mechanically stable and exhibit good water uptake strongly dependent on the extent of cross-linking, as expected. DeHA samples have also been selectively *N*-sulfated or *O*-sulfated: the former exhibit anticoagulant properties well exceeding those of the latter and not too inferior to those of heparin. Partially deacetylated HA is also a very useful starting product for selective *N*-sulfation and *N*- and *O*-sulfation to various extents. Quite interestingly, the *N*-sulfated partially deacetylated HA samples that have been studied exhibit excellent anticoagulant properties by far superior to those of *O*-sulfated samples and not too inferior to those typical of heparin. In the author's opinion, this may be qualitatively connected with the well-known role played by *N*-sulfation

in determining the anticoagulant properties of heparin samples (Scheme 154).[286]

Scheme 154. Partially Deacylated Hyalluronic Acid Cross-linked via U-4CR Yields Stable Hydrogels



The synthesis of negatively and positively charged polyelectrolytes from scleroglucan is described.[287] The negatively charged polymers were reticulated using the Ugi four-component condensation, obtaining negatively charged hydrogels. The positively charged polymers were reticulated using diethyl squarate (3,4-diethoxy-3-cyclobutene-1,2-dione, DES) to obtain positively charged hydrogels.

Alginate is regarded as a nontoxic, nonimmunogenic, and biodegradable polymer, which makes it an attractive candidate for biomedical applications. Rheological and structural properties of aqueous alginate during gelation via the U-4CR have been studied by Bu et al.[288] It was demonstrated that temperature, polymer, and cross-linker concentration could be utilized to tune the physical properties of the Ugi gels, e.g. **933**, such as structure, transparency, and viscoelasticity (Figure 34).

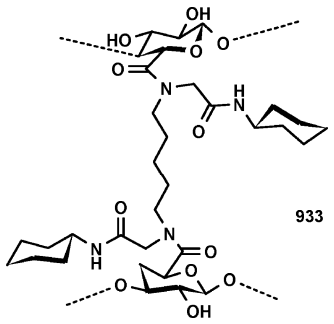


Figure 34. Cross-linked alginate by U-4CR.

Similarily, a new type of hyaluronan based polymeric network has been prepared applying the well-known cross-linking processes based on aqueous U-4CRs.[289] In this study, lysine as an ethyl ester has been used as a cross-linking agent, followed by saponification. This synthesis allowed obtaining HA hydrogels, e.g. **934**, with suitable physical properties. These hydrogels have been characterized using solid-state NMR spectroscopy and studying their swelling properties. The cross-linking degree has been evaluated by changing the molar ratio of the cross-linker lysine (Figure 35).

Wright et al. synthesized libraries of polymers using U-4CR of norbornenyl starting materials, e.g. **935**, followed by ring opening metathesis polymerization (ROMP) (Scheme 155).[290] Polymerization of these monomers **936** and **937** under the optimized conditions gave good yields of polymers

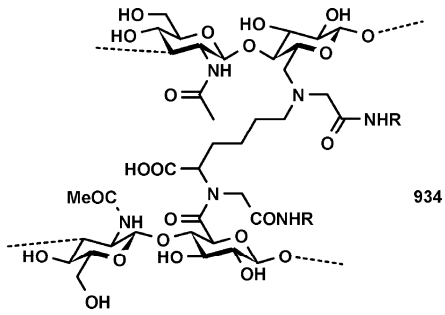
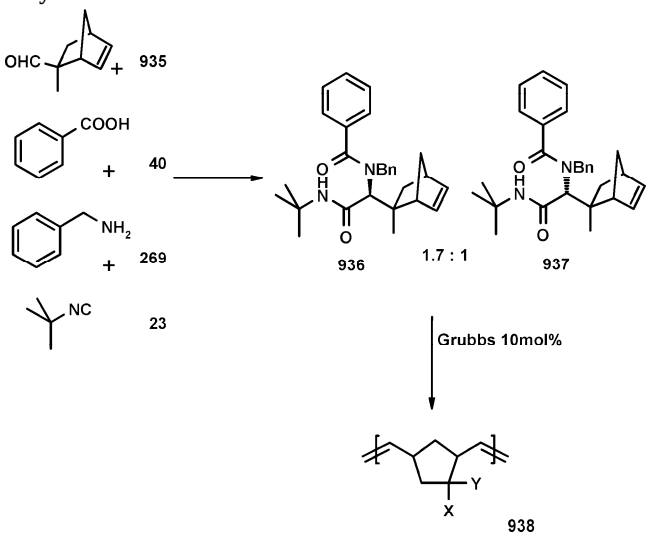


Figure 35. HA network formed by cross-linking via U-4CR using aqueous formaldehyde, cyclohexyl isocyanide, and lysine.

Scheme 155. U-4CR of Starting Materials Incorporating Cyclic Alkenes and Subsequent ROMP Afford Libraries of Polymers



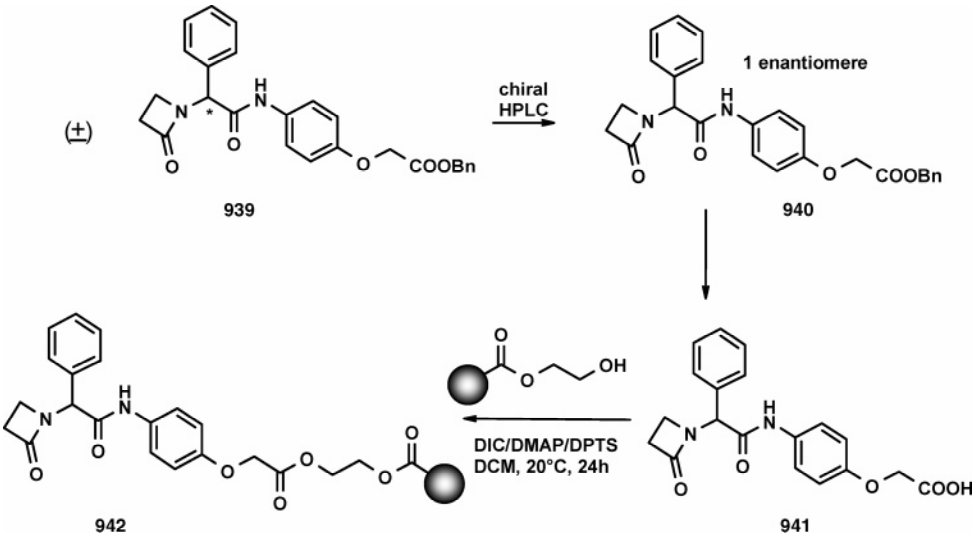
(**938**) with relatively high molecular weights and narrow dispersities, as is characteristic of ROMP based polymerizations. Determination of the glass transition temperature revealed that the polymers were highly crystalline in nature, consistent with a high degree of hydrogen bonding within the polymer. The polymerization of the chiral monomers, both as individual diastereomers and as a mixture, revealed some interesting selectivity. Polymerization of the mixture (which produces a copolymer) gave polymers of much higher molecular weights than polymerization of the individual diastereomers. The polydispersities were uniform and narrow. These polymers have structural features reminiscent of polypeptides, and the process could be extended to the preparation of chiral materials. Other variations of this strategy should be possible and could lead to a large variety of new materials.

6.5. Stationary Phases for Chromatography

The requirement to produce enantiomerically pure drugs and agrochemicals is driven by restrictive regulations, based on the often different biological activity of the two enantiomers. Moreover, the patent life of racemic products can be extended by switching to the right enantiomer ("racemic switch").

Frechèt et al. designed and prepared chiral stationary phases using selectors derived from Ugi multicomponent condensation reactions and a combinatorial approach (Scheme 156).[291] Combinatorial approaches together with high-throughput screening have been used to develop highly

Scheme 156. Application of a U-4CR To Prepare Chiral Stationary Phases for HPLC



selective stationary phases for chiral recognition. Libraries of potential chiral selectors have been prepared by the U-4CR and screened for their enantioselectivity using the reciprocal approach involving a chiral stationary phase with immobilized model target compound *N*-(3,5-dinitrobenzoyl)-*R*-L-leucine. The best candidates were identified from the library of phenyl amides of 2-oxoazetidineacetic acid derivatives, e.g. **940**. This screening also enabled specification of the functionalities of the selector desired to achieve the highest level of chiral recognition. The substituents of the phenyl ring adjacent to the stereocenter of the selector candidates exhibited the most profound effect on the chiral recognition. The best candidate was then synthesized on a larger scale, resolved into single enantiomers, e.g. **941**, using preparative enantioselective HPLC, and attached to porous poly(2-hydroxyethyl methacrylate-*co*-ethylene dimethacrylate) beads via an ester linkage to afford the desired stationary phase, e.g. **942**. Selectivities *R* as high as 3.2 were found for the separation of a variety of amino acid derivatives.

6.6. Solid-Phase MCRs

Alternatively to the synthesis of MCR libraries in solution and subsequent purification via resin capture, scavenging, or high-throughput HPLC, a growing body of literature on the solid-phase MCR, especially of resin bound isocyanides, appeared. Table 2 gives an overview of different types of resins used in isocyanide based MCRs. The corresponding applications of these are mentioned in the different sections.

Mostly, solid-phase isocyanides were prepared in a multistep procedure on the resin. Several different types of isocyanides, cleavable under different conditions, are described; some of them are commercially available. A new general strategy toward amino acid derived resin bound isocyanides involves reaction of a brominated resin with the easily available potassium salt of isocyanoacetic acid or its substituted derivatives. Thus, the strategy differs markedly from others where the isocyanide was prepared via the two-to-three-step sequence involving amination, formylation, and dehydration directly on the resin.[301] Acid and base labile variants **943** and **944** were prepared starting from 4-(bromomethyl)phenoxymethyl polystyrene and 4-(bromomethyl)-benzoic acid coupled onto aminomethyl polystyrene, respectively.

A library of *N*-substituted amino acid esters was synthesized using a solid-phase bound organic isocyanide that provides a C1 synthon to the final molecule.[302] This novel four-component, one-pot reaction delivers the final products in acceptable yields with high purities of the crude reaction products, e.g. **960**−**962**, facilitating the final purification (Scheme 157). The preparation of the isocyano resin is also described with the intermediates being controlled by ATR spectroscopy. This interesting new solid-phase methodology certainly holds the potential for multiple accesses to diverse heterocyclic motifs.

Chen et al. from Procter & Gamble Pharmaceuticals described Rink-isocyanide resin (Scheme 158).[303] The resin provides a new universal platform for Ugi multicomponent reactions. It can be conveniently prepared from Rink amine by formylation with HCOOH/diisopropylcarbodiimide and subsequent $POCl_3$/diisopropylamine dehydration. Fifty gram batches of this stable isocyanide **450** have been described in the literature. Applications were demonstrated by the traceless synthesis of diketopiperazines **963**, benzodiazepines **964**, and 5-substituted 1*H*-tetrazoles **965**. In the former two scaffolds, Fmoc-protected amino acid building blocks were reacted in a U-MCR. Cyclization with piperidine in DMF, followed by acid induced cleavage, results in library compounds in good puities and moderate to good yields. No uncyclized products were observed. *N*-Substituted α-aminotetrazoles in turn are available from the reaction of trimethylsilyl azide, an aldehyde, and a primary or seconday amine and subsequent traceless TFA cleavage. As opposed to the classical Ugi tetrazole synthesis, here, *N*-unsubstituted tetrazoles are formed. Another application is the earlier discussed Groebcke-type MCR followed by *N*-acylation under cleavage from the resin.[158]

Ley et al. reported a polymer-supported [1,3,2]-oxazaphospholidine for the conversion of isothiocyanates **966** to isocyanides **967** and their subsequent use in an Ugi reaction to form **968**.[304] Five isocyanides, e.g. **969**, were prepared in excellent yields and purities from the isothiocyanates, and the subsequent U-4CR toward 18 2-isoindolinone-7-carboxamides, e.g. **970**, afforded the array with 72−98% yields (Scheme 159).

6.7. Bioconjugates by MCR

Ziegler et al. has described the conceptual potential of the U-4CR for the easy and parallel construction of bioconjugates.[305] Thus, they investigated bovine serum albumin and

Table 2. Resin Bound Starting Materials of IMCRs

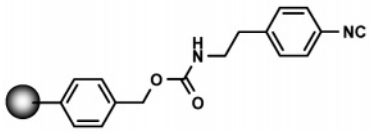
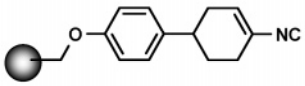
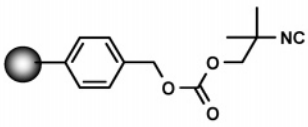
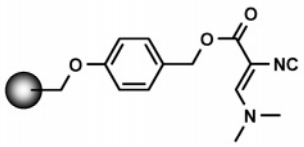
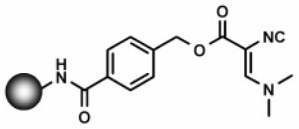
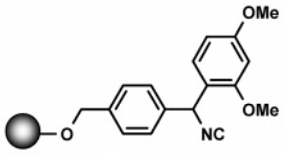
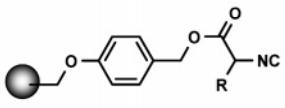
	Structure	Comments/Literature
643		isocyanide bound onto safety-catch linker resin; elemental analysis indicates a loading of 0.8 mmol/g; upon Boc-activation the product can be easily cleaved from resin with a variety of nucleophiles; useful for benzodiazepine, ketopiperazine, *N*-acyl aminoacid, dihydroquinoxalinone synthesis;[292]
514		convertible Armstrong-type isocyanide;[167] useful in the synthesis of *N*-acyl aminoacid, 'Freidinger-like' γ–lactams, and lactam-ketopiperazines;
197		Resin-bound carbonate convertible isonitrile (CCI resin) with a loading of 0.87 mmol/g; 200 g scale procedure available; cleavable under strongly basic conditions: K^{t}BuO (2 equiv, 1 M solution in THF), THF, rt, 16 h;[104,173]
943		Acid labile Wang-resin bound 3-N,N-(dimethylamino)isocyanoacrylate; loading 0.36 mmol/g; useful in thiazole, imidazole and other heterocycle synthesis; cleavable with 50%TFA/DCM; commercially available;[69,70]
944		Base labile resin bound 3-N,N-(dimethylamino)isocyanoacrylate; useful in thiazole, imidazole and other heterocycle synthesis;[69,70]
450		Rink amine type isocyano resin; 50 grams scale 2-step procedure available;[158] cleavable under strong acidic conditions; applications were demonstrated by the traceless synthesis of diketopiperazines, benzodiazepines, and 5-substituted 1*H*-tetrazoles;[158,298 298]
945		Amino acid derived isocyanides bound onto acid labile Wang resin; R = diverse α, β or γ-acids; commercially available with a variety of amino acids;[104,173]

Table 2 (Continued)

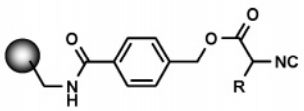
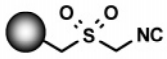
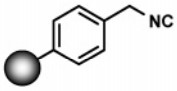
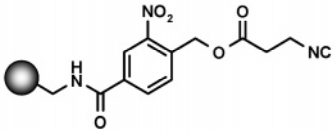
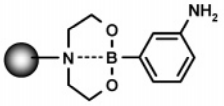
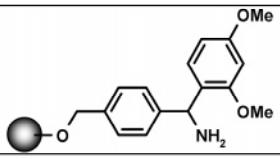
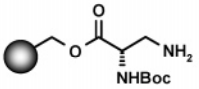
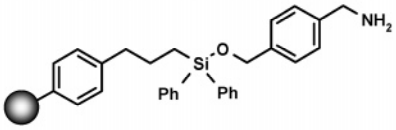
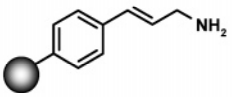
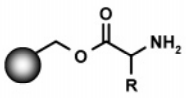
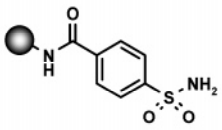
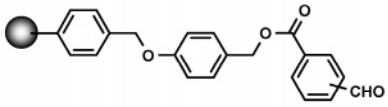
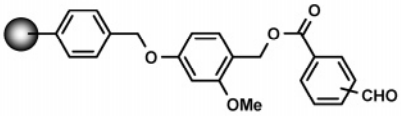
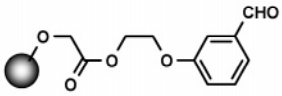
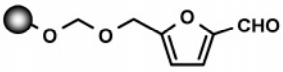
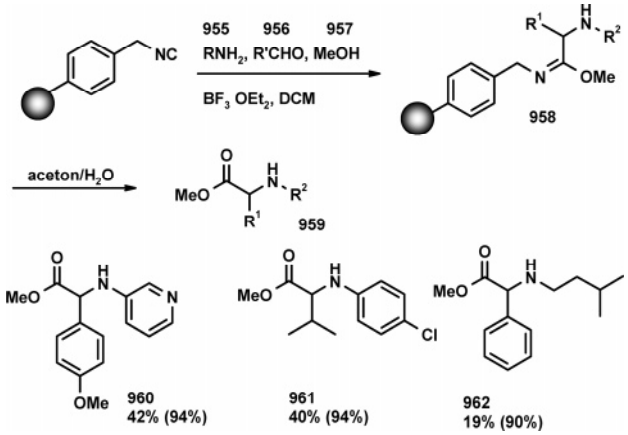
	Structure	Comments/Literature
946		Amino acid derived isocyanides bound onto base labile resin; R = diverse α, β or γ-acids; commercially available with a variety of amino acids;[104,173]
947		Van Leusen's TosMIC resin bound; prepared from polystyrene in a multistep sequential synthesis; useful in oxazol and imidazol synthesis;[293,294]
948		Aminomethyl polystyrene or TentaGel-NH_2 as starting material for the synthesis of a convertible isocyanide; reported loading 0.61 mmol/g.[297]
752		Photocleavable isocyanide resin;[245]
949		Solid phase aniline, which upon release liberates a boronic acid suitable for further transformations;[295]
866		Rink amine resin as amine component; product is acid cleavable;[296,297]
521		α-*N* protected diaminopropionic acid hydroxymethyl Merrifield resin; useful for the synthesis of β-turn mimetics;[168]
278		Solid phase benzylamine, products to be liberated with HF;[119]
950		Ugi reaction with olefinic amine inputs and subsequent traceless cleavage via ring-closing metathesis.[298] Useful for the synthesis of Freidinger lactams as β-turn mimetics.

Table 2 (Continued)

	Structure	Comments/Literature
951		Wang resin and hydroxymethyl resin bound amino acids useful for 1,4-benzodiazepine-2,5-dione and ketopiperazine synthesis respectively;[299]
356		Sulfonamide resin serves as "amine component" yielding α-aminosulfonyl amides. The products can be cleaved under acidic conditions;[137]
952		Wang type aldehyde resin; cleavage with 10% TFA/DCM; MCR products sometimes not compatible with these conditions, e.g. β-lactams;[89,90]
953		Sasrin type aldehyde resin; mildly cleavable with 1% TFA in dry DCM;[89,90]
954		An alkoxyacetyl group (AAc) linker on MPEG bound aldehyde useful in Ugi chemistry;[300] available in 1 step form commercial MPEG; cleavable with $Yb(OTf)_3$ (0.3 equiv), MeOH, rt, 4 h,
281		Acid cleavable 4-hydroxymethyl furfural bound onto MPEG useful for IMCR/Diels Alder combinations.[124]

Scheme 157. $BF_3 \cdot OEt_2$ Mediated 3-CR Affording *N*-Alkylated or Arylated α-Amino Acid Methyl Esters

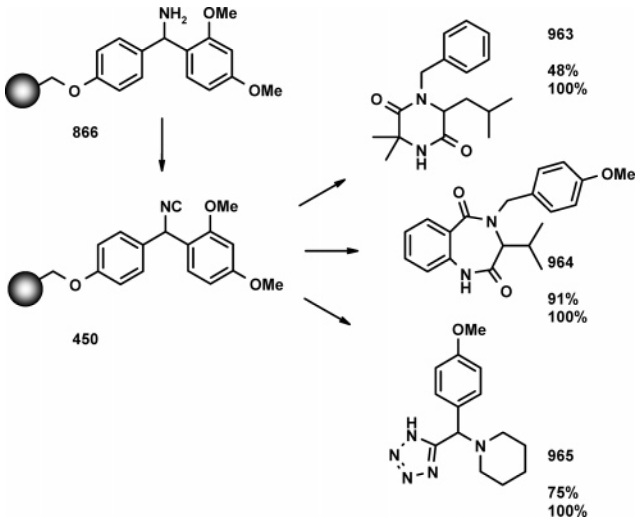


horseradish esterase as biological substrates and coupled them with diverse low molecular weight reporters such as rhodamine B **971**, biotines **972** and **974** or a glycoside **973** exemplified as different components (Figure 36). The biomolecules reacted with their amine (Lys) or carboxylic acid (Asn, Glu) side chain functionalities. For example, optimal conditions for high epitope densities in the BSA bioconjugate turned out to be 0.01−0.1 M phosphate buffer, pH 7.5. The epitope density was determined by MALDI-TOF and photometrically. The enzymatic activity of a HSE conjugate was investigated and found to be 62−95% of the initial activity. Thus, the U-4CR did not cause any dramatic loss of enzymatic activity: Taking into account the easy and unlimited variabilty of MCR chemistry, this might be a powerful approach for interesting applications of bioconjugation.

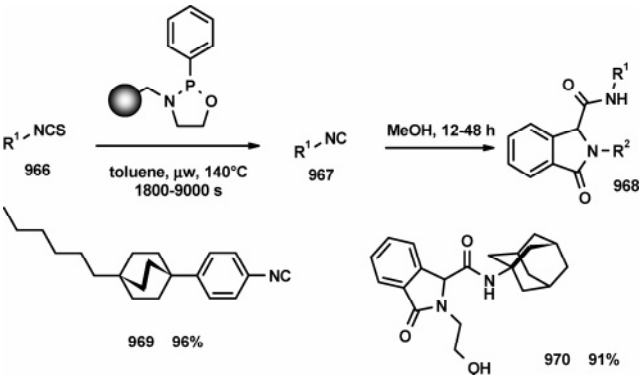
6.8. Microwave Irradiation

A solid-phase-mediated synthesis of isonitriles using a resin supported sulfonyl chloride has proven to be a highly efficient and clean technique of synthesis for this important

Scheme 158. Rink Amide Derived Isocyanide Serving as a C1 Synthone in Several Heterocycle Syntheses Using U-MCRs (Yield/Purity)



Scheme 159. Polymer Supported Desulfuration of Isothiocyanates Thus Yielding Isocyanides and Their Subsequent Transformation into Benzo Annealled γ-Lactams



class of compounds.[306] Interestingly, it was observed that the use of a Smith synthesizer and microwave irradiation gave much faster reactions, while maintaining product purity and in many cases improved yields, thereby allowing rapid access to this class of compounds for subsequent incorporation into a range of reactions, including the synthesis of isonitrile tags **977**−**979**, useful probes for a range of biological processes (Scheme 160).

Tye et al. from Evotech utilized design of experiment (DoE) methods to quickly find optimal conditions for the microwave assisted library synthesis of γ-lactams using

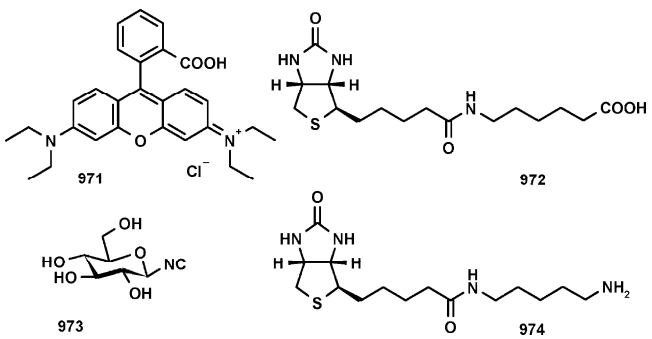
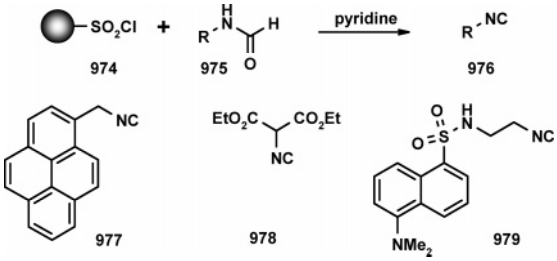


Figure 36. Useful starting materials for the synthesis of libraries of bioconjugates are dye carboxylic acids **971**, biotine educts **972** and **974**, and sugar isocyanides **973**.

Scheme 160. Polymer Supported Isocyanide Synthesis—Sulfonyl Chloride on Resins Can Be Used To Produce Isocyanides from Their Corresponding Formamides Taking Advantage of a Facilitated Work Up



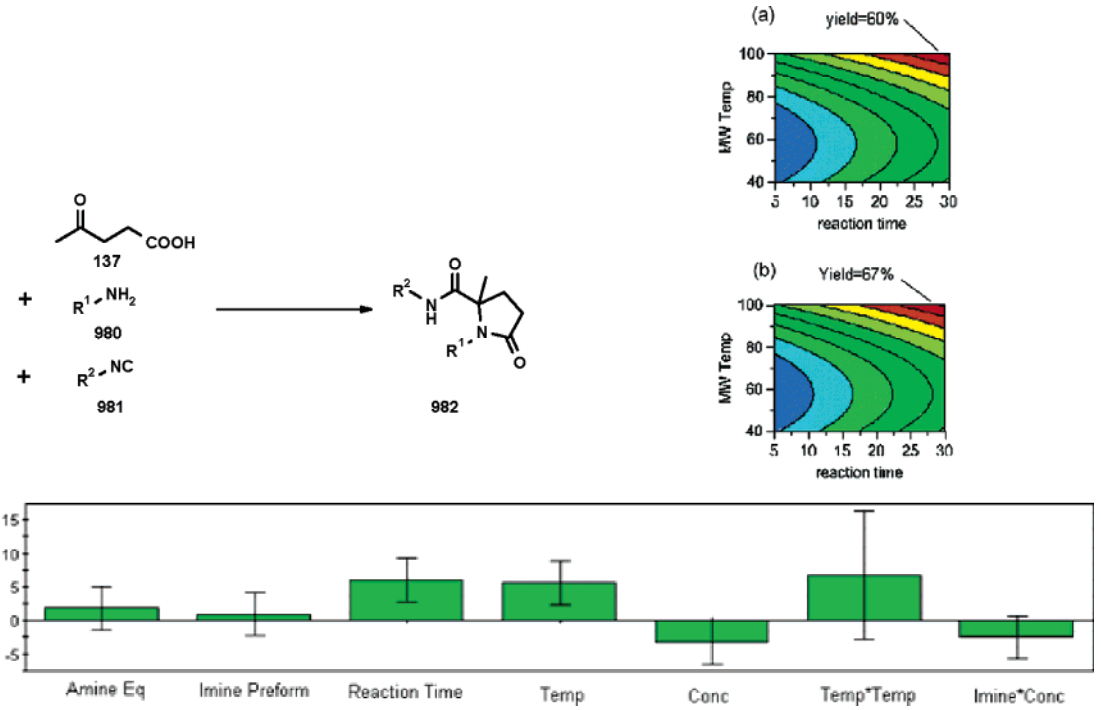
U-4C-3CR (Scheme 161).[307] Thus, they investigated factors which have profound influence on the yield of the reaction, while at the same time keeping the reaction times short (<30 min). The factors investigated were equivalents of amine, concentration, imine preformation time, microwave reaction time, and microwave temperature. With only a couple of experiments and with the help of DoE software, it was determined that the following factors are of most importance: microwave reaction time, microwave temperature, concentration, and amine equivalents. Interestingly, precondensation of the Schiff base had only negligible influence in this particular reaction. Overall, the optimized reaction conditions found are as follows: 0.2 mmol of levulinic acid, 0.3 mmol of amine, and 0.2 mmol of isocyanide in 1 mL of methanol are treated for 30 min at 100 °C in a microwave.

Although the rate accelerating power of a microwave is generally appreciated, a word of care is given here. Despite the fact that high temperature facilitates many organic reactions, IMCRs often run fast under quite mild conditions. Thus, it has been observed that using microwave in IMCR sometimes gives different reaction products. There are several considerations explaining this observation. First, several classes of isocyanides are prone to polymerization, e.g. phenylisocyanides. Since IMCRs normally are performed under high concentrations, polymerization might take place faster under high-temperature conditions. Another consideration is that the reactive α-adduct intermediate reacts with potential nucleophiles (solvent or intramolecular interactions) in a different manner temperature dependently. Intramolecular processes might compete with intermolecular reaction pathways, thus leading to oligomerization or polymerization. Thus, it is not always advisable to use microwave in MCR chemistries.

6.9. Miscellaneous

A miniaturized-synthesis and total analysis system (μSYNTAS) integrating a silicon-machined chemical microprocessor and time-of-flight mass spectrometry (TOF-MS) is used for the generation of compound libraries based on subreactions of an Ugi multicomponent reaction (MCR).[308,309] The microreactor—based on the concept of an AND logic operator—allowed the coupling of serially switched solution-phase library generation with on-line compound analysis and identification (Figure 37). In addition, the μSYNTAS allowed real-time parallel processing of MCR subreactions; in contrast to combinatorial techniques employing a solid support for reagents and products isolation, the μSYNTAS protocol required no additional preparation or work-up procedures. This approach provides an unusually high degree of control of the MCR and delivers detailed, novel information on

Scheme 161. Microwave Accelerated Synthesis of γ-Lactams—Design of Experimental Methods Was Used To Find Optimal Reaction Parameters[a]



[a] Top right: yield as a function of microwave temperature and reaction time. Bottom: the influence of the parameters on the overall outcome of the reaction. (Reprinted with permission from ref 307. Copyright 2004 The Royal Society of Chemistry.)

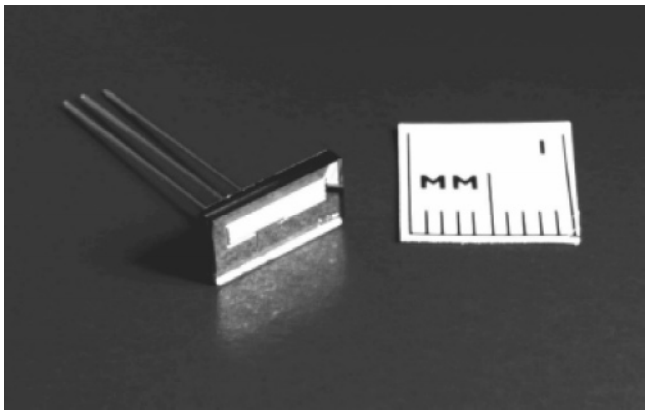
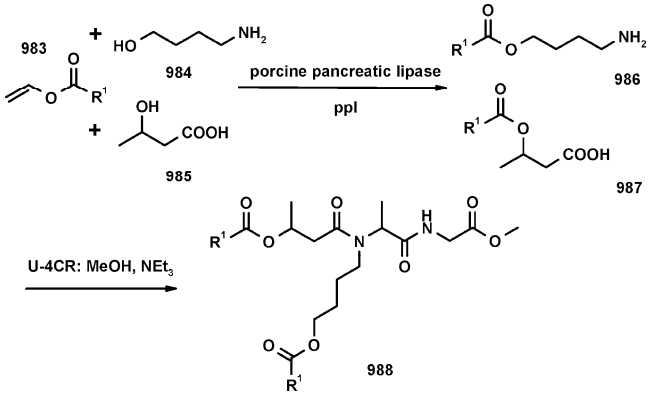


Figure 37. A glass−silicon microreactor used to prepare U-MCR libraries in a controlled fashion.

reaction intermediates in real-time. The U-4CR was performed at room temperature in a controllable fashion. Furthermore, mass spectroscopical observation of a nitrilium intermediate, cyclohexyl-(2-piperidin-1-ylethylidyne)ammonium chloride, is presented for the first time.

The chemoenzymatic preparation of a nine-member U-4CR library is described (Scheme 162).[310] The carboxylic acid and amine precursors are based on 3-hydroxybutyrate and 4-amino-1-butanol, respectively, and have been acylated selectively using a variety of acyl donors catalyzed by porcine pancreatic lipase. The enzyme is selective for the hydroxyl functionalities on both precursors, thereby yielding 3-acylbutyric acid and 4-amino-1-acyl compounds. These enzymatically generated derivatives were then subject to a U-4CR in the presence of acetaldehyde and methyl isocyanoacetate. Isolated yields of the α-(acylamino)amide Ugi products ranged from 72 to 95%. The inherent chemoselectivity of enzymatic catalysis may play an increasingly

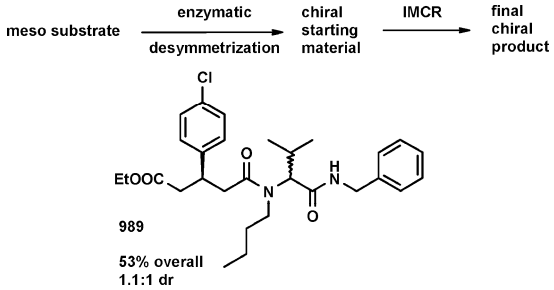
Scheme 162. Mixed MCR and Enzymatic Transformation



important role in expanding the structural diversity that can be achieved by chemical MCRs.

Another group reported on the benificial combination of IMCR and enzymatic procedures to desymmetrize prochiral carboxylic acid anhydrides (Scheme 163).[311] A new synthetic

Scheme 163. Stereoselective Synthesis Involving Enzymatic and MCR Chemistry in One-Pot



method based on combination of enzymatic desymmetrization of 3-phenylglutaric anhydrides with multicomponent

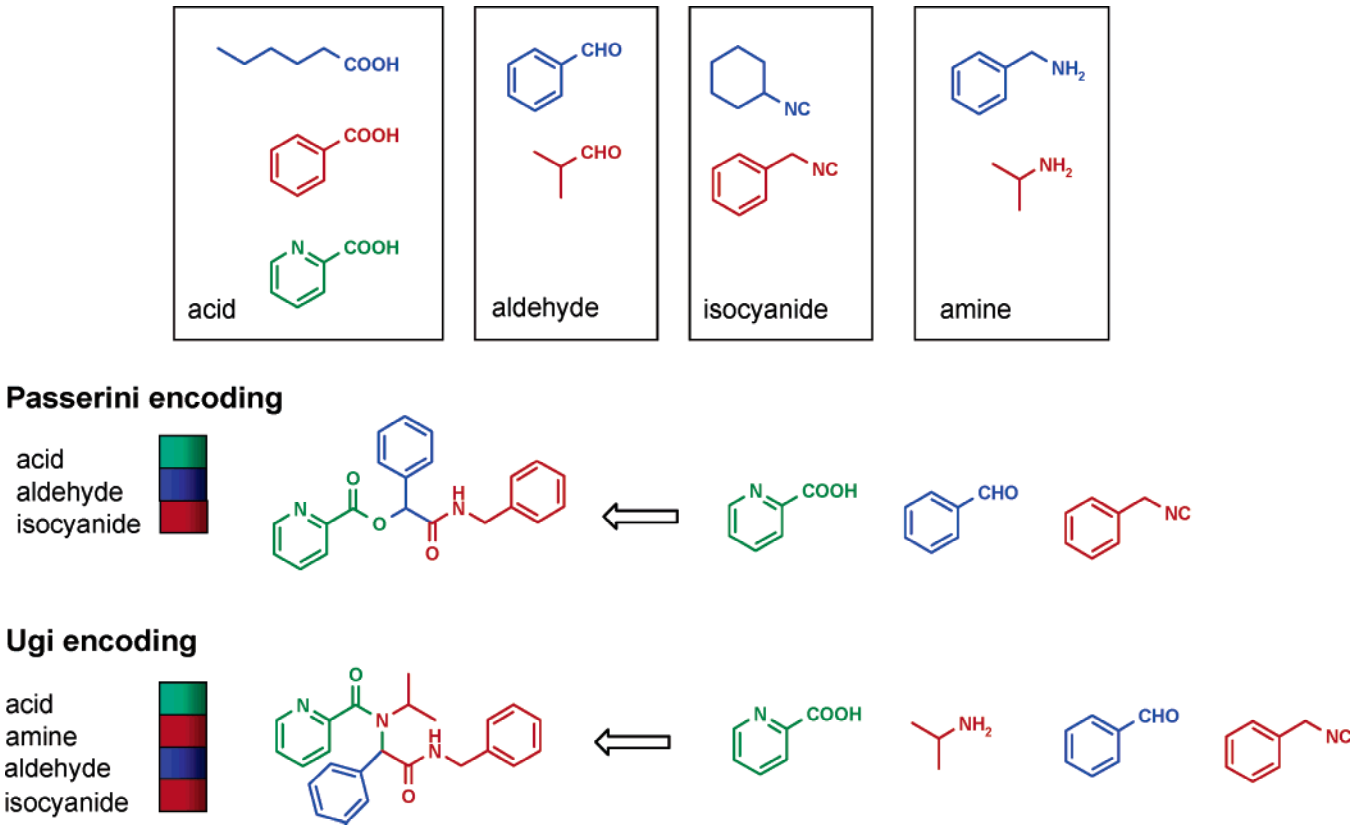


Figure 38. Color encoding of IMCRs. (Adapted from ref 312.)

condensation is outlined. Enzymatic monoesterification of glutaric anhydrides was performed, and the derived monoacids were used as substrates for subsequent Ugi and Passerini multicomponent condensations. Both reactions were combined as two-step, one-pot processes. The choice of solvent and enzyme type has an appreciable effect on the course of reactions.

MCRs have been described as being "un-encodable", making the deconvolution of libraries based on these reactions difficult. Williams described a color-encoded parallel synthesis of U- and P-MCRs (Figure 38).[312] Thus, to facilitate deconvolution of the library, each building block was assigned a color unique within its class. In addition, each reaction vessel was color bar-coded according to its constituent starting materials. For the Passerini reactions the first position on the bar code was defined as the acid component, the second as the aldehyde, and the third as the isocyanide. In the case of the Ugi reactions, the bar code was positionally defined as first, acid; second, amine; third, aldehyde; and fourth, isocyanide. These characteristic colored bar codes were then used as a means of identifying the expected products via their synthons and, hence, starting materials. This simple color bar-coding method should allow for the encoding of significantly larger libraries; for example, it is possible to encode 10.000 reaction products from a U-4CR by the use of just 10 different colors on a four-colored bar code ($10 \times 10 \times 10 \times 10$).

7. Outlook

It was Ivar Ugi in 1961 who foresaw the usefulness of isocyanide based multicomponent reactions for the synthesis of very many compounds, nowadays called chemical libraries: "Since in this condensation reaction four components react with each other, the number of possible products is quite high. Already the use of ten of each component leads to 10^4 combinations" (translated from German).[314] Clearly Ivar Ugi with his MCR chemistry heralded the age of combinatorial chemistry, 30 years before it became of use in the context of the many new targets discovered through the Human Genome Project and the interrelated High Throughput Era.

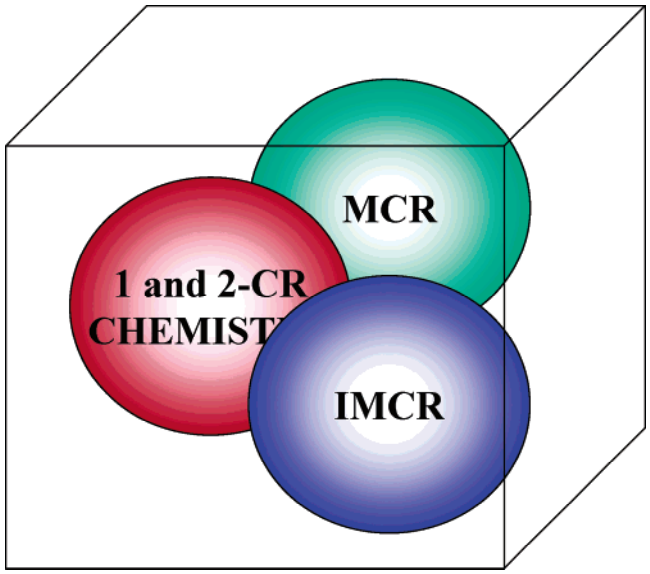
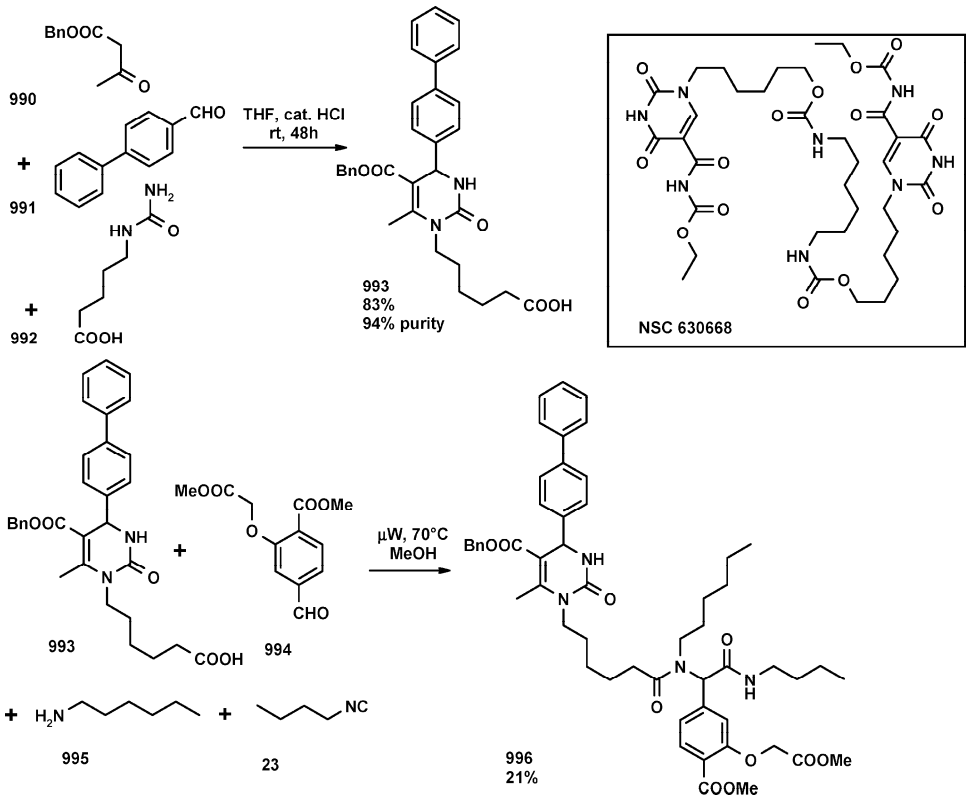


Figure 39. Combining the traditional one and two component reaction space with MCR and IMCR space provides innumerable scaffolds useful for the discovery of new materials with novel properties. Thus combining several hundred organic reactions with just 10 MCRs would result in several thousand novel and easily accessible scaffolds.

Scheme 164



Hardly a field in organic chemistry has evolved faster over only a couple of years than isocyanide based multicomponent reactions. Starting materials are no restrictions to the possible chemical space anymore, since hundreds or even thousands of educts of each class are commercially available in the meantime. However, the very large MCR space of $>10^{20}$ is only explored marginally. As a consequence of the immense functional group compatibility of IMCRs, one can easily imagine that virtually all classical reactions in organic chemistry can be combined with IMCRs to yield a plethora of scaffold possibilities (Figure 39).[313] Given that the fraction of combinations of IMCRs and traditional reactions is currently small, we can realistically expect a growing body of experimental literature contributing to a substantial percentage of all library efforts ongoing in the future. This yet to be explored chemical space would consist of the largest chemically accessible scaffold space giving access to a large physicochemical and biological property space.

However, additional techniques beyond high-throughput screening of very large chemical libraries to explore chemical space are becoming more and more important, e.g. computational screening of virtual libraries by 2D and 3D similarity, docking, and filtering. Moreover, recent work suggests that valid starting points for medchem projects can rapidly emerge out of these techniques. Together, the very large chemical space of IMCRs provides a conceptual framework within which modern chemistry based technologies will contribute to progress in medicine, material based technologies, and, finally, science based human progress.

Future research in the area of MCRs will include the discovery and design of novel MCRs, experimental improvements in solid- and liquid-phase, enantio- and diastereoselective variations, and more and more applications in drug discovery, materials science, bioconjugates, and agrochemical compounds. Research on the computational enumeration and subsequent screening of the very large MCR space will become very important.

Clearly, the preceding many examples from a short time periode of only 4 years have shown what advances have been made in the area of isocyanide based MCRs, especially in the application of this technology to important questions of human life and quality.

8. Acknowledgments

I would like to thank my former co-workers from Morphochem, Barbara Beck, Bernd Henckel, Walfrido Antuch, Katrin Illgen, Nasser Yehia, Dirk Behnke, Lutz Weber, Michael Almstetter, Robert Eckl, Martin Nicolas, Quin-Zene Chen, Yingchun Lu, Sukumar Sakamuri, Silke Bräuer, Roswita Taube, and others, for their enthusiasm to promote the idea of multicomponent reaction chemistry in all its facets.

9. Note Added in Proof

Heat shock proteins Hsc70 and Hsc40 are molecular chaperones that bind and release their protein targets in an ATP dependent manner. Hsc70 and Hsc40 contribute to tumorgenesis and are thus targets for anti-cancer drug development. Compounds have been found to modulate the ATPase activity of Hsp70. Analogues of one of these compounds (NSC 630668) were designed based on similarity and synthesized by the use of two MCRs: the Biginelli 3-CR (Bg-3CR) and the U-4CR (Scheme 164), e.g. **996**.[315] The Bg-3CR of aromatic aldehydes, *N*-mono-substituted urea, and β-ketoesters gave the corresponding dihydropyrimidinones in excellent yields, e.g. **993**. Subsequent U-4CR using the Bg-3CR product as a carboxylic acid input yielded arrays

of products, e.g. **996**. Intriguingly, compound **996** enhanced Hsp70 ATPase activity by a factor of 4.5. Thus, these compounds represent a novel class of membrane-permeable compounds useful to modulate and study Hsp70/40 dependent cellular processes and to determine whether a cellular process is chaperone-dependent.

10. Abbreviations

AAc	alkoxyacetyl linker
ACD	available chemical database
ATR	attenuated total reflectance spectroscopy
BOC	*tert*-butoxy carbonyl
BVDV	virus of bovine viral diarrhea
CCR5	CC chemokine receptor 5
CHO	Chinese hamster ovary cell line
3-CR	three-component reaction
DBU	diazabicycloundecene
DCM	dichloromethane
de	diastereomeric excess
DeHA	deacetyl hyaluronic acid
DMAD	dimethylacetylenedicarboxylate
DMAP	4-(dimethylamino)pyridine
DMF	dimethylformamide
DoE	Design of Experiment
dppf	1,1′-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
ee	enantiomeric excess
EPR	electron paramagnetic resonance
fVIIa	factor VIIa
fXa	factor Xa
GGPT	γ glutamyl transferase
HA	hyaluronic acid
HCV	hepatitis C-virus
HOBT	hydroxybenzotriazole
IMCR	isocyanide based multicomponent reaction
IMDA	intramolecular Diels−Alder
μM	micromolar
MAP	mitogen-activated pathway
MAPKAP	mitogen-activated protein kinase-activated protein kinase
MCR	multicomponent reaction
mM	millimolar
MPEG	methoxypolyethyleneglycol
MS	mass spectroscopy
MW	molecular weight
NCI-H460	National Cancer Institute cell line H460
nM	nanomolar
NMP	1-methyl-2-pyridone
PADAM	Passerini reaction/deprotection/acyl migration
P-3CR	Passerini 3-component reaction
PDC	pyridinium dichromate
PMB	*p*-methoxybenzyl
PP	polypropylene
PS-DIEA	polystyrene bound diisopropylethylamine
PS-NCO	polystyrene bound isocyanate
Pt-3CR	Petasis 3-component reaction
PyBOB	benzotriazol-1-yloxypyrrolidinophosphonium hexafluorophosphate
RANTES	regulated upon activation normal T-expressed and secreted
SAR	structure activity relationship
SASRIN	superacid sensitive resin
SPE	solid-phase extraction
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl protecting group
TEA	triethylamine
TEMPO	2,2,6,6-tetramethylpiperidinyloxy
TFA	trifluoroacetic acid
TFAA	trifluoroacetic acid anhydride
TFE	trifluoroethanol
THF	tetrahydrofuran
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
TMSCN	trimethylsilyl cyanide
TNF-α	tissue necrosis factor-α
TOSMIC	toluenesulfonylmethyl isocyanide
p-TSA	*p*-toluenesulfonic acid
U-4CR	Ugi 4-component reaction
U-5C-4CR	Ugi 5-center-4-component reaction
UDC	Ugi reaction/deprotection/cyclization

11. References

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(2) Nishiyama, Y.; Katahira, C.; Sonoda, N. *Tetrahedron Lett.* **2004**, *45*, 8539.
(3) Portlock, D. E.; Naskar, D.; West, L.; Ostaszewski, R.; Chen, J. J. *Tetrahedron Lett.* **2003**, *44*, 5121.
(4) The corresponding starting materials of these reactions are broadly commercially available, mostly in numbers exceeding 1000 (RCOOH, RNH_2, RCHO, RCOR). However, less than 1000 boronic acids and isocyanides are available at the moment.
(5) Bohacek, R. S.; McMartin, C.; Guida, W. C. *Med. Chem. Rev.* **1996**, *16*, 3.
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(9) The author has created a database of more than 500 different scaffolds amenable by MCR reactions, which is growing daily. See also http://www.organic-chemistry.org/Highlights/mcr.shtm.
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