Green Chemistry

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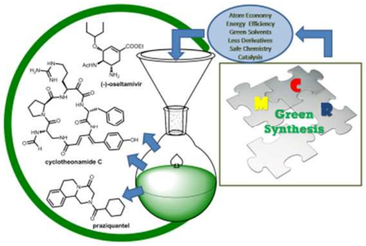

This review discusses the utility of multicomponent reactions as green chemistry methods.

Multicomponent Reactions: Advanced Tools for Sustainable Organic Synthesis

Răzvan C. Cioc, Eelco Ruijter* and Romano V. A. Orru*

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Sustainable or green chemistry has established firm ground providing essential design criteria for the development of efficient chemical syntheses of complex, high added value molecules. On the other hand, multicomponent reactions have only recently been recognized as major expansion of the synthetic chemist's toolbox. There is still little awareness, however, of the practical value of this type of reactions for meeting many of the criteria set by the green chemistry philosophy to guide organic chemists and process chemists in the design, synthesis and further development of truly sustainable manufacturing processes of medicines, food additives, catalysts or advanced materials. In this perspective we highlight the utility of multicomponent reactions as methods for green synthesis.

Introduction

Organic synthesis of valuable small molecules has come a long way since Wöhler first synthesized urea in 1828.[1] Yet, synthetic organic chemists today are just as passionate as their predecessors from those times in pursuing the challenging task of creating molecules with advanced properties and exciting chemical structures. This has served as the motivation for the discovery of novel reactivity, reagents and catalysts that enable synthetic chemists to use their creativity in designing sequences of reactions to access compounds of whatever complexity.[2] *Getting there* has been for many years synonymous with indisputable success, but in the last 30 years chemists have become more and more preoccupied about *how* they are getting there. Attributes like "concise", "efficient", "convergent", now frequent in the titles of (total) synthesis papers,[3] are surely not only catchwords but also defining criteria that chemists consider when planning their synthetic approach. In the same way, process chemists have understood their responsibility for the impact that the chemical industry has on the environment and are actively engaged in minimizing it.[4] As consequence, *green chemistry*[5] emerged in the last decades enabling synthetic and process chemists to theorize on these concepts and use them to design advanced syntheses.[6] The object of green chemistry is to reshape the way in which chemists conceive synthesis and in accordance its actions do not necessarily focus on the development of novel methods, but rather on alternative sustainable variants to existing ones and, most importantly, different synthetic strategies to include environmental considerations as early as in the process design stage.

This is where multicomponent reactions (MCRs) come into play. Multicomponent reactions combine at least three reactants[7] in the same pot to generate a product containing most (preferably all) atoms of the starting materials.[8] Their atom economy, efficiency, mild conditions, high convergence and concomitant step economy in combination with their general compatibility with green solvents would justify a central place in the toolbox of sustainable synthetic methodologies. Although an increasing number of applications of MCRs are reported in medicinal chemistry and drug discovery programmes,[9] combinatorial chemistry,[10] natural product synthesis,[11] agrochemistry,[12] and polymer chemistry,[13] there is still not a general awareness among organic chemists that MCRs are indeed able to address delicate chemical problems in an eco-friendly manner. Thus, despite the general understanding and dissemination of the chemical benefits of MCRs (convergence/divergence, diversity-oriented synthesis, library generation), the sustainability aspect of this chemistry is marginally acknowledged and reviewed in literature.[14] This review thus aims to point out the opportunities and challenges that the utilization of MCRs brings for green synthesis and process design.

Multicomponent Reactions and the Principles of Green Chemistry

Traditionally, efficiency is encoded in the synthetic chemist's mind mostly in terms of yield, selectivity and number of steps. The green chemistry perspective is, however, considerably broader and includes criteria for waste generation, use of reagents and solvents, use of hazardous chemicals, energy intensity and general safety. All these criteria are assembled in the set of 12 principles formulated by Anastas and Warner in 1998 (Figure 1).[5]

Fig. 1 Principles of Green Chemistry

In this review we would like to accompany the reader in a journey through these 12 criteria relating them to multicomponent chemistry in an attempt to demonstrate its general value for green process development but also to identify weaknesses and challenges for future research. Rather than an exhaustive coverage of literature, selected recent examples will serve to support our propositions and clarify our discussion. In the course of our discussion, it will become evident that some of the twelve principles pertain explicitly to the characteristics of the chemical reaction(s), while others are rather a matter of process optimization (chemical technology) or the nature of the reactants and products. Since only the former issue can be addressed directly by the development and optimization of synthetic methods, we will focus primarily on the corresponding green chemistry principles.

1. Waste Prevention

Designing chemical processes to minimize waste levels in the process design stage rather than dealing with downstream treatment lies at the foundation of the green chemistry philosophy. Along the multiple stages of a synthetic route, waste – in many forms – is invariably generated besides the target compounds. Including waste anticipation and prevention strategies already in the design phase of the synthesis is the sustainable way to go.

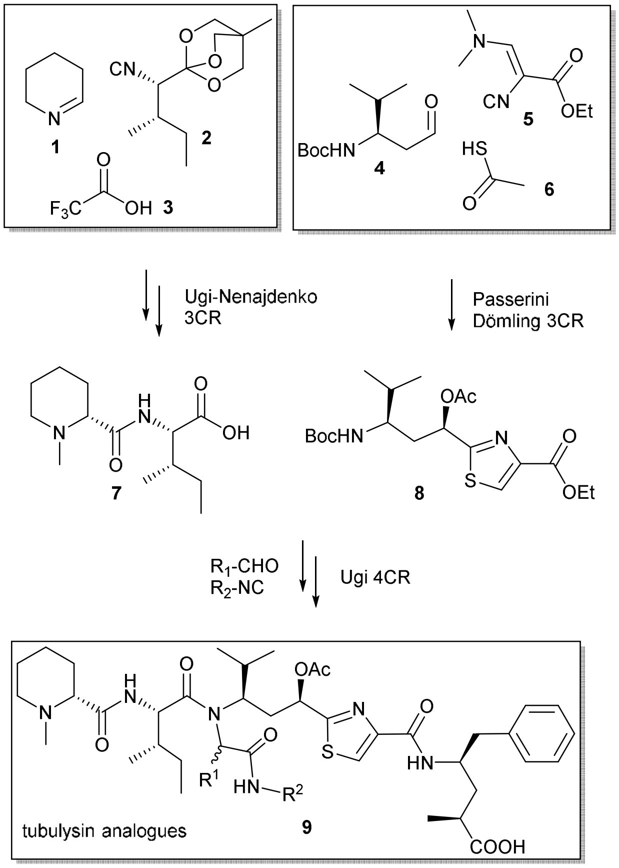
The convergent nature of MCRs is a premise for the overall waste reduction of a process not only by incorporating a highly resource-efficient step in the synthesis but also by the often dramatic shortening of the entire synthetic sequence with the positive ecological consequences thereof.

A general examination of multicomponent chemistry at the single-reaction level reveals good conversions, excellent selectivity (particularly chemo- and regioselectivity, more challenging is stereoselectivity[15]) and near stoichiometric use of reactants without any additives. Therefore, waste in the form of unreacted starting materials and side products is minimal. Next, an intrinsic feature of many MCRs is that they do not generate high molecular weight by-products as will be emphasized in the following section. Furthermore, isolation is often simple and does not make use of excessive amounts/volumes of chromatographic materials or solvents that would also add to the waste list. Table 1 captures a few representative moments of MCR history highlighting simple green chemistry metrics.

The consequence of a reaction program consisting of elementary condensation/addition stages is that by-products arise only as simple small molecules, often water and generally speaking alcohols, amines, or common salts. This has a dual beneficial outcome on the sustainability of the process from the waste prevention perspective: both the amount and hazardous nature of the waste generated by MCRs are minimal. For instance, arguably the most versatile of MCRs, the Ugi 4CR, yields a bis-amide product with the release of only one molecule of water as an innocuous by-product.

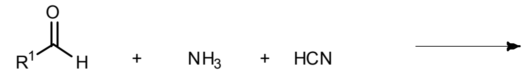
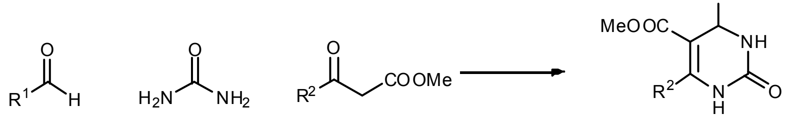
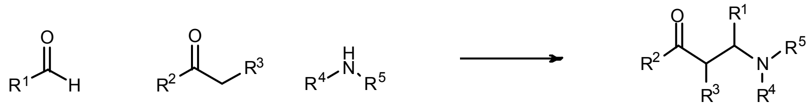
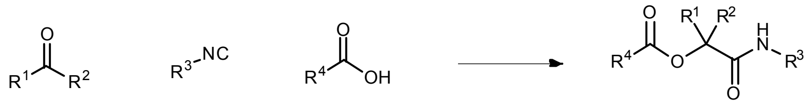
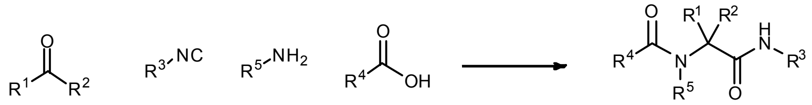
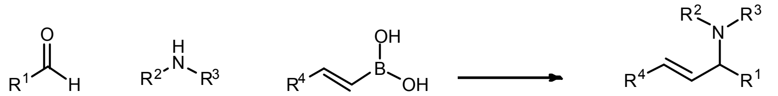
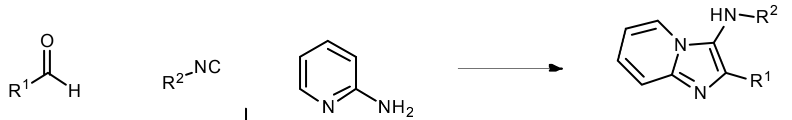
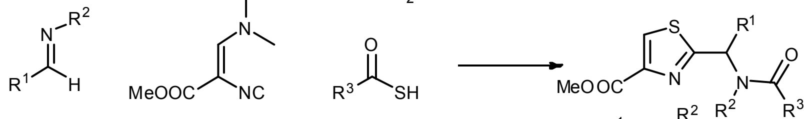
The eco-benefit of moving multistep synthesis to step-economical convergent synthetic pathways rather than a linear reaction-by-reaction route was realized long ago and the correlation of the environmental burden of a process with the number of unit operations involved is evident. The fine chemicals industry has long pursued the goal of reducing the number of stages of a process envisaging time, solvent (including solvent for cleaning the reactors) and energy savings and therefore reaction telescoping (i.e., the one-pot combination of several distinct chemical transformations) possesses high practical value.[16] In the past decade, process contraction via multiple one-pot procedures was acknowledged as viable green solution: Eli Lilly's synthesis of the anticonvulsant drug candidate LY300164[17] and Pfizer's Zoloft® improved manufacturing process[18] both received the US Presidential Green Chemistry Challenge Award.[19]

The sustainable dimension of an MCR-based synthetic strategy thus becomes comprehensible as the convergence transcends the individual reaction to the entire synthetic sequence with the immediate effect of shortening the route. The result can be remarkable: using a multiple MCR approach, Wessjohann *et al.* showed that tubulysin[20] analogues **9** with similar cytotoxicity as the natural products can be obtained in just 11 steps (longest linear sequence) by the strategic combination of a Passerini-Dömling 3CR, an Ugi 3CR and finally an Ugi 4CR (Scheme 1).[21]



Scheme 1 Multiple multicomponent approach to tubulysin analogues (Wessjohann[21]).

Table 1 Representative examples of multicomponent chemistry

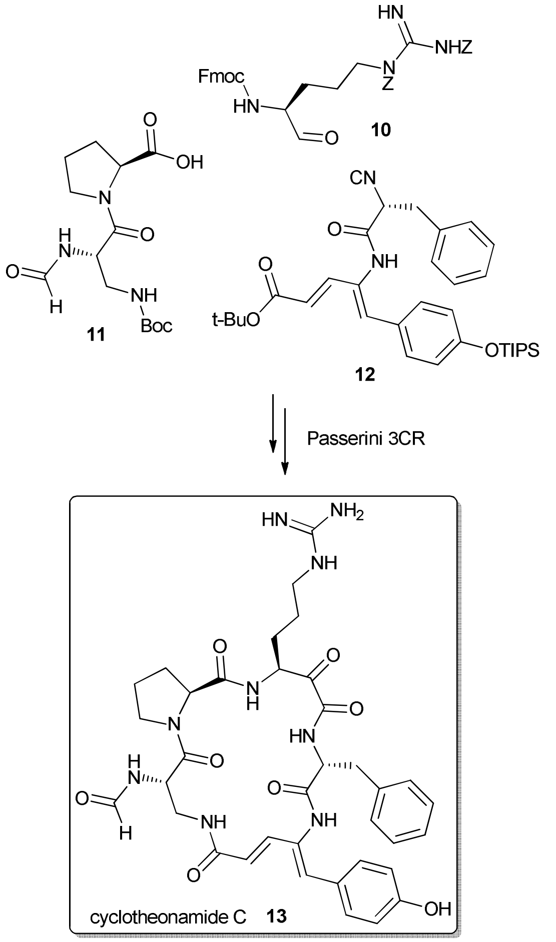
Reaction	Year	Scheme	AE[a, b]	E_{mw}[c]	Waste
Strecker[22]	1850		80%	0.26	H_2O
Biginelli[23]	1891		84%	0.20	2 H_2O
Mannich[24]	1912		89%	0.13	H_2O
Passerini[25]	1921		100%	0.00	None
Ugi[26]	1959		91%	0.10	H_2O
Petasis[27]	1993		65%	0.55	$B(OH)_3$
Groebke-Blackburn-Bienaymé[28]	1998		90%	0.11	H_2O
Passerini-Dömling[29]	2000		84%	0.19	Me_2NH
Orru[30]	2003		86%	0.16	H_2O

[a] Atom Economy = $MW_{Product}/MW_{Reactants}$; [b] calculations consider R = Me. Therefore, in practical examples the atom economy would actually be higher as the MW of reagents and products increases; [c] Environmental factor = $MW_{Waste}/MW_{Product}$; although less exact than the original E-factor based on mass,[31] this metrics is still indicative while being computed without experimental data;[32]

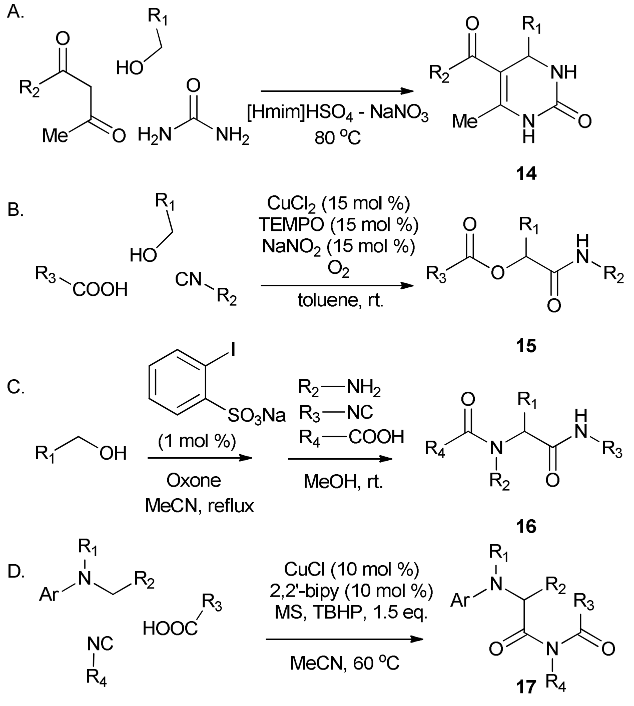
Similarly, the group of Aitken described a concise and highly convergent assembly of cyclotheonamide C **13**, a marine cyclic pentapeptide with potent serine protease inhibitory activity.[33] The Passerini 3CR, followed by deprotection and acyl migration is elegantly exploited to access the key acyclic intermediate required for the synthesis of this marine metabolite (Scheme 2).[34]

These examples serve merely to emphasize the gain in step economy attainable through multicomponent chemistry. Numerous other recent MCRs applications for the rapid and efficient preparation of natural products[11] and bioactive molecules have been reported.[9b]

Furthermore, a supplementary reduction in the number of steps in a synthetic sequence can be achieved by performing a tandem generation of one of the inputs for the multicomponent reaction, typically the aldehyde or imine component via *in-situ* oxidation. Various catalytic oxidation systems have proven compatible with MCR conditions leading to good overall yields for one-pot procedures, e.g. in the Biginelli,[35] Passerini[36] and Ugi[37] reactions (Scheme 3).

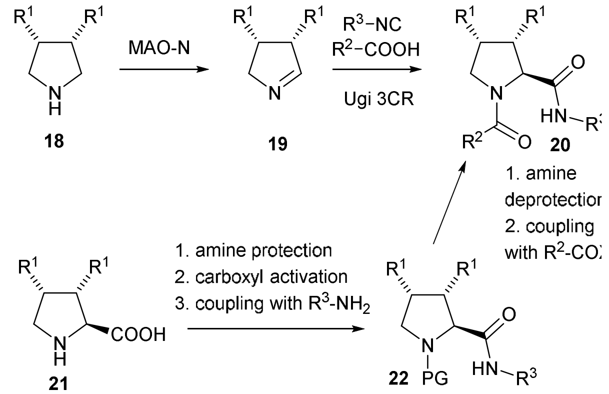


Scheme 2 Cyclotheonamide synthesis via Passerini-amine deprotection-acyl migration strategy (Aitken[34]).



Scheme 3 MCRs with *in situ* preparation of one component by oxidation.

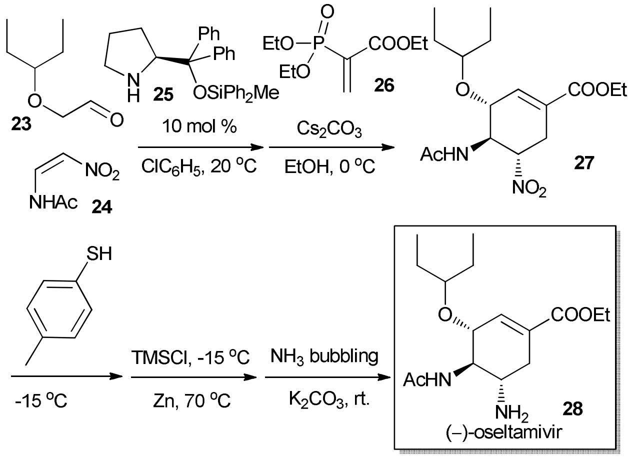
Together with step economy, these interesting methodologies are consistent with other concepts of the green philosophy. For example, sodium 2-iodobenzenesulfonate catalyses the oxidation of alcohols to aldehydes prior to the Ugi 4CR condensation under mild conditions at just 1 mol % catalyst loadings with regeneration of the hypervalent iodine active species by eco-friendly Oxone®.[37] Still, the sustainability of such processes can be pushed further by resorting to the use of enzyme catalysis instead of chemocatalysts. The green credentials of biocatalysis are well recognized[38] and its combination with MCRs would thus represent an important step towards the ideal synthesis;[39] however, successful applications of this concept are still limited.[40] For example, an engineered monoamine oxidase (MAO-N) was shown to desymmetrize cyclic *meso*-amines to enantiopure imines that can be functionalized by a stereoselective Ugi-Joullié reaction yielding optically pure 3,4-substituted prolyl peptides **20** with medicinal relevance (Scheme 4).[41] The traditional linear route towards these prolyl peptides relies on peptide-coupling strategies. These involve the use of atom-inefficient coupling reagents and wasteful protecting groups in combination with the 3,4-disubstituted proline derivative **21** as central building block, clearly inferior from a green chemistry perspective.



Scheme 4 MAO-N preparation of chiral imines and combination with MCRs compared to the traditional linear synthesis (Orru[41]).

However, the single most important sustainable advantage of step economy in organic synthesis is undoubtedly the reduction of solvent requirements. Reaction telescoping, improved work-up and isolation protocols, solvent recovery systems and multicomponent chemistry synergistically lead to a dramatic reduction of waste.[42] Such a recent example is the highly practical preparation of (–)-oseltamivir phosphate **28** (Tamiflu), one of the most important treatments for influenza.[43] Hayashi *et al.* developed a scalable process for the preparation of (–)-oseltamivir in high purity and overall yield (28%) in a remarkable one pot operation, without solvent exchange or evaporation![44] The synthesis consists of six steps conducted successively while maintaining a tight selectivity control, an unprecedented achievement for a molecule of such (stereochemical) complexity (Scheme 5). The overall yield is comparable to the yield obtained by alternative sequential routes, but it is merely half of what the same group was able to achieve previously in a process consisting of three one-pot operations.[45] These results highlight the power of multicomponent chemistry and reaction telescoping to prepare complex molecules in a concise way, without loss in yield compared to a sequential approach but with great gain in productivity and waste management.

In a similar way, densely functionalized molecules can be rapidly assembled via catalytic cascade and domino reactions.[46] These strategies are based on highly atom-efficient multiple-bond formation processes and thus can be included in the repertoire of multicomponent reaction methodology.[47] Furthermore, the synergistic use of sequential one-pot cascade reactions, multi-catalysis and MCRs is the most sustainable way to access complex molecules of practical utility with minimal generation of waste.[48] Numerous examples showing the potential of catalytic cascade reactions as green chemistry tools in the stereoselective assembly of chiral compounds are available in the recent literature.[49]



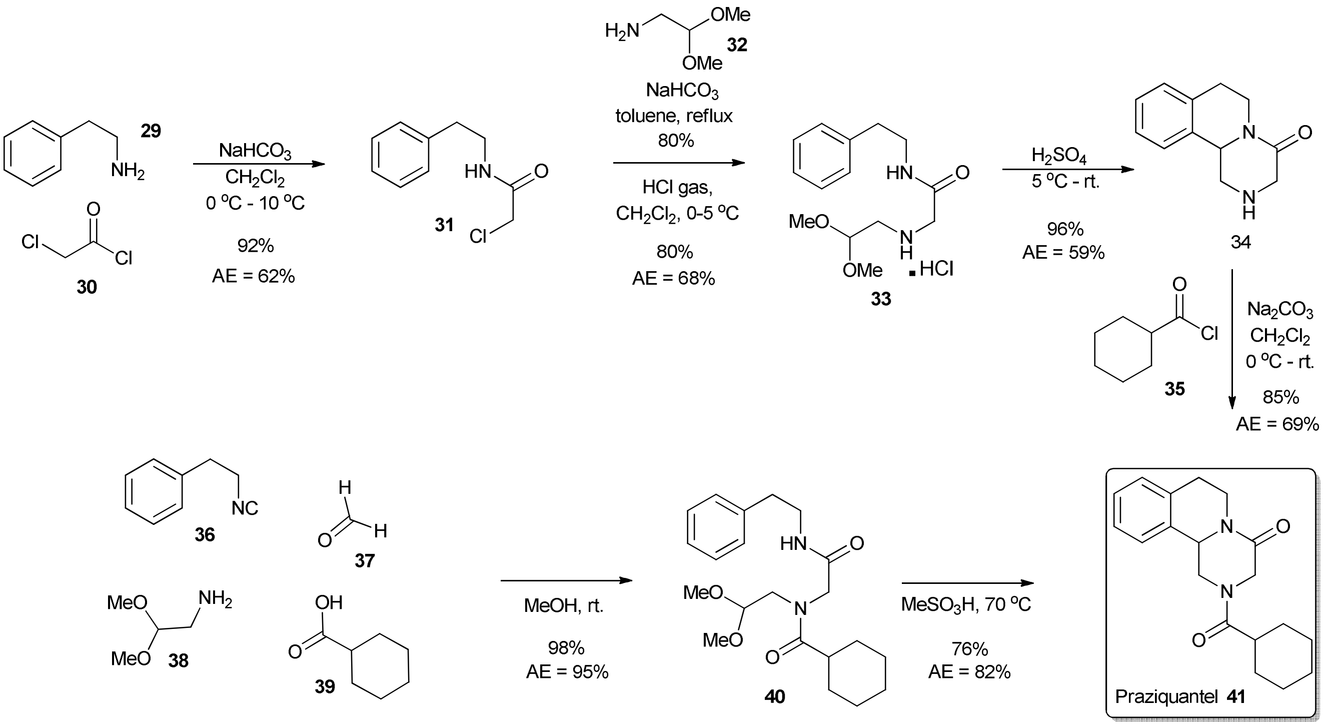
Scheme 5 Multicomponent preparation of (−)-oseltamivir (Hayashi[44]).

To conclude this section, let us consider quantitative, measurable criteria of green chemistry and visualize in figures how multicomponent chemistry anticipates and reduces waste in organic synthesis. The case study of praziquantel **41** (PZQ) is highly informative in this respect. PZQ is an anti-schistosomiasis drug present on the WHO list of essential medicines[50] and has been the subject of numerous synthetic investigations resulting in several commercial processes.[51] The most important supplier of PZQ manufactures the drug in five steps consisting essentially of amide bond formations around the key transformation which is an intramolecular *N*-acyliminium Pictet-Spengler cyclization.[52] This process is quite robust, high yielding and does not make use of particularly hazardous chemistry. Yet, the multicomponent approach is clearly superior. Based on a similar cyclization strategy, Dömling has contracted the synthesis to just two stages by preparing an already acylated intermediate via an Ugi 4CR prior to cyclization (Scheme 6).[53] The E-factor for this novel route is only 0.7 compared to 3.1 as in the commercial application, not even taking into account the reduction in solvent use. Considering the operational simplicity and facile isolation of the product, this process has great potential to enter the development phase.

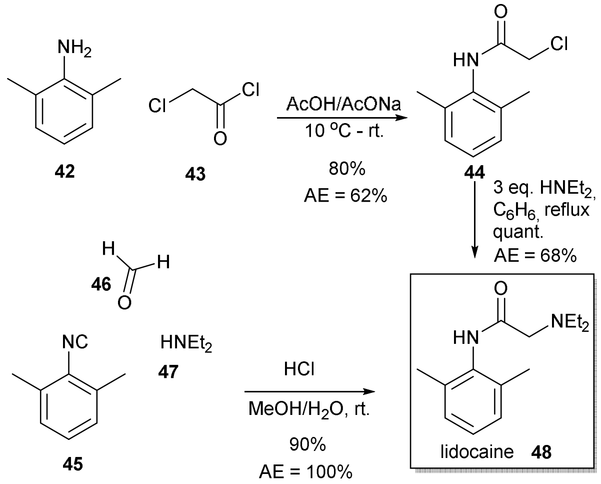
2. Atom Economy

Atom economy (AE) as a green criterion was introduced by Barry Trost in 1990.[54] Based on the examination of the number of atoms in the reagents that do end up in the structure of the product, atom economy is a simple yet useful tool to guide reaction selection. Resorting to chemistry that achieves high incorporation of the starting materials into the final product guarantees a minimal formation of waste by-products and thus represents an efficient strategy towards sustainable synthesis. To give an elementary example in this sense, addition reactions have superior atom economy over substitution reactions.

Since they typically comprise a condensation step and one or more addition steps, multicomponent reactions generally have (near-)perfect atom economy and thus represent suitable synthetic tools for addressing this green chemistry criterion.[55] Quantification reveals that most MCRs have atom economy of at least 80%, with the widely employed Passerini 3CR reaction attaining the theoretical threshold (Table 1). The Ugi 3CR reaction variant with water as acid component also proceeds with perfect atom economy and this advantage was exploited as early as the 1960s[56] in the combinatorial preparation of lidocaine **48** analogues.[57] The traditional preparation of such compounds employs chloroacetyl chloride **43** as a key building block connecting 2,6-dimethyl aniline **42** and diethylamine via classical acylation and alkylation reactions, generating waste mostly in the form of salts resulting from HCl neutralization (Scheme 7).[58]



Scheme 6 Linear vs. multicomponent synthesis of praziquantel.[53]



Scheme 7 Linear vs. multicomponent synthesis of lidocaine.

This is in fact an invariable observation for isocyanide-based multicomponent reactions (IMCR),[9f,14c,59] in which ultimately by-product-free C_{sp}^{3}- and C_{sp}^{2}- bonds to heteroatoms are generated in contrast with substitution approaches that are wasteful by definition. For instance, the virtue of the Ugi 4CR is the construction of two amide bonds. Although a plethora of methods[60] for accessing similar structures is available and countless peptide coupling reagents[61] have been reported, they all suffer from poor atom economy. Thus, where applicable, Ugi-type chemistry should be considered as a viable green alternative for amide bond formation,[62] an issue of crucial significance to the pharmaceutical industry.[63]

The revision of the synthesis of praziquantel **41**, a drug that contains two amide bonds, is illustrative in this respect: the atom economy for the MCR route is 80% with only innocuous water and methanol as by-products. This is appreciably improved compared to the 36% AE value of the commercial route in which HCl neutralization produces salt by-products inherently associated with acylation/alkylation reactions. It is noteworthy that the chemistry employed in this process is actually quite efficient in terms of yield (ranging from 80% to 96% for each of the four steps) and the stoichiometry of most steps is not disproportionate. As a consequence, waste production is essentially the result of the poor atom economy of the reactions. This example nicely reflects how the concepts of waste and atom economy are intertwined and how multicomponent reactions may address these issues.

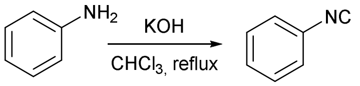
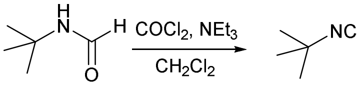
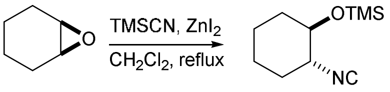
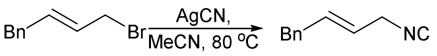
As demonstrated in this example, the intrinsic atom economy of multicomponent reactions markedly influences the greenness of a multistep target-oriented synthesis. The detrimental co-production and accumulation of stoichiometric by-products is impeded not only by a reduction in the number of required steps, but also typically the chemical manipulations that follow the MCR stage are generally more resource-efficient. The Pictet-Spengler cyclization leading directly to praziquantel after the Ugi 4CR condensation (AE = 95%) also has a good atom economy (83%), higher than any of the steps of the linear synthesis (AE ranging from 59% to 69%).

A critical look at this example immediately reveals that the starting materials are not the same for the compared routes; the multicomponent route starts from an isocyanide, while the linear route employs a primary amine. Evidently, the isocyanide (which inherently contains the energy required for the formation of e.g. an amide bond) needs to be prepared, e.g. from the corresponding primary amine. The key question in assessing the 'greenness' of isocyanide-based multicomponent approaches is thus: how green is it to prepare isocyanides? In all fairness, the synthesis of the isocyanide is often the strongest environmental limitation of multicomponent chemistry, which cannot be overlooked.

In particular, if we were to include the synthesis of the isocyanide building block **36** in the praziquantel process greenness evaluation, would our previous conclusions hold? The procedure to make this chemical follows the century-old Hoffmann method[64] refluxing 2-phenylethylamine **29** with chloroform as carbon source and excess sodium hydroxide as base in a water-dichloromethane mixture with phase transfer catalysis giving a 61% yield.[53] This protocol has obvious weaknesses: poor atom economy, substantial waste (although essentially only in the form of sodium chloride), problematic solvent. Furthermore, its scope is extremely limited and the variants designed to address this shortcoming,[65] albeit very diverse and efficient, do not show more empathy to the environment (Table 2). For instance, the highly versatile amine formylation-dehydration method consists of two steps, both atom-inefficient, noncatalytic, using hazardous reagents in excess, typically in chlorinated solvents, often wasting critical elements like phosphorous in the process. Thus, the beauty of the Ugi reaction has in fact a fair price that is paid beforehand in the isocyanide preparation. This is unequivocally the most valid argument holding down the expansion of isocyanide multicomponent reactions as truly green methods.[66]

Filling this gap requires intensive creative efforts, as the isocyanide functionality can generally be introduced via substitution or elimination rather than addition, which is contrary to the green approach. One notable exception refers to β-oxygen substituted isocyanides, that have been shown as early as 1982 to be efficiently prepared by TMSCN addition to epoxides in 100% atom economy.[67] This method has received further refinement and enantioselective versions are currently available.[68] Furthermore, TMSCN can be successfully employed directly as isocyanide equivalent in certain multicomponent reactions, relieving the ecological burden of isocyanide synthesis.[69] The limitations of these methods are obvious, but it is encouraging that progress in the more environmentally acceptable preparation of isocyanides is cumulating.

Table 2 Isocyanide preparative methods

Method	Scheme	AE
Hoffmann[64] 1867		27%
Ugi[70] 1958		21%
Gassman[67] 1982		100%
El Kaim[71] 2009		46%

3. Less Hazardous Synthesis

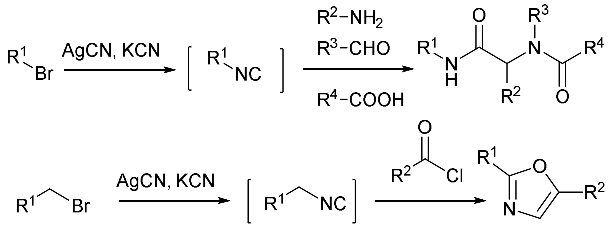
This Green Chemistry principle refers to an aspect of organic synthesis that is often overlooked, i.e., the hazards associated with the chemicals and the chemistry developed. Anastas and Warner phrased this as follows: "wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment".[5]

When it comes to industrial processes, safety is a principal objective and the intrinsic hazards of the required chemicals are closely examined to identify risks. In this respect, multicomponent reactions would generally get the green flag. Although it is a doubtful task to put labels on such diverse chemistry, it can be ascertained that most MCRs employ reactants that are fairly simple and not particularly hazardous: primary/secondary amines, aldehydes/ketones, 1,3-dicarbonyl compounds, carboxylic acids, Michael acceptors. Furthermore, problematic activation agents (e.g. oxalyl chloride, phosgene, thionyl chloride used in carboxylic acid activation) or highly reactive and unstable catalysts (organometallic species) are not characteristic. Air sensitivity of the chemical classes involved in MCRs is not a concern and the absence of moisture is typically not a stringent safety requirement (although in some case it can improve the performance of the reaction).

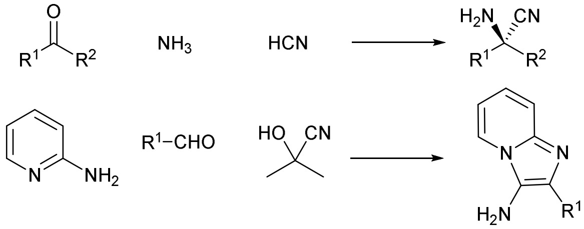
Now what about MCRs based on isocyanides? Unquestionably these peculiar nitrile isomers hold a privileged rank in the development of multicomponent chemistry, but are they correspondingly at the top of the list of chemicals of high concern in this field? Low molecular weight, volatile isocyanides smell notoriously odious[72] and, not surprisingly, their reputation has greatly suffered from their odour properties as well as their name, which suggests toxicity similar to cyanides or nitriles. However, the most comprehensive investigation of isocyanide safety, performed at Bayer AG in the 1960s, did not conclude a general toxicity for this class of compounds.[72] Isocyanides display hazard issues within the reasonable limits in comparison with other categories of chemicals; they can be transported, stored and handled with no particular precautions. Acid workup destroys any isocyanide residues by hydrolysis to formamides. Furthermore, recent methods have emerged to get around isocyanide handling: the so-called "isocyanide-free" protocols preform these infamous reagents *in situ* from activated halide derivatives and a cyanide source and follow-up chemistry proceeds satisfactorily in the same pot.[71,73] However, this methodology brings in discussion the safe use of metal cyanides which is justifiably an issue of major environmental concern (Table 3).

Table 3 Cyanides and multicomponent chemistry

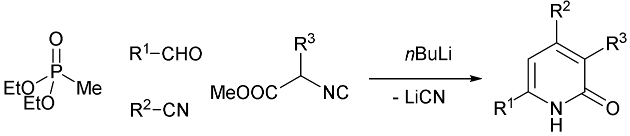
Cyanides for the synthesis of isocyanides[73]



MCRs with cyanides as inputs[74]



MCR generating cyanides[75]



Cyanides are building blocks of tremendous importance in organic synthesis[76] and their contribution to multicomponent chemistry goes far beyond the historic development of the first MCR coupling, the Strecker 3CR (Table 3). The acute toxicity of most cyanide sources (metal or organic) is common knowledge;[77] nevertheless, in certain applications cyanides are irreplaceable and thus there is only restricted room for green design to intervene here. This does not represent a severe violation of the green chemistry principles, as their application should be of course enforced only “wherever practicable”. Thus, with a thorough understanding and responsible control of the hazards, the development of cyanide-based green processes is an undeniable reality: Codexis’ multiple-enzymatic process towards the chiral intermediate required for atorvastatin using sodium cyanide in one of the steps[78] was gratified the Presidential Green Chemistry Challenge award in 2006. Exploration of the seemingly reduced possibilities for greening MCRs with cyanides has recently brought to light encouraging results, primarily with the introduction of potassium hexacyanoferrate(II) as environmentally benign cyanide source.[79] Furthermore, microreactors in flow conditions were validated as viable systems for the safe operation of multicomponent reactions involving cyanides.[80] It can thus be concluded that the design of less hazardous synthetic methodologies is an ongoing preoccupation in MCR research.

4. Safe Chemicals Design

Any chemical product should achieve the function that it has been designed for, but the sustainable view also keeps a close eye on its environmental profile, aiming to minimize it. This principle then clearly has the product molecules and their applications as focus and not the chemistry involved in making them. It is therefore not characteristic to multicomponent reactions or any other category of chemical transformations for that matter. Still, it is relevant to note that the single most important application of MCRs is library generation for drug discovery and design,[9d,9f] where the optimization of the function of the target molecule implicitly incorporates the toxicity component. By the nature of their final application, these MCR products are then safe by design.

5. Benign Solvents and Auxiliaries

Solvents are perhaps the most active area of research in green chemistry, not only because they make up by far the greatest proportion of waste,[81] but also a very significant part of the hazard issues and energy intensity of a process. The choice of solvent is often critical in multicomponent chemistry, as it may markedly influence the course of a reaction, its rate and selectivity. Nevertheless, the versatility of MCRs facilitates the selection of a green compromise solution in most cases.

The efforts of the scientific community towards the application of MCRs in eco-friendly solvents has been comprehensively reviewed in 2012.[82] The surveyed list of novel MCRs or improved variants running in water, ionic liquids, polyethylene glycol polymers (PEGs), $scCO_2$, bio-derived solvents and neat systems is impressive. Furthermore, multicomponent chemistry is well represented in another 2012 review summarizing the progress of organic synthesis in water.[83] The general compatibility of MCRs with ionic liquids was also recently demonstrated.[84] This interest devoted to multicomponent reactions in green chemistry surveys shows the privileged position that this chemistry occupies in the repertoire of sustainable synthetic tools. More importantly, however, they evidence the trend in methodology development towards a cohesive integration of the principles of green chemistry, in this particular case principles 1 and 2 that intrinsically characterize MCRs (high incorporation of reagents in products, minimum waste) with principle 5 (benign solvents).

Furthermore, in multicomponent chemistry simplified product isolation and purification can relieve an appreciable weight of the solvent burden of a process. MCRs products have many attributes that make them amenable to (re)crystallization as method of choice for purification compared to chromatography or distillation:

- ✓ the molecular weight of the product is much higher than that of the starting materials and characteristically the physical state is solid
- ✓ their structure and hence properties (*e.g.* solubility) are notably different than those of impurities or by-products
- ✓ they are either heterocyclic flat molecules with favourable packing in crystals or they are extensively decorated with polar functional groups that can engage in directed intermolecular interactions

On a laboratory scale, these beneficial properties are seldom capitalized and chromatography is frequently employed as the purification technique, but their relevance for industrial application is evident. To continue the praziquantel story, extractive workup was sufficient for advanced product purity in the multicomponent route.[53]

Clearly, the most noteworthy contribution that MCRs can bring to an industrial process as far as solvents are concerned is the global reduction of solvent levels gained by improving the step economy.

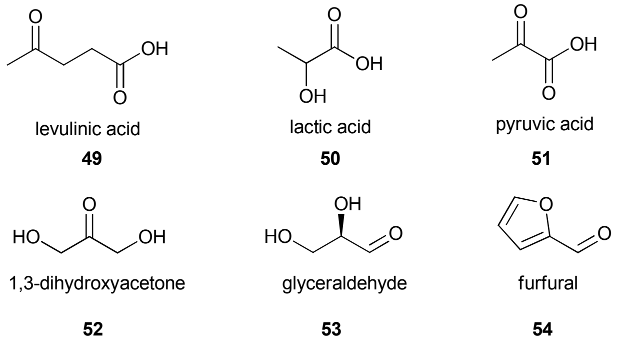
6. Energy Efficiency

Although we should be cautious to generalize, most multicomponent reactions proceed under mild conditions, typically at ambient temperatures and pressures.[9b] Occasionally, heating is imperative[85] or merely beneficial in productivity[86] while cooling prevents side product formation,[87] but extreme reaction temperatures are not at all characteristic. Furthermore, the strict exclusion of air or moisture is not necessary and thus the energy intensive solvent distillation under inert gas is redundant. Many MCRs are optimized under microwave[88] or more recently ultrasound[89] irradiation, energy sources preferable to thermal heating.[90] Moreover, the demonstrated compatibility of multicomponent chemistry with continuous operation in microreactors opens new avenues for the optimization of the process energy intensity.[91]

From a mechanistic point of view, multicomponent reactions are frequently sequences of elementary equilibrium stages ultimately pushed towards the product side by a thermodynamic driving force, such as C(II) formal oxidation to C(IV) in isocyanides, cyclization or aromatization.[65] This precludes the necessity of harsh reaction conditions on one hand and heavy heat transfer systems to absorb the released heat on the other.

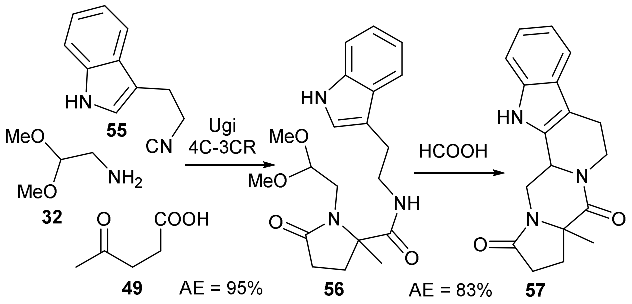
7. Renewable Feedstocks

Life on Earth can only be sustained if the resources that we use to satisfy our daily needs are renewable. When it comes to chemicals, there is much to be done here: all chemical industries vastly rely on raw materials derived from oil and natural gas. Still, the repertoire of renewable chemical inputs is steadily growing in parallel with the technological progress.[92] Most of the provided building blocks are quite elementary but do display the required reactivity handles to enable the construction of higher-complexity products (Scheme 8).



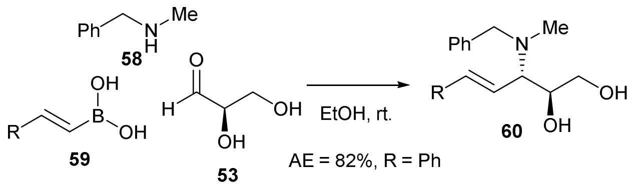
Scheme 8 Renewable building blocks for multicomponent chemistry.

Multicomponent reactions can make valuable use of these building blocks towards molecular complexity. For example, the bifunctional character of levulinic acid **49** renders this input interesting for Ugi-type chemistry generating γ-lactams;[93] coupled with a Pictet-Spengler cyclization, synthetic indole alkaloids **57** can be easily accessed (Scheme 9).[94]



Scheme 9 Levulinic acid as input in MCRs (Dömling[94]).

Another interesting study refers to the application of fatty acids and lipid-derived isocyanides in an Ugi 4CR to prepare unique types of ceramide and glycolipid architectures after the conventional attachment of a sugar residue.[95] The multicomponent approach as a tool to achieve carbohydrate-steroid conjugation has also been validated recently, again by exploration of the formidably versatile Ugi reaction.[96] In fact, sugar-based inputs have been intensively studied in Ugi condensations in the attempt to devise stereoselective versions of this important reaction but successful examples are still scarce.[97] On the other hand, reliable ways to induce diastereoselectivity in the Petasis 3CR reaction were not as intricate to develop, and sugars as well as other renewable feedstocks have found utility in this respect. Using such methodology, Wong put forward a synthetic platform towards enantioenriched sialic acids and derivatives[98] based on the pioneering studies of Petasis[99] with α-hydroxy aldehydes such as glyceraldehyde **53** (Scheme 10). Pyruvic acid[100] and 1,3-dihydroxyacetone[101] are also renewable chemicals routinely employed in Petasis 3CR.

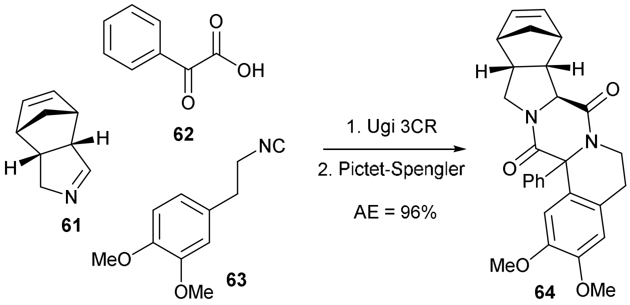


Scheme 10 Diastereoselective Petasis 3CR with glycerinaldehyde.[99]

To conclude, with a limited set of modestly functionalized chemicals that biomass processing technology can supply at the moment, it is daring to imagine that renewable starting materials will soon find a broad application in the chemical industry, but progress in this direction is building up steadily.[102]

8. Reduced Use of Derivatives

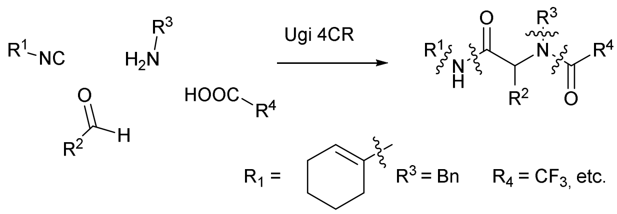
Protecting groups are still ubiquitously used in organic synthesis of more complex molecules for the advanced applications in medicine, catalysis or materials. These protecting group strategies imply supplementary stages for their introduction and removal and as protecting groups are not incorporated in end products they represent waste by definition. As MCRs proceed with high chemoselectivity and often a broad scope of functional groups are tolerated the use of protecting groups is usually unnecessary. In addition, multiple bonds are formed in a single operation, which would most likely involve the use of protecting groups in a comparable linear route. Moreover, the generally mild reaction conditions minimize problems resulting from spectator functional groups. A highlight example in this respect is the concise protecting group-free synthesis route that our group developed towards alkaloid scaffolds **64** based on an Ugi-Joullié – Pictet-Spengler sequence.[103]



Scheme 11 Multicomponent preparation of synthetic alkaloids (Orru[103]).

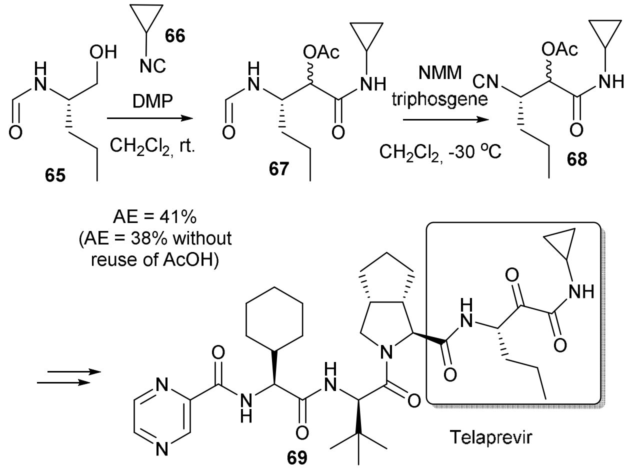
The complete exclusion of protecting groups is still highly challenging, especially when MCR sequences are employed to access high complexity products. A frequently used strategy is generically known as the reaction-deprotection-cyclization strategy (for Ugi-type condensations, Ugi-deprotection-cyclization, UDC): the conflicting reactivity of a functional group in one of the MCR inputs is masked via protection and unleashed after the MCR as basis for the generation of an extremely rich repertoire of useful scaffolds. Although not completely aligned with the 8th green chemistry principle dealing with derivatization, the overall environmental impact of such processes is significantly reduced. As the deprotection is achieved in the same pot with the reaction that it triggers such a route is still concise compared to linear alternatives (that would possibly also make use of protecting/activating groups). As a generic approach, Boc-protection delays the nucleophilic attack of an amine but many other related tactics are used in UDC.[104] Taking a closer look at the praziquantel example once more, the MCR route is in fact a UDC, this time with an aldehyde functionality numbed by acetalization.

When protecting reactive functionalities cannot be avoided, multicomponent reactions can add an additional interesting twist to green synthesis methodology. MCRs such as the Ugi 4CR and Passerini 3CR can serve to introduce protecting groups at desired positions with the correct choice of inputs. Chemically, this is achieved in a fundamentally different way with superior atom economy (*i.e.* through the reactivity of the isocyanide) than conventional methods employing activated carbonyls and excess of bases (Scheme 12).



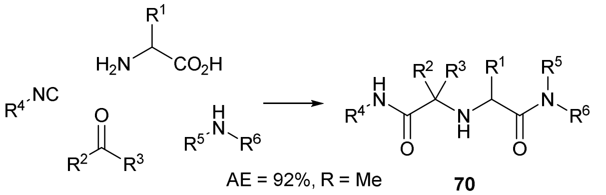
Scheme 12 Introducing protecting groups with Ugi chemistry.

For instance, the use of trifluoroacetic acid as the acid component in the Ugi 4CR[105] provides a convenient protection of the secondary amine (see also Scheme 1). Formic acid affords a cleavable formamide,[106] whereas the newly generated acetate in a Passerini 3CR masks the reactivity of an alcohol group prior to its required late stage oxidation.[107] Ingeniously, the source of acetic acid in this latter example was in fact the Dess-Martin periodinane (DMP) employed in the preparation of the aldehyde component for the MCR in an original attempt to improve the infamously low atom economy of this alcohol oxidation method (the atom utilization increases from 38% to 41%). The sequence (Scheme 13) was integrated in a highly concise preparation of the antihepatitis drug telaprevir[108] **69** that has become a landmark of the application of multicomponent reactions in green production of complex medicines.[109]



Scheme 13 MCR chemistry in the preparation of telaprevir (Ruijter[107]).

To conclude the impact of the MCR approach on diminishing the use of protecting groups/auxiliaries in synthesis, let us examine the Ugi 5C-4CR variant discovered in the group of Dömling (Scheme 14).[110] This reaction combines α-amino acids, secondary amines, aldehydes or ketones and isocyanides to yield in one step peptide-like structures **70** with fair efficiency. Alternatively, conventional chemistry would assemble this densely C-N decorated scaffold with copious use of activating agents, stoichiometric bases and carboxyl/amine protecting groups, in a multistep highly wasteful process. Multicomponent chemistry thus goes hand in hand with the optimal efficiency in the use of derivatization protocols in organic synthesis.

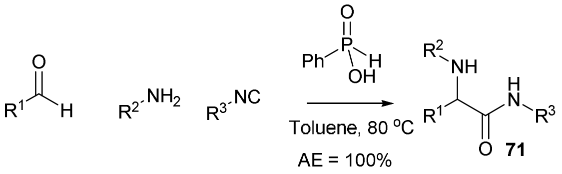


Scheme 14 Novel 5-center 4-component MCR discovered by Dömling.[110]

9. Catalysis

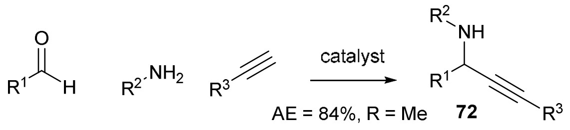
Catalysis is at the heart of the green chemistry philosophy. Catalysts enable slow reactions to proceed and drastically reduce the energy intensity of a process. When the chemistry involved allows it, the catalytic version of a process invariably generates less waste than the version using stoichiometric activating reagents. Some classes of MCRs (*e.g.* Ugi-type) can be advantageously run under mild conditions without the need of any catalyst, but for other reaction types catalysis has indeed often proven beneficial and sometimes indispensable. The development of efficient catalytic systems represents one of the most active areas in green multicomponent chemistry research.[111] Catalysis in MCRs diverges in multiple directions: Brønsted[112] and Lewis acids,[113] organocatalysts,[114] metal complexes,[115] heterogenous catalysts,[116] biocatalysts[117] and (magnetically recoverable) nanoparticles[116,118] have been employed.

Given the central position that imines occupy in multicomponent chemistry, their catalytic activation towards nucleophilic attack constitutes a major research focus. Phenyl phosphinic acid was found to be an excellent catalyst for the 100% atom economical Ugi 3CR variant between aldehydes, primary amines and isocyanides yielding α-amino amides **71** (Scheme 15).[112h] Other Brønsted acids have been shown to promote this synthetically useful condensation and its extension to the four-component one-pot preparation of α-amino amidines.[112a] The greenness of this transformation was improved even further by the group of Kumar who demonstrated the efficiency of boric acid to catalyse the reaction in aqueous media.[112e] Going beyond Brønsted acid catalysis, this Ugi 3-component coupling can be also promoted by Lewis acids.[113a]



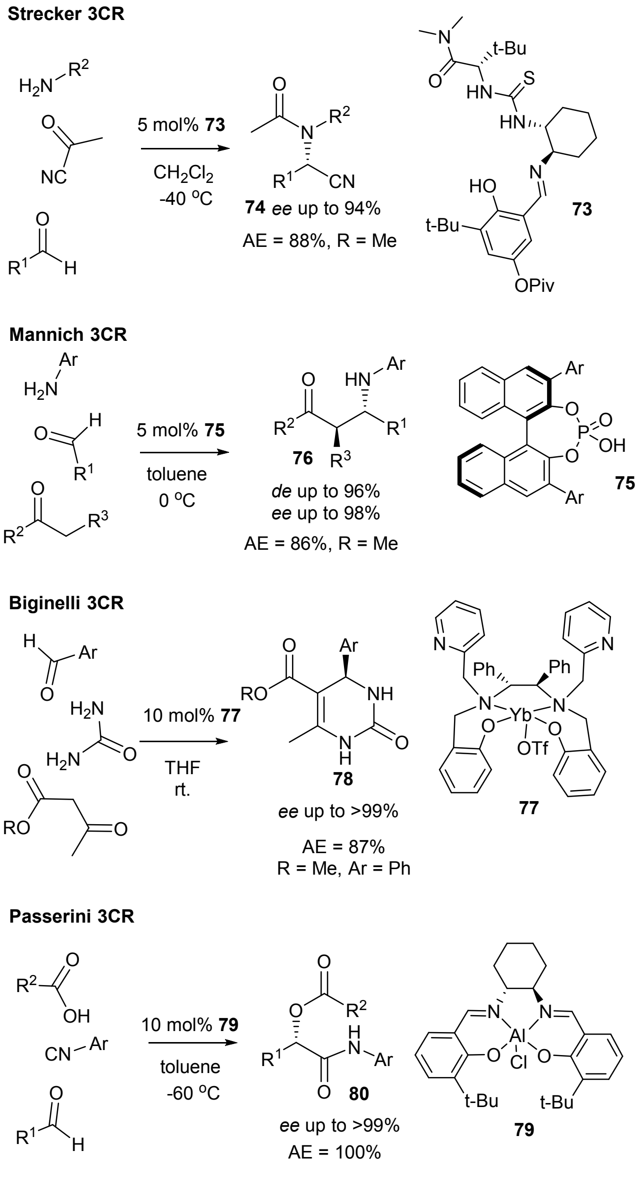
Scheme 15 Catalytic Ugi 3-component reaction (List[112h]).

From the green perspective, resin-bound catalysts have a higher practical impact due to their easy separation and recycling compared to molecular Brønsted acids. In this respect, Amberlyst A21 was successfully applied in the eco-friendly preparation of the interesting heterocyclic scaffolds dihydropyrano[2,3-*c*]-pyrazoles.[112b] Continuing with easily recoverable heterogenous catalysts, the green preparation of propargylic amines **72** via the A^3 coupling reaction (amine, aldehyde, alkyne, Scheme 16) has received considerable attention. Two recent examples highlight the suitability of heterogenized gold complexes as well as copper nanoparticles supported on TiO_2 for the efficient three-component synthesis of propargylic amines at very low catalyst loadings. Similarly, magnetic catalysts are popular choices in green multicomponent synthesis, for instance in the preparation of pharmaceutically relevant diazepines[118b,118c] or dihydropyridines via the Hantzsch condensation.[118a] Under oxidative conditions, these so-called Hantzsch esters can be oxidized to pyridines, a property that was exploited by Constantieux *et al.* to prepare single regioisomers of polysubstituted pyridines in one-pot, under dual molecular sieves and activated carbon catalysis.[116]



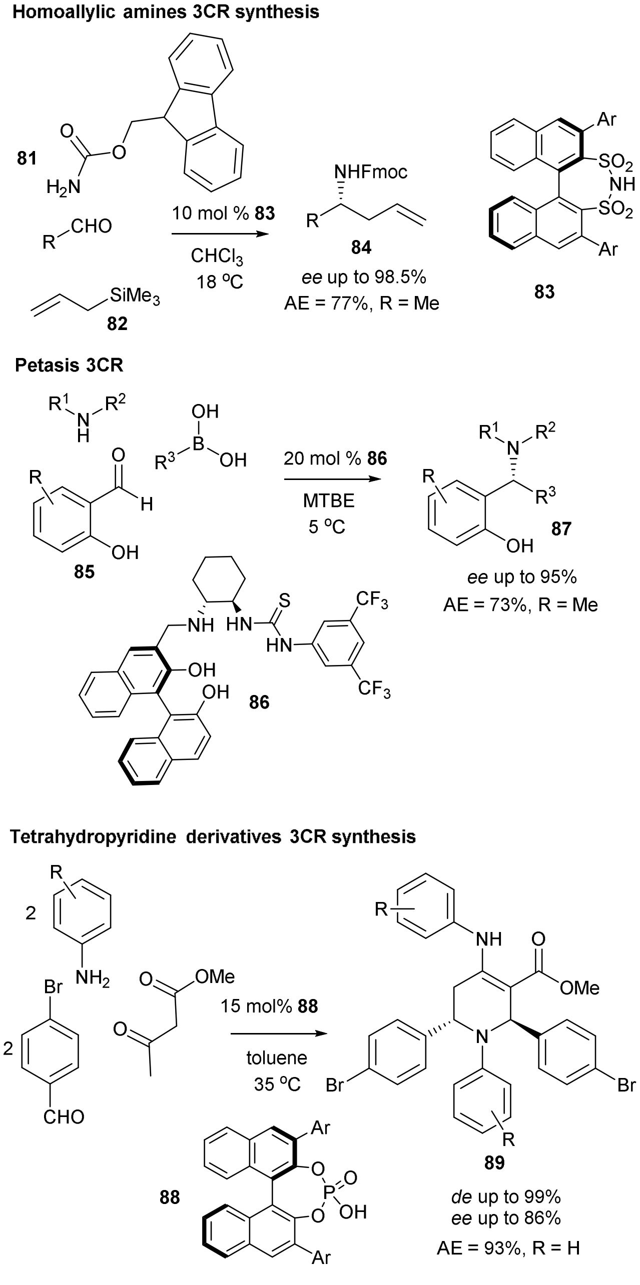
Scheme 16 3-component coupling of aldehydes, amines and alkynes.

As for chiral compounds, asymmetric synthesis is clearly the green approach compared to wasteful resolution of racemic mixtures. In many MCRs new chiral centres are created and thus the quest for enantioselectivity is a major preoccupation in multicomponent chemistry.[15,119] Proficient solutions can be provided by organocatalysis, a discipline in rapid development also due to the recognition of its green virtues.[120] In the past decade, organocatalytic multicomponent protocols embedding green concepts have been implemented for many of the known MCRs classes. Scheme 17 lists a few important examples of catalytic asymmetric MCRs using organocatalysis or chiral Lewis complexes .[121]



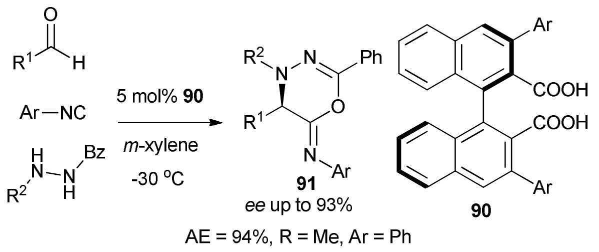
Scheme 17 Catalytic enantioselective versions of some representative MCRs.

To cite just a few recent success stories of organocatalysis and MCRs, chiral phosphoric acids **88** have been applied in the synthesis of enantioenriched biologically relevant tetrahydropyridines,[114a,114c] a thiourea-BINOL catalyst **86** promotes the enantioselective Petasis reaction[114d] and a chiral disulfonimide **83** allows the preparation of homoallylic amines **84** in optically pure form[114b] (Scheme 18). Numerous other examples testify that catalytic asymmetric multicomponent chemistry is an emerging research field.[122]



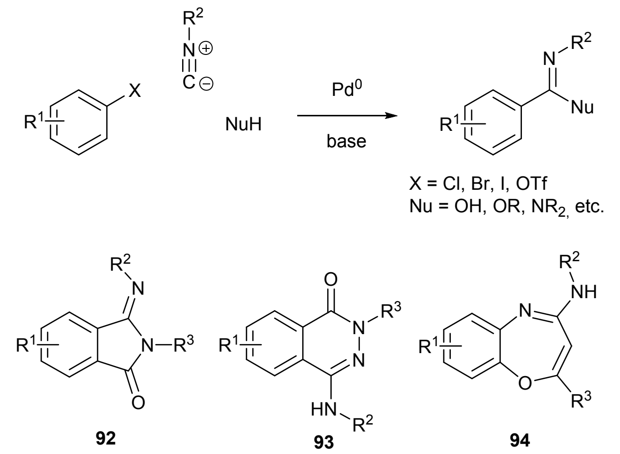
Scheme 18 Recent progress in organocatalytic multicomponent chemistry

Despite tremendous progress in this field, a milestone in MCR chemistry remains to be resolved: the catalytic enantioselective Ugi 4CR reaction. Recent achievements testify for the engagement of researchers to meet this challenge,[114e-g] although a general protocol is still the key missing piece in the puzzle of organocatalytic MCRs (Scheme 19).



Scheme 19 Novel organocatalytic Ugi-type 3CR (Maruoka[114e]).

A distinct class of catalytic MCRs arises from metal-mediated cross-coupling processes involving isocyanide insertion. Exploiting the special reactivity of the "divalent" carbon in isocyanides, this chemistry is essentially an extension of the well-acknowledged cross-coupling methodology in which the isocyanide is captured in between the coupling partners (Scheme 20).



Scheme 20 Palladium catalyzed isocyanide insertion and representative MCR products.

Such processes are inherently multicomponent, although many significant advances are actually two component intramolecular variants. Various catalytic systems have been successfully probed in this chemistry[123] and in particular palladium has opened new horizons.[124] Despite the aforementioned sustainability issues of isocyanides and those relating to the use of transition metals such as palladium, this type of chemistry provides by far the most efficient and sustainable synthetic routes toward the resulting complex heterocyclic scaffolds.

Biocatalysts provide a truly sustainable alternative to e.g. transition metal catalysts and hold unprecedented potential in green synthesis.[38] Surprisingly (or not), enzymes have found application even in promoting multicomponent reactions, with numerous and diverse examples in recent literature.[117] Unquestionably it is enzyme promiscuity and not native function behind these experimental results, but a closer inspection of these benchmark examples easily correlates mechanistically the enzyme catalytic machinery with the chemistry at hand: imine formation, nucleophilic addition, dehydration, hydrolysis, etc. Predicting the extent of the future superposition of biocatalysis and MCR is difficult, but enzymes may just be the long sought answer to some of the crucial issues in multicomponent chemisty (*e.g.* enantioselective Ugi 4CR[117d]).

10. Design for Degradation

Just like the 4th principle, this concept refers to product and not process design and therefore it is less meaningful to assess the capabilities of a particular chemistry from this perspective. Nevertheless, a brief analysis of typical MCR products emphasizes the high density of carbon-heteroatom bonds (with amides and esters very well represented) which are susceptible to degradation by microorganisms. Conversely, a great deal of structures are (aromatic) heterocycles that are presumably problematic for the environment from the biodegradability point of view.

11. Real-Time Analysis for Pollution Control

The last two green chemistry principles are primarily process-oriented and find the most relevance in industrial applications. Real-time monitoring of what goes on in a (multi cubic meter) reactor is indispensable in accident prevention and pollution control, as the signalled anomalies can be promptly managed. One highly reliable and yet generally overlooked way to achieve this is by resorting to continuous flow organic synthesis. Flow chemistry is in fact a crucial technique for green process development and it provides many other appealing opportunities besides the intrinsic compatibility with real-time process analysis, like in heat transfer issues connected to a given reaction.[125] But can multicomponent reactions be run under flow conditions? Deceptively a rather unfamiliar fact, the merger of MCRs and flow chemistry is indeed not only a well established methodology[126] but also an acknowledged essential prospect for the future of modern organic synthesis.[127]

12. Inherently Safe Chemistry for Accident Prevention

Dissecting all the facets of safety in an area as diverse as multicomponent chemistry is a daunting task. Nevertheless, reviewing the application of the previous green chemistry principles to MCRs emphasizes their good overall behaviour when it comes to safety: high temperatures or pressures are not required, highly toxic or corrosive reagents are only exceptionally used, automation in flow reactors with *in situ* monitoring is applicable. The reactions are characteristically only moderately exothermic and comparatively slow, and the probability for runaways is accordingly reduced. Multicomponent chemistry is robust, scalable and operationally simple and thus a justified option to consider in inherently safe process design. Still, its application demands increased awareness on the often crucial importance of details (*e.g.* order and moment of addition of reagents) that may arise from the complex sequence of chemical events taking place in order to correctly assemble the desired product.

Summary and outlook

The evaluation of the performance of multicomponent reactions with regard to the green chemistry recommendations ascertains good compatibility of this chemistry with sustainable organic synthesis. It is noteworthy that the majority of the green criteria are intrinsic characteristics of MCRs. Some of the gaps have been clearly identified and the quest for solutions is ongoing. Most importantly, examples of successful union of several green methods (MCRs and biocatalysis, MCRs and green solvents, MCRs in flow) are steadily building up and recommend MCRs for the design of environmentally-benign chemical processes: indeed, the power of the green chemistry principles to influence the impact that the chemical industry has on our planet is fully unleashed when they are coherently integrated.

In this respect, the green performance of multicomponent chemistry (or, more precisely, IMCRs) would benefit from the improvement of preparative methods for isocyanides. The synthetic organic community is active in solving this problem and a remarkable step forward was achieved by integrating isocyanide generation, extraction and purification with the subsequent multicomponent reaction in a continuous flow microfluidic setup.[128] This system allows the diverse chemistry of isocyanide-based MCRs to be applied in a safe and robust setup avoiding direct manipulation of isocyanide inputs. Another recent conceptual advance in this direction describes the direct synthesis of isocyanides from tertiary alcohol derivatives and TMSCN under Lewis acid catalysis.[129] These approaches score high in terms of productivity, but the issues of waste remain to be tackled.

Multicomponent reactions thus represent valuable tools in the repertoire of sustainable synthetic methods and their synergistic utilization with other green technologies would bring organic chemists one step closer to the ideal synthesis. Almost as old as Wöhler’s preparation of urea, the diverse and versatile multicomponent chemistry has the potential to be a modern answer to *how* to perform sustainable organic synthesis on both laboratory and industrial scale.

Acknowledgements

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List of abbreviations

2,2'-bipy	2,2'-bipyridine
AE	atom economy
binol	1,1'-bi-2-naphthol
Boc	*tert*-butyloxycarbonyl
Bz	benzoyl
DMP	Dess-Martin periodinane
E_{mw}	environmental factor based on molecular weight
Fmoc	fluorenylmethyloxycarbonyl
Hmim	1-methylimidazolium
IMCR	isocyanide-based multicomponent reactions
MAO-N	monoamine oxidase
MCR	multicomponent reaction
MS	molecular sieves
NMM	*N*-methylmorpholine
PEG	polyethylene glycol
Piv	pivaloyl
PZQ	praziquantel
$scCO_2$	supercritical carbon dioxide
TBHP	*tert*-butylhydroperoxide
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TIPS	triisopropylsilyl
TMSCN	trimethylsilyl cyanide
Ugi 4C-3CR	Ugi 4-center 3-component reaction
UDC	Ugi-deprotection-cyclization
WHO	World Health Organization
Z	benzyloxycarbonyl

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Department of Chemistry & Pharmaceutical Sciences and Amsterdam
Institute for Molecules, Medicines and Systems (AIMMS),
VU University Amsterdam, De Boelelaan 1083, 1081 HV Amsterdam,
The Netherlands. E-mail: e.ruijter@vu.nl; r.v.a.orru@vu.nl;
Fax: +31 20 598 7488; Tel: +31 20 598 7447/7462