university of groningen

University Medical Center Groningen

University of Groningen

Multicomponent Reactions, Union of MCRs and Beyond

Zarganes-Tzitzikas, Tryfon; Chandgude, Ajay L.; Dömling, Alexander

Published in:
Chemical Record

DOI:
10.1002/tcr.201500201

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2015

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Zarganes-Tzitzikas, T., Chandgude, A. L., & Dömling, A. (2015). Multicomponent Reactions, Union of MCRs and Beyond. *Chemical Record*, *15*(5), 981-996. https://doi.org/10.1002/tcr.201500201

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the “Taverne” license. More information can be found on the University of Groningen website: https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment.

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Download date: 28-04-2023

Record Review

DOI: 10.1002/tcr.201500201

THE CHEMICAL RECORD

Multicomponent Reactions, Union of MCRs and Beyond

Tryfon Zarganes-Tzitzikas, Ajay L. Chandgude, and Alexander Dömling*[a]

ABSTRACT: Multicomponent reactions (MCRs), which are located between one- and two-component and polymerization reactions, provide a number of valuable conceptual and synthetic advantages over stepwise sequential approaches towards complex and valuable molecules. To address current limitations in the number of MCRs and the resulting scaffolds, the concept of union of MCRs was introduced two decades ago by Dömling and Ugi and is rapidly advancing, as is apparent by several recently published works. MCR technology is now widely recognized for its impact on drug discovery projects and is strongly endorsed by industry in addition to academia. Clearly, novel scaffolds accessible in few steps including MCRs will further enhance the field of applications. Additionally, broad expansion of MCR applications in fields such as imaging, materials science, medical devices, agriculture, or futuristic applications in stem cell therapy and theragnostics or solar energy and superconductivity are predicted.

Keywords: drug discovery • isocyanides • medicinal chemistry • molecular diversity • multicomponent reactions

Dedicated to the 65th birthday of Prof. Julia Stephanidou-Stephanatou

1. Multicomponent Reactions

Reactions in organic chemistry can be classified according to the number of participating starting materials. There are one-component reactions (1CRs), two-component reactions (2CRs), multicomponent reactions (MCRs) and polymerizations (Figure 1). An example of a one-component reaction is the classical Claisen rearrangement.[1] One-component reactions involve one starting material and if necessary a catalyst and yield one or two products. In a two-component reaction two starting materials are combined into one product.[2] Reactions involving three or more starting materials are known as MCRs. Prototypical examples are the Mannich reaction and the Ugi reaction.[3] According to a generally accepted definition, "MCRs are reactions with three and more starting materials where the majority of the atoms of the starting materials are incorporated into the product."[4] An important subgroup of MCRs is the so-called unions of MCRs, where an MCR is combined with a secondary reaction, e.g., an MCR, in the same flask, enhancing the diversity and potential usefulness of the reactions.[5] MCRs bridge one- and two-component reactions with polymerizations, where one or several starting materials combine repetitively to form a polymer of varying length. The majority of organic textbook chemistry consists of one- and two-component reactions and polymerizations. Surprisingly, the wealth of MCRs is not adequately represented in modern teaching of organic chemistry despite the many contemporary and important applications in chemistry. This short review gives a personalized glimpse of modern MCRs with a focus on higher MCRs and some intriguing recent applications underscoring the immense potential of navigating the MCR space.[6]

[a]A. Dömling
Department of Drug Design
University of Groningen (The Netherlands)
E-mail: a.s.s.domling@rug.nl

 © 2015 The Chemical Society of Japan & Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

1.1. Classes of MCRs

Many of the classical MCRs are named reactions and all have proven their wide applicability in chemistry with multiple commercial products on the market (Table 1).

TaniaPhos for example is a commercial application of the Mannich 3CR. It is a chiral ligand for a catalyst used in asymmetric hydrogenations and can be synthesized from the (*R*) Ugi amine in two steps.[7] The (*R*) Ugi amine can be synthesized via a Mannich reaction between ferrocene, dimethylamine and acetaldehyde (Table 1, entry 1).[8]

α,α-Disubstituted amino acids have attracted increasing attention as unnatural amino acid analogues due to their applications in peptidomimetics and the de novo design of proteins. The Strecker 3CR was used for the synthesis of (*S*)-*N*-ethoxycarbonyl-α-methylvaline, where 3-methyl-2-butanone and NaCN were treated with NH_4Cl in the presence of $MgSO_4$ in NH_3/MeOH at 30°C. Further steps involved the formation of the tartrate salt and the preparation of the (*S*)-2-ethoxycarbonylamino-2,3-dimethylbutyric acid dicyclohexylamine salt (Table 1, entry 2).[9]

The Passerini reaction affords the fungicidal compound mandipropamid in just two steps. The first step involves the Passerini reaction of an in situ synthesized isocyanide, an aldehyde and a carboxylic acid to form the α-acyloxycarboxamide. The second step involves the alkylation with propargyl bromide to yield Micora (mandipropamid) (Table 1, entry 3).[10]

Lidocaine (Xylocaine) is a very popular local anesthetic. Its synthesis can be accomplished by the Ugi 3CR of formaldehyde, diethylamine and 2,6-dimethyl-phenylisocyanide. This synthesis constitutes an early application of an MCR in the production of a commercial drug (Table 1, entry 4).[11]

Prostaglandins have antioxidant and ionophoric activities. The Pauson–Khand 3CR has been used as the key step for the regio- and stereoselective synthesis of prostaglandin B_1. The Pauson–Khand reaction involved a silyl-protected propargyl acetylene, ethylene and octacarbonyl dicobalt as a carbon monoxide source to afford the 3-*tert*-butyldimethylsilyloxymethyl-2-substituted-cyclopent-2-en-1-one at room temperature in good yield (Table 1, entry 5).[12]

The p38 MAP kinase is involved in the inflammatory pathway and its inhibitors have been widely investigated as potential drugs. 1,4,5-Trisubstituted imidazoles were synthesized as p38 MAP kinase inhibitors using the van Leusen 3CR of an α-substituted tosylmethyl isocyanide, a primary amine

Tryfon Zarganes-Tzitzikas was born in Thessaloniki, Greece, in 1988. He obtained his B.Sc. degree in Chemistry from the Aristotle University of Thessaloniki in 2010. In March 2012 he received his M.Sc. degree with an emphasis on organic chemistry under the guidance of Prof. J. Stephanidou-Stephanatou and Prof. K. Tsoleridis from the Aristotle University of Thessaloniki. Since July 2012 he has been pursuing his Ph.D. in medicinal chemistry under the guidance of Prof. Alexander Dömling in the Drug Design Group at the University of Groningen, Netherlands.

Ajay L. Chandgude was born in Pune, India, in 1988. He completed his B.Sc. Pharmacy degree at the University of Pune, India, in 2010 and his M.Tech. degree in Pharmacy at the National Institute of Pharmaceutical Education and Research (NIPER), Mohali, India, in 2012. During his master's degree he worked on the project "MCR for the synthesis of imidazoheterocycles" in the research group of Prof. S. K. Guchhait. He is now pursuing his Ph.D. under the guidance of Prof. Alexander Dömling in the Drug Design Group at the University of Groningen, Netherlands. For his Ph.D. studies he was awarded an Erasmus Mundus Ph.D. Scholarship.

Alexander Dömling has held the chair for Drug Design at the University of Groningen since 2011. He studied chemistry and biology at the Technische Universität München and obtained his Ph.D. under the guidance of Ivar Ugi. After a postdoc under a Humboldt Fellowship in the group of the Nobel Laureate Barry Sharpless, he founded the biotech company Morphochem and later Carmolex Inc. After his habilitation he worked as full professor at the University of Pittsburgh in the School of Pharmacy. His interests are centered around multicomponent reaction (MCR) chemistry and its application to problems in drug design. His special focus is on MCR-centered pharmacophore methods, structure-based drug design and MCR-centered fragment-based drug design. He is the author of more than 150 scientific articles, reviews and book contributions. He has applied for more than 30 patents. His long-term vision is to bring a novel drug to patients in an indicated area of unmet medical needs.

 © 2015 The Chemical Society of Japan & Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

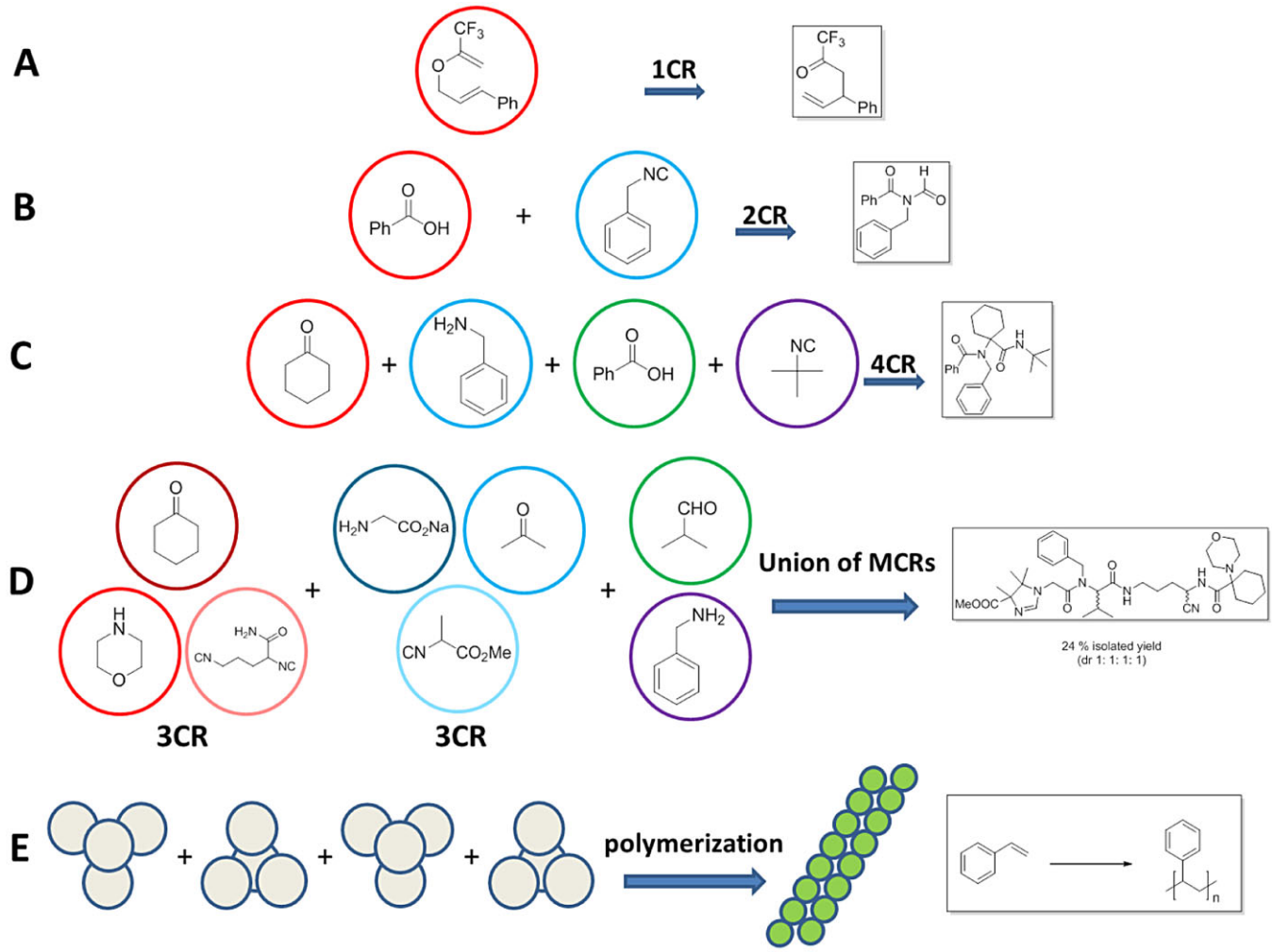


Figure 1. Schematic representation of various reactions based on the number of starting materials.

and an aldehyde in the presence of a base. The reaction has been reported on a 500 kg batch scale to provide enough material for phase III clinical trials (Table 1, entry 6).[13]

The Gewald 3CR generally affords bioisosteres of anthranilic acids. 2-Amino-3-carbonyl thiophene is the starting material for the synthesis of several drugs, such as olanzapine (Zyprexa), an atypical antipsychotic drug. This thiophene-phenol bioisostere can be easily prepared by the Gewald 3CR using cyanoacetamides, α-methylene active aldehydes or ketones, and sulfur (Table 1, entry 7).[14]

The Hantzsch 3CR was used for the synthesis of the calcium channel blocker nifedipine (Procardia). Synthesis of the dihydropyridine derivative involved condensation of a 2-nitrobenzaldehyde with two equivalents of methyl acetoacetate and ammonia (Table 1, entry 8).[15]

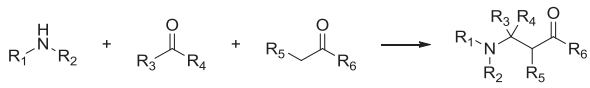
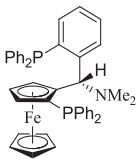
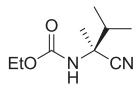
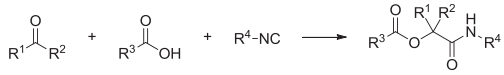
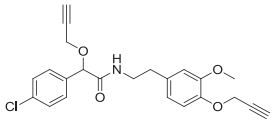
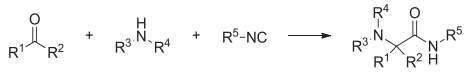
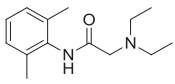
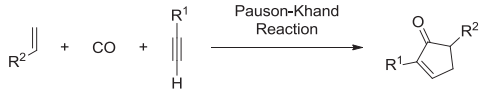
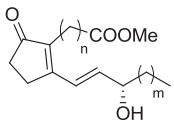
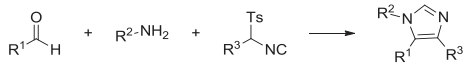
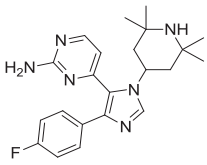
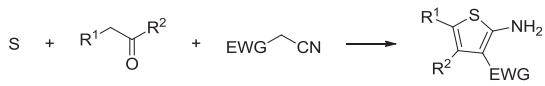
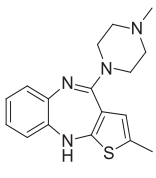
Ezetimibe (Zetia) is a lipid-lowering compound that selectively inhibits the intestinal absorption of cholesterol. It is synthesized by using the Staudinger 3CR as a key reaction. The imine formed from *p*-fluoroaniline and benzyloxybenzaldehyde was treated with methyl 5-chloro-5-oxopentanoate in the presence of tributylamine and toluene to form the β-lactam ring. This reaction involves the formation of an intermediate ketene that undergoes a [2 + 2] cycloaddition reaction with the imine to regioselectively form the β-lactam ring, giving the trans isomer as the major product (Table 1, entry 9).[16]

2. Multicomponent Reactions and Subsequent Transformations

Many MCRs have been described in the past one and a half centuries and recently many fundamental advances in finding new MCRs have been made. A strategy to enhance the size and

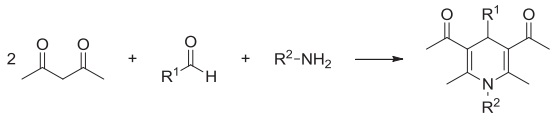
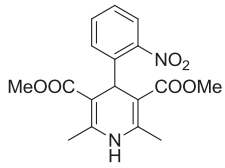
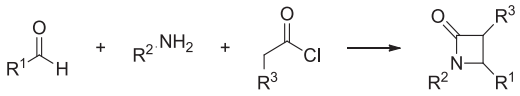
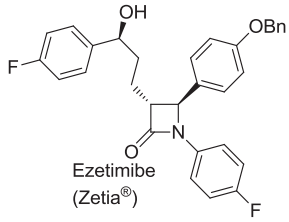
 © 2015 The Chemical Society of Japan & Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Table 1. Examples of named MCRs and their application to the synthesis of commercial products.

Entry	Named reaction	Reaction	Product
1	Mannich 3CR[3a,7]		 TaniaPhos®
2	Strecker 3CR[9]		 (*S*)-*N*-ethoxycarbonyl-α-methylvaline
3	Passerini 3CR[10]		 Micora (Mandipropamid®)
4	Ugi 3CR[11]		 Lidocaine (Xylocain®)
5	Pauson–Khand 3CR[12]		 **PPB$_1$-I** n = 7, m = 1 **PGB$_1$** n = 6, m = 4 Prostaglandin B1
6	Van Leusen 3CR[13]		 P38 MAP Kinase Inhibitor
7	Gewald 3CR[14]		 Olanzapine (Zyprexa®)

 © 2015 The Chemical Society of Japan & Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Table 1. continued

Entry	Named reaction	Reaction	Product
8	Hantzsch 3CR[15]		 Nifedipine (Procardia®)
9	Staudinger 3CR[16]		 Ezetimibe (Zetia®)

diversity of current MCR chemical space is the concept of combining an MCR and a subsequent secondary reaction; examples include postcondensations and the Ugi–deprotection–cyclization (UDC) strategy.[17] Herein, bifunctional orthogonally protected starting materials are used and cyclizations can take place in a secondary step upon deprotection of the orthogonal functional groups. Many different scaffolds have been recently described using this strategy. A recent example of such a postcondensation strategy is shown in Scheme 1. It is based on a recently discovered variation of the Ugi reaction of α-amino acids (**1**), oxo components (**2**), and isocyanides (**3**), now including primary or secondary amines (**4**), and can afford highly substituted isoindolones (**5**), pyrrolidinediones (**6**), and di- (**7**), tri- (**8**), and tetracyclic (**9**) scaffolds reminiscent of the alkaloids quinocarcin and notoamide B. The MCR is stereoselective as the chiral α-amino acid can be used with stereoretention (Scheme 1).[18]

3. Union of Multicomponent Reactions

The term "union of MCRs" was coined by Dömling and Ugi in their publication "The Seven-Component Reaction" describing the one-pot combination of a modified Asinger 4CR[19] and the Ugi 4CR (Scheme 2).[20]

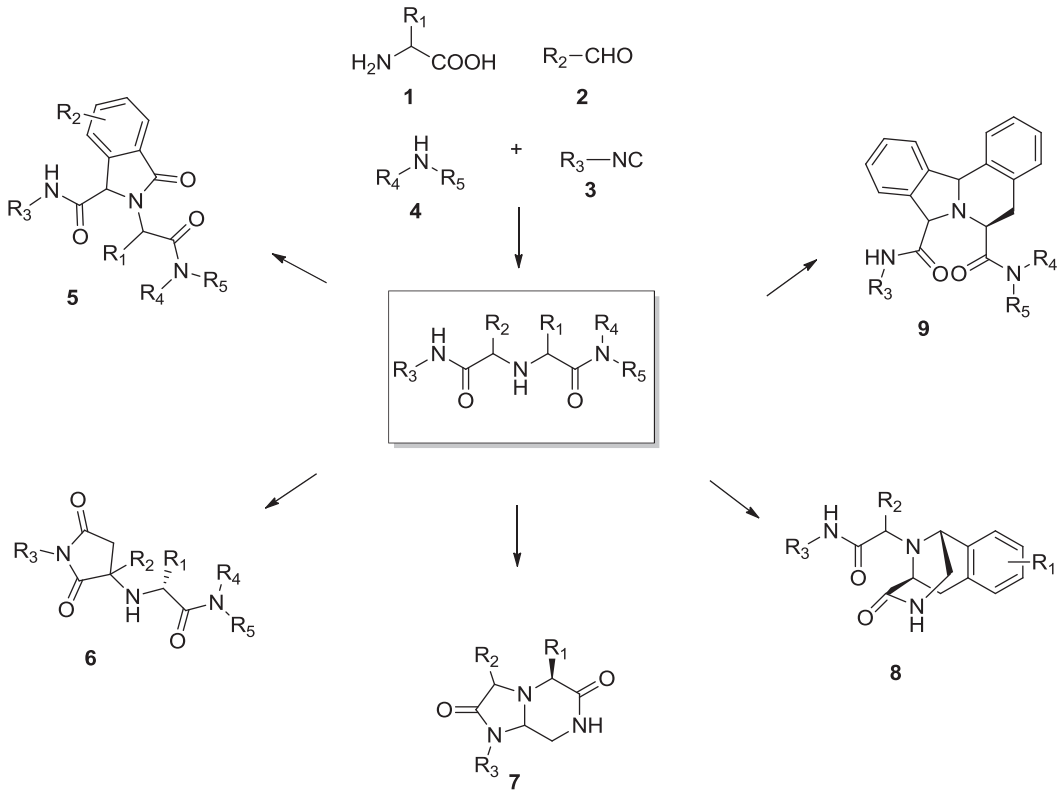
The union of MCRs is a strategy for the rational design of novel MCRs combining two (or more) different types of MCRs in a one-pot process. The presence of orthogonal reactive groups in the product of the primary MCR, which is either formed during the primary MCR or present in one of the inputs, allows the union with the secondary MCR.[21] The union of MCRs is an intriguing concept to increase even more the complexity and efficiency and provide new scaffold types. Several new examples have been elaborated recently.

Besides various 5CRs and 6CRs, the first example of an eight-component reaction, currently the highest number of different compounds used in a one-pot procedure, was published by the Orru group in 2009.[22] This 8CR unifies three different MCRs, with nine new bonds formed, creating highly complex and structurally versatile drug-like compounds with eleven points of diversity (Scheme 3).

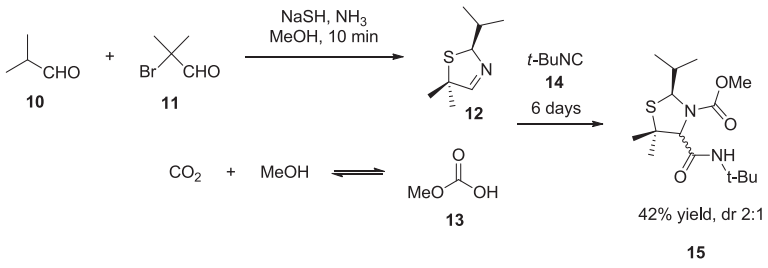
In the first of the three MCRs, imidazoline intermediate **19** was formed through a three-component reaction utilizing the sodium salt of glycine (**18**), which provided the carboxylic acid handle for the subsequent Ugi 4CR.[23] The *N*-(cyanomethyl)amide intermediate **23** was accessed via a second three-component reaction.[24] Here the authors made use of the difference in reactivity of the two isocyanides in 2,5-diisocyanopentanamide (**20**) to produce compound **23** in good yield, carrying an isocyanide handle for the subsequent MCR. Multicomponent products **19** and **23** could be formed either in separate reaction vessels (sequential manner) or in a single reaction vessel. In the case of a one-pot procedure, first the formation of **19** was established, and then the second set of starting materials was added to give intermediate **23**. Finally, the reaction mixture was neutralized to activate the carboxylic acid, and a final set of reagents (i.e., the aldehyde and amine) was added, generating the final product **24** in an impressive 24% yield (85% yield per bond-forming step).

One of the first MCRs combining more than four different components making use of an orthogonal functionality was reported by Bienaymé in 1998.[25] In a modified

 © 2015 The Chemical Society of Japan & Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 1. Postcondensation examples involving an Ugi 5C-4CR reaction.



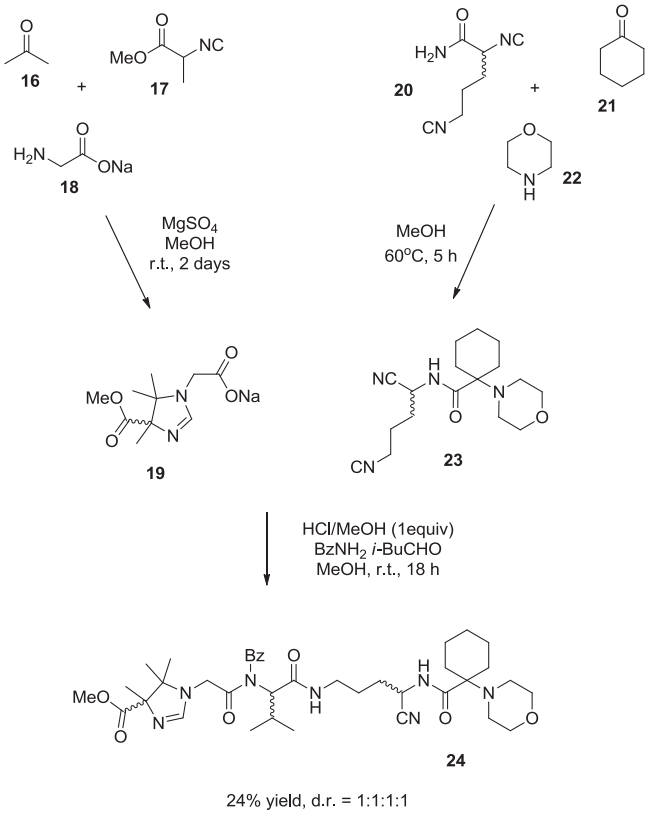
Scheme 2. "The seven-component reaction" (Asinger–Ugi 7CR).

Bredereck reaction, the secondary amine morpholine (**25**), *N*-formylimidazole diethyl acetal (**26**) and methyl isocyanoacetate (**27**) were reacted to produce the intermediate isocyanide (**28**) exclusively as the (*Z*) stereoisomer (Scheme 4). After the subsequent addition of a carboxylic acid (e.g., benzoic acid) and an aldehyde (e.g., cyclohexane carboxyaldehyde), a Passerini 3CR takes place, resulting in the formation of product **29** as a racemic mixture in a fair yield (30%), representing an 80% yield per bond-forming step (five new bonds).

The combination of a Petasis 3CR[26] and an Ugi 4CR (Pt-U-6CR) was recently described by Portlock and co-workers (Scheme 5).[27] With six new bonds formed and the introduction of six points of diversity, dipeptide amides **34** could be obtained as 1:1 mixtures of racemic diastereomers with yields ranging from 80 to 95% per bond-forming step. As shown in Scheme 5, the amino acid **33**, formed by the Petasis 3CR, serves as the carboxylic acid component in the subsequent Ugi 4CR. Despite the readily achievable high structural diversity, a solvent change was necessary for the second MCR to proceed, hence limiting the applicability of this approach in the rapid preparation of structurally diverse, drug-like compound libraries. To overcome this drawback, the same authors showed that this reaction sequence could be translated to a solid support, thus allowing the exploration of a larger chemical space, though at the cost of one point of diversity as a result of the linkage to the resin.[28]

 © 2015 The Chemical Society of Japan & Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Another interesting example of creating complexity and structural diversity by the combination of two successive MCRs was published recently by Al-Tel and co-workers (Scheme 6).[29] By combining the Groebke–Bienaymé–Blackburn reaction,[30] an acid-mediated isocyanide addition to 2-iminopyridines yielding fused pyridine-imidazoles (**38**), with a Passerini 3CR or an Ugi 4CR, a 5CR or 6CR was developed, generating structurally diverse (up to ten points of diversity), highly substituted, drug-like heterocyclic compounds **39** and **40**, respectively, in an efficient manner (>90% yield per bond-forming step). The formylbenzoic acids **36** reacted with 2-aminopyridines **35** and isocyanides **37** selectively on the aldehyde group and the benzoic acid moiety was left intact. Thus, the orthogonal reactivity of the carboxylic acid in the Groebke–Bienaymé–Blackburn reaction was used as a functional handle in the subsequent Ugi or Passerini MCRs.



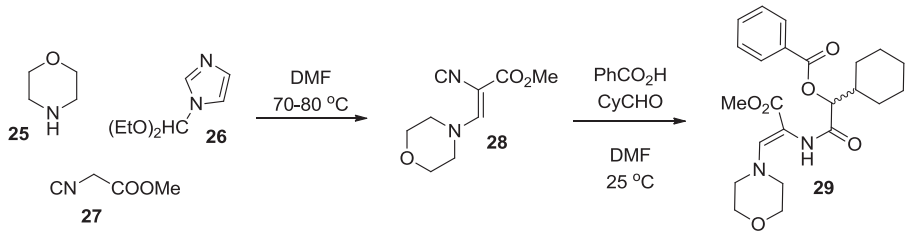
Scheme 3. Combination of three multicomponent reactions leading to an 8CR.

4. Recent MCR Applications

Several interesting recent applications of MCR chemistry going beyond simple combinatorial applications are discussed in the following.

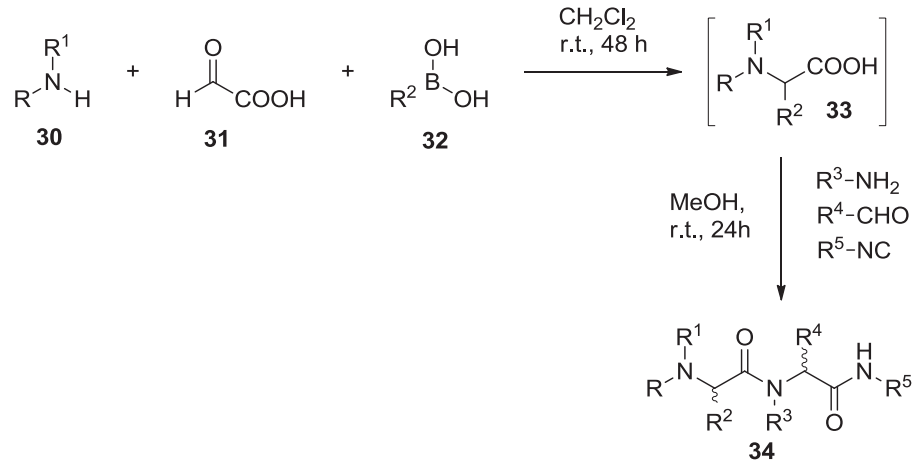
Large-Scale Pharmacophore-Based Virtual Screening of MCR Libraries: AnchorQuery

Two decades ago, MCR chemistry was generally neglected in the pharmaceutical and agrochemical industries. The knowledge of these reactions was often low and it was generally believed that MCR scaffolds were associated with a lack of useful drug-like properties, e.g., absorption, distribution, metabolism, excretion, and toxicity (ADMET). During the time of combinatorial chemistry, however, MCRs offered a major technology to reliably produce large compound libraries to fill the screening decks. Nowadays, MCR technology is widely recognized for its impact on drug discovery projects and is strongly endorsed by industry as well as academia.[31] These examples show that pharmaceutical and agrochemical compounds with preferred ADMET properties and superior activities can be engineered based on MCR chemistry. The very high compound numbers per scaffold available via MCRs may be regarded as a friend or foe. On the one hand, it can be fortunate to have an MCR product as a medicinal chemistry starting point, since a fast and efficient SAR elaboration can be accomplished; on the other hand, the known chemical space based on MCRs is incredibly large and can neither be screened nor exhaustively synthesized with reasonable efforts. The currently preferred path to medicinal chemistry starting points in industry, high-throughput screening (HTS), however, is an expensive process with rather low efficiency, yielding hits often only in low double-digit or single-digit percentages. Modern postgenomic targets often yield zero hits. Furthermore, the initial hits are often not amenable to elaboration due to their

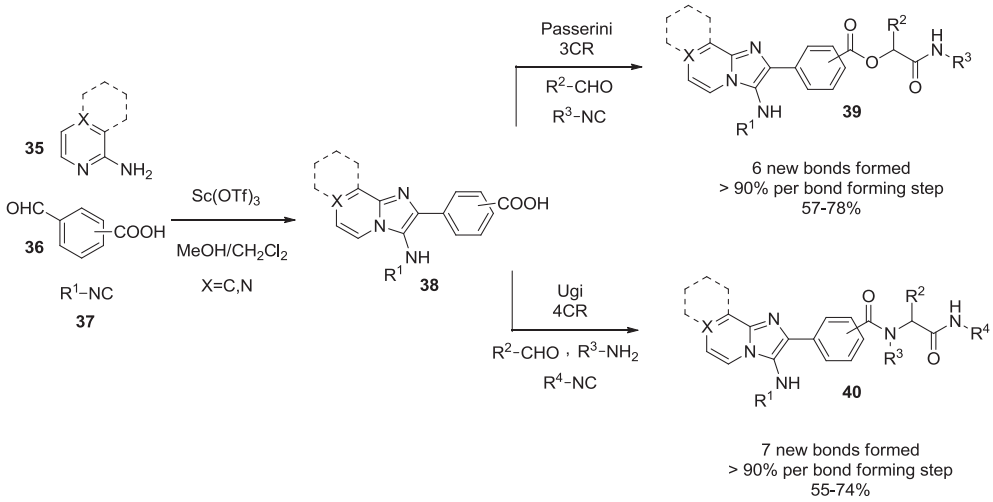


Scheme 4. Combination of a Bredereck reaction and a Passerini 3CR.

 © 2015 The Chemical Society of Japan & Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 5. Combination of the Petasis 3CR and Ugi 4CR.



Scheme 6. Combination of the Groebke–Bienaymé–Blackburn 3CR with the Passerini 3CR or Ugi 4CR.

complex multistep synthesis. Thus, neither the screening of even a very small fraction of the chemical space accessible by the classical Ugi 4CR and other scaffolds nor the synthesis is possible. Recent advances in computational chemical space enumeration and screening, however, allow for an alternative process to efficiently foster a very large chemical space. The free web-, anchor-, and pharmacophore-based server AnchorQuery (http://anchorquery.ccbb.pitt.edu/), for example, allows for the screening of a very large virtual MCR library with over a billion members.[32] AnchorQuery builds on the role that deeply buried amino acid side chains or other anchors play in protein–protein interactions. Based on the efficient and convergent nature of MCR chemistry, proposed virtual screening hits can be instantaneously synthesized and tested. This software was instrumental to the discovery of multiple potent and selective MCR-based antagonists of the protein–protein interaction between p53 and Mdm2 (Figure 2).[33,34] Thus, computational approaches to screen MCR libraries will likely play a more and more important role in the early drug discovery process in the future. An increasing amount of high-resolution structural information on MCR molecules bound to biological receptors is becoming available. With the advent of structure-based design and fragment-based approaches in drug discovery, access to binding information of MCR molecules to their receptors is becoming crucial. Once the binding mode of an MCR molecule is defined, hit-to-lead transitions become more facile, time to market can be shortened, and the attrition rate in later clinical trials can be potentially reduced with the knowledge to engineer the physicochemical properties of the target compounds.

Active compounds were reported based on anchoring of a 6-chloroindole moiety onto Trp23 of p53 in the p53–Mdm2

 © 2015 The Chemical Society of Japan & Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

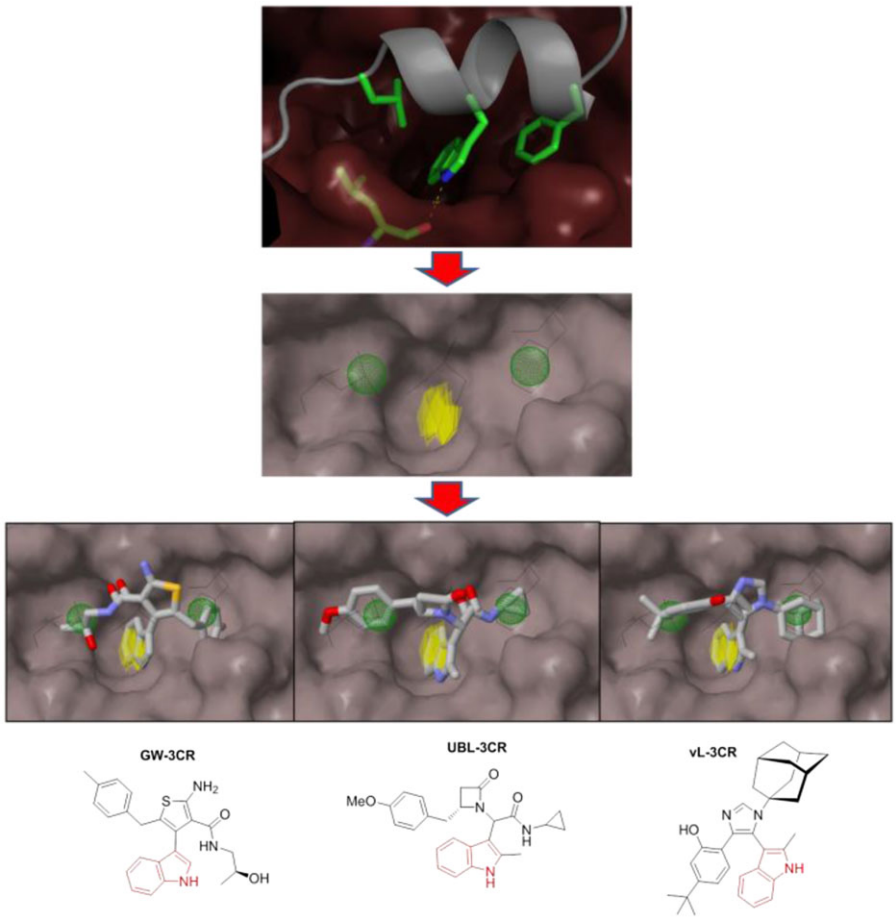


Figure 2. The use of AnchorQuery in structure-based drug discovery. Top: The endogenous interaction of p53 in Mdm2 with the hot spot amino acids Phe19, Trp23 and Leu26. Middle: Pharmacophore modeling and screening of a very large virtual library of MCR products allow for the efficient discovery of novel and potent scaffolds. Bottom: Three MCR molecules mimicking the p53 interaction with Mdm2.

interaction, designed through special computational software AnchorQuery and synthesized through Ugi and other multicomponent chemistry.[35,36] The most potent compounds were **41** (PDB: 3TJ2), **42** (PDB: 4MDQ), and **43** (PDB: 4MDN) with IC_{50} values of 400 nM, 1.2 μM, and 600 nM, respectively (Scheme 7).

Compounds **41** and **42** mimic three distinct amino acids of p53 (Phe19, Trp23, and Leu26), but compound **43** induced an additional hydrophobic pocket on the Mdm2 surface and unveiled for the first time a four-point binding mode (Figure 3).[37]

Besides applications in structure-based drug design and medicinal chemistry, MCR chemistry has recently also found application in the design and synthesis of libraries with unusual 3D and physicochemical properties for applications in high-throughput screening campaigns, such as the European Lead Factory (https://www.europeanleadfactory.eu/).

Natural Products

The use of MCRs in natural product synthesis is currently very much underinvestigated, but several recent examples are discussed in the following.

While the Bucherer–Bergs and the related Strecker synthesis are well-established methods for the one-pot synthesis of natural and unnatural amino acids and provide some very early examples of MCR-triggered natural product syntheses, the complex antibiotic penicillin was synthesized 50 years ago in a highly convergent approach by Ivar Ugi using two MCRs, the Asinger reaction and his own reaction (Scheme 8).[38]

Although early examples of the advantageous use of MCRs in the deliberate total synthesis of complex natural products led the way, their use has been neglected for decades and only recently realized by a few organic chemists.[39–44]

 © 2015 The Chemical Society of Japan & Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

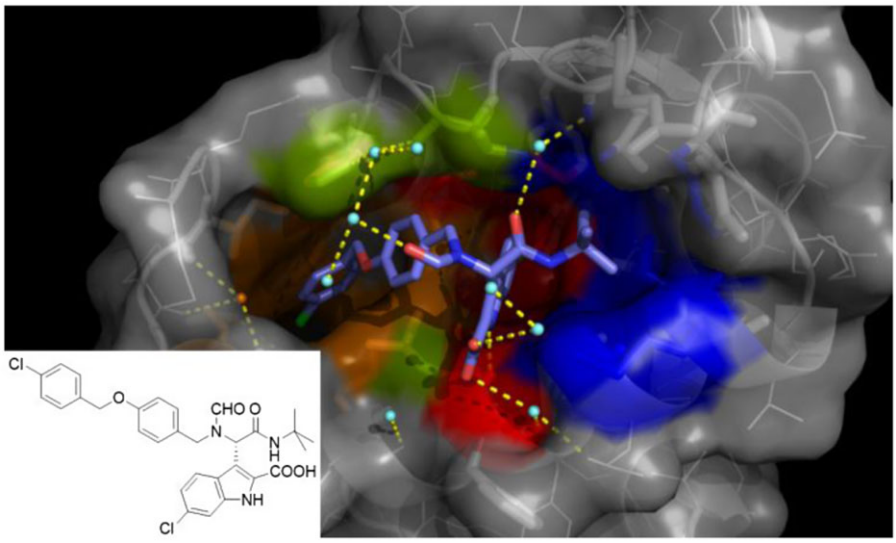
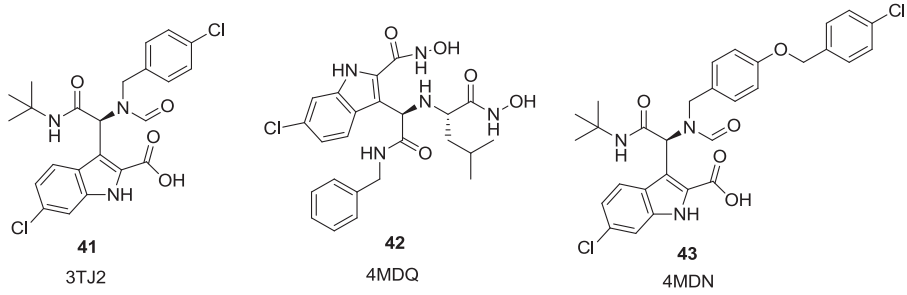
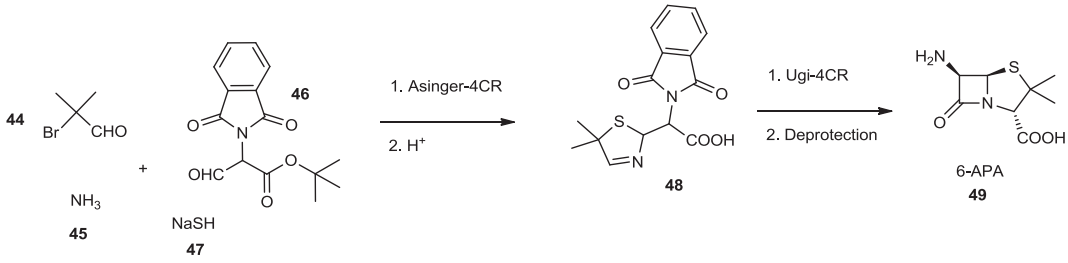


Figure 3. A potent p53–Mdm2 antagonist comprising four pharmacophore points based on the Ugi 4CR, discovered with AnchorQuery technology (PDB: 4MDN). The hot spots of the protein–protein interaction of p53 (green sticks) on Mdm2 (reddish surface) are shown, with different ligand areas important for the ligand–protein interaction projected onto the receptor surface and represented by different colors: isocyanide, blue; aldehyde, red; amine, green and orange. The acid component (formic) does not make major contributions but rather points into solvent.



Scheme 7. p53–Mdm2 inhibitors synthesized by the Ugi 4CR.

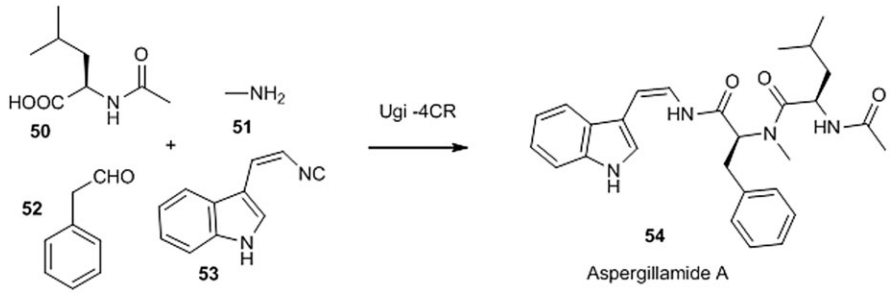


Scheme 8. Penicillin synthesis via the union of the Asinger 4CR and the Ugi 4CR.

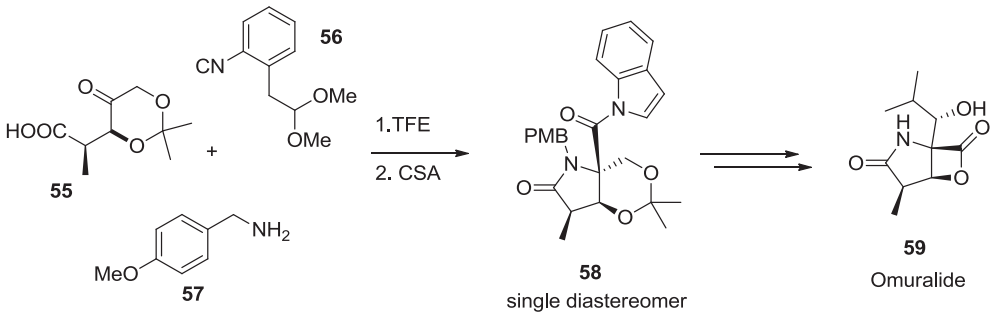
A novel MCR approach towards aspergillamide A (**54**) was described by Dömling et al. using an Ugi 4CR between *N*-acetylleucine (**50**), methylamine (**51**), phenylacetaldehyde (**52**) and (*E*/*Z*)-3-(2-isocyanoethenyl)indole (**53**), and the natural product was obtained in one step (Scheme 9).[45]

The natural product and proteasome inhibitor omuralide (**59**) has been synthesized in a stereocontrolled manner using an intramolecular U-4CR of the ketocarboxylic acid **55** as a key step (Scheme 10).[46] Here, a novel convertible isocyanide, 1-isocyano-2-(2,2-dimethoxyethyl)benzene (**56**), was used,

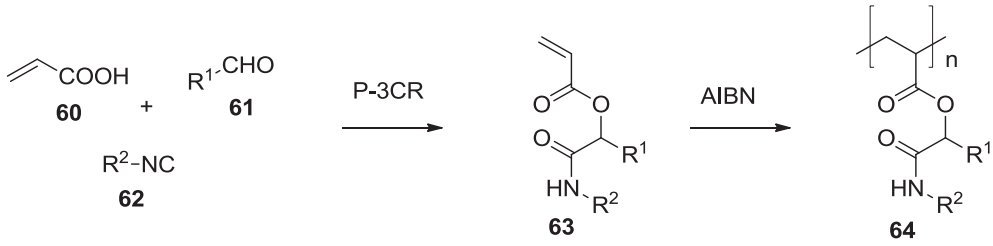
 © 2015 The Chemical Society of Japan & Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



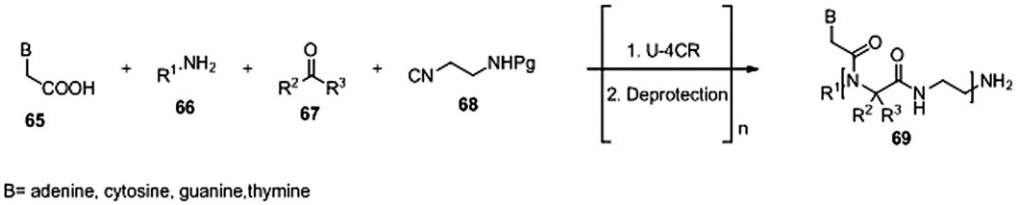
Scheme 9. Synthesis of aspergillamide A via the Ugi 4CR.



Scheme 10. Synthesis of omuralide using an Ugi 4CR as a first step.



Scheme 11. Macromolecule synthesis via the Passerini 3CR.



Scheme 12. MCR approach to PNA polymers.

which was introduced independently by two groups. The *p*-methoxybenzylamine (**57**) is used as an ammonia surrogate. The indole acyl of the intermediate **58** resulting from the convertible isocyanide can be cleaved under very mild conditions to produce the final product.

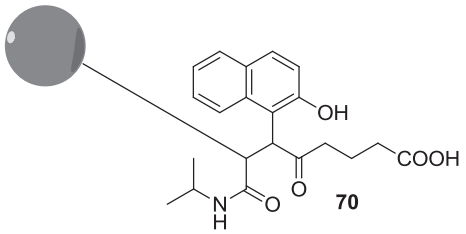
Polymers—Materials

Another application of MCR chemistry far from being leveraged to its full extent is in materials science. Precise engineering of macromolecular architectures is of utmost importance for

 © 2015 The Chemical Society of Japan & Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

designing future materials. Like no other technology, MCRs can help to meet this goal. Recently, the synthesis of sequence-defined macromolecules **64** without the utilization of any protecting group using a Passerini 3CR has been described (Scheme 11).[47]

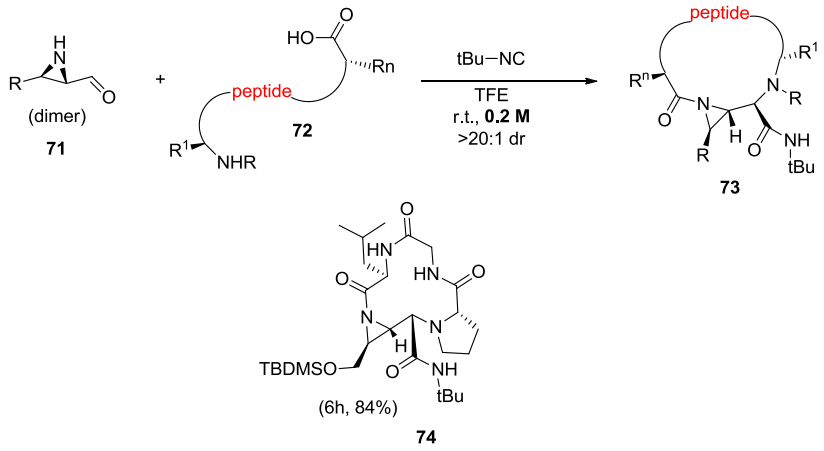
Another sequence-specific polymer synthesis with biological applications is that of the peptide nucleic acids (PNAs), which are metabolically stable and can recognize DNA and RNA polymers. This can be accomplished by the Ugi 4CR (Scheme 12).[48]

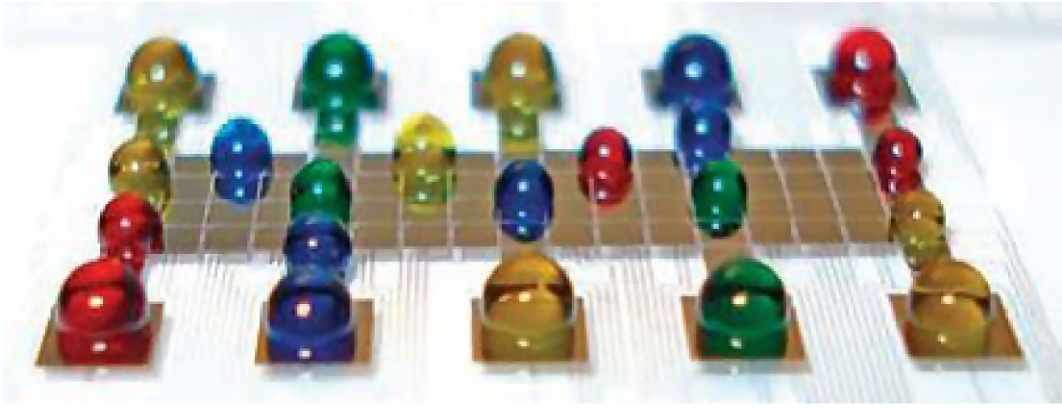


Scheme 13. Ugi-modified stationary phase.

Yet another application of MCRs in materials science might underscore the potential opportunities to uncover. Stationary phases modified with Ugi molecules have been recently introduced to efficiently separate immunoglobulins (Igs).[49] Currently, more than 300 monoclonal antibodies (mAbs) are moving toward the market. However, the efficient and high-yielding cleaning of the raw fermentation brew is still a holy grail in technical antibody processing. Thus, it is estimated that approximately half of the fermentation yield of mAbs is lost during purification. Ugi-modified stationary phases **70** (Scheme 13) have been found in this context to be far superior to purification protocols based on natural Ig-binding proteins, which are expensive to produce, labile, unstable, and exhibit lot-to-lot variability.

Fluorescent pharmacophores were discovered by the Groebke–Bienaymé–Blackburn MCR (GBB-3CR) with potential applications as specific imaging probes using a droplet array technique on glass slides.[50] Another group described the discovery of BODIPY dyes for the in vivo imaging of phagocytotic macrophages and their assembly by MCRs.[51]





Scheme 14. Macrocycle synthesis via MCRs.

 © 2015 The Chemical Society of Japan & Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Synthesis of Macrocycles

The structures of macrocyclic synthetic compounds and natural products recently became en vogue due to their many potential advantages over low-molecular-weight compounds. Macrocycles can have improved binding to receptors and can even target features of proteins that are otherwise difficult to handle, such as protein–protein interactions, due to their large and flat surface area. Moreover, some macrocycles show enhanced transport properties due to their chameleon-like behavior in hydrophobic and hydrophilic environments. This behavior can be triggered by conformational changes induced by a shift between intra- and intermolecular hydrogen bonding.

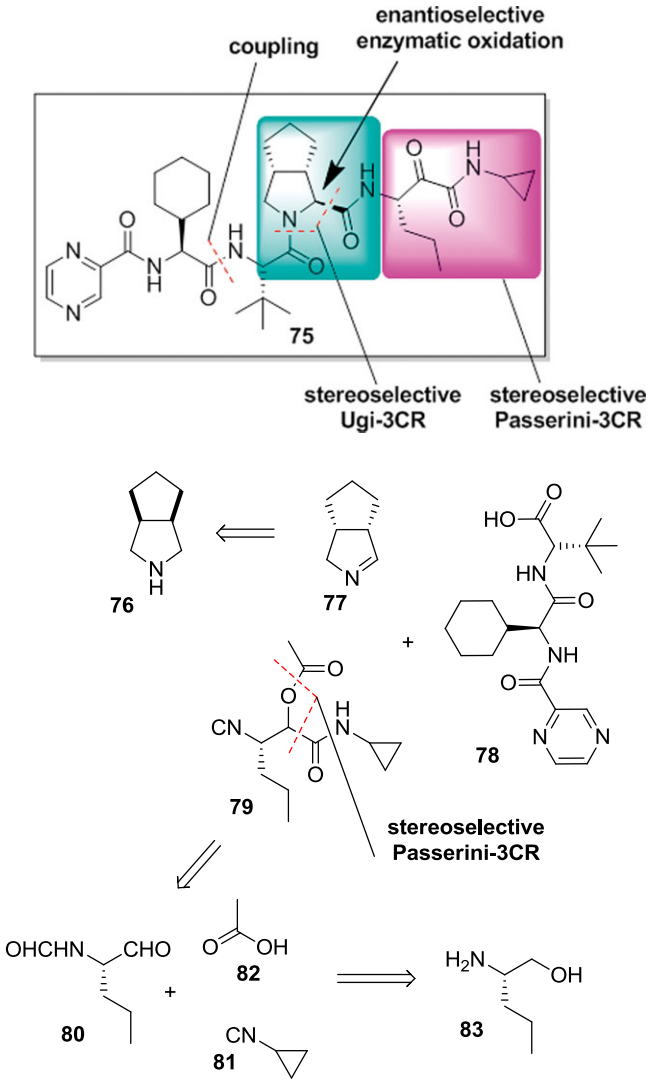
Modular MCR chemistry is very well suited to the fast and efficient synthesis of a diverse range of macrocycles. Pioneers of using MCRs for the macrocyclization step were Failli and Immer, who synthesized bioactive cyclic hexapeptides via an Ugi MCR of *N*-*C*-terminal-unprotected linear hexapeptides.[52] Later many other groups contributed to macrocycle synthesis via MCRs. A recent outstanding example consists of the macrocycle synthesis of Yudin[53] involving amphiphilic aziridinoaldehydes (**71**) in Ugi-type reactions (Scheme 14).

The macrocycle synthesis is diverse in terms of ring size and starting materials. An interesting application of the macrocyclization in very small volumes has been recently disclosed.[54]

Applications in the Pharmaceutical and Agrochemical Industries

Other worthwhile applications of MCRs in medicinal chemistry are in routes scouting for shorter, convergent, and cheaper syntheses. An excellent showcase example is the synthesis of the recently approved HCV protease inhibitor Incivek (telaprevir, **75**). This complex compound is industrially produced using a lengthy, highly linear strategy relying on standard peptide chemistry that exceeds 20 synthetic steps. Orru et al. were able to reduce the length and complexity of the synthesis of Incivek by almost half using a biotransformation and two MCRs as the key steps (Scheme 15).[55a,b] Recently, Riva et al. reported a second MCR approach towards Incivek using an enantioselective enzymatic desymmetrization.[55c]

Another example is the convergent synthesis of the schistosomiasis drug Biltricide (praziquantel, **89**) using key Ugi and Pictet–Spengler reactions (Scheme 16).[56] Clearly, more synthetic targets are out there, which can be potentially accessed in a more convergent and cheaper way using MCR chemistry, thus potentially benefiting the patient.

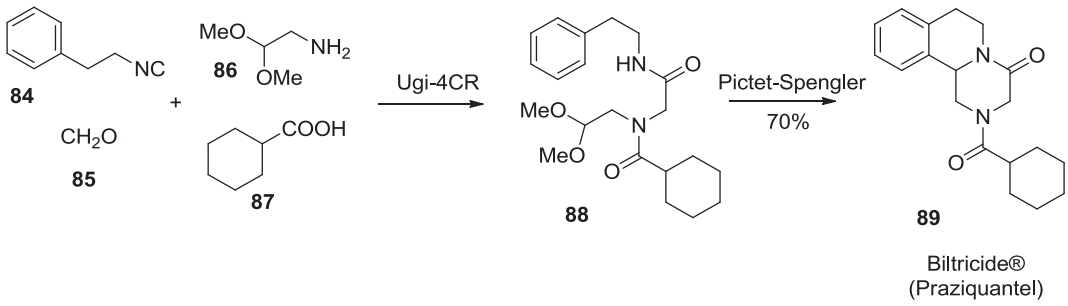


Scheme 15. MCR approach towards Incivek (telaprevir).

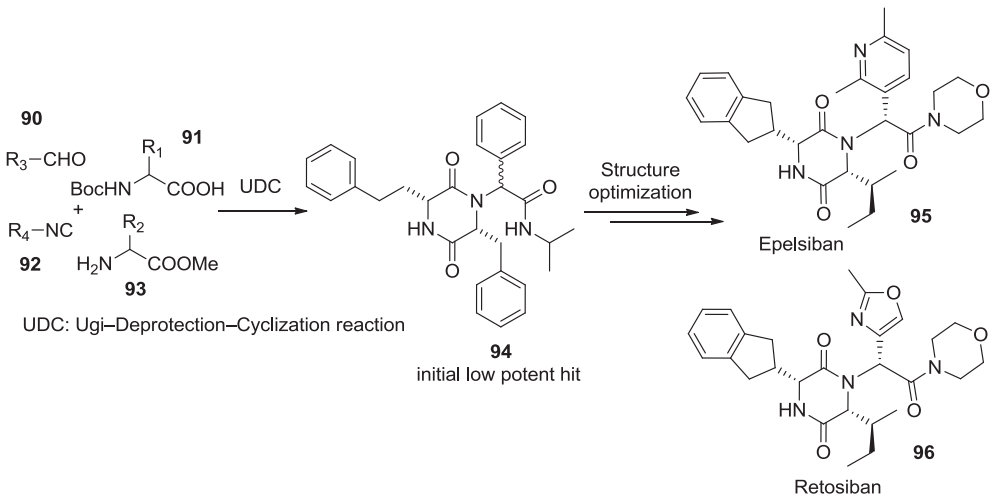
Clinical Candidates

Preterm labor is the major reason for neonatal morbidity and occurs in 10% of all births worldwide. Currently, antagonistic derivatives of the neurohypophyseal nonapeptide hormone oxytocin are used to control preterm labors; however, they are associated with the typical disadvantages of peptide drugs, such as a lack of oral bioavailability, short half-life and potential immunogenicity. The diketopiperazine (DKP) scaffold **94** was discovered in a HTS campaign that, after further medicinal chemistry optimization, developed into the first clinical class of low-molecular-weight oxytocin antagonists retosiban (**96**) and epelsiban (**95**), which are currently undergoing human clinical trials. The latter is also the first oxytocin antagonist drug developed for the treatment of premature ejaculation in men (Scheme 17).[57]

 © 2015 The Chemical Society of Japan & Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 16. Biltricide (praziquantel) synthesis using key Ugi 4CR and Pictet–Spengler reactions.



Scheme 17. Oxytocin antagonists produced via the UDC methodology.

Interestingly, they show superior activity for the oxytocin receptor and selectivity toward the related vasopressin receptors than the peptide-based compounds currently used clinically. Perhaps against the intuition of many medicinal chemists, the Ugi diketopiperazines are orally bioavailable, while the currently used peptide derivatives are i.v. only and must be stabilized by the introduction of terminal protecting groups and unnatural amino acids.

Because of the convergent and efficient nature of the MCR chemistry, detailed SAR studies of the scaffold substituents could be performed, giving rapid access to all eight stereoisomers of this Ugi DKP backbone in a landmark paper involving Ugi chemistry.[58]

5. MCRs: Quo Vadis?

The immense scaffold diversity coupled with the ease of access of many different compounds and the resulting straightforward optimization protocols make MCR chemistry an almost perfect technology to solve many of the issues of modern life. Whereas MCRs have recently found broad acceptance in general organic and medicinal chemistry, other science and technology domains still do not appreciate the outstanding opportunities that MCRs offer. We predict MCRs to become even more popular, especially if new applications become introduced. Some foreseen new fields of MCR chemistry are wordled in Figure 4.

Acknowledgements

The Dömling laboratory is generously funded by the University of Groningen, the Innovative Medicines Initiative (grant agreement no. 115489), the Qatar National Science Foundation (NPRP 6-065-3-012), the National Institute of Health (1R01GM097082-01) and Carmolex Inc. We are highly indebted to Erasmus Mundus for a Ph.D. scholarship to A. Chandgude.

 © 2015 The Chemical Society of Japan & Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

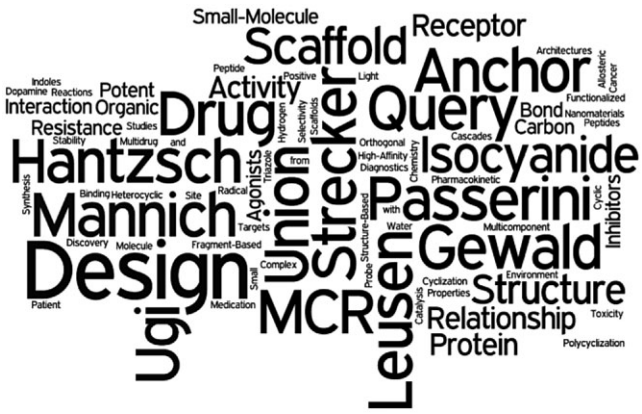


Figure 4. Wordoodle for MCRs.

REFERENCES

[1] a) L. Claisen, *Ber. Dtsch. Chem. Ges.* **1912**, *45*, 3157–3166; b) V. R. Annamalai, E. C. Linton, M. C. Kozlowski, *Org. Lett.* **2009**, *11*, 621–624.

[2] X. Li, S. J. Danishefsky, *J. Am. Chem. Soc.* **2008**, *130*, 5446–5448.

[3] a) C. Mannich, W. Krösche, *Arch. Pharm.* **1912**, *250*, 647–667; b) I. Ugi, R. Meyr, U. Fetzer, C. Steinbrückner, *Angew. Chem.* **1959**, *71*, 386; c) I. Ugi, C. Steinbrückner, *Angew. Chem.* **1960**, *72*, 267–268; d) I. Ugi, *Angew. Chem. Int. Ed. Engl.* **1962**, *1*, 8–21.

[4] I. Ugi, A. Dömling, W. Hörl, *Endeavour* **1994**, *18*, 115–122.

[5] A. Dömling, I. Ugi, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 563–564.

[6] a) E. Ruijter, R. Scheffelaar, R. V. A. Orru, *Angew. Chem. Int. Ed.* **2011**, *50*, 6234–6246; b) R. Kakuchi, *Angew. Chem. Int. Ed.* **2014**, *53*, 46–48; c) L. El Kaïm, L. Grimaud, *Eur. J. Org. Chem.* **2014**, 7749–7762.

[7] a) W. Chen, W. Mbafor, S. M. Roberts, J. Whittall, *J. Am. Chem. Soc.* **2006**, *128*, 3922–3923; b) W. Chen, S. M. Roberts, J. Whittall, A. Steiner, *Chem. Commun. 2006*, 27, 2916–**2918**; c) D. Marquarding, H. Klusacek, G. Gokel, P. Hoffmann, I. Ugi, *J. Am. Chem. Soc.* **1970**, *18*, 5389–5393; d) L. F. Battelle, R. Bau, G. W. Gokel, R. T. Oyakawa, I. Ugi, *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 138–140; e) L. F. Battelle, R. Bau, G. W. Gokel, R. T. Oyakawa, I. K. Ugi, *J. Am. Chem. Soc.* **1973**, *95*, 482–486.

[8] a) G. W. Gokel, P. Hoffmann, H. Klusacek, D. Marquarding, E. Ruch, I. Ugi, *Angew. Chem.* **1970**, *82*, 77–78; b) G. W. Gokel, I. Ugi, *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 191.

[9] a) A. Strecker, *Liebigs Ann. Chem.* **1850**, *75*, 27–45; b) J. T. Kuethe, D. R. Gauthier, G. L. Beutner, N. Yasuda, *J. Org. Chem.* **2007**, *72*, 7469–7472.

[10] a) M. Passerini, L. Simone, *Gazz. Chim. Ital.* **1921**, *51*, 126–129; b) M. Passerini, G. Ragni, *Gazz. Chim. Ital.* **1931**, *61*, 964–969; c) L. Banfi, R. Riva, *Org. React.* **2005**, *65*, 1–140; d) C. Lamberth, A. Jeanguenat, F. Cederbaum, A. De Mesmaeker, M. Zeller, H.-J. Kempf, R. Zeun, *Bioorg. Med. Chem*. **2008**, *16*, 1531–1545.

[11] I. Ugi, C. Steinbrückner (Astra AB), DE-1103337, **1961**.

[12] a) P. L. Pauson, I. U. Khand, *Ann. N. Y. Acad. Sci.* **1977**, *295*, 2–14; b) A. Vazquez-Romero, L. Cardenas, E. Blasi, X. Verdaguer, A. Riera, *Org. Lett.* **2009**, *11*, 3104–3107.

[13] a) A. M. Van Leusen, J. Wildeman, O. H. Oldenziel, *J. Org. Chem. 1977*, 42, 1153–**1159**; b) J. Sisko, *J. Org. Chem.* **1998**, *63*, 4529–4531.

[14] a) K. Gewald, E. Schinke, H. Böttcher, *Chem. Ber.* **1966**, *99*, 94–100; b) J. K. Chakrabarti, T. M. Hotten, D. E. Tupper, Patent EP 454436, **1991**; c) K. Wang, D. Kim, A. Dömling, *J. Comb. Chem.* **2010**, *12*, 111–118.

[15] a) A. Hantzsch, *Ber. Dtsch. Chem. Ges. 1881*, 14, 1637–**1638**; b) F. Bossert, W. Vater, *Naturwissenschaften* **1971**, *58*, 578; c) F. Bossert, H. Meyer, E. Wehinger, *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 762–769.

[16] a) H. Staudinger, *Justus Liebigs Ann. Chem.* **1907**, *356*, 51–123; b) S. B. Rosenblum, T. Huynh, A. Afonso, H. R. Davis, N. Yumibe, J. W. Clader, D. A. Burnett, *J. Med. Chem.* **1998**, *41*, 973–980; c) C. Palomo, J. M. Aizpurua, I. Ganboa, M. Oiarbide, *Eur. J. Org. Chem.* **1999**, 3223–3235.

[17] a) C. Hulme, V. Gore, *Curr. Med. Chem*. **2003**, *1*, 51–80; b) W. Erb, L. Neuville, J. Zhu, *J. Org. Chem.* **2009**, *74*, 3109–3115.

[18] a) K. Khoury, M. K. Sinha, T. Nagashima, E. Herdtweck, A. Dömling, *Angew. Chem. Int. Ed.* **2012**, *51*, 10280–10283; b) M. K. Sinha, K. Khoury, E. Herdtweck, A. Dömling, *Chem. Eur. J.* **2013**, *19*, 8048–8052; c) M. K. Sinha, K. Khoury, E. Herdtweck, A. Dömling, *Org. Biomol. Chem.* **2013**, *11*, 4792–4796.

[19] F. Asinger, M. Thiel, *Angew. Chem.* **1958**, *70*, 667–683.

[20] A. Dömling, I. Ugi, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 563–564.

[21] A. Dömling, *Curr. Opin. Chem. Biol.* **2000**, *4*, 318–323.

[22] N. Elders, D. van der Born, L. J. D. Hendrickx, B. J. J. Timmer, A. Krause, E. Janssen, F. J. J. de Kanter, E. Ruijter, R. V. A. Orru, *Angew. Chem. Int. Ed.* **2009**, *48*, 5856–5859.

[23] N. Elders, E. Ruijter, F. J. J. de Kanter, M. B. Groen, R. V. A. Orru, *Chem. Eur. J.* **2008**, *14*, 4961–4973.

[24] N. Elders, E. Ruijter, F. J. J. de Kanter, E. Janssen, M. Lutz, A. L. Spek, R. V. A. Orru, *Chem. Eur. J.* **2009**, *15*, 6096–6099.

[25] H. Bienaymé, *Tetrahedron Lett*. **1998**, *39*, 4255–4258.

[26] N. A. Petasis, I. A. Zavialov, *J. Am. Chem. Soc.* **1997**, *119*, 445–446.

[27] D. E. Portlock, R. Ostaszewski, D. Naskar, L. West, *Tetrahedron Lett.* **2003**, *44*, 603–605.

[28] D. E. Portlock, D. Naskar, L. West, R. Ostaszewski, J. J. Chen, *Tetrahedron Lett*. **2003**, *44*, 5121–5124.

[29] T. H. Al-Tel, R. A. Al-Qawasmeh, W. Voelter, *Eur. J. Org. Chem.* **2010**, 5586–5593.

[30] a) H. Bienaymé, K. Bouzid, *Angew. Chem. Int. Ed. 1998*, 37, 2234–**2237**; b) K. Groebke, L. Weber, F. Mehlin, *Synlett* **1998**, *6*, 661–663; c) C. Blackburn, B. Guan, P. Fleming, K. Shiosaki, S. Tsai, *Tetrahedron Lett.* **1998**, *39*, 3635–3638.

 © 2015 The Chemical Society of Japan & Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

[31] A. Dömling, W. Wang, K. Wang, *Chem. Rev.* **2012**, *112*, 3083–3135.
[32] D. Koes, K. Khoury, Y. Huang, W. Wang, M. Bista, G. M. Popowicz, S. Wolf, T. A. Holak, A. Dömling, C. J. Camacho, *PLoS One* **2012**, 7, e32839.
[33] A. Czarna, B. Beck, S. Srivastava, G. M. Popowicz, S. Wolf, Y. Huang, M. Bista, T. A. Holak, A. Dömling, *Angew. Chem. Int. Ed.* **2010**, *49*, 5352–5356.
[34] M. Bista, S. Wolf, K. Khoury, K. Kowalska, Y. Huang, E. Wrona, M. Arciniega, G. M. Popowicz, T. A. Holak, A. Dömling, *Structure* **2013**, *21*, 2143–2151.
[35] Y. Huang, S. Wolf, D. Koes, G. M. Popowicz, C. J. Camacho, T. A. Holak, A. Dömling, *ChemMedChem* **2012**, *7*, 49–52.
[36] A. Dömling, Patent Application WO 2012/033525 A3, **2012**.
[37] Y. Huang, S. Wolf, B. Beck, L.-M. Köhler, K. Khoury, G. M. Popowicz, S. K. Goda, M. Subklewe, A. Twarda, T. A. Holak, A. Dömling, *ACS Chem. Biol.* **2014**, *9*, 802–811.
[38] I. Ugi, *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 810–819.
[39] a) B. Beck, S. Hess, A. Dömling, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1701–1705; b) W. Wang, S. Joyner, K. Khoury, A. Dömling, *Org. Biomol. Chem.* **2010**, *8*, 529–532.
[40] T. Fukuyama, B. D. Robins, R. A. Sachleben, *Tetrahedron Lett.* **1981**, *22*, 4155–4158.
[41] J. E. Semple, P. C. Wang, Z. Lysenko, M. M. Joullié, *J. Am. Chem. Soc.* **1980**, *102*, 7505–7510.
[42] S. Takiguchi, T. Iizuka, Y. Kumakura, K. Murasaki, N. Ban, K. Higuchi, T. Kawasaki, *J. Org. Chem.* **2010**, *75*, 1126–1131.
[43] S. Wan, F. Wu, J. C. Rech, M. E. Green, R. Balachandran, W. S. Horne, B. W. Day, P. E. Floreancig, *J. Am. Chem. Soc.* **2011**, *133*, 16668–16679.
[44] B. B. Toure, D. G. Hall, *Chem. Rev.* **2009**, *109*, 4439–4486.
[45] B. Beck, S. Hess, A. Dömling, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1701–1705.
[46] a) C. B. Gilley, M. J. Buller, Y. Kobayashi, *Org. Lett.* **2007**, *9*, 3631–3634; b) O. Kreye, B. Westermann, L. A. Wessjohann, *Synlett* **2007**, *20*, 3188–3192; c) J. Isaacson, C. B. Gilley, Y. Kobayashi, *J. Org. Chem.* **2007**, *72*, 3913–3916; d) S. Lage, I. Villaluenga, N. Sotomayor, E. Lete, *Synlett* **2008**, *20*, 3188–3192.
[47] S. C. Solleder, M. A. R. Meier, *Angew. Chem. Int. Ed.* **2014**, *53*, 711–714.
[48] A. Dömling, K. Z. Chi, M. Barrere, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2871–2874.
[49] J. M. Haigh, A. Hussain, M. L. Mimmack, C. R. Lowe. *J. Chromatogr. B.* **2009**, *877*, 1440–1452.
[50] O. N. Burchak, L. Mugherli, M. Ostuni, J. J. Lacapère, M. Y. Balakirev, *J. Am. Chem. Soc.* **2011**, *133*, 10058–10061.
[51] A. Vázquez-Romero, N. Kielland, M. J. Arévalo, S. Preciado, R. J. Mellanby, Y. Feng, R. Lavilla, M. Vendrell, *J. Am. Chem. Soc.* **2013**, *135*, 16018–16021.
[52] A. Failli, H. Immer, M. Götz, *Can. J. Chem*. **1979**, *57*, 3257–3261.
[53] R. Hili, V. Rai, A. K. Yudin, *J. Am. Chem. Soc.* **2010**, *132*, 2889–2891.
[54] M. J. Jebrail, A. H. C. Ng, V. Rai, R. Hili, A. K. Yudin, A. R. Wheeler, *Angew. Chem. Int. Ed.* **2010**, *49*, 8625–8629.
[55] a) A. Znabet, M. M. Polak, E. Janssen, F.J. J. de Kanter, N. J. Turner, R. V. A. Orru, E. Ruijter, *Chem. Commun.* **2010**, *46*, 7918–7920; b) T. Zarganes-Tzitzikas, A. Dömling, *Org. Chem. Front.* **2014**, *1*, 834–837; c) L. Moni, L. Banfi, A. Basso, L. Carcone, M. Rasparini, R. Riva, *J. Org. Chem.* **2015**, *80*, 3411–3428.
[56] H. Cao, H. Liu, A. Dömling, *Chem. Eur. J.* **2010**, *16*, 12296–12298.
[57] A. D. Borthwick, D. E. Davies, A. M. Exall, D. G. Livermore, S. L. Sollis, F. Nerozzi, M. J. Allen, M. Perren, S. S. Shabbir, P. M. Woollard, P. G. Wyatt, *J. Med. Chem*. **2005**, *48*, 6956–6969.
[58] a) A. D. Borthwick, D. E. Davies, A. M. Exall, R. J. Hatley, J. A. Hughes, W. R. Irving, D. G. Livermore, S. L. Sollis, F. Nerozzi, K. L. Valko, M. J. Allen, M. Perren, S. S. Shabbir, P. M. Woollard, M. Aprice, *J. Med. Chem*. **2006**, *49*, 4159–4170; b) T. Zarganes-Tzitzikas, P. Patil, K. Khoury, E. Herdtweck, A. Dömling, *Eur. J. Org. Chem.* **2015**, *1*, 51–55.

Received: May 5, 2015
Published online: September 11, 2015

 © 2015 The Chemical Society of Japan & Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim