Chapter 1

Multicomponent Reaction Design in Quest for Molecular Complexity and Diversity

Abstract: In the past decade it has been extensively demonstrated that multicomponent chemistry is an ideal tool to create molecular complexity. Furthermore, combination of these complexity-generating reactions with follow-up cyclization reactions led to scaffold diversity, which is one of the most important features of diversity-oriented synthesis. Scaffold diversity has also been created by the development of novel multicomponent strategies. Four different approaches will be discussed (single reactant replacement, modular reaction sequences, condition-based divergence, and union of multicomponent reactions), which all led to the development of new multicomponent reactions and higher order multicomponent reactions, thereby addressing both molecular diversity and complexity.

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1.1 Complexity and Diversity

The importance of small molecules\textsuperscript{[1]} in contemporary chemical biology and medicinal research is undisputed. Studying the interaction of small molecules with biological systems, is crucial for understanding all fundamental processes of life, both in health and disease.\textsuperscript{[2]} Synthetic organic chemists enable access to structurally complex and functionally diverse sets of small molecules and thus supply the feedstock for advanced chemical biology and medicinal research studies.

Current drug discovery involves the screening of small molecules for their ability to bind to a pre-selected protein target (found by biological methods).\textsuperscript{[3]} This is rather time-consuming and leads to the development of drugs for only a small selection of protein targets. The ultimate goal, however, is to identify molecular modulators for all cellular processes, which emerge from growing insights in genome biology, including non-classical biological targets that are currently considered “undruggable”.\textsuperscript{[4]} This can be done by screening small molecules for their ability to modulate a biological pathway in cells or organisms, without considering a specific protein target. This will result in the simultaneous identification of the therapeutic protein target and its chemical modulator.\textsuperscript{[3]}

\textbf{Figure 1.} Representation of (a) Target-Oriented Synthesis (TOS), (b) Combinatorial Chemistry and (c) Diversity-Oriented Synthesis (DOS) in chemical space.\textsuperscript{[2]}

Since the protein target and the chemical modulator are unknown, for this drug development strategy methodologies are required that lead to structurally complex and diverse small molecules covering a broad region of the so-called “chemical space”.\textsuperscript{[2,5,6]} This is one of the main focuses of diversity-oriented synthesis (DOS, Figure 1c).\textsuperscript{[2,7–9]}
aim of DOS, *i.e.* to access as many points in the chemical space, differs very much from target-oriented synthesis (TOS, Figure 1a) and combinatorial chemistry (Figure 1b), which access just a single point or dense region in chemical space. TOS is especially used in drug discovery involving pre-selected protein targets and makes use of retro-synthetic analysis.[3] TOS primarily relies on nature to discover small bioactive compounds. After isolation and characterization of a natural product, it can become a target for chemical synthesis. Closely related to this approach is combinatorial chemistry, which often uses these natural products or other known drugs, as a starting point to obtain a collection of molecules derived from the parent skeleton (focused libraries), for example by changing substituents around a common skeleton.

In contrast to retrosynthetic analysis used for TOS and combinatorial chemistry, DOS requires “forward synthetic planning” that enables the conversion of simple starting materials into complex and diverse products. Molecular complexity (generally found in natural products) seems to be extremely important to obtain an optimal perturbation function and specificity of action of the chemical modulators on their protein targets.[2,9]

The goal of achieving *molecular diversity* can be divided in three different diversity elements: (a) appendage diversity (combinatorial chemistry), (b) stereochemical diversity, and most importantly (c) scaffold diversity (Figure 2).[2]

*Appendage* diversity (Figure 2a) is the central feature of combinatorial chemistry and involves the introduction of different appendages to a common molecular skeleton. Although diversity is generated, these compounds all have a common molecular skeleton, thereby displaying related chemical information in the 3D space (same molecular shape) resulting in a limited amount of potential binding partners.

![Figure 2. The three different elements of molecular diversity.](Image)
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For DOS, it is especially important to create compounds that display diverse 3D information. This can be realized by developing synthetic pathways that incorporate the two other diversity elements, stereochemical and scaffold diversity. *Stereochemical* diversity (Figure 2b) involves the generation of as many stereoisomers of the same molecule, however not as mixtures, but selectively. For this, stereoselective reactions are required that allow selective access to different stereoisomers by for example changing the stereochemistry of the catalyst or the chiral substrates. Finally, *scaffold* diversity (Figure 2c), probably the most important element of diversity, is the generation of a collection of products with different molecular skeletons (scaffolds). This can for example be realized by changing the reagents added to a common substrate (reagent-based approach) or by transforming a collection of similar substrates having different appendages with suitable pre-encoded skeletal information, using similar reaction conditions (substrate-based approach).[2,10]

For DOS to succeed, highly efficient (max. 3-5 reaction steps), versatile, and robust synthetic methodologies are needed. This requires new concepts and novel design approaches that focus on complexity and diversity generation and do not require protective group manipulations: a clear challenge for the synthetic organic chemist.

![Figure 3](image.png)

**Figure 3.** Schematic illustration of a multicomponent reaction leading to a complex product.

A powerful strategy to address these challenges involves the use of multicomponent reactions (MCRs), which are reactions of at least three different simple reagents reacting in a well-defined manner to form a single product (Figure 3).[11] This highly convergent methodology allows molecular complexity to be created by the facile formation of several new covalent bonds in a one-pot transformation. Using MCRs, the number of functional group manipulations towards a given complex molecular target is minimized, thus avoiding the use of protective groups. At the same time MCRs proceed with remarkably high atom economy[12] and low E factors[13]. As such, syntheses involving MCRs save
time and energy (step efficiency) and quite closely approach the concept of the ideal synthesis, making them very useful to apply in DOS.\cite{11c}

### 1.2 Multicomponent reactions

The first important MCR was developed by Strecker in 1850 (Scheme 1).\cite{14} In this reaction ammonia, an aldehyde and hydrogen cyanide combine to form α-cyano amines 1, which upon hydrolysis form α-amino acids 2. Also heterocyclic compounds were obtained using multicomponent reactions. An example of this is the Hantzsch reaction, discovered in 1882.\cite{15} This reaction is a condensation of an aldehyde with two equivalents of a β-ketoester in the presence of ammonia resulting in the formation of dihydropyridines 3. A comparable reaction is the Biginelli reaction, founded in 1893.\cite{16} This reaction is a three-component reaction (3CR) between an aldehyde, a β-ketoester and urea to afford dihydropyrimidines 4.

**Scheme 1.** Overview of some of the first reported MCRs.

Another well-known 3CR is the Mannich reaction, developed in 1912, in which formaldehyde or a non-enolizable aldehyde and an amine form an intermediate Schiff
base which subsequently reacts with an α-acidic compound, to afford β-amino carbonyl 5.[17]

A few years later, Passerini developed a new 3CR towards α-acyloxy amides 9 which are formed by reacting an aldehyde or ketone 6, a carboxylic acid 8 and an isocyanide 7 (Scheme 2).[18] Since the first synthesis of isocyanides (formerly known as isonitriles[19]) in 1858, the Passerini three-component reaction (P-3CR) was the first MCR involving this reactive species. It has become one of the renowned examples of an important subclass of MCRs, the isocyanide-based MCRs (IMCRs). Especially important for the Passerini reaction, but also for a lot of other IMCRs, is the ability of isocyanides to form α-adducts, by reacting with nucleophiles and electrophiles (at the carbon atom). The nucleophilic character of the isocyanide carbon can be explained by the filled non-bonding σ-orbital. The electrophilic character is explained by the empty π*-orbital possessing a high orbital coefficient on carbon (Figure 4).[20] Even though the isocyanide carbon is nucleophilic, good electrophiles such as protonated carbonyls or iminium ions are typically required for a reaction to occur (as becomes also clear from the mechanism of the Passerini reaction).[21]

Figure 4. Frontier orbitals of the isocyanide, explaining the reactivity of this important functional group in multicomponent chemistry.

The Passerini reaction is typically carried out at high concentrations of starting materials in aprotic solvents (generally DCM), at or below room temperature. The reaction shows a broad substrate scope and variation of all three components is extensively possible. Since the Passerini reaction is accelerated in aprotic solvents, it is assumed that the reaction follows a non-ionic pathway. The most plausible mechanism of the reaction is depicted in Scheme 2.[18,20] Initially, a loosely bound hydrogen bonded adduct 10 is formed, from the carboxylic acid 8 and the carbonyl compound 6. The next step is the formation of the α-adduct 11 by reaction of the isocyanide with the nucleophilic
carboxylate and the electrophilic protonated carbonyl compound. \( \alpha \)-Adduct \( 11 \) then rearranges to give \( \alpha \)-acyloxy amide \( 9 \).

![Scheme 2. The Passerini and Ugi MCRs and their proposed mechanisms.](image)

About forty years later, in 1959, Ugi developed a four-component variant of this reaction that involves an aldehyde or ketone \( 6 \), a carboxylic acid \( 8 \), an amine \( 12 \) and an isocyanide \( 7 \) yielding \( \alpha \)-acylamino amide \( 13 \) (U-4CR, Scheme 2).\[^{22}\] Like the Passerini reaction, the Ugi reaction shows a high substrate scope. The reaction is favored in polar protic solvents and is usually performed in methanol, though several other solvents have been reported.\[^{20,23}\] Although different mechanisms have been reported,\[^{11g}\] the Ugi reaction will presumably proceed via nitrilium ion intermediate \( 15 \), formed by a reaction of the isocyanide \( 7 \) with the \( \textit{in situ} \) generated iminium ion \( 14 \). Subsequent trapping of \( 15 \) with the carboxylate \( 16 \) generates the instable \( \alpha \)-adduct \( 17 \), which undergoes an intramolecular acylation called the Mumm rearrangement to afford \( \alpha \)-acylamino amide \( 13 \).\[^{21,24}\]
1.3 Molecular diversity involving MCRs

As already became clear from the previous examples, MCRs are ideal to obtain complex products in an easy way. However, DOS also requires molecular diversity (appendage, stereochemical and scaffold diversity), which can as well be accomplished using MCRs. MCRs are ideal to achieve appendage diversity, because all individual components can be varied to create a large library of products that have the same skeleton but differ in the substituents around it. If, for example, a four-component reaction is considered and 40 inputs of all four components are combined, this will result in \(4^4 = 2\,560\,000\) reaction products.[25]

To create stereochemical diversity within MCRs there is a need for stereoselective (or -specific) reactions. Since many MCRs involve flat intermediates, like imines and \(\alpha,\beta\)-unsaturated ketones, they result in the formation of racemic products. Moreover, often mixtures of diastereomers are obtained if more than one stereogenic centre is formed.

However, there are several examples known of asymmetric induction, by the use of chiral building blocks (diastereoselective reactions). For example, it has been successfully applied to the Strecker, Mannich, Biginelli, Petasis, Passerini, Ugi, and many other MCRs, which has been excellently reviewed by Yus and co-workers.[26] Enantioselective MCRs, which generally proved to be much harder, have been performed with chiral organometallic catalysts and organocatalysts.[26,27]

An interesting example that shows the possibility of stereochemical diversity, is the Mannich reaction involving organocatalysis (Scheme 3).[28-30] By changing the nature of the organocatalyst (L-Proline (20) vs. (3R,5R)-5-methyl-3-pyrrolidinecarboxylic acid (25)) the \((2S,3S)\)-syn and \((2S,3R)\)-anti diastereomers 21 and 26 could be formed selectively in high diastereo- and enantioselectivities. The difference in stereochemical outcome of the two reactions can be explained by the different steric influence of the pyrrolidine ring. For L-proline (Pathway A), enamine conformation 24 is favored over 23 due to steric hindrance of the carboxylic acid and the double bond in conformation 23.

The facial selection (the re face of the enamine reacts with the si face of the imine) is controlled by the carboxylic acid, which activates the imine (transition state I). For organocatalyst 25 the steric bulk is on the 5-position of the pyrrolidine ring instead of the 2-position. This results in a favored enamine conformation 29, with the carboxylic acid and the enamine double bond to the same side. The carboxylic acid will direct the
approach of the enamine to the imine (transition state II) similarly as described for L-proline, resulting in the formation of anti-diastereomer 26.

Evidently, by taking the enantiomers of the organocatalyst the two enantiomeric products 22 and 27 (depicted in grey) are accessible, making it possible to access all 4 possible stereoisomers for this MCR.[29,31]

Scheme 3. Introduction of stereochemical diversity in the Mannich reaction applying organocatalysis.

Regarding scaffold diversity it is evident that any single MCR does not lead to multiple scaffolds, since ideally, three or more components combine to form a single product (one of the criteria for MCRs). As a result several research groups have introduced scaffold diversity by combining MCRs with cyclization reactions, as illustrated in Figure 5.[32,33]

This concept of introducing scaffold diversity by intramolecular cyclizations is nowadays commonly referred to as the build/couple/pair strategy, introduced by Schreiber in 2008.[34] The build phase involves the (asymmetric) synthesis of (chiral) building blocks containing orthogonal sets of functionalities that can be used for the coupling and subsequent pairing reactions. In this stage, smart selection of building blocks will lead to a large number of different scaffolds in the pairing (cyclization) stage. The couple phase involves intermolecular coupling reactions that combine the different building blocks, resulting in densely functionalized substrates ready for use in the pairing phase. Considering MCRs as coupling reactions, there is a need for versatile MCRs that are able to use a lot of different substrates (high functional group tolerance/broad substrate scope). Furthermore, it would be ideal that the MCR can provide every possible
stereoisomer selectively, to obtain stereochemical diversity. The *pair* phase involves intramolecular coupling reactions (functional group pairing reactions\(^{[35]}\)) that join the functional groups that were strategically planned in the build phase. Carefully adapting the reaction conditions in this pairing phase leads to pairing of different functional groups, resulting in the formation of a variety of different scaffolds.

**Figure 5.** The generation of scaffold diversity, by combining MCRs with cyclization reactions according to the build/couple/pair strategy.\(^{[36]}\)

Since the build/couple/pair strategy requires versatile MCRs it is not surprising that the Ugi four-component reaction is often used for this purpose as coupling reaction. A wide variety of Ugi (*couple*) post-cyclization reactions (*pair*) are reported, to afford an impressive range of nitrogen heterocycles (for selected examples, see Scheme 4).\(^{[32,37-43]}\) As is clear from the scheme, by variation of the Ugi building blocks and applying the proper cyclization reaction, different scaffolds are accessible in only two to three steps. For example, if 4-bromo-1H-indole-3-carbaldehyde, allylamine, 3-butenolic acid and isopropyl isocyanide are used as Ugi inputs, the two retained alkene functionalities in Ugi product 33 allow ring-closing metathesis to afford 34. This product possesses an aryl bromide and an alkene functionality that can undergo a second cyclization by a subsequent intramolecular Heck reaction occurring with excellent diastereoselectivity to afford 35 in 59% overall yield (product is racemic).\(^{[37]}\) In some of the examples, *i.e.* Ugi/Diels-Alder and Ugi/Pictet-Spengler, the reactions were performed in a single pot (although step-wise), but in the majority of the examples the Ugi intermediate was first isolated.
Scheme 4. The introduction of scaffold diversity by the Ugi-4CR (couple) and follow-up cyclization reactions (pair).

A second, very elegant, example of build/couple/pair strategy in DOS is performed by Schreiber and co-workers (Scheme 5). This example uses the Petasis reaction of (S)-lactol 42, L-phenylalanine methyl ester (43) and (E)-2-cyclopropylvinylboronic acid (44) as coupling reaction, followed by a propargylation to obtain the densely functionalized substrate 46 in >99% de. Although the Petasis reaction was not sufficient to introduce all required functionalities, making an additional coupling step necessary, it can easily introduce stereochemical diversity. This is because the anti-diastereomer is exclusively formed, directed by the α-hydroxy functionality of the intermediate imine. By combining both enantiomers of the lactol and the amino acid, 4 stereoisomers are accessible.
Scheme 5. The use of the Petasis 3CR as coupling reaction and several pairing reactions to afford 15 distinct scaffolds.

As is common for the build/couple/pair strategy, the scaffold diversity is created in the pairing phase. Remarkably, Schreiber was able to use every single functionality of 46. Seven different highly selective pairing reactions were performed, to obtain seven different scaffolds (A-G), which is quite remarkable since they are all obtained from one
single substrate. To come back to a term earlier introduced, this is an example of a reagent-based approach since a single substrate is converted by different reaction conditions, producing a diversity of scaffolds.\textsuperscript{[34]}

Products \( \text{F} \) and \( \text{G} \) were in turn substrates for subsequent pairing reactions to obtain multicyclic compounds \( \text{J}, \text{N}, \text{K}, \text{O} \) and \( \text{H} \). Finally products \( \text{B}, \text{J} \) and \( \text{H} \), which all comprise a diene functionality could be further converted by a subsequent Diels-Alder reaction with \( 4\text{-methyl-1,2,4-triazolin-3,5-dione} \) to obtain the highly complex products \( \text{I}, \text{M} \) and \( \text{L} \). This example shows that by applying the build/couple/pair strategy a collection of 15 highly diverse (and complex) scaffolds can be obtained in only three to five steps.\textsuperscript{[45]}

### 1.4 Novel multicomponent strategies towards scaffold diversity

From the previous examples it is clear that scaffold diversity can be achieved using MCRs and post condensation cyclizations. However, during the last decade much work has also been devoted to obtain scaffold diversity by using MCR strategies exclusively. Besides scaffold diversity, this has also lead to the development of a number of novel MCRs. These new multicomponent design strategies, to achieve scaffold diversity, can be divided into four main approaches:

- Single Reactant Replacement (SRR)
- Modular Reaction Sequences (MRS)
- Condition-Based Divergence (CBD)
- Union of MCRs (MCR\(^2\))

As will be clear from the following examples, many of these are illustrations of rationally designed MCRs that could generally only succeed because of chemists’ insight into mechanisms and functional group reactivities, although some MCRs are still found serendipitously.
1.4.1 Single Reactant Replacement (SRR)

The Single Reactant Replacement strategy (SRR, Figure 6), a phrase first introduced by Ganem, involves the development of new MCRs by systematic assessment of the mechanistic or functional role of each component in a known MCR.\(^{[46]}\) In this method one reactant C is substituted for reactant D that displays a similar chemical reactivity mode required for the multicomponent condensation with A and B. By incorporation of an additional reactivity or functionality into D, the resulting MCR might be directed to a different outcome, leading to scaffold diversity.\(^{[46]}\)

![Figure 6. Schematic representation of the Single Reactant Replacement (SRR) strategy to scaffold diversity.](image)

Probably one of the first examples of SRR is performed by Ugi and co-workers, who replaced the carbonyl component 6 of the Passerini reaction by a different electrophile, \textit{i.e.} imine 47, which resulted in the well-known Ugi reaction affording 13 (Scheme 6).\(^{[22]}\) Ugi furthermore replaced the carboxylic acid (8) input of the Ugi reaction by different acidic components 48 to afford various different scaffolds (Scheme 6).\(^{[47]}\) It is required that the selected components are sufficiently acidic (to activate the imine) but their conjugated bases should still be able to attack the intermediate nitrilium ion as a nucleophile. Consequently, Ugi was able to use HNCO and HNCS to afford hydantoinimides (49a) and thiohydantoinimides (49b), respectively. These are formed from the corresponding \(\alpha\)-adducts, by an intramolecular acylation. Also hydrazoic acid was used, resulting in the formation of tetrazole 50 by spontaneous cyclization of the \(\alpha\)-adduct. By applying water or hydrogen selenide the corresponding \(\alpha\)-adducts are transformed by tautomerization, to obtain the final products 51a and b, respectively.
Scheme 6. One of the first examples of Single Reactant Replacement performed by Ugi and co-workers.

In a related approach, Ganem and co-workers changed the carboxylic acid in the Passerini reaction for a Lewis acid (TMSOTf, 53) to activate the carbonyl compound 6. Reaction of several carbonyls, morpholinoethylisonitrile 52 and Zn(OTf)$_2$/TMSCl (which forms TMSOTf in situ) resulted in the formation of $\alpha$-hydroxyamide 56 (Scheme 7). Ganem realized that a neighbouring stabilizing group like in this example the morpholine ring, was required to stabilize the nitrilium ion 54 (formed by attack of the isonitrile to the activated carbonyl), since simple isonitriles did not result in any reaction.[48]

These mechanistic insights lead Ganem to study other donating groups at the isocyanide component, applying e.g. isocyanate esters or amide (57). Indeed the esters and amides were able to function as stabilizing group, leading to the formation of ethoxy- and morpholinooxazoles 60.[48]

Further SRR could be achieved by replacing carbonyl 6 to iminium ion 61, which resulted in the formation of bis-amino oxazoles 65 (catalyzed by a Brønsted acid).[49] Finally, our research group serendipitously discovered the formation of $N$-(cyanomethyl)amides 70 when primary $\alpha$-isocyano amide 67 was used as an input (Scheme 7, SRR$^4$, Brønsted
acid was applied only with primary amines). The mechanism of this reaction will be
discussed further in paragraph 1.4.3.

![Scheme 7](image)

**Scheme 7.** Four successive single reactant replacements, resulting in four new scaffolds.

Another nice example of SRR is depicted in Scheme 8. The original reaction was
developed by Diels and Harms in 1936. Reaction of isoquinoline 71 with dimethyl
acetylenedicarboxylate (DMAD, 72) initially forms zwitterionic intermediate 73, which
then undergoes a Michael addition/Mannich reaction domino sequence with a second
equivalent of DMAD to form benzoquinolizine 74. This is, however, not a true 3CR
reaction, since two components are identical. In 1967, Huisgen reported three variations
of this reaction in which intermediate 73, a 1,4-dipole, is trapped with several different
dipolarophiles, such as dimethyl azocarboxylate 75, diethyl mesoxalate 77 and
phenylisocyanate 79 to form tricyclic scaffolds 76, 78 and 80, respectively. Other
examples of replacement of the second equivalent of DMAD have been published by Nair
et al. who applied 2,5-dimethyl-1,4-benzoquinone 81 to obtain spiro[1,3]oxazino[2,3-
a]isoquinoline derivative 82, N-tosylimines 83 to afford 2H-pyrimido-[2,1-
alisoquinolines 84 and arylidinemalononitriles 85 to yield tetrahydrobenzoquinolizine derivatives 86.\textsuperscript{[53-55]} Recently, Yavari et al. reported a 3CR to pyrrolo[2,1-a]alisoquinolines 88, by reacting 71, 72 and aroylnitromethanes 87 in good yields.\textsuperscript{[56]} The reactions reported here, obtained by SRR, are all one-pot three-component reactions. For additional MCRs involving intermediate 73, see ref 57.

\begin{center}
\includegraphics[width=\textwidth]{scheme_8.png}
\end{center}

\textbf{Scheme 8.} Replacement of DMAD in the original reaction to 74, by different third components yielding several new isoquinoline based MCRs. The differentiating component in each reaction is indicated in bold.

From the reported examples in this paragraph\textsuperscript{[58]} it is clear that SRR is a fast way of developing new MCRs and is extremely useful for application in DOS, since it can quickly afford many different scaffolds.
1.4.2 Modular Reaction Sequences

The second MCR development strategy leading to scaffold diversity involves Modular Reaction Sequences (MRS, Figure 7) which is closely related to SRR but involves a versatile reactive intermediate that is generated from substrates A, B, and C by an initial MCR. This intermediate is then reacted 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 92 as an intermediate to scaffold diversity which is generated in situ from a phosphonate 89, a nitrile 90 and an aldehyde 91 via a 3CR involving a Horner-Wadsworth-Emmons (HWE) reaction (Scheme 9). In 1995, Kiselyov reported the first MCR involving this 1-azadiene which he reacted with sodium or potassium salts of aryl substituted acetonitriles 93 to afford 2-amino pyridines 94 in 61-72% yields (3 examples, R¹ = H, R² = R³ = Ar). Furthermore, he reacted the 1-azadiene with sodium enolates of methyl aryl ketones 95 to afford 2,4,6-substituted pyridines 96 in 63-67% yield (3 examples, R¹ = H, R² = R³ = Ar). Ten years later, Kiselyov published an elaboration of this work, by reacting 1-azadiene 92 with amidines (97, R⁴ = alkyl, aryl) and guanidines (97, R⁴ = NHR) to afford polysubstituted pyrimidines 98 in 22-73% yield. This MCR proved to have a rather high substrate scope since all components could be varied to some extent (19 examples, R¹ = H, alkyl, Ph, R² = R³ = Ar). Furthermore, the one-pot reaction of 92 with 5-amino
pyrazoles (99, X = N, Y = C) and 2-amino imidazoles (99, X = C, Y = N) resulted in the formation of bicyclic compounds 100 and 101 (12 examples, 52-77%, R¹ = H, R² = R³ = Ar). In another one-pot procedure Kiselyov reacted 92 with the dianion of methyl imidazolyl acetates 102 to yield imidazo[1,2-a]pyridines 103 (12 examples, 54-75%, R¹ = H, R² = R³ = Ar). Our group has also contributed to these 1-azadiene derived MCRs by reacting 92 with isocyanates 104 to selectively afford functionalized 3,4-dihydropyrimidine-2-ones 105 (29 examples, 15-90% yield) and triazinanone diones 106 (17 examples, 25-91% yield) depending on the nature of the isocyanate (Scheme 9). The use of isocyanates with strongly electron-withdrawing groups (Ts, p-NO₂Ph, CO₂Me, C(O)Ph) resulted in

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the exclusive formation of the dihydropyrimidinones 105, while isocyanates with less electron-withdrawing (Ph, PMP) or donating substituents (Et, benzyl) resulted in the formation of triazinane diones 106. Dihydropyrimidinones are most likely formed by nucleophilic attack of the 1-azadiene nitrogen to the isocyanate (with electron-withdrawing substituent), followed by cyclization. On the other hand, when isocyanates with less electron-withdrawing or 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, thermodynamically favored, six-membered triazinane diones. Both reactions showed to have a broad substrate scope (appendage diversity) and the R² and R³ substituents could be varied extensively. However, variation of the R¹ substituent was limited (only H and Me).

A modification of the dihydropyrimidinone MCR was performed by applying isothiocyanates 107 as the fourth component, which resulted in the formation of 2-aminothiazines 108 which upon microwave heating could rearrange (Dimroth rearrangement) to dihydropyrimidine-2-thiones 109.[67]

A second example that uses modular reaction sequences was reported by Zhu and co-workers (Scheme 10). They combined the bis-amino oxazole (113) MCR with primary amines, discussed earlier in the SRR paragraph (Scheme 7), with a subsequent N-acylation using α,β-unsaturated acyl chloride 114 (fourth component) affording polysubstituted pyrrolopyridinones 119.[68,69] After acylation and upon heating, the formation of 119 can be explained by an intramolecular Diels-Alder reaction affording bridged tricyclic intermediate 116. Subsequent base-catalyzed retro-Michael cycloreversion, with loss of morpholine (117) and final tautomerization gives 119.

A variation of this reaction involving the same intermediate oxazole MCR product 113, uses activated alkynoic acid derivatives 120 as the acylating agent (fourth component).[70] The resulting intermediate again undergoes an intramolecular Diels-Alder reaction, followed by a retro-Diels Alder, resulting in the loss of nitrile 123 and giving dihydrofuropyrrolone 124. The furan moiety in this product is a diene that can react with dienophile 125 (fifth component) in a second Diels-Alder reaction, to give hexasubstituted benzenes 127 after loss of water. Since these steps all occurs in one pot, this reaction has evolved from a three- to a five-component reaction by applying a very elegant modular reaction sequence. All together, three different highly functionalized
scaffolds have been developed, originating from a single three-component reaction towards bis-amino oxazoles.

![Scheme 10](image)

**Scheme 10.** Modular reaction sequences reported by Zhu and co-workers, involving an initial bis-amino oxazole MCR.

In summary, modular reaction sequences have proven to be extremely useful for the fast generation of scaffold diversity. It can be argued that these examples belong to the SRR strategy. However, since the intermediate is formed by a MCR, we have divided this as a separate strategy. The generation of the intermediate via a MCR gives the possibility for easy appendage diversity, since generally all the components can be varied.

### 1.4.3 Condition-Based Divergence

Condition-Based Divergence in MCRs (CBD, Figure 8) generates multiple molecular scaffolds from the same starting materials by merely applying different conditions. It is evident that for reactions involving simultaneous molecular interactions of three or more components, different potential reaction pathways leading to different products are
accessible. A good MCR follows one pathway selectively. However, it is certainly of great interest to modulate the selectively to a different pathway by changing the reaction conditions, which is the major goal of CBD.\[71]\n
For example, depending on the catalyst, solvent or temperature that is used, a set of inputs A, B and C may react \textit{via} different pathways to produce distinct scaffolds. As can be understood this is not a simple task, which is expressed by the limited amount of reported examples.

![Schematic representation of the Condition Based Divergence (CBD) strategy to scaffold diversity.](image)

\textbf{Figure 8.} Schematic representation of the Condition Based Divergence (CBD) strategy to scaffold diversity.

In 2008 Liu \textit{et al.} demonstrated this concept by the organocatalytic asymmetric one-pot 3CR of aldehydes 128 (generally aromatic), diethyl \(\alpha\)-aminomalonate 129 and nitroalkenes 130 (Scheme 11).\[72\] By altering the organocatalyst they could selectively obtain either Michael addition product 132 or \([3+2]\) dipolar cycloaddition product 134. In the absence of a catalyst, reaction control generally proved to be poor.\[73\] Initially, for both reaction pathways, \(\alpha\)-imino esters are formed \textit{in situ} by a reaction of the aldehyde with the \(\alpha\)-aminomalonate. The use of organocatalyst 131, which activates both the \(\alpha\)-imino ester (producing an azomethine ylide) and the nitroalkene \textit{(via} a doubly hydrogen-bonded interaction), resulted in the selective formation of Michael adduct 132 with high enantioselectivity (16 examples, 48-95\%, 94-98\% \(ee\)). This product is stable and does not react further to form the cycloaddition product 134.

When on the other hand, organocatalyst 133 (possessing a bulky 2,5-diaryl-pyrrole moiety) is applied, product 134 was selectively formed by a highly diastereo- and
enantioselective 1,3-dipolar cycloaddition (11 examples, 56-90%, \(dr > 99:1\) endo-selective, 60-91% ee). This reaction most likely involves activation of the nitroalkene by the thiourea, via the earlier mentioned doubly hydrogen-bonded interaction, followed by a concerted attack of the \textit{in situ} formed azomethine ylide (in this case the ylid is not produced by, nor coordinated to the organocatalyst because of the bulky, non-basic pyrrole group, but is most likely formed \textit{via} a 1,2-prototropic rearrangement\(^{[74]}\).

![Scheme 11. Reaction control in the 3CR of aldehydes diethyl \(\alpha\)-aminomalonate and nitroalkenes.](image)

Although Liu \textit{et al.} established the formation of two different reaction products starting from the same three components, the degree of structural diversity is rather limited, since Michael product 132 is formally an intermediate to 134 (although this product is presumably not formed step-wise but concerted). Nevertheless, both products are formed under high stereocontrol, and the enantiomeric products are theoretically accessible by taking the enantiomeric organocatalysts giving rise to stereochemical diversity.

In 2008, Chebanov \textit{et al.} reported an excellent example of condition-based divergence by the multicomponent reaction of 5-amino pyrazoles 135, cyclic 1,3 diketones 136 and aromatic aldehydes 137 (Scheme 12).\(^{[71,75]}\). 5-Amino pyrazoles 135 have at least three non-equivalent nucleophilic centers (N1, C4, NH\(_2\)), but the authors were able to drive the reaction to three distinct scaffolds 139, 142 and 144 by changing the reaction conditions. Under reflux conditions in ethanol, a mixture of 139 and 144 was always obtained. However, performing the reaction at 150°C in a sealed vessel (MW or conventional heating) in the presence of NEt\(_3\) led to the exclusive formation of Hantzsch product 139.
(8 examples, 70-91% yield). This indicates that the Hantzsch product is most likely the thermodynamic product in this transformation.

Scheme 12. Tuning the 3CR to three different scaffolds by adapting the reaction conditions.

Although a thorough mechanistic study was not performed, the reaction likely proceeds via intermediate 138, which upon loss of water provides Hantzsch product 139. In their search for the optimal base for the selective formation of 139, the authors unexpectedly found a different reaction product, namely 142 (9 examples, 38-75% yield). This product is formed when a nucleophilic base such as sodium ethoxide or potassium tert-butoxide was used instead of NEt₃ (under otherwise identical reaction conditions as for the formation of 139). The formation of 142 is explained by a nucleophilic attack of the alkoxide to intermediate 138 followed by a ring-opening/recyclization.
Conversely, neutral and ambient conditions lead to the formation of the kinetically controlled Biginelli product 144 (8 examples, 51-70%). The authors found that sonication was required to obtain the final product, since simple stirring of the three components at rt did not result in any desired reaction. They explained this observation by the improved mass transfer through cavitation phenomena.\[76\] This reaction presumably involves intermediate 143.

Recently, our group also contributed to CBD to develop MCRs as a tool for DOS. By judicious selection of the reaction conditions, the 3CR between α-acidic isocyanides 145 (isocyano amides\[77\] and isocyano esters\[78\]), carbonyl components 6 and primary amines 146 could be directed towards either 2H-2-imidazolines 150 or trisubstituted oxazoles 152 (Scheme 13).\[79\]

**Scheme 13.** Directing the MCR of α-acidic isocyanides, carbonyl components and primary amines towards 2H-2-imidazolines 150 and trisubstituted oxazoles 152 and their proposed mechanisms.

By applying 2 mol% AgOAc as the catalyst, 2-imidazolines 150 were obtained selectively, while the use of a Brønsted acid (for R^4 = NR_2) or a polar aprotic solvent (for R^4 = OR) selectively provided the corresponding oxazoles 152. The formation of 2-imidazolines 150 can be mechanistically explained by coordination of the isonitrile
carbon to Ag\(^+\), which enhances the \(\alpha\)-acidity of the isocyanide (Pathway A), and reduces the nucleophilicity of the isonitrile carbon (preventing pathway B). Upon loss of a proton the isocyano \(\alpha\)-anion 147 can undergo a Mannich type addition to the iminium ion 148, followed by cyclization to form 2-imidazoline 150 after a final proton shift.

When, on the other hand, a Brønsted acid is applied (Pathway B), the slight decrease in pH will lower the concentration of the isocyanide \(\alpha\)-anion, thereby making the imidazoline pathway less favorable (Pathway A). Since the imine is activated by the Brønsted acid, the isonitrile carbon of 145 can attack the iminium ion 148 as a nucleophile, leading to nitrilium intermediate 151. After proton abstraction and cyclization oxazole 152 is formed. For isocyano esters however, the use of methanol and Brønsted acid was not sufficient to exclusively form the oxazole, since polar protic solvents turned out to promote the formation of 2-imidazolines.\(^{[80]}\) The use of aprotic solvents seemed to be the best choice for directing the 3CR with isocyano esters to the trisubstituted oxazoles (best results were obtained with DMF).

An elaboration of this work involves the 3CR between primary \(\alpha\)-isocyano amides 67, carbonyl components 6 and primary amines 146, which could be directed towards either 2\(H\)-2-imidazolines 153 or \(N\)-(cyanomethyl)amides 156 by Ag\(^+\) catalysis versus Brønsted acid mediated reaction, respectively (Scheme 14).\(^{[50]}\)

\[\text{Scheme 14. Directing the MCR towards 2\(H\)-2-imidazolines 153 and \(N\)-(cyanomethyl)amides 156 and the suggested mechanism for the formation of \(N\)-(cyanomethyl)amides 156.}\]

The selective formation of \(N\)-(cyanomethyl)amides 156 (also earlier mentioned in the SRR approach, Scheme 7) can be rationalized by the same criteria as the formation of trisubstituted oxazoles 152 (Scheme 13), since the use of a Brønsted acid, prevents the
formation of 2-imidazolines 153 by the decreased pH. By applying a Brønsted acid, the reaction initially proceeds via the same mechanism as for the oxazole MCR. However, when intermediate 155 is formed, it does not tautomerize to form the 5-amino oxazole 157. Instead, proton abstraction at the exocyclic imine nitrogen and subsequent ring opening gave the corresponding N-(cyanomethyl)amides 156. Again Ag⁺ catalysis promotes the formation of 2-imidazolines 153, for the same reasons as discussed before.

In conclusion, the CBD approach makes it possible to obtain scaffold diversity starting from the same reaction inputs by adapting the temperature, reaction promoter or solvent.

1.4.4 Union of MCRs

The Union of MCRs (MCR², Figure 9) is a fourth strategy for the rational design of novel MCRs that combines two (or more) different types of MCRs in a one-pot process.

![Figure 9](image)

**Figure 9.** Schematic representation of the Union of MCRs (MCR²) strategy to scaffold diversity.

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 union with the secondary MCR.¹¹g,¹⁸¹ By varying the secondary MCR (for example by addition of inputs E/F or G/H), diverse (and complex) scaffolds will be available, making this strategy excellent for application in DOS.
The combination of MCRs in one pot is not new. It was first introduced by Dömling and Ugi who developed a seven-component reaction (7CR) that was basically a one-pot combination of a modified Asinger 4CR and Ugi 4CR (scheme 15).\cite{82}

**Scheme 15.** Asinger 4CR-Ugi 4CR, a one-pot 7-component reaction.

In this 7CR, an $\alpha$- or $\beta$-bromo/chloro aldehyde 158, NaSH/NaOH, NH$_3$, another aldehyde 161, an isocyanide 166, CO$_2$, and a primary alcohol (solvent) are combined to afford 167 efficiently. However, NaSH/NaOH, NH$_3$ and CO$_2$ are invariable components in this reaction which limits the substitutional diversity (appendage diversity) and thereby the scope of the MCR.

**Scheme 16.** Mechanism of the Ugi-5C-4CR $\cup$ Passerini-3CR.
Another example also reported by Ugi and co-workers, is the combination of an Ugi Five Center Four Component Reaction (U-5C-4CR) with a Passerini-3CR (Scheme 16). This one-pot procedure uses an α-amino acid (L-aspartic acid, 168) as a 2-center-1-component input, which explains the origin of the U-5C-4CR. The reaction mechanism most likely involves an initial condensation of the amino functionality of the α-amino acid 168 with the aldehyde 169 to form iminium ion 171. After α-addition, intermediate 172 is formed which cannot undergo the Mumm rearrangement. This is why the solvent methanol acts as a competing nucleophile, to form derivative 174. This compound still has a free carboxylic acid, which can undergo a (much slower) P-3CR in the same pot to afford 175. The drawback of this procedure is that two equivalents of the aldehyde and isonitrile inputs are used, which also limits the substituent variability.

In 2010, Westermann and co-workers reported the one-pot combination of the Ugi and Ugi-Smiles 4CRs by the use of a reactant that contains both a carboxylic acid and a 2-nitrophenol (176) or 2-hydroxypyridine moiety. Although the Ugi 4CR was found to be relatively fast compared 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 than in the Ugi-Smiles reaction) afforded the desired products 178 and 179 in relatively low yield, Scheme 17, compared to the pseudo-7CR approach where the same isocyanide, aldehyde, and amine input were used for both reactions.

Scheme 17. One-pot seven-component Ugi/Ugi-Smiles reaction by Westermann and co-workers.

In 2009, our group demonstrated that the union of MCRs can also be used to obtain complexity as well as scaffold diversity (Scheme 18). The strategy is based on the abovementioned 3CR to 2H-2-imidazolines (reacting an isocynano ester, aldehyde or ketone and an amine) that shows extraordinary functional group and solvent compatibility. By incorporation of a second orthogonally reactive group in one of the starting materials, this MCR can be coupled to a second MCR.
This concept has been demonstrated by the use of diisocyanide 180 in the 2-imidazoline MCR. The two isocyanide functionalities in 180 show intrinsic different reactivities, resulting in the chemoselective formation of 2-imidazoline 181. The retention of the isocyanide moiety in 181 provides an handle for subsequent isocyanide based MCRs.

Scheme 18. Union of MCRs using diisocyanide 180 in the initial 2-imidazoline MCR.

The goal of obtaining different final scaffolds has been demonstrated by varying the secondary isocyanide based MCR. Since the 2-imidazoline MCR can be performed in a wide range of solvents, the solvent of the one-pot procedure will be selected based on the optimal solvent for the secondary MCR. For example, the 2-imidazoline MCR has been combined with the Passerini MCR to give 184 and 185. This one-pot MCR reaction has
been performed in CH$_2$Cl$_2$, since this is the best solvent for the Passerini reaction. The initial MCR could also be combined with the Ugi 4CR (in MeOH) to give 188, an Ugi variant[87] (in MeOH) using the tethered keto acid, levulinic acid (192), to give 193 and with a recently reported 3CR towards highly substituted 1,6-dihydropyrazine-2,3-dicarbonitrile derivatives[88] (in EtOH), to yield 191.

The possibility of obtaining scaffold diversity by the union of MCRs has been further demonstrated using the \(N\)-(cyanomethyl)amide 3CR\(^{[50]}\) (discussed earlier) as the primary MCR.\(^{[85]}\) By applying the primary \(\alpha\)-isocyano amide derivative of 180, this MCR could be connected to the Passerini, the Ugi and the Ugi Smiles\(^{[89]}\) MCRs resulting in various new scaffolds.

Interestingly, it was even possible to combine the 2-imidazoline and the \(N\)-(cyanomethyl)amide 3CRs with the Ugi 4CR to afford a novel eight-component reaction, which is a landmark in this field.\(^{[85]}\)

In conclusion, the union of MCRs has proven to be a useful tool to achieve complex scaffolds in a simple one-pot procedure. Furthermore, our group has demonstrated that by choosing MCRs that show unique solvent and functional group tolerance as the primary MCR, these can be easily coupled to various secondary MCRs to produce several new scaffolds.

### 1.5 Concluding remarks

Diversity-oriented synthesis of small molecules is a great challenge for synthetic organic chemists. DOS requires the development of new methodologies that generate scaffold diversity in addition to appendage and stereochemical diversity.

MCRs have been demonstrated to be extremely useful for DOS, since these complexity-generating reactions can easily be combined with several follow-up cyclization reactions resulting in the rapid synthesis of diverse (heterocyclic) scaffolds. Furthermore, novel MCR design strategies have emerged as important tools to generate scaffold diversity. Four different approaches (SRR, MRS, CBD and MCR\(^2\)) have been applied, which all led to the development of new MCRs and higher order MCRs, thereby addressing both molecular diversity and complexity.
Most examples described in paragraph 1.4, however, did not address the concept of stereoselectivity, since nearly all products obtained were isolated as racemic mixtures and/or mixtures of diastereomers. The development of stereoselective multicomponent reactions (to be able to introduce stereochemical diversity) remains a major challenge for the future.

### 1.6 Outline of this thesis

From this first chapter it became clear that MCRs as complexity-generating reactions are additionally very useful to rapidly generate multiple molecular scaffolds. In Chapter 2, the development of a new 4CR will be described, which is an elaboration on the 1-azadiene-derived modular reaction sequences, discussed in this introduction chapter (Scheme 9). This new MCR uses isocyanoacetates (a.k.a. isocyno esters) as the fourth reaction component, to generate isonitrile-functionalized 3,4-dihydropyridin-2-ones (3,4-DHP-2-ones). An optimization study was performed and the scope of the reaction was investigated. The preservation of the isonitrile functionality allows follow-up isonitrile based multicomponent chemistry (union of MCRs), resulting in the development of higher-order MCRs, as described in paragraph 1.4.4. The combination of the DHP-2-one 4CR with the Passerini 3CR to yield conformational constrained depsipeptides will be discussed in Chapter 3. This resulted in the formation of a new 6CR. In Chapter 4 the combination of the DHP-2-one MCR with the Ugi 4CR was investigated, which led to the serendipitous discovery of a new MCR towards dihydrooxazolopyridines (DHOPs). The scope and limitations of this unprecedented MCR have been explored. By an initial alkylation of the DHP-2-one scaffold, the Ugi 4CR could still be performed giving the possibility for the formation of conformationally constrained peptides. Because of the high similarity of the DHP-2-one scaffold with the so-called Freidinger lactams (turn mimetics), Chapter 5 describes the examination of the DHP-2-one scaffold to function as a turn-inducer, which was established by NMR spectroscopy and X-ray diffraction. The research described in Chapter 6 demonstrates the application of the DHP-2-one 4CR in the synthesis of constrained DHP-2-one containing cyclic RGD peptides. This chapter includes both the details of the synthesis and an extensive conformational analysis.
1.7 References and Notes


[4] Molecules/interactions that are considered to be “undruggable”, comprise transcription factors, regulatory RNAs, interactions between proteins (especially intracellular) and between proteins and DNA. There are only about 500 “druggable” targets: Schreiber, S. L. Nature 2009, 457, 153-154.

[5] The chemical space is a multidimensional area with each dimension defined by a descriptor which can be molecular weight, polarity, solubility, membrane permeability, binding constant, H-bonding properties etc. and encompasses all small carbon-based molecules that could in principle be created: Dobson, C. M. Nature 2004, 432, 824-828.


[13] The E factor is defined as the mass ratio of waste (everything but the desired product) to desired product. For a recent overview, see: Sheldon, R. A. Green Chem. 2007, 9, 1273-1283.


Although the authors used a pre-formed imine, there are several examples known of proline catalyzed one-pot three component Mannich reactions. However if aromatic aldehydes are used in this one-pot procedure, the obtained Mannich products had to be reduced (by NaBH₄) to the corresponding alcohols to avoid epimerization during isolation: (a) Hayashi, Y.; Tsuboi, W.; Ashimine, I.; Urushima, T.; Shoji, M.; Sakai, K. Angew. Chem. Int. Ed. 2003, 42, 3677-3680; (b) Córdova, A. Synlett 2003, 23-41.
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[58] In addition to the examples reported here there are several other publications that apply SRR to achieve new scaffolds, thereby discovering new MCRs: (a) Weber, L. Multicomponent Reactions; (eds. Zhu, J.; Bienaymé, H.), Wiley-VCH: Weinheim, 2005, Chapter 10 and references therein. (b) Mironov, M. A. QSAR Comb. Sci. 2006, 25, 423-431 and references therein. (c) ref 46.


[61] The use of phosphonates with large R^1 substituents resulted in a significant decrease in yield, 22-39% for R^1 = Ph and i-pentyl.


[73] Ref 72 and references mentioned therein.


[75] Several other research groups have been involved in MCRs with aminoazoles, 1,3-diketones and aldehydes. For a recent overview see: Chebanov, V. A.; Gura, K. A.; Desenko, S. M. *Top. Heterocycl. Chem.* 2010, 23, 41-84 and references cited therein.

[76] Propagation of ultra sound waves into the liquid medium results in a series of high-pressure (compression) and low-pressure (rarefaction) cycles, with rates depending on the frequency. During the low-pressure cycle, high-intensity ultrasonic waves generate small vacuum bubbles in the liquid, which can reach a volume at which they are not stable anymore resulting in a violent collapse. This phenomenon is termed cavitation: (a) Mason, T. *J. Chem. Soc. Rev.* 1997, 26, 443-451. (b) Cravotto, G.; Cintas, P. *J. Chem. Soc. Rev.* 2006, 35, 180-196.

[77] It has to be noted that the formation of oxazoles using isocyanamides has been well studied by Zhu and co-workers (see ref 49). With the work of Elders et al. the oxazole MCR has been expanded with a wide range of isocyanan esters. The MCR with isocyanan amides can now also be directed to the 2-imidazolines.

[78] The directing properties of the MCR involving isocyano esters could exclusively be performed using α-aryl isocyanate esters, since the use of α-alkyl isocyanate esters always resulted in the formation of 2-imidazolines, in various solvents, even without AgOAc, see ref 80 and Elders, N. PhD thesis 2010, Vrije Universiteit Amsterdam.


[86] The α-isocyanide is α-acidic and will react in the 3CR to yield 2H-2-imidazolines, while the other isocyanide is an aliphatic isocyanide and remains unaffected.


