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INTRODUCTION: MULTICOMPONENT STRATEGIES

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GENERAL INTRODUCTION

The goal of this book is to provide an overview of the most useful and noteworthy examples of multicomponent reactions (MCRs) published in this field between 2005 and 2014, in order to attract the attention of a wide range of readers. Previous examples are collected in an exceptional book edited by Zhu and Bienaymé, published in 2005 [1]. Since then, a great number of interesting and important reviews have also been written, and they will be cited throughout this book. For this reason, only the most pivotal examples will be reported and commented on in order to avoid repetitions.

MCRs are widely defined as reactions in which three or more components are added to a single vessel at the same time to lead to a final product that contains most of the atoms from the starting reagents. Therefore, these reactions encompass a sequence of more than one chemical transformation without the necessity of changing the reaction media after each transformation. It is not surprising then that MCRs lead to great molecular diversity and allow for the creation of libraries of small organic molecules while requiring less time and effort when compared with step-by-step procedures [2]. This is especially attractive for the pharmaceutical industry, for which the easy creation of large libraries of compounds with possible biological activity is a priority.

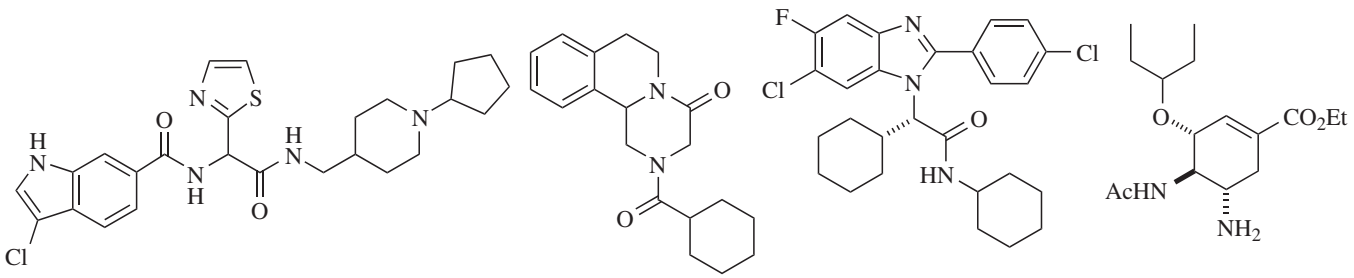
The significance of these processes can be observed in the large number of publications that have appeared in this field over the last decade. Also, the biological utility of compounds synthesized with MCRs has been confirmed by the discovery of many molecules with remarkable biological activity (Fig. 1.1) [7].

Over the last decade, interest in performing sustainable chemistry has drastically increased [8]. The application of ingenious strategies to synthesize complex scaffolds and highly substituted molecules, combining molecular diversity [9] with ecocompatibility [10], has been the main focus of many scientific groups. In effect, the rational design of reactions that transform simple and readily available substrates into complex structures in a single reaction is one of the current major challenges in organic synthesis. In this context, MCRs have become one of the best established approaches for reaching this goal, since these strategies imply atom economy [11] and bond-forming efficiency [12].

There are some authors that consider the reaction between bitter almond oil and ammonia, carried out by Laurent in 1838, as the first MCR [13]. This mixture could promote a condensation of ammonia, hydrogen cyanide, and benzaldehyde, resulting in an α-aminonitrile intermediate that, once formed, reacts with another molecule of benzaldehyde to give its corresponding Schiff base. However, in the compositions reported by the authors, none of the examined products lined up with the MCR's possible products, neither the α-aminonitrile nor its subsequent Schiff base. Therefore, the Strecker reaction could be considered the first reported MCR, due to the fact that it was the first time that an author was able to determine the structure of a product formed in a MCR.

Since the development of the Strecker reaction in 1850 [14], a great number of interesting MCRs have been reported, and amidst them, some of the most significant reactions are displayed in Table 1.1. In the following chapters, these pioneering reactions will be extensively discussed.

Multicomponent Reactions: Concepts and Applications for Design and Synthesis, First Edition. Edited by Raquel P. Herrera and Eugenia Marqués-López.

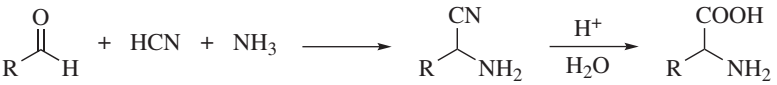


Factor Xa inhibitor | Praziquantel | Farnesoid X receptor agonist | (–)-Oseltamivir

FIGURE 1.1 Examples of drugs synthesized with MCRs: factor Xa inhibitors [3], praziquantel [4], farnesoid X receptor agonists [5], and (–)-oseltamivir [6].

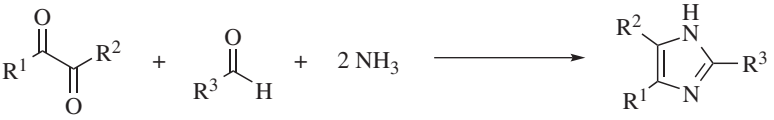
TABLE 1.1 Some historically significant MCRs

Strecker [14], 1850



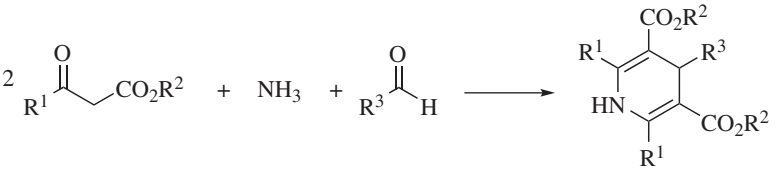
Synthesis of α-amino acids

Debus-Radziszewski [15], 1858, 1882



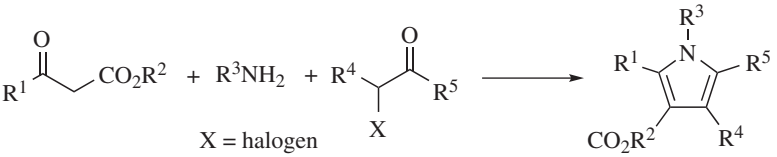
Synthesis of imidazoles

Hantzsch [16], 1881



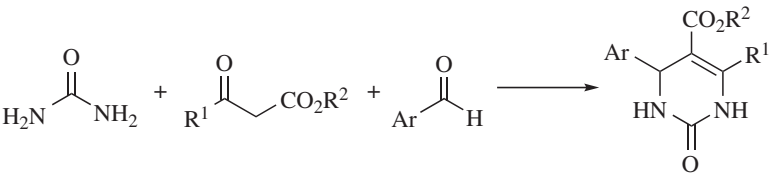
Synthesis of 1,4-dihydropyridines

Hantzsch [17], 1890



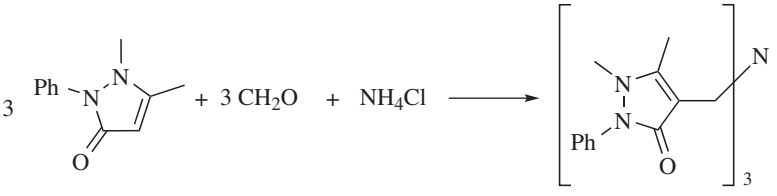
Synthesis of pyrroles

Biginelli [18], 1891



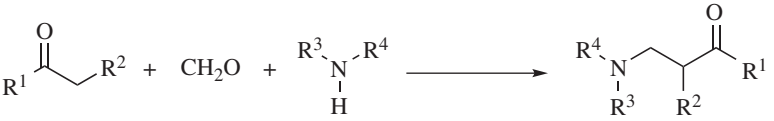
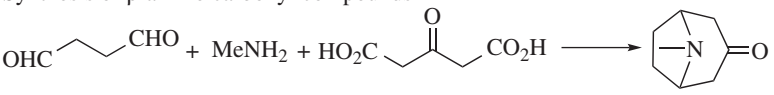
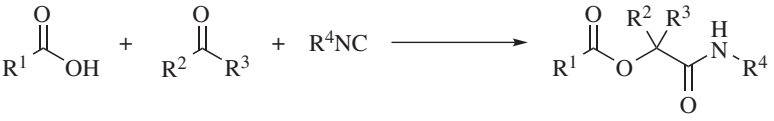
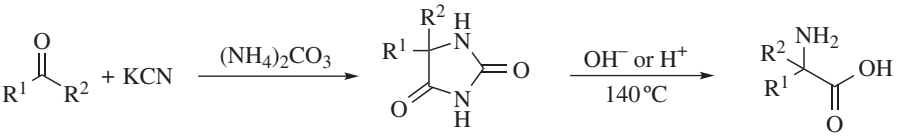
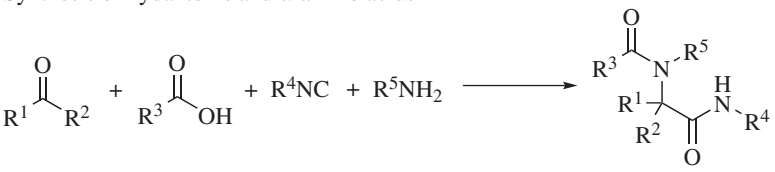
Synthesis of dihydropyrimidones

Mannich [19], 1912



Synthesis of an antipyrine-derived tertiary amine

Table 1.1 (*continued*)

Mannich [20], 1917	 Synthesis of β-amino carbonyl compounds
Robinson [21], 1917	 Synthesis of tropinone
Passerini [22], 1921	 Synthesis of α-acyloxy amides
Bucherer–Bergs [23], 1929–1934	 Synthesis of hydantoins and α-amino acids
Ugi [24], 1959	 Synthesis of α-*N*-acylamino amides

1.1 BASIC CONCEPTS

Some of the basic concepts related to MCRs are briefly described in the following text in order to familiarize the reader with this field and its characteristics.

1.1.1 Clarifying Terminology: One-Pot, Domino/Cascade, Tandem, and MCRs

The previous terms are probably familiar for most chemists, but they have crucial differences that are important to know in order to distinguish each term from the others. The term one-pot reaction includes reactions that involve multiple chemical transformations between reagents that are carried out in a single reactor. Thus, MCRs fall into the category of one-pot reactions due to the sole reactor required for carrying out the reaction and that there are multiple chemical transformations involved.

Furthermore, Fogg and dos Santos categorized the different types of multicatalyzed one-pot reactions in 2004 [25], some years after Tietze set the definition of domino reactions [12]. In this categorization, domino/cascade catalysis, tandem catalysis, and multicatalytic one-pot reactions were distinguished depending on certain factors, such as the moment when the (pre)catalysts are added and the number of catalytic mechanisms involved (Fig. 1.2). Generally speaking, domino/cascade and tandem catalyses are one-pot reactions where all the components are introduced at the same time at the beginning of the reaction, while in multicatalytic one-pot reactions, all of the reaction's components are not added at the same time. Another requirement for domino/cascade and tandem catalyses is that all successive transformations must occur as a consequence of the intermediate generated in the previous reaction step. In Fogg's classification, domino/cascade and tandem catalyses are differentiated by the number of catalytic mechanisms present in the reaction.

With all the aforementioned concepts defined, it has been made clear that MCRs are one-pot reactions that might also fall under the category of domino/cascade or tandem reactions. A reaction is a domino/cascade or tandem MCR when it has the characteristics of one of these types of reactions in addition to including three or more reagents that react to form a final product.

1.1.2 Using Rational Design to Discover New MCRs

Designing new multicomponent approaches in a less haphazard and more rational manner is vital for increasing the limited scaffold diversity obtained by the MCRs reported

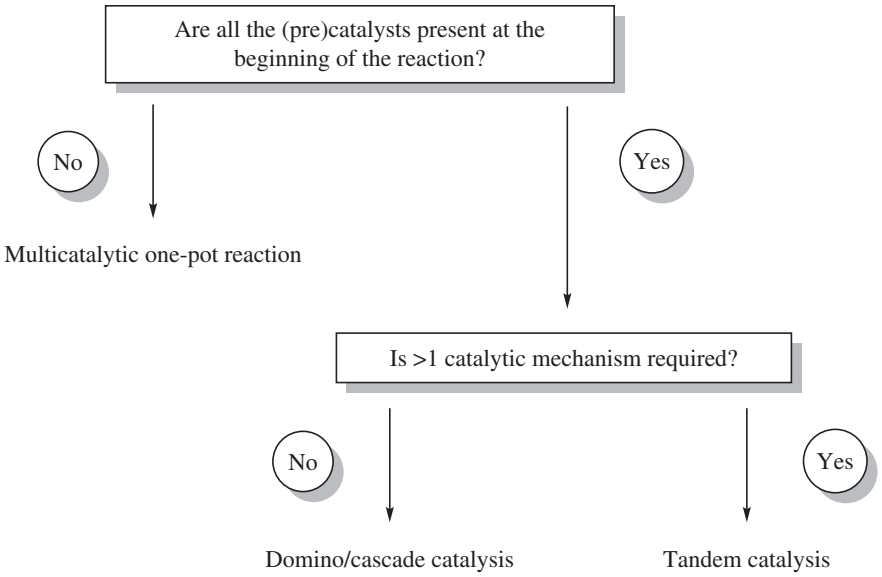


FIGURE 1.2 Fogg's simple classification of one-pot processes involving multiple catalytic transformations.

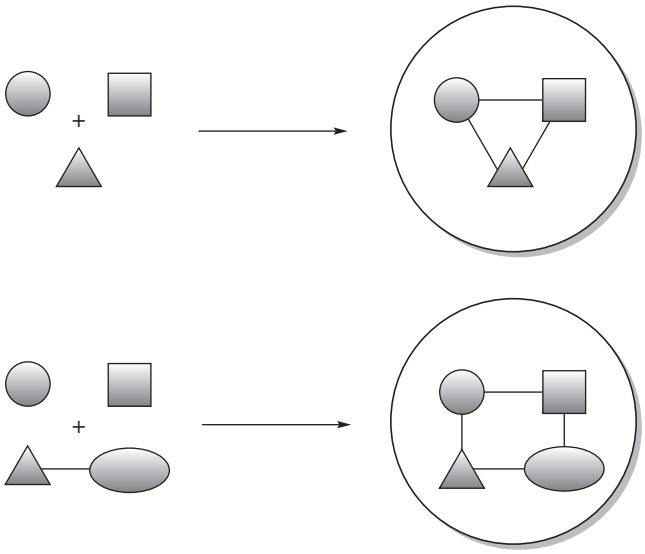


FIGURE 1.3 Single reactant replacement method for MCRs.

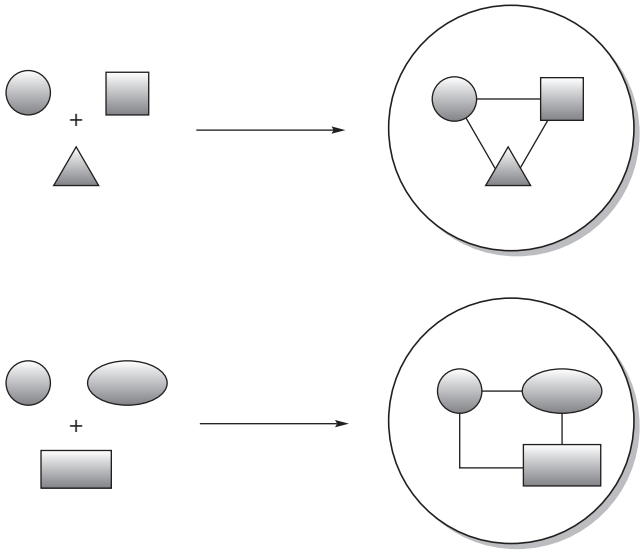


FIGURE 1.4 Example of a reaction-operator strategy carried out by changing two substrates.

until now. To do so, five different methods, most of them excellently explained by Orru and coworkers in their review [2b], have been developed to discover new MCRs: single reactant replacement (SRR), reaction-operator strategy, modular reaction sequences (MRS), condition-based divergence (CBD), and combination of MCRs (MCR^2).

1.1.2.1 SRR This strategy was first proposed by Ganem [26] and involves the replacement of one reactant with a different reactant that shows the same essential reactivity with other reagents, carrying out the same role in the reaction mechanism (Fig. 1.3). This approach has been demonstrated to be a valuable tool, providing different final adducts by incorporating additional functionalities in the reactants.

1.1.2.2 Reaction-Operator Strategy In this approach, defined by Mironov [27], there is a simultaneous replacement of two or more reagents with different reagents that show the same essential reactivity (Fig. 1.4). The name of this strategy comes from the comparison of chemical reactions with mathematical functions: in reactions, a reaction operator would be the equivalent to a function operator in mathematics. This reaction operator is introduced as an algorithm in a computer-controlled system, whose function is to find new reactions by using preexisting reactions as a starting point with the help of reaction preparation and analytical automated systems.

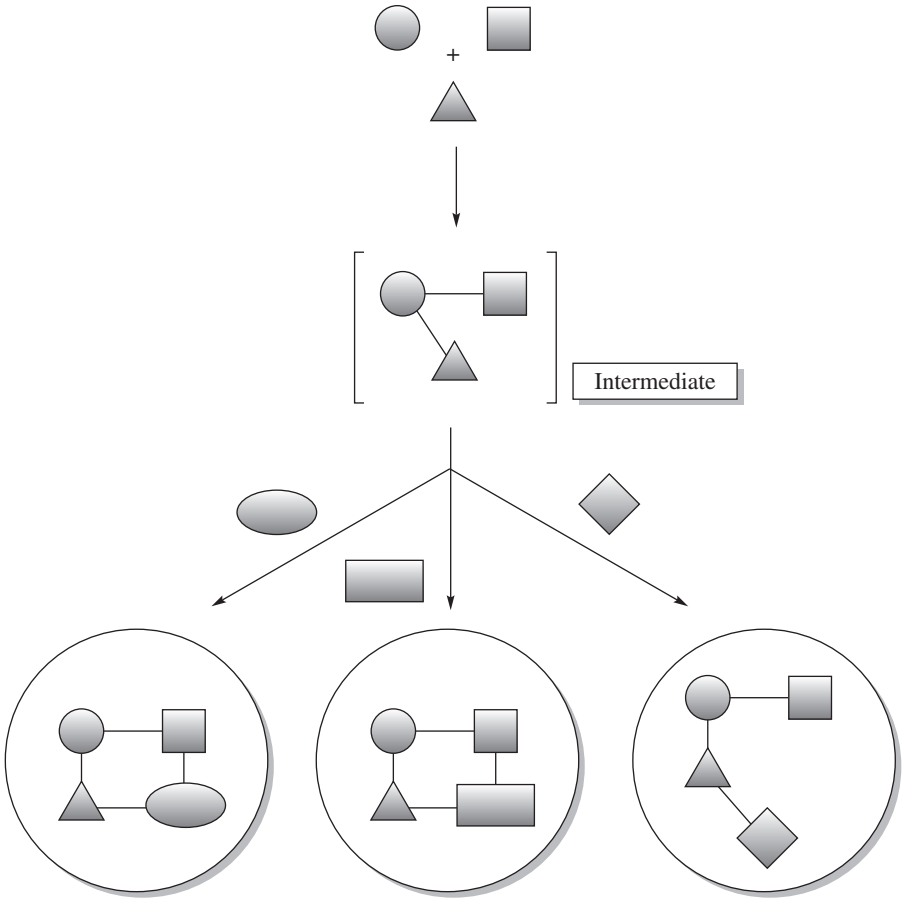


FIGURE 1.5 Modular reaction sequence approach in MCRs.

1.1.2.3 MRS This third approach involves a versatile reactive intermediate that is initially generated though a MCR from different substrates [28]. This compound is further treated *in situ* with a range of different compounds to produce a diverse set of more complex structures (Fig. 1.5). This divergent synthesis approach is very useful for rapidly generating scaffold diversity, creating large compound libraries.

1.1.2.4 CBD The use of specific catalysts, solvents, or additives could guide a reaction along different pathways, producing distinct final adducts (Fig. 1.6). There are some examples of MCRs that have different major products based on their reaction conditions [29]; however, it is uncommon to achieve a wide variety of adducts through this method. Many of these examples were discovered serendipitously, which is reflected in the limited number of reported examples. Although this approach is not frequently used, it is an efficient strategy for obtaining products with an attractive variety of scaffolds by simply varying reaction conditions.

1.1.2.5 MCR² The final strategy for the rational design of innovative MCRs is the combination of two or more different types of MCRs (Fig. 1.7) [30]. In this combinatorial chemistry approach, a certain compound with different functionalities that participates in a MCR reacts not only with the reagents of this MCR but also reacts with a molecule from a different MCR. When the results of each individual MCR are known, it might be possible to predict what products would be obtained from mixing both MCRs *via* a linker molecule. However, scientists should always take into consideration whether reactions that involve these linkers are reversible or not. In fact, this is a crucial parameter to be studied in order to make any MCR² work properly and to attain the best possible results.

1.1.3 Discovering New MCRs with Automated Combinatorial Reaction Finding

An appealing approach to discover innovative MCRs is to use the automated combinatorial reaction finding method, due to the large number of reactions that it studies simultaneously. This combinatorial chemistry approach combines mechanized analytical and reaction preparation systems in order to study the products from a large number of MCRs that are being carried out at the same time in separate well plates [31].

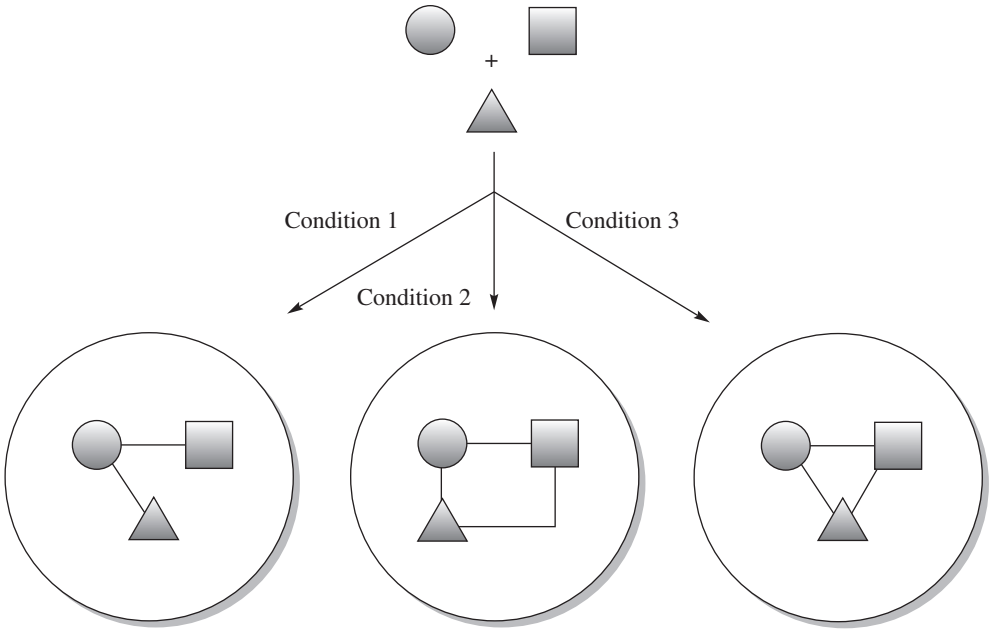


FIGURE 1.6 Divergence in MCRs achieved through changing reaction conditions.

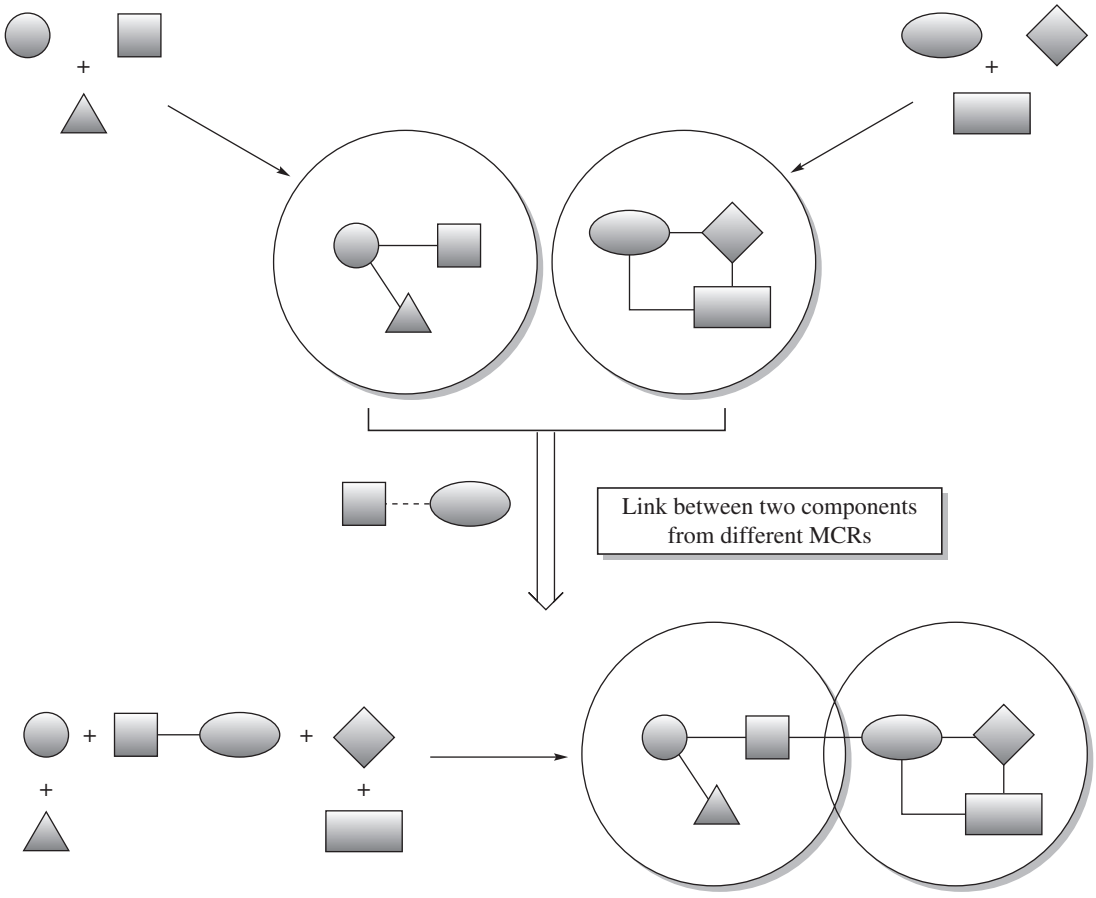


FIGURE 1.7 Combination of two MCRs.

In this approach, a robotic dispensing system prepares the reactions, then they are studied *via* automated high-performance liquid chromatography (HPLC) and/or mass spectroscopy (MS) systems, and finally, the data is collected and evaluated by a computer. This may save a considerable amount of time, since the exploration of such large number of reactions without using computer-controlled processes would require an enormous amount of time.

1.1.4 Computational and Analytical Tools to Study MCRs

Even though serendipity has always played a pivotal role in the discovery of new types of MCRs, the steady increase of publications in the last decade indicates an emergence of new ways to design MCRs in a more rational way. There are some tools that can help researchers to make decisions when performing MCRs. For example, there are computational programs that predict the main product when different starting reagents are put together in a reaction, enabling the creation of huge virtual compound libraries [31].

However, designing an enormous amount of products to synthesize is not very practical, since preparing and testing every product would require a considerable amount of time. Fortunately, there are computational programs that deal with this challenge. These programs sift through the virtual libraries that compile the resultant products from specific MCRs, selecting those products that may have biological activity. The ability to use these programs to target specific biological activities makes them especially appealing for drug discovery [32]. The results obtained after these filtering steps must always be verified through experimental work; however, doing these computational studies first can save time and effort.

Another strategy is using analytical techniques to study MCRs. There are diverse techniques that have appeared recently and are still being developed, such as coupling liquid chromatography, MS, and nuclear magnetic resonance (LC–MS–NMR) [31, 33]. These techniques allow having a better knowledge of the crude reaction mixture, making it possible in many cases to identify by-products, intermediates, and main products. This is helpful for interpreting the mechanisms that govern these MCRs, which helps researchers to predict whether or not certain changes in the reactants would result in variations in the final structures. Also, knowing different MCR mechanisms might help to predict whether a MCR^2 will have favorable results or not.

1.1.5 Diversity-Oriented Synthesis and Biology-Oriented Synthesis

Diversity-oriented synthesis (DOS) was defined by Schreiber in 2000 [34]. He referred to synthetic processes that contain only a few steps (~3–5) and are planned with a forward planning strategy rather than designed with a retrosynthetic analysis. The reason behind this is that products obtained using this approach are not aimed at one specific biological target, which makes a retrosynthetic analysis to create products that bind to specific sites useless. This approach proposes that in order to address biological targets that are innocuous to drugs currently being used, researchers should synthesize new designs that are not based in natural products, since natural products only interact with specific biological targets [35].

In 2006, Waldmann and coworkers introduced the concept of biology-oriented synthesis (BIOS) [36]. This approach's goal is to enable small organic molecules to bind to proteins by mimicking certain core structures found in natural products [37]. This is accomplished by adding the part of a natural product's structure that commonly binds to a certain protein to a small organic molecule, thus allowing it to bind to that protein.

Both of the aforementioned concepts are interesting because they could be useful for discovering new molecules with promising biological activity. However, in order to be successful, they require the synthesis of a great number of different compounds, since there are a huge number of variations among the synthesized structures that might drastically change their biological activity. MCRs have proven to be useful in DOS and BIOS due to the fact that libraries with a large amount of drug candidates can be created through easy approaches [38]. Synthesizing many different compounds through MCRs is especially appealing when the reactions are combined with high-throughput screening [5, 39]. This is an easy, fast, and effective way to generate a large group of diverse compounds which properties, biological or other, can be readily tested.

For this reason, MCRs are crucial tools along with DOS and BIOS. The development of these two promising areas will undoubtedly depend on the development of MCRs within these fields.

1.1.6 Optimization of MCRs

As previously stated, MCRs are reactions where more than two starting materials react in one single vessel. Since the collision of three or more independent molecules is highly unlikely, MCRs typically involve a number of basic reactions with individual mechanisms, each one normally requiring different reaction conditions.

In 1997, Ugi proposed a classification system for MCRs based on the reversibility of their individual reactions [40]. These reversibility parameters play an important role in the results obtained in MCRs, and they change depending on the reaction's conditions. Optimizing these conditions is a really challenging aspect because the best conditions for a specific individual reaction are not usually the best conditions for the developed MCR, since optimizing one of the chemical

transformations generally results in changes in the efficiency of the other transformations. For this reason, a compromise must be found through the exploration and optimization of different reaction parameters, such as solvent, concentration, and temperature.

This optimization step may represent one of the most difficult tasks for developing new MCRs. However, recent developments in MCRs within other areas of chemistry, such as computational chemistry or analytical chemistry, have provided valuable tools for saving time and resources in the MCR optimization process. For example, certain computational programs, used in combination with the mechanized analytical and reaction preparation systems mentioned before, can expedite the optimization process of a MCR and drastically increase the yields obtained [31]. These computational programs use genetic algorithms, whose function is to change reaction parameters over successive sets of reactions depending on the results obtained in the previous set. This combination of genetic algorithms with automated systems has also proven to be very useful in drug discovery, since they can be used to optimize the values of a specific biological activity found in a MCR's products [41].

1.2 CATALYSIS IN MCRs AND VARIOUS SYNTHETIC APPROACHES

Many MCRs require a catalyst or a source of radiation to promote the formation of the desired products. The catalysts employed may have different functions, such as giving the desired stereocontrol [42], leading to the formation of a certain compound over the others, or simply ensuring that the reaction can be performed. In this section, different types of catalysis employed in MCRs will be discussed briefly, as well as different methods that improve the efficiency of these reactions.

1.2.1 Organocatalysis in MCRs

Chiral organocatalysis is a really attractive tool for performing effective reactions while avoiding the use of metals. Normally, organocatalysts contaminate less and are less toxic than organometallic catalysts because they do not include metals within their structures, which is beneficial for industries that try to avoid using metals, such as the pharmaceutical industry.

There are many different organocatalysts that have been used efficiently in asymmetric MCRs [43]. These organocatalysts have different ways of interacting with molecules, from forming covalent bonds with substrates, such as prolines, to interacting through hydrogen bonds, such as (thio) ureas. Many examples of how these types of organocatalysts are used in MCRs will be discussed in detail in Chapter 2.

1.2.2 Organometallic Catalysis in MCRs

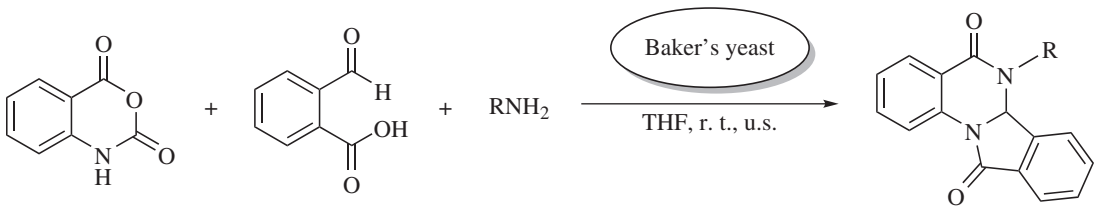
Organometallic catalysis has many advantages over the other types of catalysis. Metal catalysts display good results in an extensive range of reactions, achieving an alluring combination of short reaction times and excellent results. This area of catalysis has been more developed than the others and, therefore, has a bigger number of examples within the field of MCRs [44]. There are many cases of metals that have been effectively employed in MCRs as catalysts, such as palladium, rhodium, and ruthenium, among many others. Numerous examples of interest will be disclosed in Chapter 3.

1.2.3 Biocatalysis in MCRs

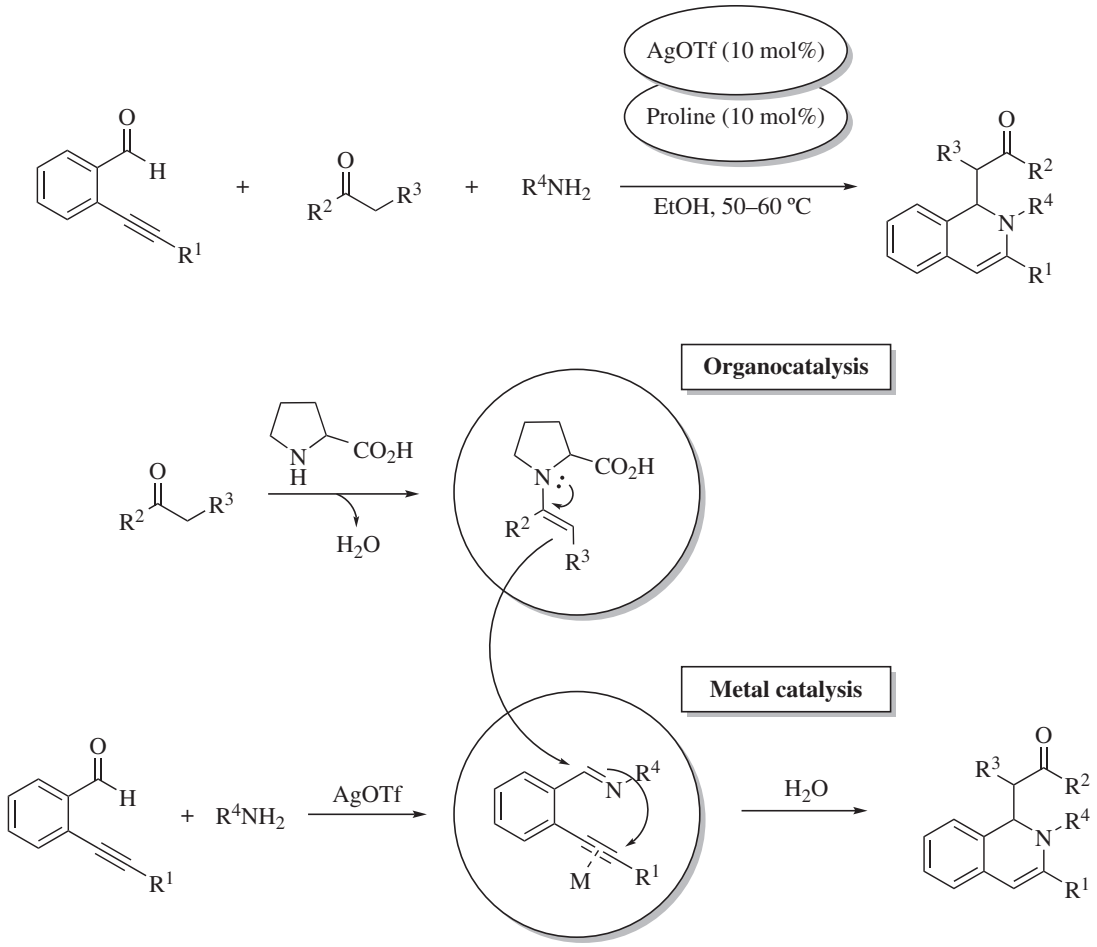
Biocatalysis refers to the use of enzymes or whole cells as catalysts in chemical reactions. This type of catalysis does not have as many publications as the other types of catalysis, but there are noteworthy examples where biocatalysts have been used in MCRs with very good results [45]. Even though only a small number of examples have been discovered so far, their promising results make biocatalysis an area of great interest among the scientific community. Due to the high specificity of enzymes for certain substrates, a high stereocontrol can be achieved in these reactions. Also, it is possible to obtain a specific product out of all the possible final products, even in reactions in which none of the other types of catalysis obtain acceptable results (Scheme 1.1).

1.2.4 Combining Different Types of Catalysis

MCRs are not restricted to the use of only one type of catalysis. Combining different types of activation facilitates the synthesis of compounds that are difficult to obtain when



SCHEME 1.1 Biocatalyzed synthesis of isoindolo[2,1-*a*]quinazolines carried out by Raval and coworkers using baker's yeast as the catalyst [45a].



SCHEME 1.2 Cocatalyzed MCR using a metal catalyst and an organocatalyst along with the proposed mechanism [46].

using just one type of catalysis (Scheme 1.2) [46]. Furthermore, results of certain MCRs may be improved by shortening reaction times and by procuring higher yields and more stereocontrol, making this a promising approach that calls for further research.

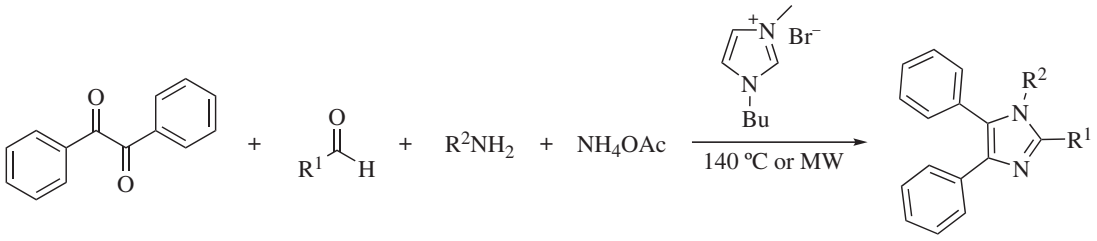
1.2.5 Other Methods

There are a large number of MCRs that use alternative approaches to enhance their results; some remarkable examples will be covered in Chapter 11. One of the most common strategies is using microwave (MW) radiation in the reactions. Heating reactions with this source of radiation has enormous advantages over normal heating methods because, when using a polar solvent, the reaction media is heated up more efficiently, causing shorter reaction times [47]. For this reason, MW radiation can sometimes substitute a catalyst that would otherwise be necessary in certain MCRs to achieve good results in short reaction times (Scheme 1.3).

Another strategy employed to obtain better results is performing reactions with ultrasonication (Scheme 1.4). Ultrasound irradiation is especially useful in reactions where the starting reactants are nearly insoluble in the reaction media (multiphasic systems), when volatile gases are generated in the reaction, and in reactions that involve radical or ionic species [50].

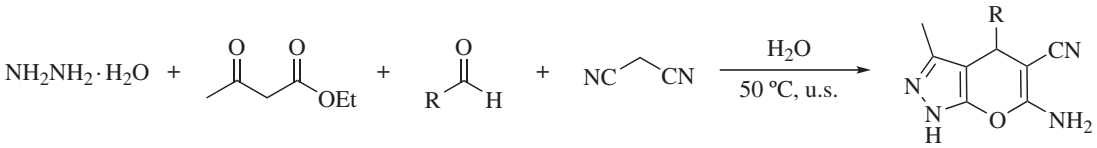
Solid-phase synthesis is another useful method for the synthesis of products that is now being applied to MCRs [51]. Solid-phase synthesis is the synthesis of compounds through reactions in which the final products are attached to a solid support. Once the products are obtained, these compounds are separated from the support after the by-products have been removed from the reaction media through simple washing steps (Scheme 1.5). This feature can simplify the reaction's work-up process, requiring only filtration and further treatment to free the product from the support, avoiding the necessity of other more tedious purification processes while saving time and resources. This approach is very appealing for the easy and rapid creation of compound libraries when combined with automated reaction preparation systems [2a, 52].

Other methods that can be effectively employed in MCRs are infrared (IR) and photochemical irradiations. These approaches are useful in specific circumstances where reactants



	Time	Yield
Conventional heating	1.5–5 h	82–93%
Microwave irradiation	3–8 min	82–93%

SCHEME 1.3 MCR using either conventional heating or microwave irradiation and the results observed by Hasaninejad and coworkers [48].



	Time	Yield
Normal stirring conditions	1–5 h	70–86%
Ultrasonication	15–40 min	79–95%

SCHEME 1.4 Synthesis of dihydropyrano[2,3-*c*]pyrazoles under ultrasound irradiation [49].

absorb those types of radiation, promoting their reaction with other reagents. There are only several examples of MCRs using these techniques [53], but further research may reveal new potential ways of synthesizing new complex molecules.

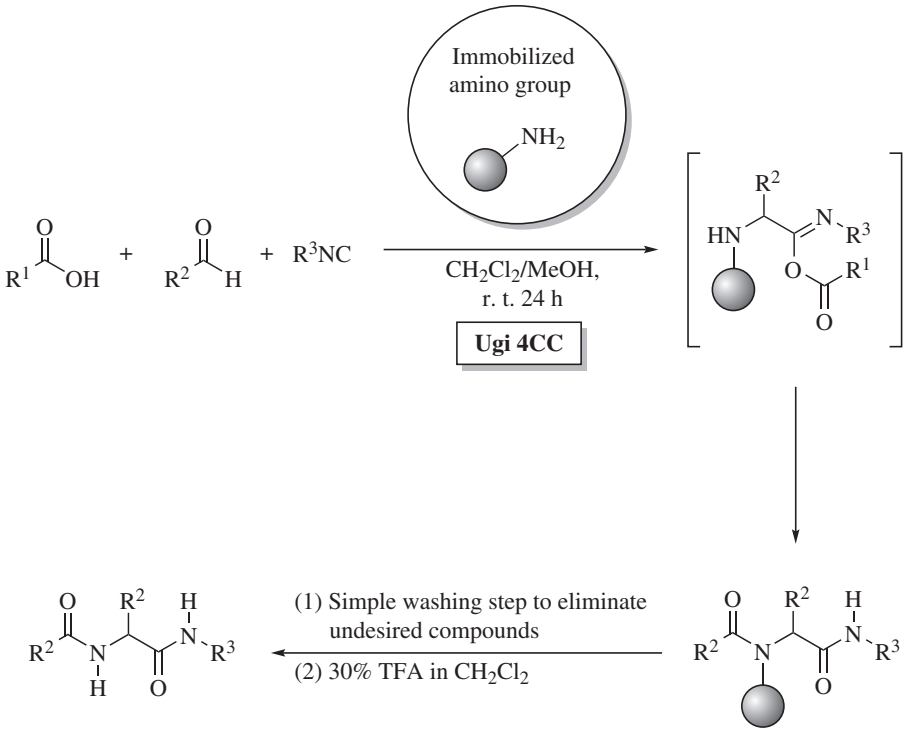
1.3 GREEN CHEMISTRY

MCRs are in agreement with the basic concepts of green chemistry set by Anastas and Warner in 1998 [54], providing final complex products in one step through novel synthetic strategies that are environmentally friendly. Some appealing advantages of using MCRs are the generation of a smaller amount of waste, the conservation of resources, and the reduction in the energy required. All these advantages have brought MCRs into the focus of researchers whose goal is developing pioneering green chemistry processes. Throughout this section, some techniques recently used in MCRs that adhere to the standards set by green chemistry will be discussed.

1.3.1 Atom Economy

Atom economy, a concept that was introduced by Trost in 1991, measures the efficiency of a reaction by comparing the amount of the targeted final product to the amount of other products generated [11]. This concept presents the need to design reactions where the majority of the reactants are incorporated into the desired product. This approach is preferred over others, such as breaking down a complex reactant to obtain a product, due to the fact that in the latter approach, even when reaction yields are 100%, the rest of the starting material normally is wasted.

MCRs are clear examples of successfully applied atom economy. In these reactions, different molecules are converted into a complex product in an efficient way. Thus, the development of MCRs also implies the development of atom-economical reactions.



SCHEME 1.5 Syntheses of a large number of compounds having the same base structure through Ugi four-component condensations carried out by Armstrong and coworkers [51b].

1.3.2 Using Green Solvents

The use of green solvents in chemical reactions is a topic that has been concerning chemists throughout history [55]. There are many publications and ongoing research projects regarding this issue. In fact, researchers have always aimed to perform reactions with environmentally friendly solvents, especially if they are reusable and/or recyclable. Some examples of green solvents used in MCRs are water [56], ionic liquids (ILs) [57, 58], and bio-based solvents [56]. These solvents are not only environmentally friendly, but they also present fascinating properties that sometimes lead to unexpected results that would be difficult to obtain using other common solvents. Many innovative and interesting cases will be explored in Chapter 11 and throughout the rest of the book.

1.3.3 Solventless MCRs

Performing effective solventless reactions has been a challenging topic in many fields of chemistry, and there is a lot of ongoing research on these reactions. Implementing reactions in the absence of solvents is a textbook example of a green synthetic strategy in which the elimination process for waste generated by the solvent is no longer necessary. However, working without solvents can complicate the mixing process and make it more difficult for the substrates to react.

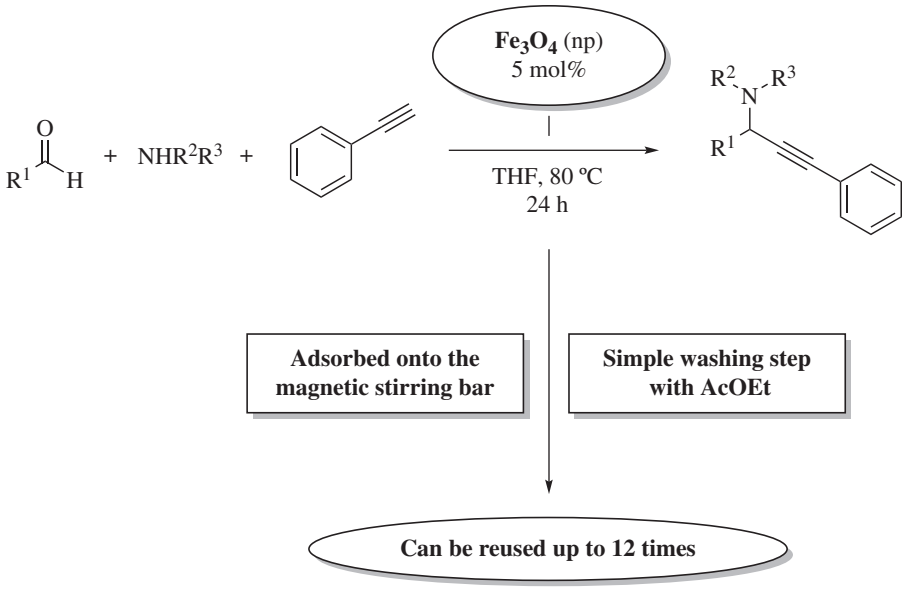
Many examples of MCRs have been performed without incorporating a solvent [59, 60]. The techniques that have had the best results in these reactions are mechanochemical procedures [61], MW irradiation [62], and IR irradiation [53].

1.3.4 Heterogeneous Catalysis in MCRs

Heterogeneous catalysis is really interesting not only because of multiphasic systems' intriguing characteristics but also because the catalysts are easy to recover and reuse. Reusable catalysts bring economic advantages to the table; they can reduce the costs of the reaction since they can be reutilized in subsequent reactions.

The most common strategy for synthesizing reusable catalysts is attaching the desired catalyst to a specific support, such as resin or silica, which makes them insoluble in many solvents. These supports do not degrade in solutions, allowing them to be separated easily by filtration at the end of the reaction and then reused in a subsequent reaction. A similar method is to use catalysts that are not soluble in the reaction media. Where, again, a simple filtration process is all that is required to separate the catalysts.

Also, another emerging approach used in MCRs that involves easily recoverable catalysts is the use of magnetic particles as catalysts or as supports for catalysts (Scheme 1.6). The enormous interest in this type of particle comes mainly from how effortless it is to recover these particles from the



SCHEME 1.6 MCR using reusable magnetic particles as the catalyst [63a].

reaction media using magnets. There are many examples of MCRs that use magnetic particles. In some of these examples, the catalysts are compatible with water, and in others, they show promising results in solventless reactions [63].

1.4 IMPORTANCE AND EVOLUTION

MCRs represent a pivotal step in the development of modern chemistry. Unfortunately, many of the aforementioned reactions have only been extensively explored in their racemic version. With all the development that asymmetric catalysis has experienced over the years, new strategies have come to light, which will enable researchers to perform these previously racemic MCRs with stereocontrol.

Moreover, with the growing interest in using green chemistry to design cleaner organic reactions, mild, energy-efficient, and atom-economical processes will be the standards for chemistry in the near future. Also, other methods, already in use, will be improved in order to follow this trend in the pharmaceutical sector, aiming to synthesize drugs through more environmentally friendly reactions. MCRs have already been used for the synthesis of a handful of biologically active products with successful results (see Chapter 6). Further efforts are required to convert these procedures into competitive processes that can be implemented in the synthesis of a wide range of biologically active compounds.

The future of this area will most likely rely on the development of techniques that save time, energy, effort, and resources, as well as decrease the amount of waste generated in reactions. The development of the aforementioned computational and analytical techniques will play a vital role in future advances in MCRs. When using these techniques, it becomes easier to focus on the most valuable products of a certain MCR, shortening the time required for obtaining products with specific characteristics. Furthermore, these techniques expedite the study of products that result from a set of MCRs and the creation of novel reactions.

Also, there are already many examples of MCRs that employ methodologies from green chemistry, such as using reusable catalysts, recyclable solvents, and mechanochemical processes. The increase in the use of these techniques and green solvents in MCRs shows that these reactions will evolve along with green chemistry.

All the reasons mentioned previously make MCRs a valuable and competitive source for synthesizing biologically active products and other compounds with interesting uses in both minor scale and industrial research.

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