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Multicomponent Reactions for a Sustainable Organic Synthesis

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1.1 Introduction

1.1.1 Green Chemistry and Sustainability

The 12 Green Chemistry principles, theorized in 1998 by Paul Anastas and John Warner, have been a key reference for generations of chemists to achieve a more responsible development of chemical processes and products [1]. The first principle, stating that "*It is better to prevent waste than to treat or clean up waste after it has been created*," represents the reading key of all the efforts done by the scientific community so far: "reducing or, even better, preventing waste" is a must in the optimization of current chemical processes. The other principles somehow indicate the fields of intervention, such as the need for efficient metrics to compare the greenness of different processes, as well as the need for safer syntheses, chemicals, solvents, and auxiliaries (even better if the latter two can be either minimized or avoided). Renewable feedstocks should be preferred when their exploitation is viable, and renewable energy sources, such as solar-derived light and electricity, have become increasingly attractive. Derivatization (including the use of protecting groups) should be made unnecessary via either robust and versatile chemistry or efficient and selective catalysis, preferably not based on precious metals (the performance of abundant base-metal catalysts must be evaluated). Alternatively, organic catalysts are a relevant topic in sustainability-oriented research, as also witnessed by the 2021 Nobel Prize shared by Prof. B. List and D. MacMillan for asymmetric organocatalysis. Technological advances are also essential in: (1) enabling the design of (bio)degradable products, which should not persist in the environment, and (2) providing high-performance instrumentation

suitable for real-time analysis of chemical processes intended to increase their safety and prevent pollution and accidents. It follows that *Green Chemistry* defines how to achieve *sustainability*, which is the ultimate goal and applies to different endeavors, notably human health and ecosystems [2]. In between, *green engineering* bridges these two concepts by taking a broader look at manufacturing systems (feasibility, economics, green metrics) via life cycle analysis (LCA).

1.1.2 Green Chemistry Features of Multicomponent Reactions

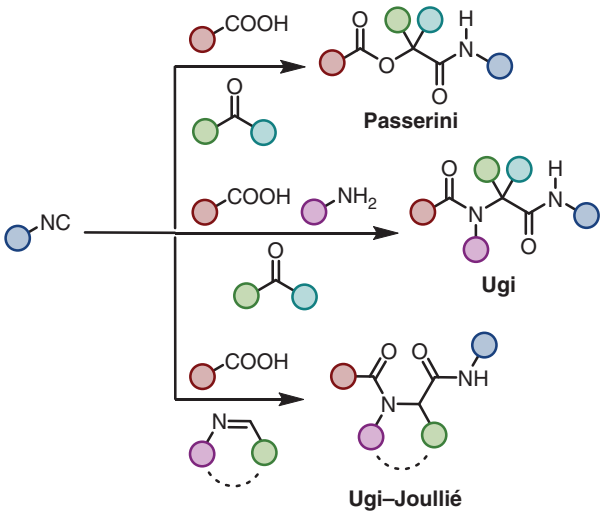
Multicomponent reactions (MCRs) are defined as "*reactions where more than two starting materials are converted to a product, and the product contains most of atoms of the educts*" [3]. This definition readily highlights some hallmarks of MCRs, such as atom economy and convergence. Atom economy is a valid green metric to evaluate waste minimization and is calculated as the ratio between the molecular weight of the product and the molecular weight(s) of (all) the starting material(s) [4, 5]. Convergence is a good parameter to compare the synthetic efficiency of different processes [6]: let's consider a three-step synthesis toward product ABCD. Notwithstanding a 90% yield for each step, the overall yield is 72%. If the product ABCD is assembled via a convergent approach featuring the parallel synthesis of AB and CD, followed by the coupling of AB and CD, the overall yield is 81%. This implies that convergent processes lead, for their intimate nature, to higher yields with respect to linear syntheses. By involving at least three different components, MCRs are also able to generate molecular diversity and complexity. More in detail, diversity is enabled by the availability (at reasonable prices) of as many different starting materials as possible, whereas greater complexity can be achieved by coupling a multicomponent condensation with additional (one-pot two-step) reactions, such as acid-, base-, or metal-promoted (macro)cyclizations [7, 8]. Furthermore, MCRs represent reactions integrated over time and space, being also defined as "*mix-and-go*" reactions. They indeed rely on a set of different sub-reactions occurring in the same flask in a given, well-defined sequence toward the formation of one final product [3]. Their ease of performance makes them excellent candidates for combinatorial chemistry, showing very often exquisite substrate scope in high-throughput experimentation. Importantly, they can be performed at a nanogram scale, e.g., in automated synthetic platforms [9–11], or up to a kilogram scale in the production of active pharmaceutical ingredients (APIs). As for manufacturing processes, guidelines to improve and/or change a synthetic route based on so-called SELECT criteria are provided [12]: **S**, safety to run on scale, with minimum **E**, environmental impact, **L**, legal, no infringement of intellectual property, **E**, economics (meet the development budget and the target cost of goods), **C**, control of operating parameters, **T**, throughput (availability of raw materials, space-time yields). MCRs can excellently meet all the SELECT criteria. However, complementing other robust methodologies representing dominant reactions in *hit* and *lead* identification and optimization (e.g., amide bond formation and Suzuki–Miyaura couplings) [13], MCRs are an appealing choice in medicinal chemistry [14–16]. Several reactions pertain to the class of MCRs,

including Mannich, Biginelli, Hantzsch, Strecker, etc. [17–21]. Notably, quite often such processes are instrumental to the forging of heterocyclic scaffolds [22].

Overall, in a more holistic view, MCRs can cross some areas for improvement in the pursuit of global sustainability as indicated by the UN Sustainable Development Goals (SDGs), such as: clean energy (goal 7), industry, innovation, and infrastructure (goal 9), responsible consumption and production (goal 12), climate action (goal 13), life below water (goal 14) and life on land (goal 15), whereas the present chapter and the whole current book project aims at contributing to quality education (goal 4).

Despite their great potential, MCRs are still perfectible. Their innate green chemistry features can be dramatically improved by exploiting enabling technologies such as photochemistry [23–28], electrochemistry [24, 29, 30], sonochemistry [31–33], mechanochemistry [34], microwave chemistry [35, 36], flow chemistry [37, 38], and biocatalysis [39–41]. Additionally, such processes can be carried out under solvent-free conditions [42] or in water [43–45], fostering the green character of the inherent transformations. Isocyanides are key intermediates in most MCRs [46, 47]. The reason is due to the extraordinary reactivity of the isocyano group that allows for a unique pattern where both an electrophile and a nucleophile react at the same atom to form the so-called α-adduct. Scheme 1.1 collects the most important MCRs arising from isocyanides.

The aim of this chapter is to discuss the improvement in sustainability (when possible) in representative MCRs, making use of green media (e.g., water or solvent-free conditions) or due to the adoption of enabling technologies. In particular, the discussion will be focused on MCRs involving isocyanides as the reaction partners (e.g., Passerini, Ugi, and the Ugi–Joullié reactions, Scheme 1.1) [48]. The selection is



Scheme 1.1 Isocyanides in MCRs.

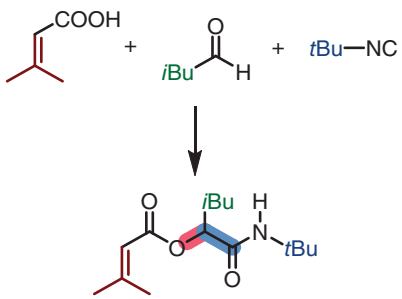
a personal choice of the authors and does not pretend to be exhaustive. For a more comprehensive treatment of the topics, the reader is referred to the respective chapters of the current book and references cited therein.

1.2 Passerini Reaction

The Passerini reaction is the first isocyanide-based MCR (IMCR) considered (Scheme 1.1). The process is the one-pot construction of an α-acyloxy carboxamide by the combination of an isocyanide, a carbonyl derivative (either an aldehyde or a ketone), and a carboxylic acid, followed by the Mumm rearrangement [49–54]. The use of water as the solvent (in place of troublesome organic media) has been demonstrated to have a beneficial effect on the reaction outcome. In fact, adduct **1** was obtained in only 45% yield (at 50% conversion) in DCM after 18 hours of reaction (Scheme 1.2). On the contrary, the adoption of water led to an almost quantitative yield at 100% conversion in only 3.5 hours [43]. Moreover, **1** is poorly soluble in water, allowing for its trivial isolation in good purity.

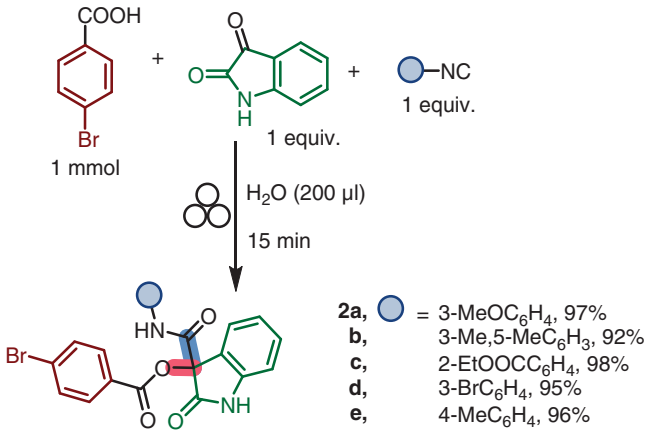
Mechanochemistry may be helpful in performing the Passerini 3-CR (three-component reaction), particularly when the use of bulky ketones (or isocyanides) renders the reaction slow or ineffective. Thus, the preparation of biologically relevant oxindoles **2a–e** (Scheme 1.3) characterized by a quaternary benzylic center, starting from benzoic acids, isatin, and substituted isocyanides, was initially tested under solvent-free conditions [55]. A high-speed vibration milling with a double agate ball (6 mm diameter) in an agate jar was adopted in this case. The process was, however, unsuccessful and required a liquid-assisted grinding (LAG) agent. Among these agents, water was found superior with respect to other common organic solvents (e.g., toluene and methanol). By adopting this simple protocol, Passerini adducts **2a–e** were formed in very high yields (>90%) after only 10–15 minutes [55].

Solvent-free high-speed ball milling (HSBM) conditions were, however, successfully applied to the preparation of α-acyloxy carboxamides starting from benzoic acids, benzaldehydes, and *t*-butyl isocyanide. Very eco-friendly



1, 45% (18 h, 50% conversion, DCM)
95% (3.5 h, 100% conversion, H_2O)

Scheme 1.2 Rate acceleration in water in the synthesis of **1**.



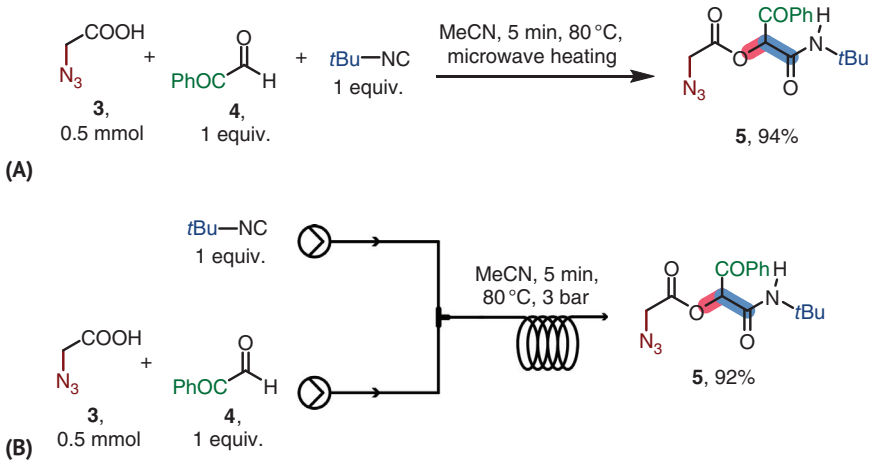
Scheme 1.3 Mechanochemical preparation of oxindoles **2a–e**.

conditions, characterized by high atom economy with no generation of toxic by-products, were possible thanks to this approach [56]. Similarly, a solvent-free Passerini reaction using grinding led to azulene derivatives bearing a carboxamide unit [57].

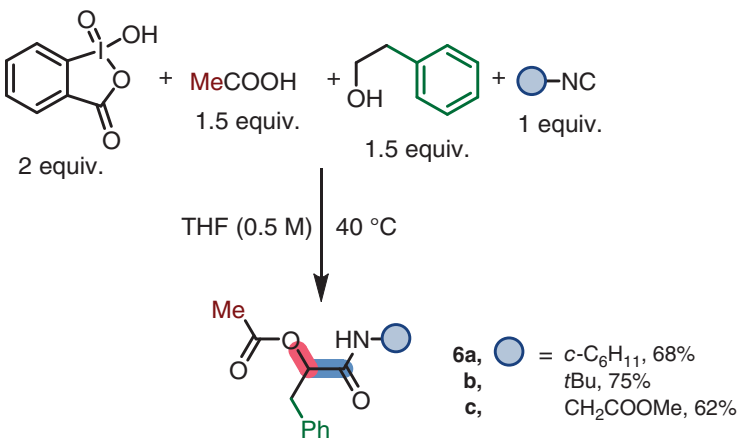
Solvent-free conditions were beneficial even when the preparation of the Passerini adducts was realized under microwave irradiation (the reaction was completed within 30 seconds at 120 °C) [58] or under ultrasound-promoted conditions [59]. In the latter case, sterically congested Passerini adducts were formed and, while the usual reaction conditions (with DCM as the solvent) required a very long reaction time (more than two weeks), the adoption of sonochemistry (sonic horn power = 1200 W, irradiation frequency = 25 kHz) allowed to obtain the hoped for amides in less than 40 minutes under solvent-free conditions [59].

The synthesis of α-acyloxy ketones (having a structural motif present in several APIs or natural products) may be pursued by a Passerini reaction having recourse again to microwave irradiation, but also under continuous flow conditions [60]. Flow chemistry is a key enabling technology toward the design of sustainable transformations, including isocyanide-based multicomponent processes, and holds significant promise for the scale-up and industrialization of the underlying synthetic protocols [37, 38]. Thus, α-acyloxy ketones containing an α-carboxamide moiety may be easily accessed in a one-pot process starting from arylglyoxal **4**, an isocyanide, and a substituted carboxylic acid (e.g., azidoacetic acid **3**, Scheme 1.4). Gratifyingly, it was found that the reaction was completed in only five minutes with a similar reproducible yield (92–94%), both using microwave irradiation (Scheme 1.4A) or under flow conditions (Scheme 1.4B). Moreover, the Passerini adduct **5** was easily isolated by simple elimination of the solvent from the resulting mixture.

A different approach to improve the greenness of the Passerini reaction is the *in situ* preparation of the carbonyl partner from the corresponding alcohol. Such a novel protocol is particularly useful when the carbonyl derivative (mostly, aldehydes) is difficult to handle or unstable, thus increasing the overall synthetic



Scheme 1.4 Synthesis of α-acyloxy ketones via Passerini 3-CR (A) upon microwave heating under batch conditions, and (B) under continuous flow conditions.



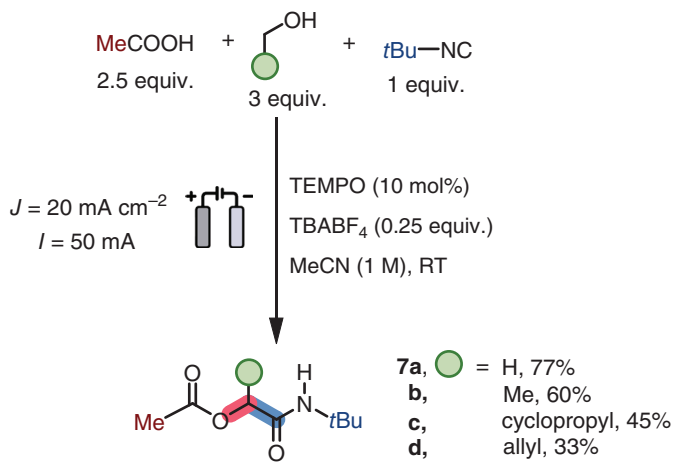
Scheme 1.5 One-pot oxidative Passerini reaction.

efficiency and versatility of the described MCR. One of the first examples pertaining to this strategy involved an alcohol oxidation promoted by 2-iodoxybenzoic acid (IBX, Scheme 1.5) [61]. Thus, the reaction partners were added to a suspension of IBX in tetrahydrofuran (THF) and heated at 40 °C to deliver compounds **6a–c** in good to satisfying yields. Such an oxidative Passerini three-component reaction (P-3CR) was carried out under heterogeneous conditions due to the poor solubility of IBX in the chosen reaction medium. This aspect prevented any undesirable oxidation of the isocyanide and allowed for the easy separation of IBX and its reduced form, iodosobenzoic acid (IBA), by simple filtration through a celite pad [61].

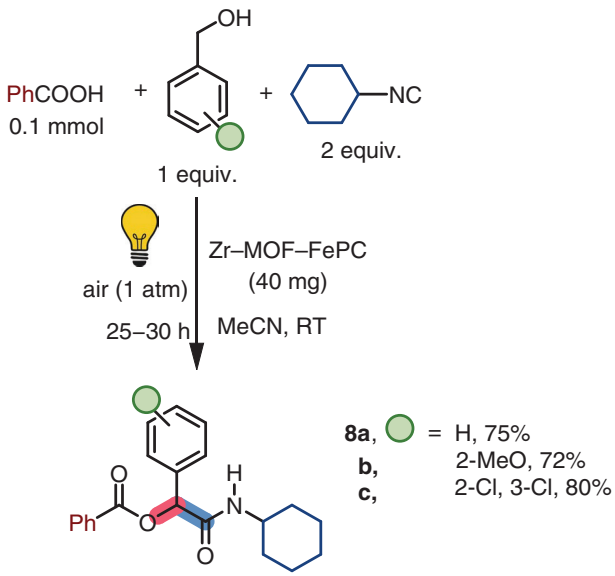
A more elegant way to generate the carbonyl partner *in situ* is by having recourse to electrochemistry. This technique allows for the fine-tuning of reaction pathways by modulating the redox state of reactants, avoiding the generation of toxic by-products (often associated with the use of stoichiometric oxidants) and thus promoting atom economy and reducing hazardous waste streams.

In this case, the aldehyde required for the reaction has been obtained from the corresponding alcohol by an indirect anodic oxidation, where (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) had the role of key redox mediator (Scheme 1.6). The electrochemical apparatus consisted of an undivided cell having a carbon graphite anode and a stainless-steel cathode; the reaction was carried out under amperostatic conditions (20 mA cm^{-2}) with the help of tetra-*n*-butylammonium tetrafluoroborate as supporting electrolyte. Then, α-acyloxycarboxamides **7a–d** were formed in variable yields depending on the alcohol used [62].

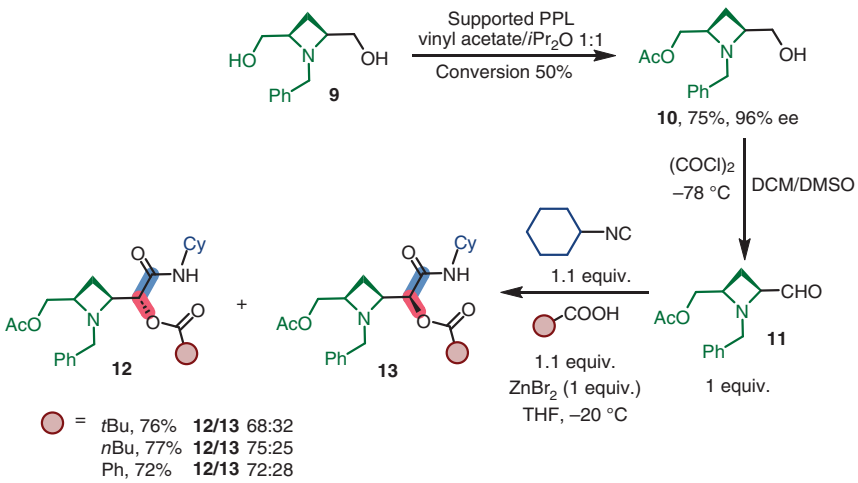
The oxidation of alcohols may be likewise induced under photocatalytic conditions. In one such example, the photocatalyst was a porous multifunctional zirconium-based metal organic framework (MOF) that was later derivatized by incorporating Fe(III) complexes. The resulting MOF (Zr–MOF–FePC, PC=2-pyridinecarboxaldehyde) was an efficient heterogeneous photocatalyst for the conversion of alcohols into aldehydes under UV light irradiation (from a high-pressure mercury lamp) [63]. Thus, different benzyl alcohols were converted *in situ* into the corresponding benzaldehydes for the preparation of amides **8a–c** in good yields after 25–30 hours of irradiation (Scheme 1.7). The heterogeneous conditions enabled the easy recovery (by simple centrifugation) of the multifunctionalized photocatalyst, which was found active for at least two additional catalytic cycle tests, demonstrating the stability of the MOF material during the course of the reaction [63].



Scheme 1.6 Electro-induced Passerini 3-CR.



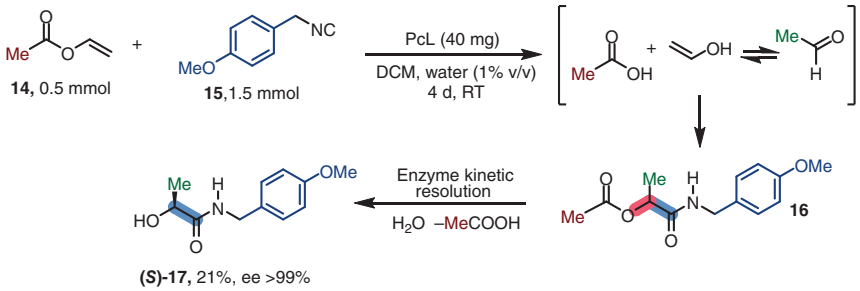
Scheme 1.7 Zr–MOF–FePC-catalyzed one-pot tandem photooxidative Passerini reaction.



Scheme 1.8 Passerini adducts from biocatalytically derived chiral azetidines.

The adoption of biocatalysis, e.g., for the desymmetrization of starting materials and products, is a potent tool to compensate for the lack of enantioselectivity usually observed in typical multicomponent processes. Diastereoselectivity, on the other hand, depends on the reaction type and substrates' chemical nature, and can greatly vary across different MCRs.

An example pertaining to this approach is described in Scheme 1.8 [64]. The first step was the synthesis of enantiopure azetidine-2-carboxyaldehyde **11**. This



Scheme 1.9 Enzyme-promoted three-step one-pot synthesis of α-hydroxy carboxamides.

compound was in turn prepared by lipase-catalyzed acetylation of **9** to give chiral nonracemic azetidine **10** [65] followed by Swern oxidation. Aldehyde **11** was then subjected to Passerini conditions, except for the addition of zinc bromide as a promoter that increased the diastereoselectivity in **12**/**13** formation. A final cyclization step gave access to polyfunctionalized heterocycles (not shown) [64].

In a related paper, chiral aldehydes obtained from desymmetrized erythritol gave Passerini adducts that were easily converted into densely functionalized, polyoxygenated heterocycles [66].

An elegant application of biocatalysis in MCRs was demonstrated in the enantioselective preparation of α-hydroxy carboxamides (an important source of optically active natural and unnatural amino acids). The strategy involved a three-step one-pot tandem process, wherein vinyl ester **14** was initially hydrolyzed in solution by *Pseudomonas cepacia lipase* (PcL) to release two components of the Passerini 3-CR, namely acetic acid and acetaldehyde (Scheme 1.9). The presence of a minimal amount of water was crucial to ensure the enzymatic hydrolysis that allowed the *in situ* generation of a difficult-to-handle reagent, such as low-boiling and irritant acetaldehyde. The presence in solution of isocyanide **15** led to racemic α-acyloxy carboxamide **16** that was subjected to *in situ* enzymatic kinetic resolution to form exclusively the (*S*)-enantiomer of α-hydroxy carboxamide **17** [67].

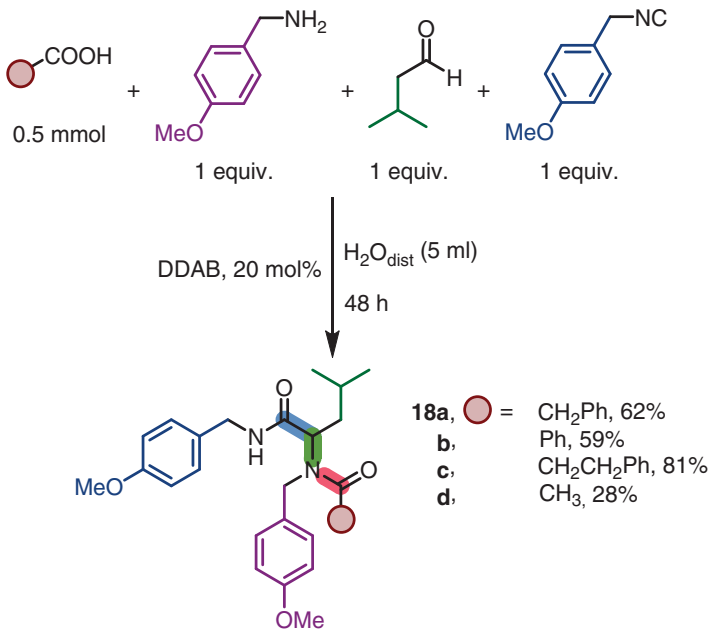
1.3 Ugi Reaction

The Ugi reaction [68] makes use of four different partners (U-4CR), namely an aldehyde, an amine, a carboxylic acid, and an isocyanide, and gives access to α-aminoacyl carboxamide derivatives. Accordingly, given the ubiquity of this motif in biologically active compounds, it is difficult to exaggerate the importance of this transformation in pharmaceutical applications, in particular for the preparation of APIs [69, 70]. At the same time, the Ugi reaction has been conveniently adopted in natural product synthesis [71] and has been recognized as a valuable tool on the route to diverse indole-containing derivatives [72]. An additional variant to the classic U-4CR process is the corresponding three-component (U-3CR) version, which is based on an amine, a carbonyl compound

(aldehyde or ketone), and an isocyanide, the carboxylic acid being omitted. Thus, equally important α-amino amide scaffolds are smoothly obtained from such a combination [73, 74].

As observed in the case of the Passerini reaction, the Ugi reaction can be effectively realized by adopting water as the medium [43]. Along this line, an intriguing opportunity is the adoption of an aqueous vesicle system, obtained through the addition of surfactants in distilled water. Thus, the best results were obtained when the process was carried out for 48 hours in the presence of didodecyldimethylammonium bromide (DDAB, 20 mol%) vesicles, which allowed to prepare adducts **18a–d** in good to excellent yields (Scheme 1.10). Notably, spontaneous formation of crystals was observed in the case of product **18a**, which fell out from the reaction mixture and could be easily separated by filtration. Furthermore, the corresponding filtrate solution containing the surfactant could be reused for additional reaction runs [75]. The adoption of neat water as the reaction medium was demonstrated as a convenient choice also in the case of the U-3CR variant. This strategy allowed to obtain complex chromanones in an environmentally friendly manner by adopting a catalytic amount of HCOOH (5 mol%) to promote the transformation of interest [76].

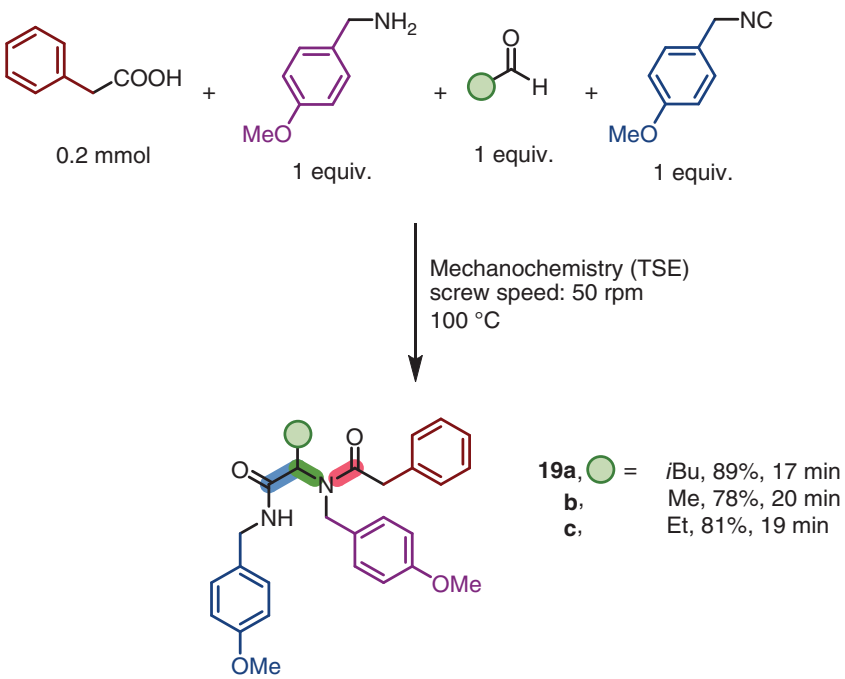
Ugi reactions have been demonstrated to take place under solvent-free conditions as well. In one instance, the adoption of a mechanochemical approach based on twin screw extrusion (TSE) operated at 50 rpm and 100 °C cleanly led to the preparation of α-aminoacyl carboxamide derivatives **19a–c** in good yields



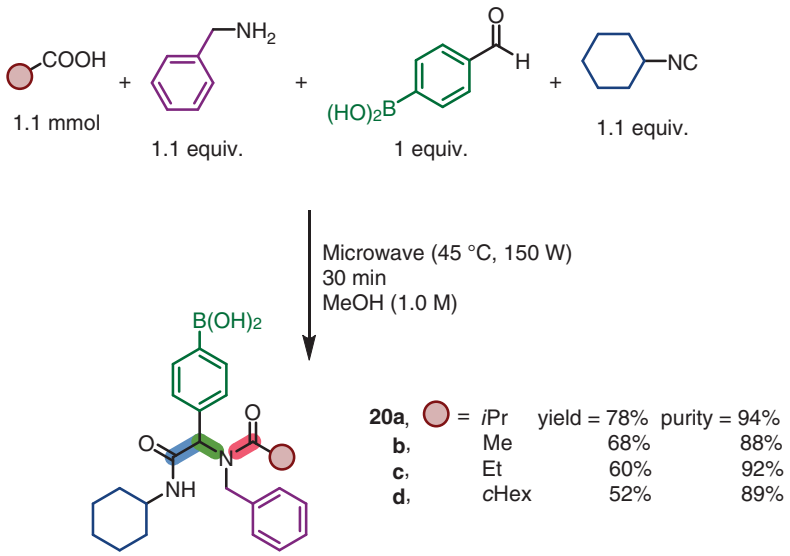
Scheme 1.10 Adoption of surfactants in distilled water for the preparation of adducts **18a–d**.

(Scheme 1.11), showing a superior performance with respect to classic techniques. Thus, the adducts of interest were obtained in high yields and purity, within a short reaction time [77]. Along the same line, a LAG strategy based on MeOH was adopted to perform a Ugi reaction under HSBM mechanochemical conditions [56]. In another instance, an elegant synthesis of privileged heterocyclic peptidomimetics 2,5-diketopiperazines and α,β-unsaturated-γ-lactams was reported, which leveraged on a mechanochemical domino strategy, encompassing an initial U-4CR protocol, followed by post-transformation of the first-formed adducts. Noteworthy, the reactions took place in high overall yields in a very short reaction time (only six minutes) [78].

Microwave irradiation proved beneficial in promoting the Ugi reaction, as demonstrated in the synthesis of arylboronic acid analogs of phenylglycine, enabling the preparation of boron-containing chemical libraries. As shown in Scheme 1.12, products **20a–d** were obtained upon 30 minutes microwave irradiation (45 °C, 150 W) starting from (4-formylphenyl)boronic acid. The latter compound was initially mixed with benzylamine in MeOH and stirred for five minutes at room temperature. Next, the chosen carboxylic acid and cyclohexyl isocyanide were added to the reaction mixture, which was finally subjected to microwave irradiation. Notably, although HPLC purification of the desired products was typically performed, a simple liquid/liquid extraction was found sufficient to deliver **20a–d** in excellent purity (Scheme 1.12) [79]. At the same



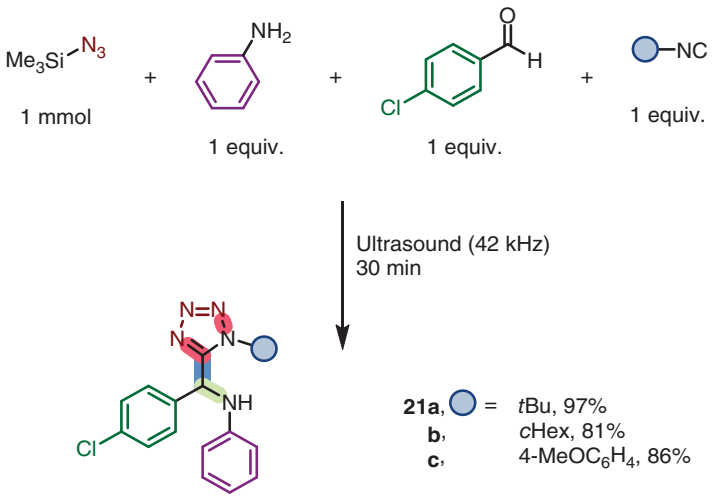
Scheme 1.11 Solvent-free mechanochemical preparation of adducts **19a–c** by means of TSE.



Scheme 1.12 Microwave-assisted synthesis of arylboronic acid analogs of phenylglycine **20a–d**.

time, microwave-assisted Ugi-type transformations have been exploited for the preparation of important heterocyclic scaffolds, including lactams [80] and dibenzo[*c*,*e*]azepinones [81], starting from levulinic acid and substituted 2′-formylbiphenyl-2-carboxylic acids, respectively, as bifunctionalized starting materials. Interestingly, a design of experiments (DoE) approach was adopted in the former case for the rapid and efficient optimization of the reaction protocol [80]. Another intriguing application relates to the microwave-assisted one-pot two-step synthesis of dihydroquinoxalinones on a polymeric support based on polyethylene glycol (PEG). The protocol relied on the combination of aldehydes, Fmoc-protected α-amino acids, isocyanides, and a soluble polymer-supported 4-fluoro-3-amino benzoate ester. After the U-4CR step, Fmoc-deprotection was followed by intramolecular cyclization to afford novel bicyclic quinoxalin-2-ones. Interestingly, product isolation and purification were easily performed via precipitation and washing [82].

Another enabling technology compatible with the Ugi reaction is sonication. Along this line, the Ugi-azide variant, making use of trimethylsilylazide ($TMSN_3$) in place of the carboxylic acid, has been reported to take place in an ultrasound-accelerated fashion to deliver 1,5-disubstituted tetrazoles. Among the different conditions tested, an excellent performance was observed when the reaction was realized by combining equimolar amounts of the starting materials under solvent-free conditions upon sonication (42 kHz) for 30 minutes at 25 °C. As a result, excellent yields of tetrazoles **21a–c** were obtained (Scheme 1.13) [83]. According to analogous ultrasound-assisted strategies, several tetrazole-containing scaffolds have been prepared under catalyst- and solvent-free conditions [84–86]. Overall, the

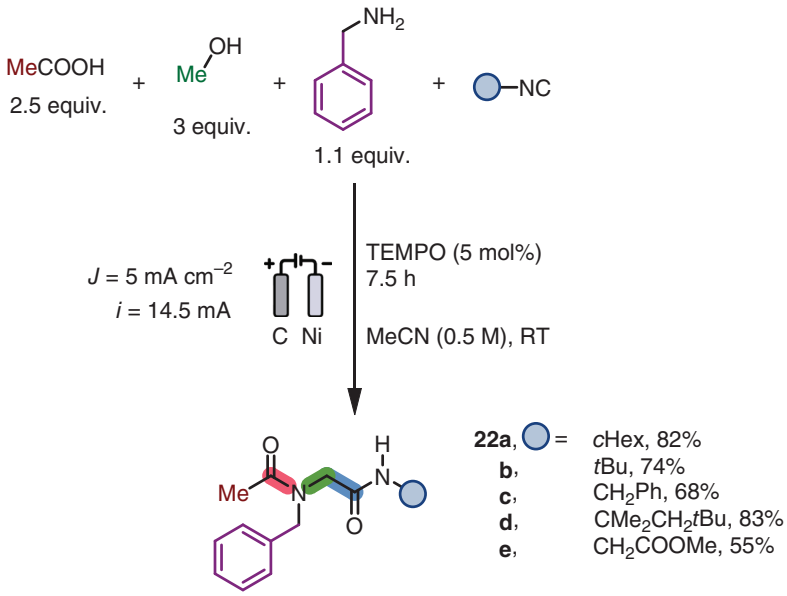


Scheme 1.13 Ultrasound-accelerated synthesis of 1,5-disubstituted tetrazoles **21a–c** via Ugi-azide reaction.

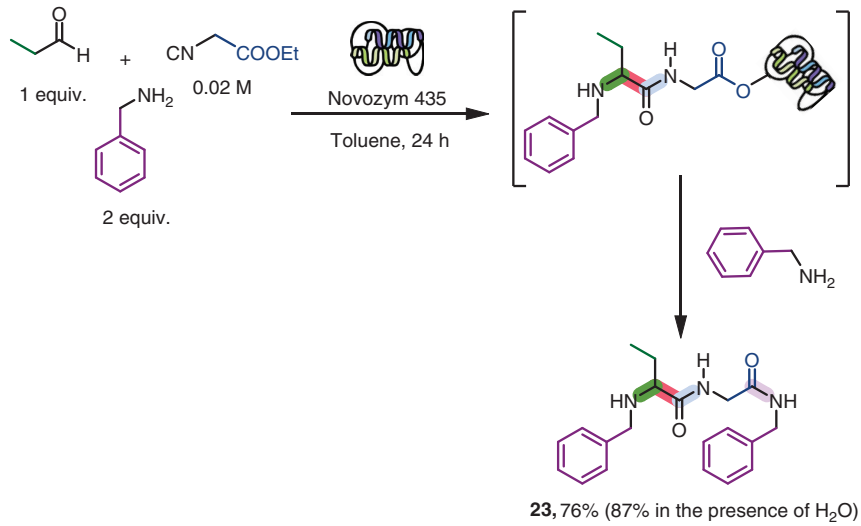
U-4CR protocol can be implemented with minimum synthetic effort and is compatible with a large variety of conditions, including the adoption of aqueous or solvent-free media, as well as the combination with microwave or ultrasound irradiation. Such versatility, associated with its simplicity, demonstrates the intrinsic green character of the transformation and renders it appropriate for undergraduate organic chemistry laboratories [87].

As mentioned for the Passerini reaction, also in the case of the Ugi transformation, it is possible to generate *in situ* one of the starting materials required to unleash the MCR transformation of interest. This is the case of an electrochemical TEMPO-catalyzed protocol recently reported, which employed alcohols as aldehyde surrogates. Thanks to this extremely chemoselective transformation, a library of Ugi adducts was rapidly obtained, skipping the need to handle unstable and/or toxic aldehydes. As shown in Scheme 1.14, products **22a–e** were prepared by adopting an amperostatic operation mode (i = 14.5 mA, j = 5 mA/cm^2) for 7.5 hours in an undivided cell setup, with no need for additional electrolytes. The products were obtained in good to excellent yields, and the protocol could be easily scaled up, as demonstrated by the preparation of **22a** in 75% yield at the gram scale (1.08 g of Ugi adduct obtained from 5 mmol of isocyanide) [88].

Ugi-type transformations can be promoted by means of biocatalytic approaches. This strategy is particularly convenient in the case of the U-3CR variant, lacking the carboxylic acid. As shown in Scheme 1.15, Novozym 435 (20%) allowed to obtain dipeptide **23** in very good yield (76% of isolated product) by reacting benzylamine, propanaldehyde, and ethyl isocyanoacetate for 24 hours in toluene. From the mechanistic point of view, it has been proposed that the isocyanide ester group reacted with a serine fragment in the active site of the enzyme to enable the reactivity and was finally hydrolyzed thanks to the reaction with a second equivalent of the



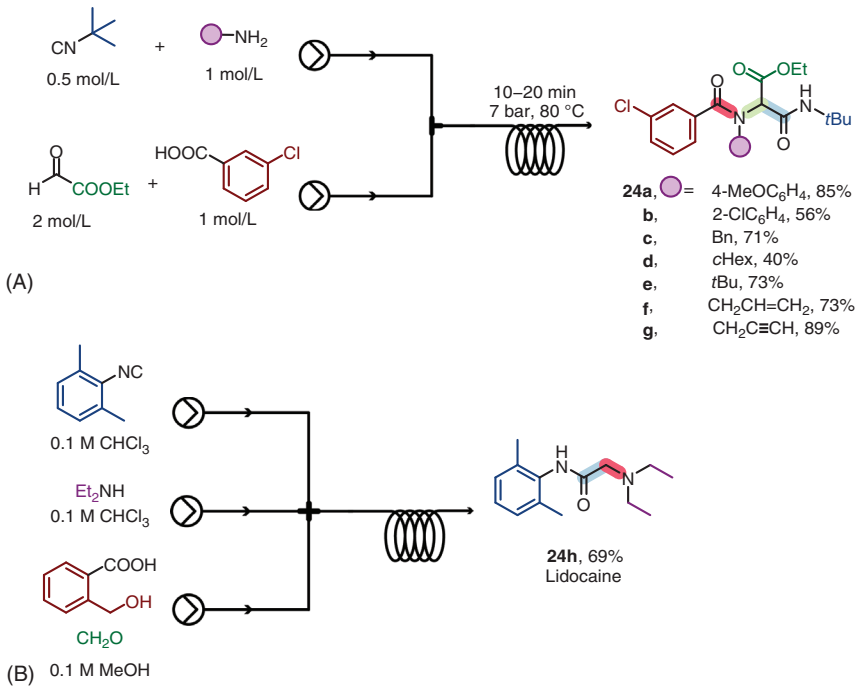
Scheme 1.14 Electrochemical TEMPO-catalyzed oxidative Ugi reaction.



Scheme 1.15 Biocatalytic preparation of dipeptide **23** via a U-3CR transformation.

employed amine. Interestingly, the addition of water (0.5%v/v) allowed to increase the yield of **23** to 87% [89]. In a follow-up study, it was demonstrated that the structure of the isocyanoester has a key role in dictating the reaction outcome, with the screened enzymes showing a preference for short-chain derivatives [90].

Flow conditions may help to shorten the reaction time of Ugi-type transformations, as shown in Scheme 1.16. Thus, α-amino-1,3-dicarbonyl compounds **24a–g**



Scheme 1.16 Ugi-type transformations under continuous flow conditions applied to the preparation of (A) α-amino-1,3-dicarbonyl compounds (**24a–g**) and (B) lidocaine drug (**24h**).

were readily obtained by injecting the four starting materials through two different channels in a 250 μl microreactor glass chip at 80 °C and 7 bar, with a 20-minute residence time (Scheme 1.16A) [91]. An analogous strategy has been adopted in the development of the continuous flow multistep preparation of cyclic peptoids via a U-4CR/Cu-catalyzed Huisgen azide-alkyne cycloaddition sequence [92]. Flow conditions proved beneficial also to overcome the challenges related to the concomitant adoption of ammonia and formaldehyde, thanks to the use of hexamethylenetetramine (HMTA) as a surrogate. Thanks to the excellent control of temperature and reaction time associated with flow conditions, it was possible to easily scale up the synthetic protocol [93]. Finally, the local anesthetic and antiarrhythmic drug lidocaine has been rapidly assembled via a telescoped U-4CR strategy, where the isocyanide was also synthesized under flow conditions, delivering **24h** in 69% yield (Scheme 1.16B) [47].

1.4 Ugi–Joullié Reaction

Another IMCR discussed in this chapter is the so-called Ugi–Joullié reaction (a notable variant of the above-described Ugi reaction). First developed in 1982 by Joullié and co-workers, it consists of a three-component process in which cyclic imines are employed in place of the amine and carbonyl partners

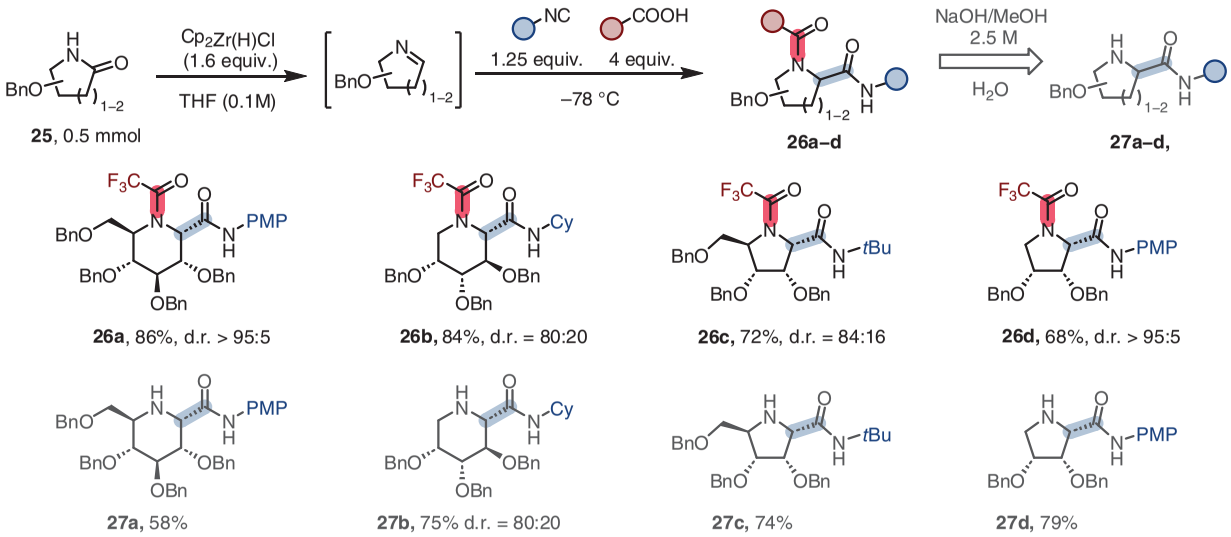
(Scheme 1.1) [94]. This strategic modification not only results in high diastereoselectivity but also effectively addresses a major limitation related to the traditional Ugi reaction, i.e., the pronounced conformational flexibility typical of its products. The incorporation of an *N*-heterocyclic structure, however, dramatically increases structural rigidity, making the Ugi–Joullié reaction a valuable strategy for drug-design applications, including the synthesis of nature-inspired glyco- and peptido-mimetics [95, 96].

Several methods for the synthesis of the desired cyclic imines have been reported, including the *N*-chlorination/elimination sequence applied to secondary amines, the deoxygenation of cyclic nitrones, or the Staudinger/*aza*-Wittig cyclization of azido-aldehydes [95, 97]. A significant alternative, however, is the *in situ* generation of the prerequisite imine, so as to possibly allow a one-pot process. Along this line, a strategy involving the deoxygenative reduction of carbohydrate-derived lactams has been proposed, on the route to polyhydroxylated piperidine and pyrrolidine peptidomimetic scaffolds [97]. In detail, treatment of a variety of easily obtained chiral gluco-lactams **25** with Schwartz's reagent $Cp_2Zr(H)Cl$ in THF easily provided the corresponding imines, which were then readily employed in a Ugi–Joullié reaction by addition of the desired isocyanide and TFA to the reaction mixture at −78 °C. Trifluoroacetamides **26a–d**, obtained in moderate to good yields and high diastereomeric ratios, could also be smoothly converted to free amines **27a–d** through basic hydrolysis (Scheme 1.17).

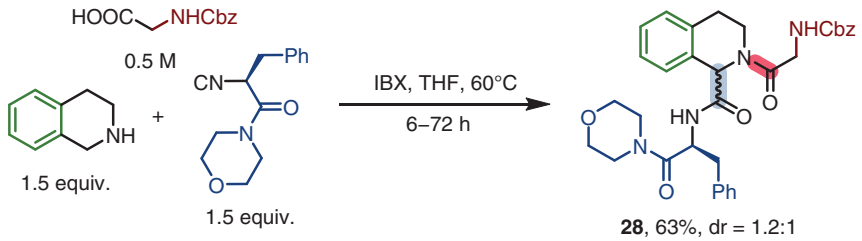
The oxidative transformation of amines is also a valid strategy for the *in situ* generation of the corresponding imines [98]. This approach provides a protocol for the concomitant N and C1 functionalization of tetrahydroisoquinoline (THIQ), in which this substrate could be converted to a reactive imine/iminium ion by an IBX-mediated oxidation. Subsequently, such intermediates underwent a Ugi–Joullié MCR, reacting with an isocyanide and a carboxylic acid, to afford 1,2-diacylated adducts in good to excellent yields, including tripeptide **28** (63% yield, Scheme 1.18).

Similar conditions have also been reported for the diastereoselective oxidative Ugi-type transformation, adopted for the synthesis of several *N*-acylprolyl amide derivatives **29a–d**, starting from the corresponding *meso*-pyrrolidines (Scheme 1.19) [99]. The employment of IBX as a mild, selective, and efficient oxidant, alongside the possibility to directly functionalize the α-carbon atom of amines in a highly diastereoselective fashion (so as to obtain various dipeptides as possible drug candidates), highlights the significance of this process.

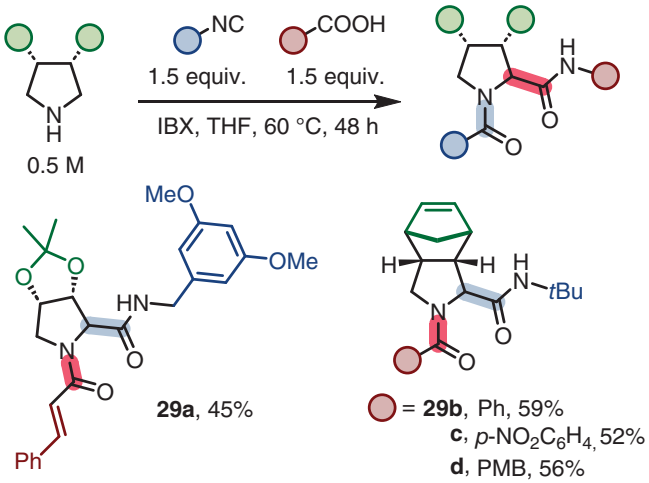
An elegant and attractive approach for obtaining enantiomerically enriched imines is by means of chemoenzymatic syntheses [100]. An Amano PS lipase was adopted, inside a complex convergent synthetic strategy, for the desymmetrization of *meso* precursors (e.g., **30**) to smoothly obtain both enantiomers of the desired imine. Chiral imine **31** was subsequently employed in a Ugi–Joullié process with complex carboxylic acids and enantiopure isocyanides (obtained through a multistep route). Diversity-oriented synthesis of densely functionalized pyrrolidines (**32a**,**b**, possibly carrying pharmacologically relevant appendages) with complete control of the relative and absolute configuration was therefore pursued (Scheme 1.20).



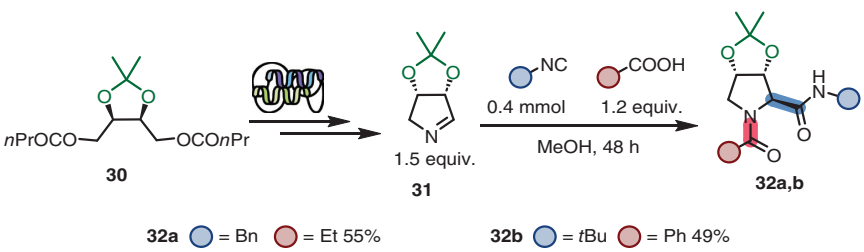
Scheme 1.17 One-pot reductive Ugi–Joullié functionalization of carbohydrate-derived lactams, followed by amide hydrolysis.



Scheme 1.18 One-pot oxidative Ugi–Joullié functionalization of THIQ.

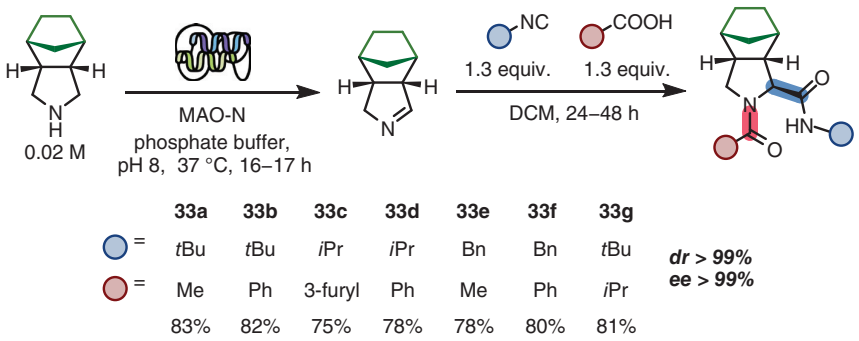


Scheme 1.19 One-pot oxidative Ugi–Joullié functionalization of *meso*-pyrrolidines.



Scheme 1.20 Chemoenzymatic synthesis of enantiomerically enriched imines employed in the synthesis of densely functionalized pyrrolidines.

Monoamine oxidase N (MAO-N) from *Escherichia coli* is another enzyme suitable for the preparation of enantiomerically enriched cyclic imines, by desymmetrization of the corresponding pyrrolidines, in a very good yield and *ee* [101]. The optically pure imine was easily obtained under mild conditions (37 °C; phosphate buffer, pH 8) and used for the following step without the need for complex



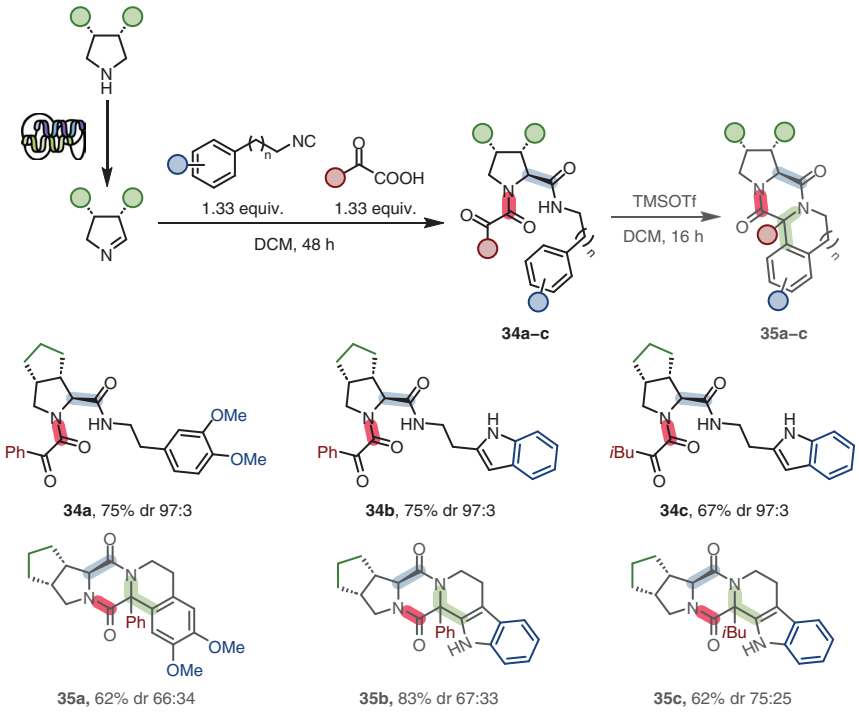
Scheme 1.21 Enzymatic desymmetrization of amines for the preparation of enantiomerically enriched imines, subsequently employable as substrates in IMCRs.

purification. A wide variety of 3,4-*cis*-substituted 1-pyrrolidines **33a–g** (structurally analogs, among others, to Wennemers-type organocatalysts) was then accessed in yields up to 83% with a complete diastereoselectivity (Scheme 1.21).

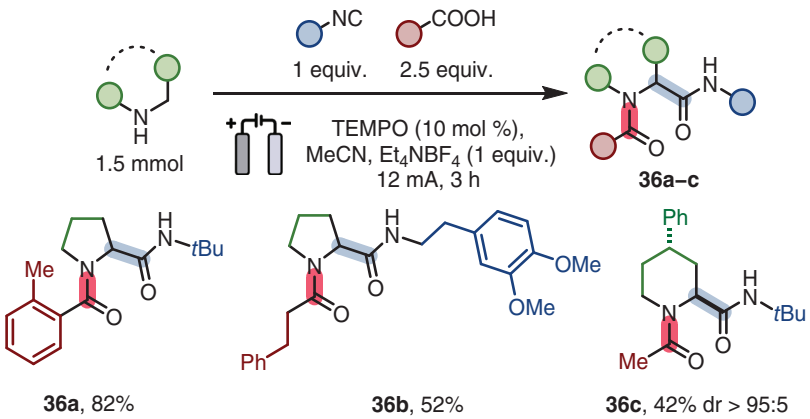
The same research group later reported a similar methodology, in which the enzymatic desymmetrization step (also in this case, mediated by MAO-N) was followed by a Ugi–Joullié MCR/Pictet–Spengler-type cyclization sequence, to eventually yield several 2,5-diketopiperazines (DKPs) [102]. The first two steps (i.e., the oxidative desymmetrization and the multicomponent process) led to highly functionalized and optically pure 3,4-*cis*-substituted prolyl peptides **34a–c**. These compounds underwent a Pictet–Spengler cyclization in the presence of trimethylsilyl trifluoromethanesulfonate, providing alkaloid-like polycyclic compounds **35a–c** in moderate to excellent yields and diastereomeric ratio (Scheme 1.22).

An additional oxidative approach for the generation of cyclic imines is the electrochemical, TEMPO-catalyzed, *in situ* conversion of the corresponding amine [103]. This methodology showed a particularly appreciable functional-group tolerance. As shown in Scheme 1.23, the reaction was performed under amperostatic conditions, adding to an undivided cell (equipped with a graphite working electrode and a Ni counter electrode) the reaction partners, in the presence of tetraethylammonium tetrafluoroborate as the electrolyte. Employing the reported strategy, several α-carbamoylated products (including **36a–c**) were isolated in moderate to good yields. A complete chemoselectivity was observed when using *N*-Boc-protected amino acids as reaction partners: no product resulting from the insertion of the isocyanide at the *α*-position of the Boc-protected nitrogen was detected.

Photosensitization is another possible strategy for the oxidative preparation of the desired imine under sustainable conditions, through the mild and practical conversion of secondary benzylic amines. Thus, THIQ was easily converted by oxidation to the corresponding imine, promoted by singlet oxygen ($^1O_2$), smoothly generated by the help of a tetraphenylporphyrin (H_2TPP) photosensitizer, irradiated with a 300 W tungsten lamp [104]. Following this protocol, a variety of imines

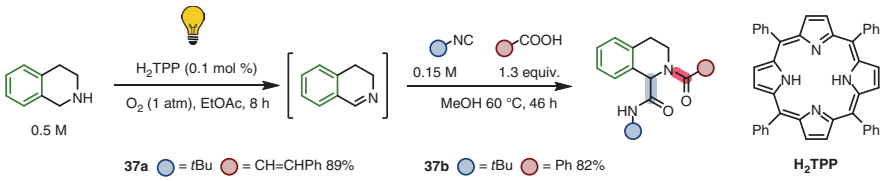


Scheme 1.22 Enzymatic desymmetrization of amines for the tandem IMCR/Pictet–Spengler reaction.



Scheme 1.23 Electrocatalyzed TEMPO-mediated Ugi–Joullié reaction.

was obtained in 90–99% yield with a remarkable purity, without *N*-oxide or nitrone contamination. As an example, THIQ was directly employed for further functionalization in a Ugi–Joullié reaction to give **37a** and **37b** in good yields (Scheme 1.24).



Scheme 1.24 Photosensitized Ugi–Joullié reaction.

The formation of side-products arising from competing reactions, and the degradation of the reaction intermediates (in particular, imines), is a challenge in classical Ugi–Joullié processes performed under batch conditions. To overcome this drawback, a continuous flow protocol has been recently developed, allowing for rapid mixing and efficient temperature control, combined with an increased overall efficiency and reduced waste formation [105]. In such work, a cost-effective flow reactor was assembled from HPLC components (i.e., a piston pump and a six-port injector) and a self-made 15 ml tubular reactor, immersed in a silicone oil bath for heating. In this way, several spiroindolenine derivatives, including **38a–c**, were obtained in moderate yields (Scheme 1.25A).

Moreover, this protocol was further extended into a telescoped segmented continuous flow strategy for the synthesis of spiroindolenine (from cyclohexane carboxaldehyde and phenylhydrazine hydrochloride) [105, 106]. The apparatus comprised an in-line purification system coupled with a 0.2 ml mixing chip, in which the so-formed imine was combined with the selected (protected) amino acid and the isocyanide (Scheme 1.25B). This system allowed to synthesize four different peptidomimetics (**38b–e**) in good yields, in about 100 minutes of reaction time.

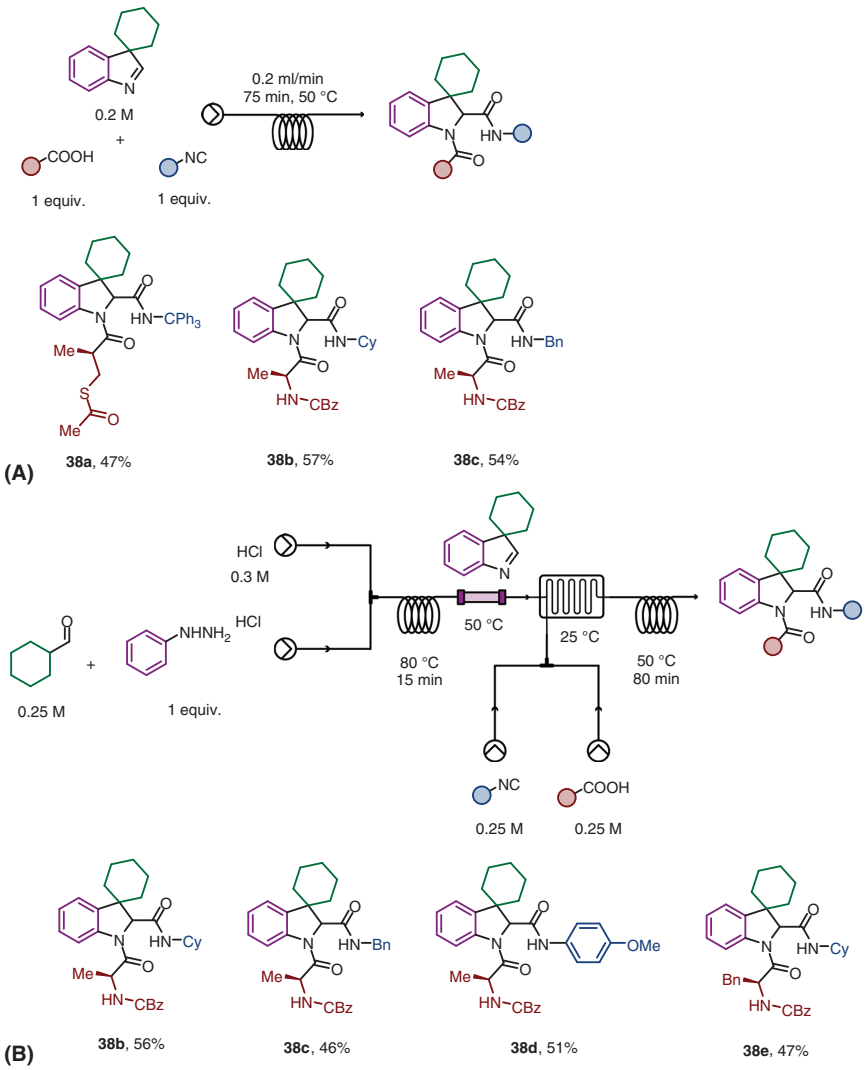
1.5 Greenness of MCRs in Drug Preparation

As previously stressed, MCRs are deemed green reactions par excellence. To verify if this concept corresponds to the truth, a strict comparison with other common chemical approaches is mandatory. The best approach is to evaluate the calculated green parameters for a given synthesis (e.g., of a drug) performed through a classical synthetic approach or via an MCR protocol, as detailed in the examples below.

The first case study is related to the preparation of Amenamevir, a Helicase-Primase Inhibitor for the optimal treatment of Herpes Zoster [107]. This oxadiazolephenyl-containing bioactive derivative has been industrially prepared starting from carboxylic acid **39** and 2,6-dimethylaniline **40**, following the route presented in Scheme 1.26 [69, 108, 109].

An alternative route was later proposed, having recourse to a U-4CR protocol by simply mixing the same acid and aniline along with formaldehyde and isocyanide **41** (Scheme 1.27) [69, 110].

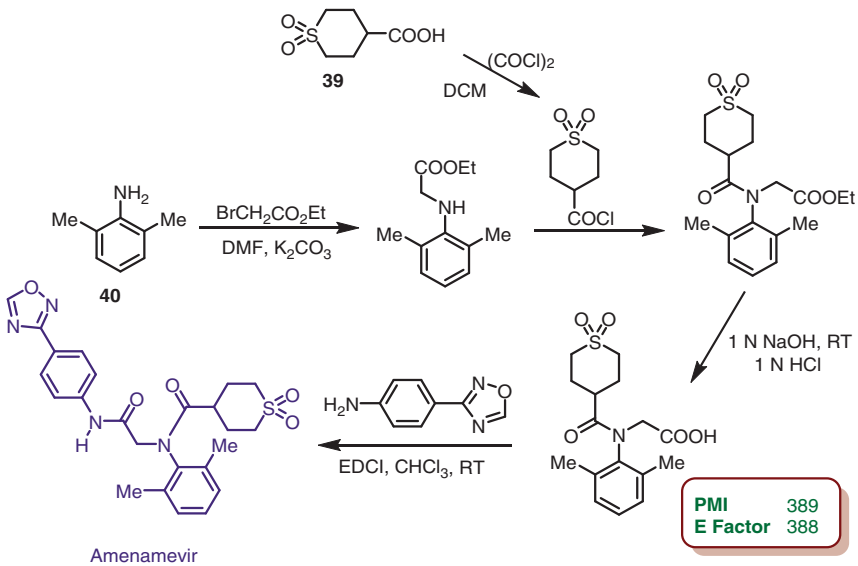
The apparent advantage from the eco-sustainable point of view of the latter approach has been demonstrated through the calculation of different green metrics.



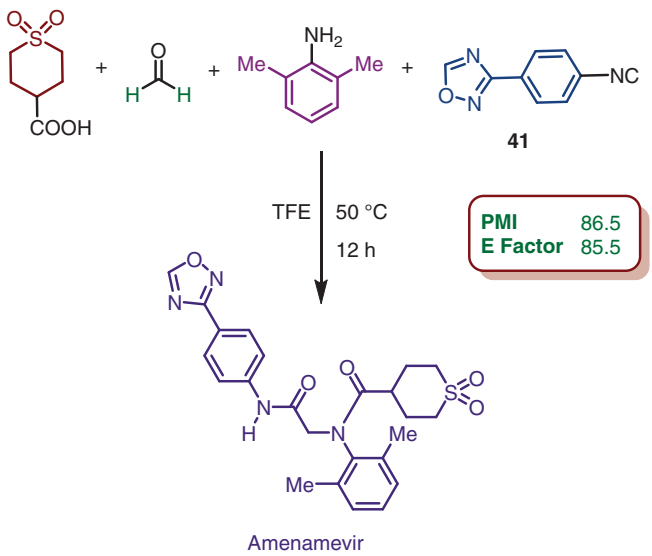
Scheme 1.25 Ugi–Joullié reaction under (A) continuous flow and (B) telescoped flow conditions.

For the two syntheses, two parameters were calculated, *viz*. Process Mass Intensity (PMI, total mass of materials (kg)/mass of product (kg)) and the *E*-factor (mass of waste (kg)/mass of product (kg)) [2]. The lower the PMI and *E*-factor, the more eco-friendly the process is. As apparent from Schemes 1.26 and 1.27, the parameters related to the U-4CR reaction are consistently more favorable with respect to those calculated for the industrial route (lower PMI and *E*-factor).

A further example deals with the synthesis of Telaprevir (a protease inhibitor belonging to the class of antiviral drugs) used for the treatment of hepatitis C [111].

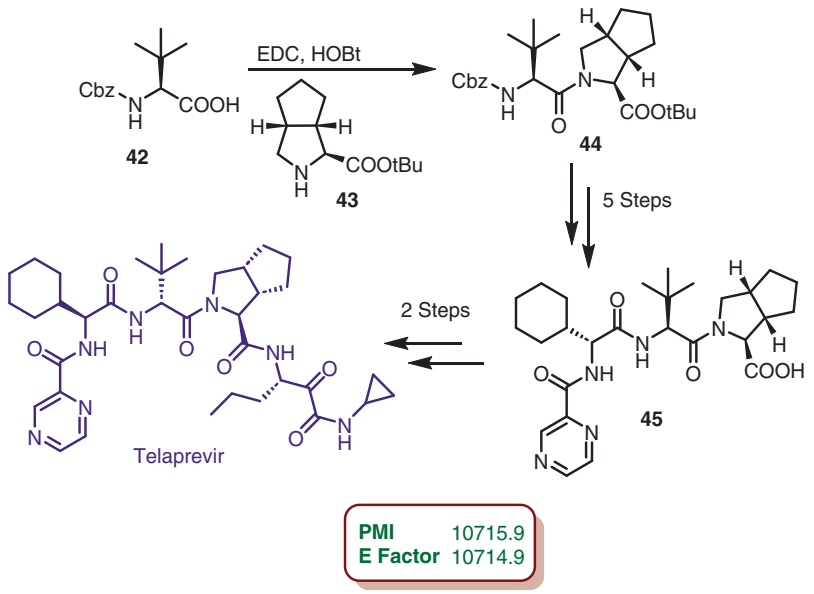


Scheme 1.26 Industrial synthesis of Amenamevir.



Scheme 1.27 Preparation of Amenamevir via U-4CR protocol.

The proposed approach for the preparation of the final tetrapeptide is sketched in Scheme 1.28 and starts from *N*-Cbz-L-*t*-leucine **42**, which is coupled with bicyclic aminoester **43** to yield the protected dipeptide **44**. An additional elaboration step introduced the pyrazine (compound **45**) and the *N*-cyclopropylacetamide moieties



Scheme 1.28 Industrial synthesis of Telaprevir.

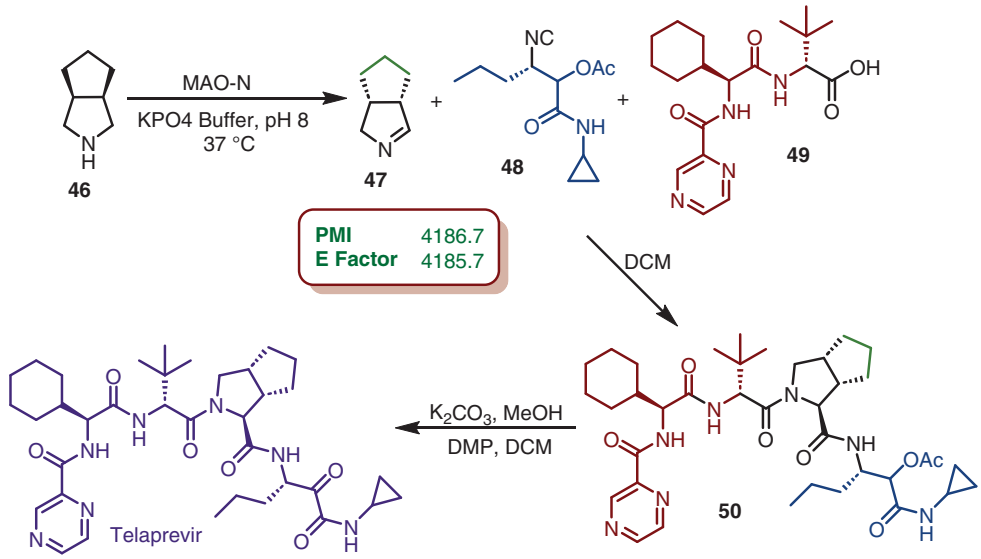
to ultimately afford the desired drug [112]. Unfortunately, the green parameters indicate that such a synthesis needs implementation (very high values of PMI and *E*-factor) [69].

The merging of biocatalysis and MCRs allows for the development of a greener approach, as illustrated in Scheme 1.29. The key point here is the adoption of a monoamine oxidase N (MAO-N) (from *Aspergillus niger*, optimized by directed evolution) to induce an enzymatic desymmetrization of *meso*-pyrrolidine **46** to afford imine **47**. The latter compound initiated a Ugi–Joullié reaction upon combination with isocyanide **48** and acid **49** to give intermediate **50**, whose OAc group was converted into a carbonyl by oxidation with Dess–Martin periodinane (DMP) [113]. Of note is the eco-sustainable advantage of this route, which markedly improved all the determined green metrics parameters (compare the values reported in Schemes 1.28 and 1.29) [69].

In a similar way, the adoption of MCRs was advantageous also in the preparation of Atorvastatin (a statin drug employed to prevent cardiovascular disease) [114] and in the preparation of Ivosidenib (an inhibitor that targets the mutant isocitrate dehydrogenase 1 enzyme) [10, 11].

1.6 Conclusion and Outlook

As apparent from the examples reported in this chapter, MCRs are elective processes for the sustainable synthesis of organic compounds. Among MCRs, those using isocyanides have a prominent role, given the unique reactivity patterns



Scheme 1.29 MCR-based synthesis of Telaprevir.

offered by this functional group. In recent years, it has been demonstrated that the greenness of a given MCR-based process may be improved by having recourse to enabling technologies. Such approaches allow the *in situ* formation of one of the partners of the MCR starting from easily available reagents. Alcohols may be then oxidized to give carbonyl derivatives (to be exploited in the Passerini or Ugi reaction), while amines may be converted into imines to promote Ugi–Joullié reactions. Isocyanide-based MCRs have been adopted in key steps along the synthesis of different drugs (e.g., Amenamevir, Telaprevir, etc.), showing better green metrics parameters with respect to common synthetic routes. We therefore expect that the use of MCRs in sustainable synthetic endeavors will play an increasingly important role in the near future.

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