Multicomponent Reactions

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Multicomponent Reaction Design in the Quest for Molecular Complexity and Diversity

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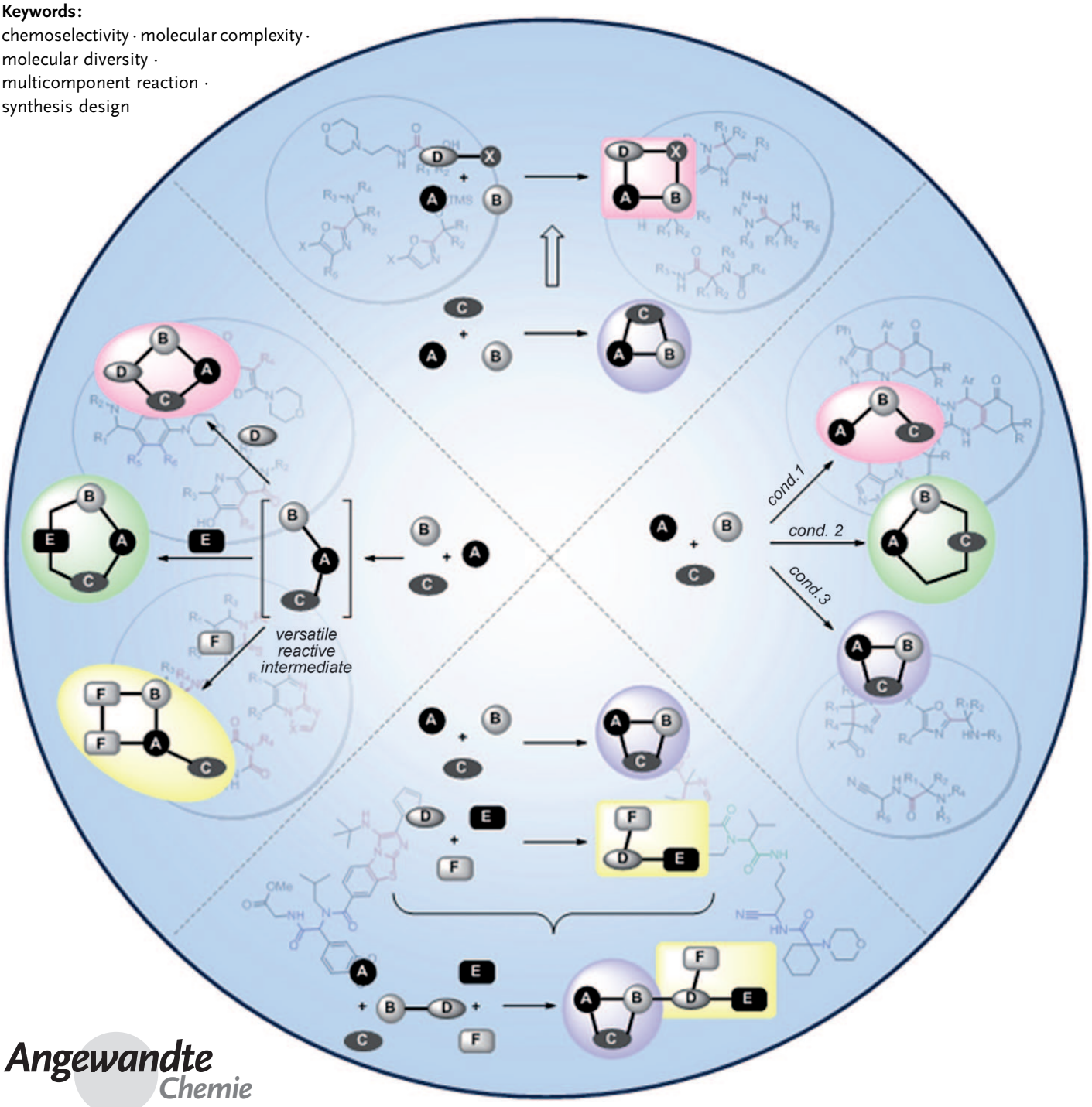
Keywords:
chemoselectivity · molecular complexity · molecular diversity · multicomponent reaction · synthesis design



Multicomponent reactions have become increasingly popular as tools for the rapid generation of small-molecule libraries. However, to ensure sufficient molecular diversity and complexity, there is a continuous need for novel reactions. Although serendipity has always played an important role in the discovery of novel (multicomponent) reactions, rational design strategies have become much more important over the past decade. In this Review, we present an overview of general strategies that allow the design of novel multicomponent reactions. The challenges and opportunities for the future will be discussed.

From the Contents

1. Introduction 6235
2. Rational Design Strategies for MCRs 6237
3. Towards stereoselective MCRs 6243
4. Summary and Outlook 6244

1. Introduction

The importance of small organic molecules in contemporary chemical biology and medicinal research is undisputed. Studying the interaction of such small molecules with biological systems and the perturbation of a certain biological ground state they may cause is crucial for understanding all the fundamental processes in health and disease. Synthetic organic chemists provide access to structurally complex and functionally diverse sets of compounds and thus supply the feedstock for advanced research in chemical biology. The goal is to identify potent and selective molecular modulators of all cellular processes, including the growing number of non-classical biological targets considered "undruggable"—that is, cannot be addressed with medication.[1]

It is, however, an arduous task to find even a single one of these modulators in the vastness of chemical space. Chemical space can be described as a representation of all (small) molecules in a multidimensional space in which the descriptors can be any property other than the molecular structure.[2] These can include for example, molecular weight, polarity, solubility, membrane permeability, binding constants, hydrogen-bonding properties, etc. The molecular diversity within a set of compounds is consequently reflected in the dispersion in chemical space. Estimates of the total number of small molecules (MW < 500) that can in theory be prepared from a handful of elements (C, H, N, O, S) range from 10^{60} to 10^{200}—numbers that vastly exceed our comprehension.[3] Fortunately, compounds with biological activity are not spread out evenly throughout chemical space, but rather concentrated in a confined section ("biological activity space").[4] However, finding compounds with novel biological activity in this vast space is like finding a needle in a haystack. To increase the odds, the molecular diversity between the library members should be as great as possible within the boundaries of biological activity space. To break down the complex notion of molecular diversity we can distinguish three fundamental levels of diversity: a) appendage diversity (combinatorial chemistry), b) stereochemical diversity, and c) scaffold diversity (Figure 1).

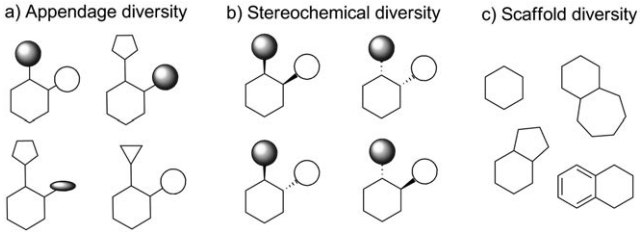


Figure 1. The three fundamental levels of molecular diversity: appendage, stereochemical, and scaffold diversity

Appendage diversity (Figure 1a) involves the introduction of different appendages to a common molecular skeleton (scaffold). However, since all the compounds have the same molecular skeleton, they have very similar molecular shapes and display relevant chemical information in a narrow range of 3D space (same molecular shape). This results in limited overall diversity. Stereochemical diversity (Figure 1b) involves the selective generation of as many stereoisomers of the same molecule as possible. For this, stereospecific reactions are required. Different stereoisomers are selectively accessible, for example, by changing the stereochemistry of the catalyst and/or chiral starting materials. Scaffold diversity (Figure 1c) is probably the most important element of diversity; it involves the generation of a collection of compounds with different molecular skeletons (scaffolds). This can be realized by changing the reagents added to a common substrate (reagent-based approach) or by transforming a collection of substrates having suitable pre-encoded skeletal information under similar reaction conditions (substrate-based approach).

Unlike molecular diversity, which can be readily quantified on the basis of structural and physicochemical properties, molecular complexity is a less tangible property that is hard to quantify. It involves not only the number and types of atoms in the molecule, but also their connectivity. A prominent factor in molecular complexity is stereochemical (3D) structural information. Classical combinatorial chemistry products are flat, aromatic heterocyclic compounds, which contain no 3D structural information. In contrast, compounds isolated from natural sources (natural products) have more macro-

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cyclic and diverse polycyclic ring systems, as well as a wealth of 3D structural information. Interestingly, increasing the molecular complexity in an array of compounds inherently leads to higher diversity. This observation has inspired two concepts that advocate the importance of molecular complexity: DOS and BIOS.

In 2000, Schreiber introduced the concept of diversity-oriented synthesis (DOS).[5] This basic concept involves short reaction sequences (3–5 steps) combined with a forward planning strategy (rather than a retrosynthetic analysis). In DOS, natural product likeness refers to the molecular complexity in terms of, for example, the number and type of rings and stereocenters rather than actual resemblance to naturally occurring compounds. In fact, Schreiber argues that, to address "undruggable" targets, compounds should not be too similar to natural products, since most of these act on the same "classical" biological targets.[1] Several years later, Waldmann and co-workers introduced the concept of biology-oriented synthesis (BIOS).[6] The rationale behind BIOS is that typical natural product fragments have a high probability of binding to protein domains. Since proteins are built up in a modular fashion from a limited number of domains and fold types, similar (natural product) small molecules can be expected to bind to evolutionarily (but not functionally) related proteins.[7]

Both concepts have proven useful strategies for the discovery of novel biological activity. Their success rates in the future will greatly depend on the availability of synthetic methods that allow the straightforward realization of DOS and BIOS concepts by addressing all the fundamental levels of molecular diversity. A sufficiently large collection of compounds with considerable molecular diversity and complexity is required to fulfill the requirements of potency and selectivity. For DOS and BIOS to be successful, the number of synthetic steps is limited for practical reasons and highly efficient synthetic methods with a strong focus on bond construction and functional group compatibility are required. Particularly useful reactions are those that involve multiple bond formation, such as tandem and multicomponent reactions. In this Review we will discuss strategies for the rational design of new multicomponent reactions[8–13] as powerful tools for the realization of DOS and BIOS.

A multicomponent reaction (or MCR) is defined as a reaction in which three or more compounds react in a single operation to form a single product that contains essentially all of the atoms of the starting materials (with the exception of condensation products, such as H_2O, HCl, or MeOH). Since the collision of three or more independent molecules is highly unlikely, MCRs typically involve a number of subreactions. In many cases, most of the intermediate steps are equilibrium reactions and only the final step is an irreversible process, such as a C–C bond formation or a rearrangement. The oldest multicomponent reaction according to current standards is the Strecker reaction of amines, aldehydes, and cyanide to give α-aminonitriles.[14] Other MCRs that were discovered long ago, such as the Biginelli[15,16] and Ugi[17–19] reactions, saw a true renaissance during the age of combinatorial chemistry. It has since been increasingly recognized that such applications of MCRs suffer from the classical pitfall of combinatorial chemistry: the focus on appendage diversity. Consequently, the design and discovery of new MCRs is vital to address scaffold diversity in compound collections.

Currently, the major issues concerning the use of MCRs as tools in chemical biology are: 1) limited scaffold diversity, and 2) poor stereocontrol. The former is addressed by the continuous discovery of novel MCRs. Although serendipity has always played an important role in the discovery of new MCRs, the emergence of a more rational design approach in recent years is reflected in the number of scientific publications in the past two decades that deal with MCRs (Figure 2).

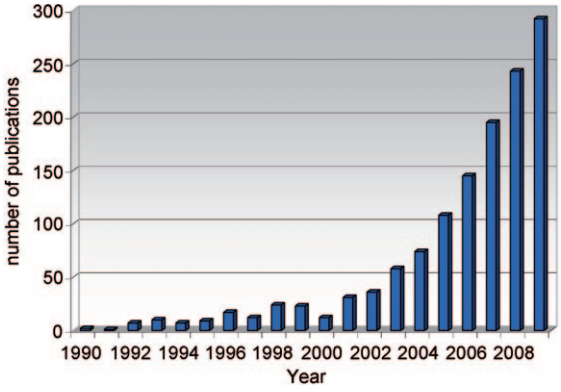

Figure 2. Number of publications dealing with MCRs in the period 1990–2009 (results are derived from a Web of Knowledge query on "component reaction").

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A very effective strategy to increase scaffold diversity without developing new MCRs is the combination of existing MCRs with complexity-generating reactions, in particular cyclization reactions.[20] To achieve significant variation of the resulting scaffolds, the so-called build/couple/pair strategy (Figure 3) has been used.[21]

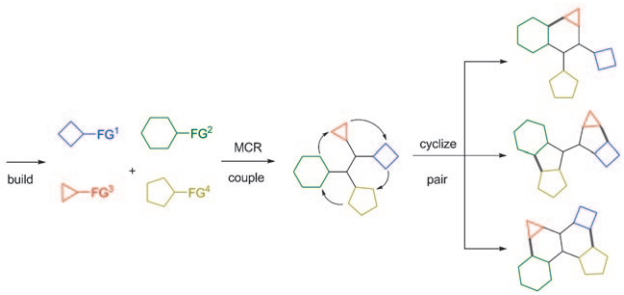

Figure 3. The generation of scaffold diversity by combining MCRs with cyclization reactions according to the build/couple/pair strategy.[20,21]

As an example of the efficiency of this approach, Scheme 1 summarizes the use of the Ugi four-component reaction (U-4CR)[17–19] as the coupling phase to afford compounds **1**–**6**, after which a number of cyclization reactions (including cycloadditions and palladium-catalyzed cross-coupling reactions) are used in the pairing phase to afford an impressive range of nitrogen heterocycles (**7**–**14**).

Another elegant example of the use of MCRs in the build/couple/pair strategy was described by Schreiber and coworkers, who used the Petasis 3CR[22] for the construction of a single cyclization precursor.[23] This compound could undergo seven distinctly different cyclization types (based on the addition of certain reagents or catalysts), followed by a series of further scaffold modification reactions to afford a total of 15 different scaffolds. Interestingly, the highly diastereoselective Petasis 3CR also allows control over the absolute configuration, so that this approach can also address stereochemical diversity.

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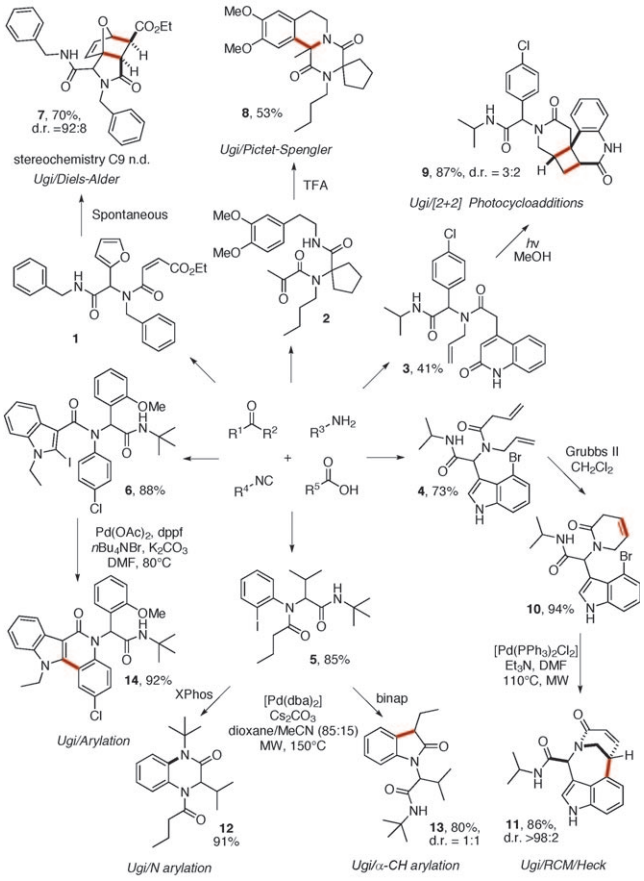


Scheme 1. The introduction of scaffold diversity by the Ugi-4CR (coupling) and follow-up cyclization reactions (pairing). New bonds formed in the pairing reactions are indicated in red. binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl, dba = *trans*,*trans*-dibenzylideneacetone, dppf = 1,1′-bis(diphenylphosphanyl)ferrocene, n.d. = not determined.

2. Rational Design Strategies for MCRs

Although the above examples demonstrate the potential of post-MCR cyclization strategies to increase molecular diversity and complexity, the most straightforward approach to address the issue of limited scaffold diversity is the rational design of novel (multicomponent) reactions. Four strategies for the design of novel multicomponent reactions are represented schematically in Figure 4: a) Single reactant replacement (SRR); b) modular reaction sequences (MRS); c) conditions-based divergence (CBD), and d) combination of MCRs (MCR^2).

2.1. Single Reactant Replacement

The phrase "single reactant replacement" (SRR, Figure 4a) was first coined by Ganem[24] and involves the development of new MCRs by systematic assessment of the mechanistic or functional role of each component in a known MCR. It involves the replacement of one reactant (C) with a different reactant (D-X) that displays the same essential reactivity mode required for the multicomponent condensa-

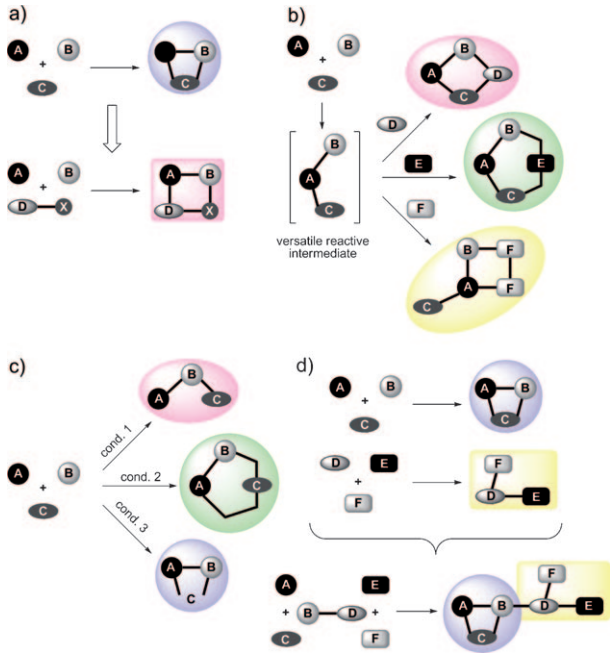
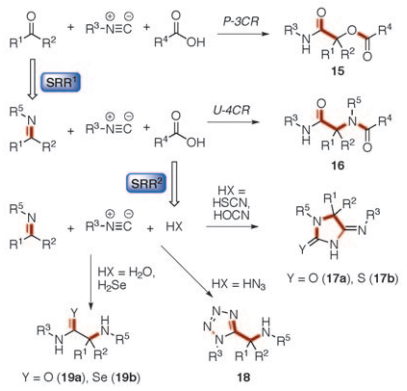


Figure 4. Design strategies for the development of novel multicomponent reactions. a) Single reactant replacement; b) modular reaction sequences; c) divergent MCRs through changing the conditions; d) combination of MCRs.

tion with A and B. By incorporating additional reactivity or functionality into D, the resulting MCR may be directed to a different product scaffold.

Probably one of the first examples of SRR was reported by Ugi, who replaced the carbonyl component used in the Passerini 3CR[25,26] by an imine, which resulted in the well-known Ugi reaction (Scheme 2).[17–19] Ugi also replaced the carboxylic acid input of the Ugi reaction by different acidic components to afford various different scaffolds.[18] The mechanism of the Ugi reaction is generally believed to involve protonation of the imine by a weak acid (e.g. a carboxylic acid) followed by nucleophilic addition of the isocyanide to the iminium ion. The resulting nitrilium ion is subsequently attacked by the conjugate base of the weak acid (e.g. a carboxylate), which only needs to be weakly nucleophilic. Thus, the carboxylic acid in the classical Ugi reaction may be replaced by a variety of weak inorganic acids. For example, HOCN and HSCN could be used to afford (thio)hydantoinimides **17a** and **17b**, respectively. These are formed from the corresponding α adducts by cyclization of the intermediate β-amino iso(thio)cyanates. The use of HN_3 resulted in the formation of tetrazoles **18** by spontaneous cyclization of the α adduct. When water or hydrogen selenide is used, the corresponding α adducts undergo tautomerization to afford amides **19a** and selenoamides **19b**, respectively.



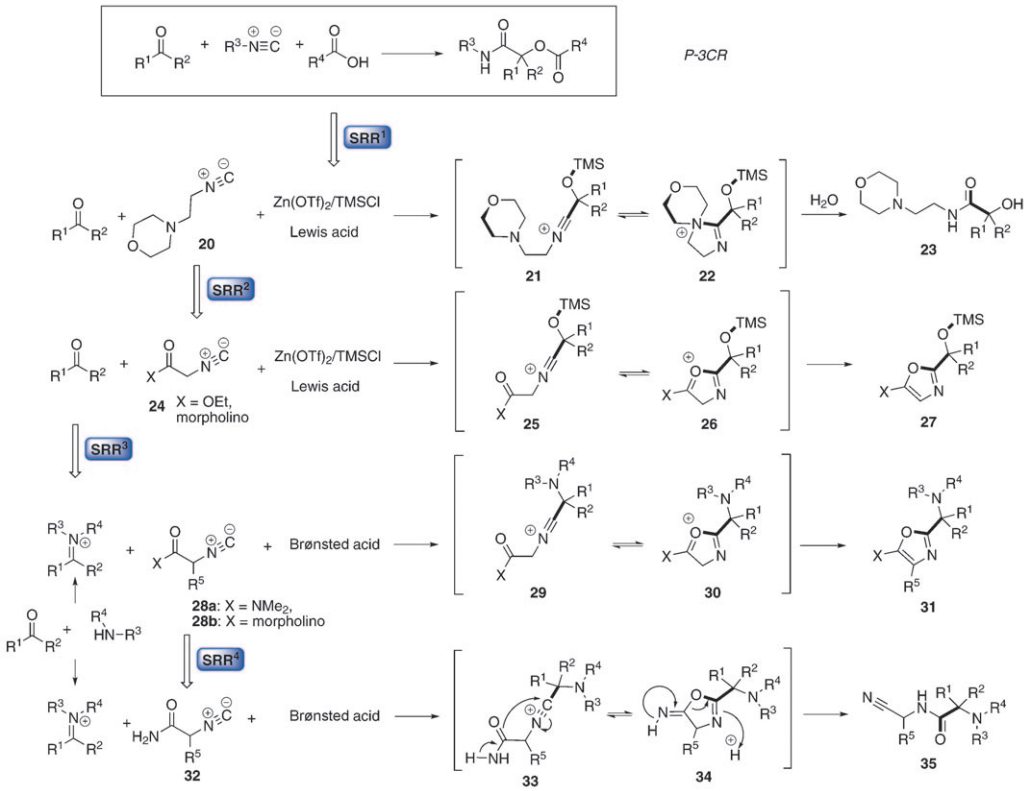
Scheme 2. Sequential SRR from the Passerini to the Ugi reaction (SRR^1) to Ugi variations (SRR^2).

In a related approach, Xia and Ganem changed the carboxylic acid in the Passerini reaction to a Lewis acid (TMSOTf) to activate the carbonyl component.[27] The reaction of several aldehydes and ketones, morpholinoethyl isocyanide (**20**), and $Zn(OTf)_2$/TMSCl (which forms TMSOTf in situ) resulted in the formation of α-hydroxyamides **23** (Scheme 3). A neighboring stabilizing group (such as the morpholine ring in this example) was shown to be required to stabilize the intermediate nitrilium ion **21**, since the use of simple isocyanides did not afford products **23**.[27] The involvement of cyclic intermediate **22** suggested that cyclic products may be generated when a nucleophile (e.g. a carbonyl oxygen atom) is present in the isocyanide component. Indeed, the use of isocyano esters or amides (**24**) led to the formation of ethoxy- and morpholinooxazoles **27**.[27]

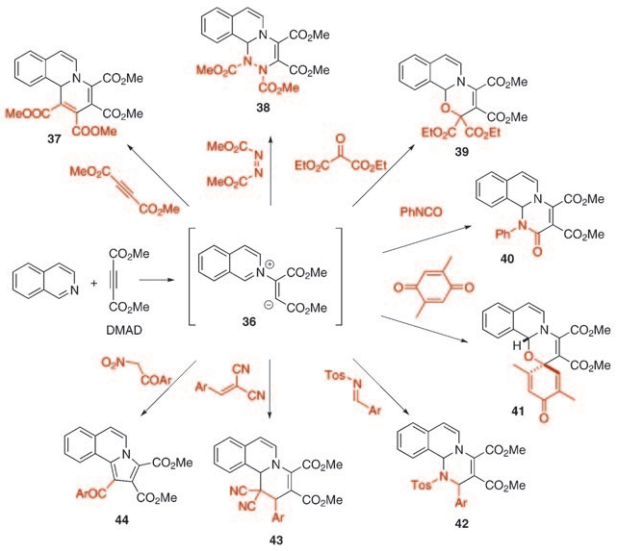
Further SRR could be achieved by replacing the aldehyde or ketone with an imine (e.g. Passerini→Ugi reaction), which resulted in the formation of diaminooxazoles **31** (by Brønsted acid catalysis).[27] It should be noted that this reaction was reported earlier by Zhu and co-workers.[28] Finally, our research group serendipitously discovered that the use of primary α-isocyano amides **32** as reactants led to the formation of *N*-(cyanomethyl)amides **35** (Scheme 3, SRR4).[29]

Another example of SRR is depicted in Scheme 4. The reaction of isoquinoline with two equivalents of dimethyl acetylenedicarboxylate (DMAD) was originally developed by Diels and Harms in 1936. The reaction proceeds through zwitterionic intermediate **36**, which then undergoes a Michael addition/Mannich reaction domino sequence with a second equivalent of DMAD to afford benzoquinolizine **37**.[30] It is hardly surprising that many other dipolarophiles react with intermediate **36** in a similar fashion. In 1967, Huisgen et al. reported three multicomponent variations of this reaction, in which intermediate **36** is trapped with several different dipolarophiles, such as dimethyl azodicarboxylate, diethyl mesoxalate, and phenyl isocyanate to form tricyclic scaffolds **38**, **39**, and **40**, respectively.[31] Other examples were reported by Nair et al., who used 2,5-dimethyl-1,4-benzoquinone to obtain spiro[1,3]oxazino[2,3-*a*]isoquinoline derivative **41**, *N*-tosylimines to afford 2*H*-pyrimido[2,1-*a*]isoquinolines **42**, and arylidinemalononitriles to yield tetrahydrobenzoquinolizine derivatives **43**.[32–34] Recently, Yavari et al. reported a new 3CR by trapping intermediate **36** with aroylnitromethanes to give benzoindolizines **44**.[35]

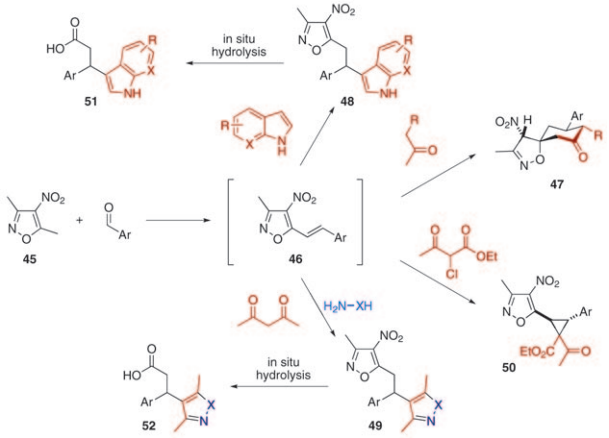
Adamo et al. also used the SRR approach based on the reactivity of 3,5-dimethyl-4-nitroisoxazole (**45**) to develop a family of MCRs. This heterocycle readily reacts with aromatic aldehydes to give the corresponding condensation products



Scheme 3. Four successive single reactant replacements resulting in four new scaffolds. Newly formed bonds in each reaction are indicated in red. OTf = trifluoromethanesulfonate, TMS = trimethylsilyl.



Scheme 4. Replacement of DMAD in the original reaction by **37**, with different third components used to yield several new isoquinoline-based MCRs. The differentiating component in each reaction is indicated in red.



Scheme 5. MCRs developed by SRR of the C-nucleophile through condensation of 3,5-dimethyl-4-nitroisoxazole (**45**) and aromatic aldehydes. The differentiating component in each reaction is indicated in red.

46 (Scheme 5), which can react with doubly enolizable ketones in a double Michael addition to give the spiroisoxazolines **47**.[36] The third component can be substituted by a variety of other carbon nucleophiles such as (aza)indoles (leading to **48**).[37] When the reaction is perfomed with acetylacetone as the nucleophile in the presence of hydroxylamine or hydrazine, the products are diheterocycles **49**.[38] Finally, ethyl 2-chloroacetoacetate can be used as the nucleophile in a domino conjugate addition/S_N2 reaction to give cyclopropanes **50**.[39] Interestingly, Adamo et al. showed that it was possible with **48** and **49** to hydrolyze the nitroisoxazole during the workup to the corresponding carboxylic acids **51** and **52**. In these cases, the reactivity of **45** in these

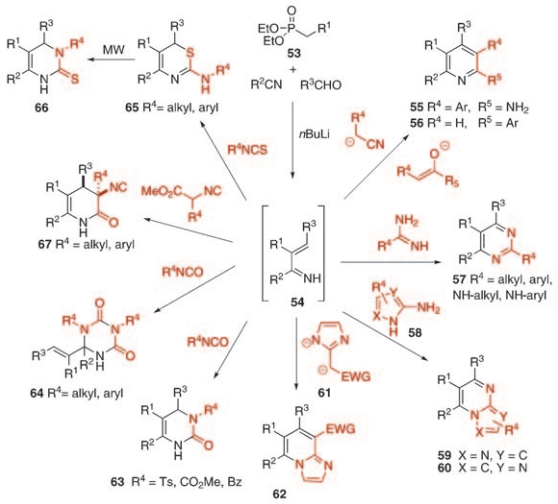
MCRs can be regarded as that of an acetate dianion equivalent.[37,38]

In summary, the SRR strategy has already proven to be great value and has evolved into a reliable approach for the design and rational development of novel MCRs.[40,41]

2.2. Modular Reaction Sequences

A second strategy for the discovery of novel MCRs involves modular reaction sequences (MRSs, Figure 4b). This approach is related to SRR, but involves a versatile reactive intermediate that is generated from substrates A, B, and C by an initial MCR.[12] This reactive intermediate is then treated in situ with a range of final differentiating components (D, E, and F) to yield a diverse set of scaffolds.

One striking example is the use of 1-azadiene **54** as the intermediate to achieve scaffold diversity.[42] The 1-azadiene is generated in situ from a phosphonate, a nitrile, and an aldehyde by a 3CR involving a Horner–Wadsworth–Emmons (HWE) reaction (Scheme 6).[43,44] In 1995, Kiselyov



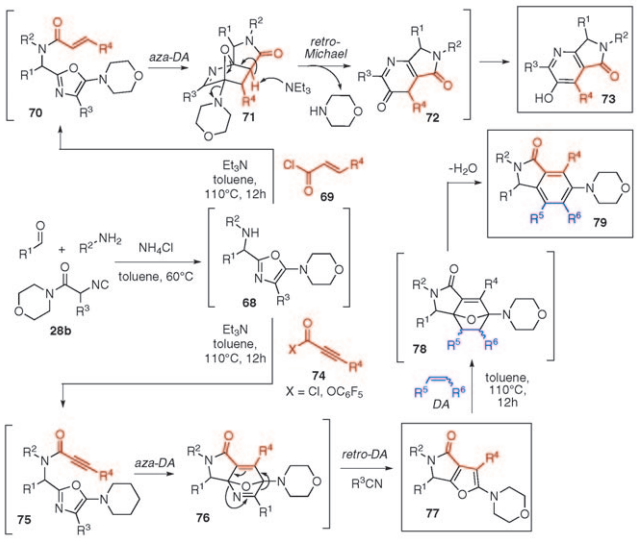
Scheme 6. Modular reaction sequence involving the 1-azadiene 3CR as the initial MCR, to which several fourth components were added. The differentiating component in each reaction is indicated in red. EWG = electron-withdrawing group.

reported the first MCR involving this 1-azadiene through its reaction with sodium or potassium salts of α-arylacetonitriles to afford 2-aminopyridines **55** (3 examples, 61–72% yield; $R^1 = H$, $R^2 = R^3 = Ar$).[45] The 1-azadiene was also treated with sodium enolates of methyl aryl ketones to afford 2,4,6-substituted pyridines **56** (3 examples, 63–67% yield; $R^1 = H$, $R^2 = R^3 = Ar$).[45] Ten years later, Kiselyov reported an extension of this work, when he treated 1-azadiene **54** with amidines (R^4 = alkyl, aryl) and guanidines (R^4 = NHR) to afford polysubstituted pyrimidines **57** in 22–73% yield. This MCR proved to have a rather high substrate scope, since all the components could be varied to some extent (19 examples; R^1 = H, alkyl, Ph, $R^2 = R^3 = Ar$).[46] Furthermore, the one-pot reaction of **54** with 5-aminopyrazoles (**58**, X = N, Y = C) and 2-aminoimidazoles (**58**, X = C, Y = N) resulted in the formation of bicyclic compounds **59** and **60** (12 examples, 52–77% yield; $R^1 = H$, $R^2 = R^3 = Ar$).[47] In another one-pot procedure, Kiselyov treated **54** with the dianion of methyl imidazolyl acetates **61** to yield imidazo[1,2-*a*]pyridines **62** (12 examples, 54–75% yield; $R^1 = H$, $R^2 = R^3 = Ar$).[48]

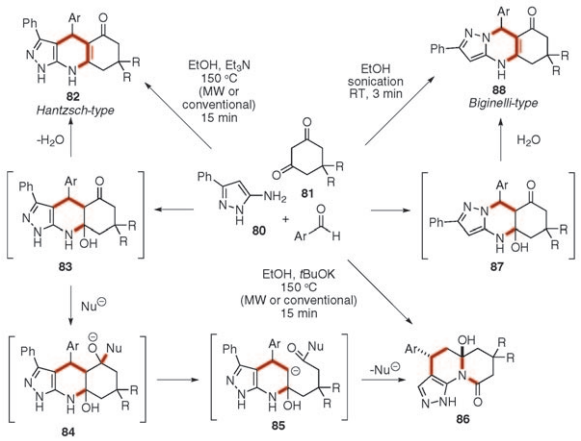
Our research group has also contributed to these 1-azadiene-based MCRs by treating **54** with isocyanates to selectively afford functionalized 3,4-dihydropyrimidine-2-ones **63** (29 examples, 15–90% yield)[49,50] and triazinane diones **64** (17 examples, 25–91% yield)[51,52] depending on the nature of the isocyanate (Scheme 6). The use of isocyanates with strongly electron-withdrawing groups (R^4 = Ts, *p*-NO_2Ph, CO_2Me, Bz) resulted in the exclusive formation of the dihydropyrimidones **63**, thus establishing a useful and versatile alternative to the well-known Biginelli 3CR.[15,16] On the other hand, isocyanates with less electron-withdrawing (R^4 = Ph, *p*-methoxyphenyl (PMP)) or electron-donating substituents (R^4 = Et, Bn) resulted in the formation of triazinane diones **64**. Dihydropyrimidones **63** are most likely formed by nucleophilic attack of the 1-azadiene nitrogen atom on the isocyanate (with electron-withdrawing substituents), followed by cyclization. On the other hand, when isocyanates with less electron-withdrawing or electron-donating substituents are used, the initial condensation product of the 1-azadiene to the isocyanate is sufficiently nucleophilic to react with a second equivalent of isocyanate. This secondary condensation product then cyclizes to afford the triazinane diones. Interestingly, the use of isothiocyanates as the fourth component resulted in the formation of 2-aminothiazines **65**, which undergo Dimroth rearrangement upon microwave heating to give dihydropyrimidine-2-thiones **66**.[53] Perhaps the most intriguing reaction in this family is the reaction of azadiene **54** with α-isocyano esters to give isocyano-substituted dihydropyridones **67**.[54,55] The retained isocyanide function allows combination with isocyanide-based MCRs for further scaffold differentiation.[56–58]

A second MCR discovery approach that uses modular reaction sequences was reported by Zhu and co-workers. They combined the diaminooxazole **68** MCR with primary amines (see also Scheme 3) with a subsequent N-acylation using α,β-unsaturated acid chlorides **69** (fourth component) to afford polysubstituted pyrrolopyridinones **73** (Scheme 7).[28,59] After acylation and heating, the formation of **73** can be explained by an intramolecular Diels–Alder reaction that affords the bridged tricyclic intermediate **71**. A subsequent base-catalyzed retro-Michael cycloreversion with loss of morpholine and aromatization gives **73**.

A variation of this reaction involving the same intermediate oxazole MCR product **68** makes use of activated alkynoic acids **74** as the fourth component.[60] The resulting intermediate undergoes an intramolecular Diels–Alder reaction followed by a retro-Diels–Alder reaction with loss of a nitrile to furnish dihydrofuropyrrolones **77**. The furan moiety in this product is a diene that can react with a fifth component (a dienophile) in a second Diels–Alder reaction to give hexasubstituted benzenes **79** after loss of water. Since all the reactions occur in one pot, this MCR has evolved from a three- to a five-component reaction through application of a



Scheme 7. Modular reaction sequences reported by Zhu and co-workers involving an initial diaminooxazole MCR. The first differentiating components are indicated in red, the second in blue.



Scheme 8. Tuning a 3CR to three different scaffolds by adapting the reaction conditions.[61] Newly formed bonds in each reaction are indicated in red. MW = microwave irradiation.

very elegant modular reaction sequence. This approach has resulted in three different highly functionalized scaffolds originating from a single 3CR.

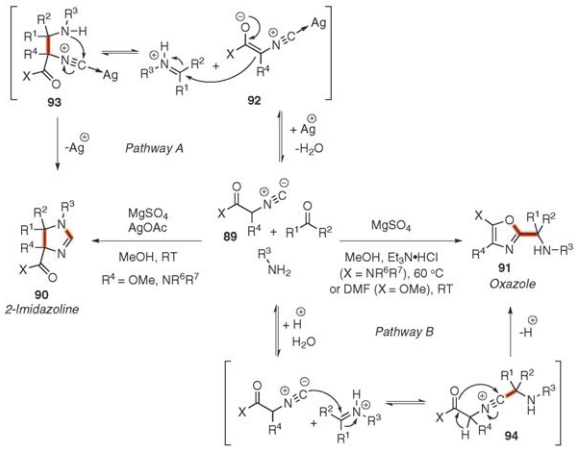
In summary, modular reaction sequences have proven to be extremely useful for the rapid generation of scaffold diversity. This strategy can be regarded as a subtype of SRR, but the unique feature of MRSs is the involvement of a single type of versatile reactive intermediate that displays divergent reactivity modes. Since the generation of the reactive intermediate is a constant, several MCRs that afford different scaffold structures can be achieved using the same experimental setup. This is an especially attractive feature of this strategy in regard to parallel synthesis and library generation: ingenious planning of modular reaction sequences allow the straightforward generation of diverse scaffold libraries.

2.3. Divergence through Changing the Reaction Conditions

Conditions-based divergence in MCRs (CBD, Figure 4c) generates multiple molecular scaffolds from the same starting materials by merely applying different conditions. Intuitively, it is not very surprising that several different potential reaction pathways leading to different products are possible for reactions involving simultaneous molecular interactions of three or more components. For example, the use of specific catalysts, solvents, or additives may direct the course of the reaction along different pathways that produce distinct scaffolds. This is certainly not possible for all MCRs. Consequently, optimizing CBD is not straightforward, which is reflected in the limited number of reported examples.

In 2008, Chebanov et al. reported an excellent example of a conditions-based divergence by the multicomponent reaction of 5-aminopyrazole **80**, cyclic 1,3-diketones **81**, and aromatic aldehydes (Scheme 8).[61] 5-Aminopyrazole **80** has at least three non-equivalent nucleophilic centers (N1, C4, NH_2), but the authors were able to direct the reaction to three distinct scaffolds (**82**, **86**, and **88**) by changing the reaction conditions. A mixture of **82** and **88** was obtained under conventional heating (reflux in ethanol), but heating to 150 °C in a sealed vessel (microwave irradiation or conventional heating) in the presence of NEt_3 led to the exclusive formation of Hantzsch product[62] **82** (8 examples, 70–91 % yield). This finding indicates that the Hantzsch product is most likely the thermodynamically favored product in this transformation. Although a thorough mechanistic study was not performed, the reaction likely proceeds via intermediate **83**, which upon loss of water affords Hantzsch product **82**. When a nucleophilic base such as sodium ethoxide or potassium *tert*-butoxide was used instead of NEt_3 (under otherwise identical conditions), a different reaction product was produced (**86**; 9 examples, 38–75 % yield). The formation of **86** can be explained by a nucleophilic attack of the alkoxide on intermediate **83** followed by ring opening/recyclization. Neutral and ambient conditions lead to the formation of the kinetically controlled Biginelli product **88** (8 examples, 51–70 %). The authors found that sonication was required to obtain the final product, since simply stirring the three components at room temperature did not result in any desired reaction.

Recently, our research group has used the CBD concept to develop MCRs as a tool for DOS. By judicious selection of the reaction conditions, the 3CR between α-acidic isocyanides **89** (isocyano amides or esters), aldehydes or ketones, and primary amines could be directed towards either 2-imidazolines **90** or trisubstituted oxazoles **91** (Scheme 9).[63] By applying 2 mol % AgOAc as a catalyst, 2-imidazolines **90** were obtained selectively, while the use of a Brønsted acid (for $X = NR_2$) or a polar aprotic solvent (for $X = OR$) provided the corresponding oxazoles **91** selectively. The formation of 2-imidazolines **90** can be mechanistically explained by coordination of the isocyanide carbon atom to Ag^+, which enhances the α acidity of the isocyanide (Pathway A), and reduces the nucleophilicity of the isocyanide carbon atom (preventing pathway B). Upon loss of a proton,



Scheme 9. Directing the MCR of α-acidic isocyanides, carbonyl components, and primary amines towards 2-imidazolines **90** and trisubstituted oxazoles **91**. Newly formed bonds in each reaction are indicated in red.

the isocyanide α-anion **92** can undergo a Mannich-type addition to the iminium ion followed by cyclization to give 2-imidazoline **90**. In contrast, addition of a Brønsted acid (Pathway B) will lower the concentration of the isocyanide α-anion, thereby making pathway A less favorable. Since the imine is activated by the Brønsted acid, the isocyanide carbon atom of **89** can attack the iminium ion, thereby leading to intermediate **94**. After proton abstraction and cyclization, oxazole **91** is formed.

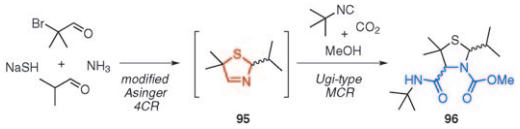
Similar CBD approaches are possible for the related 3CR of primary α-isocyano amides, aldehydes, or ketones and primary amines to give *N*-(cyanomethyl)amides **35** (see also Scheme 3). This reaction follows a similar course as the formation of oxazoles (Scheme 8). Consequently, the use of a Brønsted acid leads to selective formation of *N*-(cyanomethyl)amides **35**, while the addition of 2 mol% AgOAc leads to the exclusive formation of the corresponding 2-imidazolines.[29]

Many examples of CBD are based on serendipitous discovery. The enormous potential of CBD to generate diverse sets of scaffolds from a very small set of inputs, therefore advocates the need for explorative experimentation. However, careful consideration of the decisive factors of different reactivity modes can allow the rational design of CBD.

2.4. Combination of MCRs

The combination of MCRs (MCR^2, Figure 4d) is a fourth strategy for the rational design of novel MCRs that combine two (or more) different types of MCRs in a one-pot process. The presence of orthogonal reactive groups in the product of the primary MCR, which is either formed during the primary MCR or present in one of the inputs allows the combination with the secondary MCR.[13,64] Varying the successive MCR (for example, by addition of inputs **E**/**F** or **G**/**H**) will make diverse (and complex) scaffolds available, thus making this strategy excellent for application in DOS.

The combination of MCRs in one pot was first introduced by Dömling and Ugi who developed a seven-component reaction (7CR) by the one-pot combination of a modified Asinger 4CR[65] and the Ugi 4CR.[66] In this 7CR, an α- or β-halo aldehyde, NaSH/NaOH, NH_3, another aldehyde, an isocyanide, CO_2, and a primary alcohol (solvent) are combined to afford complex thiazolidines efficiently (e.g. **96**, Scheme 10). However, NaSH/NaOH, NH_3, and CO_2 are



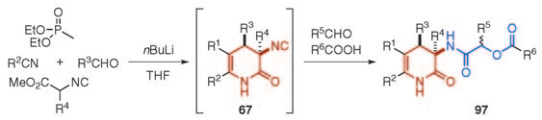
Scheme 10. Combination of the modified Asinger 4CR and an Ugi-type MCR to afford thiazolidines.

invariable components in this reaction, which significantly limits the appendage diversity and thus the scope of the MCR.

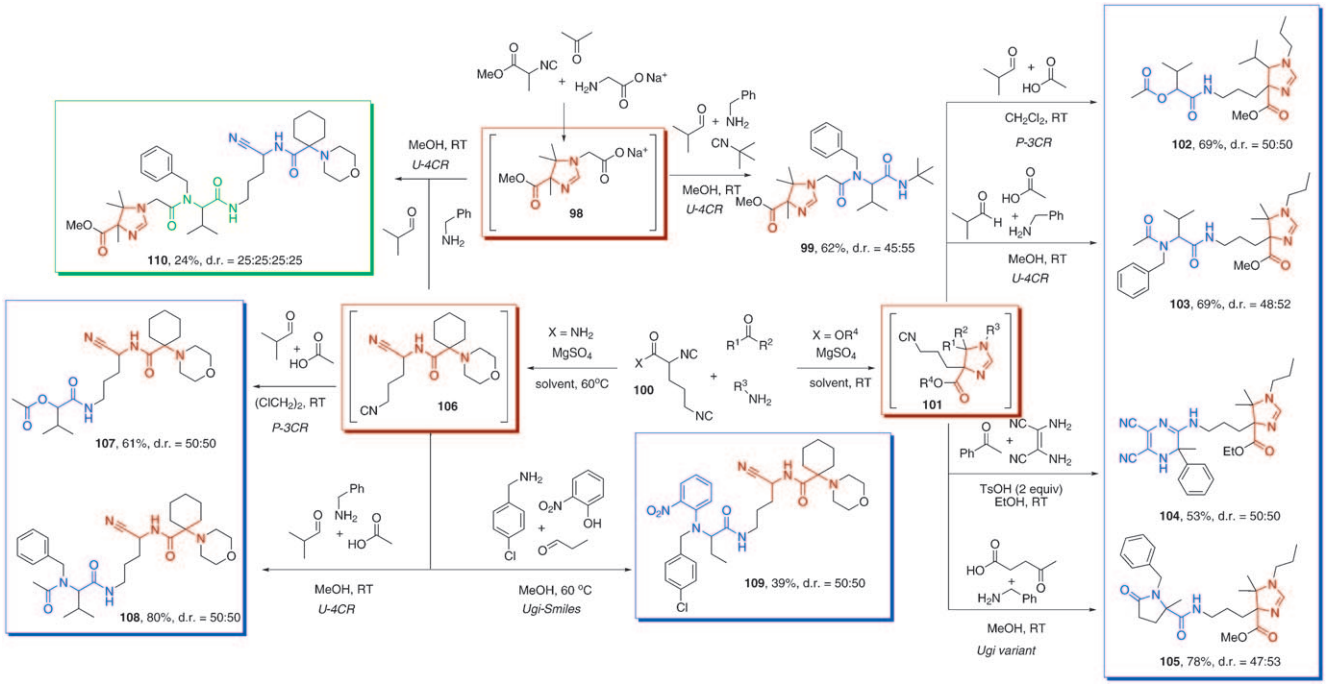
Another example was also reported by Ugi et al., namely the combination of a Ugi five-center four-component reaction (U-5C-4CR) with a Passerini 3CR.[67] This one-pot procedure uses L-aspartic acid as a two-center one-component input. Since the α adduct of an α-amino acid, an aldehyde, and an isocyanide cannot undergo the Mumm rearrangement, the solvent MeOH acts as a competing nucleophile, thereby resulting in a U-5C-4CR that leads to a methyl α-amido ester. The δ-carboxylic acid can only participate in the (much slower) Passerini 3CR. The same aldehyde and isocyanide are used in both MCRs, which limits the variability of the products.

In 2003, Portlock et al. reported the combination of the Petasis 3CR and the Ugi 4CR.[67–70] However, an intermediate solvent change was required, which limits the practicality of this approach. In 2007, we showed that the 4CR for the preparation of isocyano dihydropyridones **67** (see Scheme 6) can be combined in one pot with the Passerini 3CR to give constrained depsipeptides **97** (Scheme 11).[56] The yield of the one-pot procedure is comparable with the combined yield of the separate reactions.

In 2009, our research group demonstrated that a combination of MCRs can be used to achieve complexity as well as scaffold diversity (Scheme 12).[71] The strategy is based on the 3CRs of isocyano esters or amides, aldehydes or ketones, and amines to give 2-imidazolines[72] or *N*-(cyanomethyl)amides.[29] Both reactions show extraordinary functional group and solvent compatibility. By incorporation of a



Scheme 11. Combination of the 4CR for isocyanodihydropyridones and the P-3CR. The primary MCR scaffold structure is shown in red and the secondary scaffold in blue.



Scheme 12. Combination of MCRs based on 2-imidazoline and *N*-(cyanomethyl)amide MCRs. The primary MCR scaffold structures are shown in red, the secondary scaffolds in blue, and the tertiary scaffold in green. Primary MCR intermediates are in red boxes, double MCR (MCR^2) products in blue boxes, and the triple MCR (MCR^3) product in the green box.

second orthogonally reactive group in one of the starting materials, these MCRs can be coupled to various secondary MCRs. For example, sodium glycinate can be used in the 2-imidazoline 3CR to afford carboxylate-functionalized imidazoline intermediate **98**, which can participate in a U-4CR after protonation to give **99**.

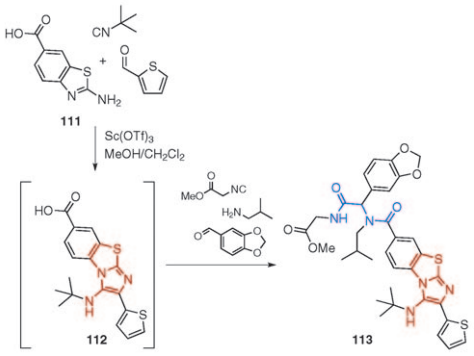
A more versatile approach involves the use of diisocyanides **100**. The two isocyanide functionalities show intrinsically different reactivities. The α-isocyanide is α acidic and more reactive, which results in the chemoselective formation of the intermediate 2-imidazoline **101** and *N*-(cyanomethyl)-amide **106**. The δ-isocyanide provides a handle for subsequent isocyanide-based MCRs. Since the 2-imidazoline MCR can be performed in a wide range of solvents, the optimal solvent for the secondary MCR can be used in each case. Consequently, intermediate isocyanoimidazoline **101** can undergo a variety of secondary MCRs, including a Passerini 3CR to give **102**, a Ugi 4CR to give **103**, an intramolecular Ugi variant[73] with levulinic acid to give **105**, and a recently reported 3CR for the preparation of 1,6-dihydropyrazine-2,3-dicarbonitrile derivatives[74] such as **104**. Similarly, intermediate isocyano-*N*-(cyanomethyl)amide **106** can undergo a Passerini 3CR to give **107**, a Ugi 4CR to give **108**, and a Ugi–Smiles[75,76] 4CR to give **109**. Finally, it even proved possible to combine three MCRs in one pot by connecting intermediates **98** and **106** (generated by two sequential, orthogonal MCRs) through a Ugi 4CR to result in the formation of **110** through a unique eight-component reaction.[71]

Westermann and co-workers recently reported the one-pot combination of the Ugi and Ugi–Smiles 4CRs through the use of a reactant that contains both a carboxylic acid and a 2-nitrophenol or 2-hydroxypyridine moiety.[77] Although the Ugi 4CR was found to be relatively fast with respect to the Ugi–Smiles reaction, a sequential Ugi/Ugi–Smiles one-pot 7CR (using a different combination of isocyanide, aldehyde, and amine in the Ugi reaction than in the Ugi–Smiles reaction) afforded the desired products in relatively low yield compared to the pseudo-7CR approach where the same isocyanide, aldehyde, and amine input were used for both reactions.

Al-Tel et al. combined the Groebke–Bienaymé–Blackburn 3CR[78–80] with Ugi or Passerini MCRs to arrive at a series of 5- and 6CRs with highly complex products.[81] An interesting feature of the Groebke–Bienaymé–Blackburn 3CR of aminoheteroaromatic compounds, aldehydes, and isocyanides is that it directly affords pharmaceutically relevant heterocyclic products (e.g. **105**, Scheme 13).

3. Towards stereoselective MCRs

One of the main limitations of MCRs as synthetic tools is the typical lack of stereocontrol. For example, a generally applicable catalytic asymmetric Ugi reaction is considered a holy grail in MCR chemistry. In practice, however, the stereoselectivity of many (isocyanide-based) MCRs is notoriously poor. Although there are some examples of catalytic asymmetric Passerini(-type) three-component reactions (P-3CR),[82–86] the enantioselectivities are generally modest and only good in specific cases, with aluminum–salen complexes being the most promising catalysts.[86] Zhu and co-workers have recently reported very promising results for their isocyanide-based MCRs for the synthesis of oxazoles.[87,88] The general problem is that many MCRs, including the U-

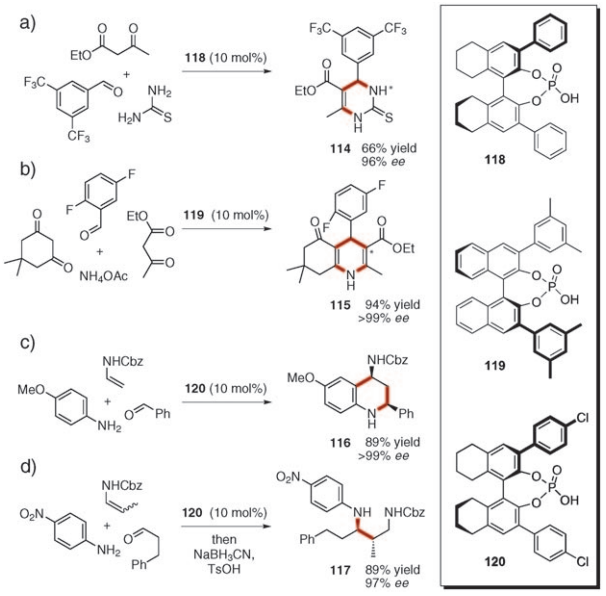


Scheme 13. Combination of Groebke–Bienaymé–Blackburn 3CR and Ugi 4CR. The primary MCR scaffold structures are shown in red and the secondary scaffolds in blue.[81]

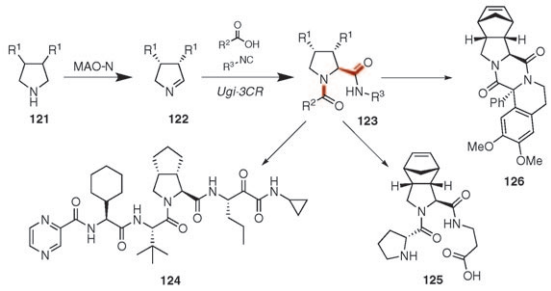
4CR, are essentially uncatalyzed. The discovery of a catalyst for a certain MCR is the important first step in the development of a (catalytic) asymmetric version.[89] For example, acid-catalyzed classical MCRs such as the Hantzsch,[62] Biginelli,[15] Povarov,[90] and Mannich[91] reactions have greatly benefited from the recent rise of chiral Brønsted acid catalysis (Scheme 14).[92–95] Other recent developments in organocatalysis have led to the development of a number of very elegant asymmetric cascade processes.[96]

Several classical MCRs have also benefitted from other developments in asymmetric organocatalysis.[97] Barbas and co-workers described how careful selection of pyrrolidine-type organocatalysts allows full control of the stereochemical diversity in the Mannich reaction.[98,99] The nature of the organocatalyst determines the stereochemical outcome of the reaction. The use of L-proline and (3*R*,5*R*)-5-methyl-3-pyrrolidinecarboxylic acid as catalysts leads to the formation of (2*S*,3*S*)-*syn* and (2*S*,3*R*)-*anti* diastereomers, respectively, in high diastereo- and enantioselectivity. The difference in the stereochemical outcome of the two reactions can be rationalized by the difference in the preferred conformation of the intermediate enamines. The facial selectivity (the *re* face of the enamine reacts with the *si* face of the imine) is controlled by the carboxylic acid, which activates the imine. Evidently, the enantiomeric products are accessible by using the opposite enantiomers of the organocatalysts, thus providing access to all four possible stereoisomers.

Exploiting the intrinsic diastereoselectivity of certain MCRs is another attractive strategy for the development of stereoselective MCRs.[11] Since the availability of chiral pool materials is limited, straightforward and reliable methods for the generation of optically pure MCR inputs are required. The (one-pot) combination of such methods with MCRs opens up exciting opportunities to address stereochemical diversity in DOS/BIOS-based library design. In this context, biocatalysis is a promising, yet virtually unexplored method. Recently, we used a monoamine oxidase to desymmetrize *meso*-pyrrolidines to the corresponding 1-pyrrolines, which then react in a highly diastereoselective Ugi-type MCR (Scheme 15).[100] Moreover, we were able to exploit this



Scheme 14. a) Organocatalytic asymmetric Biginelli 3CR using chiral phosphoric acid **118**.[93] b) Organocatalytic asymmetric Hantzsch 4CR using chiral phosphoric acid **119**.[92] c) Organocatalytic asymmetric Povarov 3CR using chiral phosphoric acid **120**.[94] d) Organocatalytic asymmetric Mannich 3CR using chiral phosphoric acid **120**.[95] Newly formed bonds are indicated in red. Cbz = benzyloxycarbonyl, Ts = 4-toluenesulfonate.



Scheme 15. Oxidative desymmetrization of *meso*-pyrrolidines by monoamine oxidase N (MAO-N) from *Aspergillus niger* and subsequent Ugi-type MCR in the synthesis of organocatalysts (e.g. **125**),[100] synthetic alkaloids (e.g. **126**),[103] and the hepatitis C drug candidate telaprevir (**124**).[101] Newly formed bonds in the MCR are indicated in red.

method in a short and efficient asymmetric synthesis of the important hepatitis C drug candidate (HCV NS3 protease inhibitor) telaprevir (**124**),[101] as well as a Wennemers-type organocatalyst for asymmetric Henry reactions (**125**)[100,102] and polycyclic alkaloid-type compounds (e.g. **126**).[103]

4. Summary and Outlook

Many classical MCRs involve 1) the unique reactivities of isocyanides[8] (e.g. Passerini, Ugi), or 2) the combination of β-dicarbonyl compounds, amines, and aldehydes (e.g. Hantzsch, Biginelli).[104–106] Variations on these themes have led to the discovery of many interesting MCRs. However, options for further expansion of this repertoire are limited. Future

strategies for the development of new MCRs will most likely focus more on the one-pot combination of sequential, orthogonal reactions. For example, (multicomponent) reactions with high functional group and solvent compatibility allow their straightforward one-pot combination with other reactions, thereby leading to highly atom- and step-economical procedures. Furthermore, modular reaction sequences allow stepwise expansion of scaffold diversity. Some MCR purists may claim such sequential one-pot reactions are not true multicomponent reactions, since the reagents can not all be added simultaneously. In our opinion, it is more practical to consider what we wish to achieve with an MCR, that is, a practical, atom-economic, one-pot procedure that delivers complex products with high variability. For this purpose, a true MCR must: 1) involve a true one-pot procedure without intermediate workup or solvent change; 2) incorporate essentially all of the atoms of the reactants into the product, with the exception of small condensation by-products, and 3) involve only inputs that can be independently varied. In addition, the variability of each of the components should be sufficient to ensure a high overall appendage diversity.

Recent advances in homogeneous catalysis (and especially organocatalysis) offer a bright future for the development of novel catalytic (asymmetric) MCRs. Our growing insights in the fundamental (and conditional) reactivity of functional groups will lead to the development of many chemo-, regio-, and stereoselective MCRs in years to come. It should, however, be noted that this fundamental understanding is based on many decades of curiosity-driven research, which will continue to be required for future innovation in synthetic strategies. Moreover, it will lead to the serendipitous discovery of many more new reactions—for as much as we may know, chemistry always has new and intriguing surprises in store.

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