



Research Article

## Green Organic Synthesis via Multicomponent Reactions

G. Bosica<sup>\*1</sup>, K. Baldacchino<sup>1</sup>, R. Abdilla<sup>1</sup> and R. De Nittis<sup>1</sup>

<sup>1</sup>Laboratory of Green Synthetic Organic Chemistry, Department of Chemistry, University of Malta, Msida, Malta

**Abstract.** The success of the modern pharmaceutical industry is largely due to the remarkable achievements of organic synthesis over the last century. However, many of these reactions were developed at a time when the toxic properties of many reagents and solvents were not known and waste minimisation and sustainability were not significant issues. By the latter half of the 1980s, the worldwide chemical industry knew that it had to clean up its act: its environmental reputation was terrible. In the past two decades, the Green Chemistry movement has helped industry become much cleaner. Green chemistry efficiently utilises (preferably renewable) raw materials, eliminates waste, and avoids the use of toxic and/or hazardous reagents and solvents in the manufacture and application of chemical products. There are several ways in which organic synthesis can be carried out in line with the Green Chemistry principles and, among these, multicomponent reactions under green conditions prove to be useful and versatile tools. Recent examples of applications will demonstrate the molecular diversity that can be obtained from this green synthetic approach.

**Keywords:** Green chemistry, organic synthesis, heterogeneous catalysis, one-pot multicomponent reaction

### 1 Introduction

#### 1.1 What is Green Chemistry?

In the 1980s and 1990s, several environmentally conscious terms entered the chemical arena. Specifically, after Anastas and Warner's contributions in 1998, the use of green chemistry has clearly been growing rapidly in a linear fashion (Linthorst, 2010). Green Chemistry can be generally described as "the design of chemical products and processes to reduce or eliminate the use and generation of hazardous substances" (Anastas et al., 1998). Rather than a separate field of chemistry, Green Chemistry is a philosophy, a way of thinking which should be applied

to the design, manufacture and application of chemical products. This is by no means an easy task, as most chemicals are not benign, making the development of a fully "environmentally-friendly" process practically impossible. Therefore, in order to reduce the environmental impact caused by chemical processes, rather than trying to only achieve the perfect environmentally-benign synthesis, twelve guiding principles were developed in order to facilitate chemists in designing more sustainable chemical processes (Anastas et al., 2010). The fundamental idea behind green chemistry is the awareness that it is better to prevent waste than to treat or clean up after it is formed, as specified in the first and most important of the twelve principles (Anastas et al., 1998). Quite recently, Paul T. Anastas and Julie B. Zimmerman published an alternative "Periodic Table" highlighting key elements present in Sustainable and Green Chemistry (Anastas et al., 2019). This format was an interesting approach towards explaining the multifaceted nature of Green Chemistry. In fact, the table summarises the general approaches taken in green chemistry and engineering into element-group type categories and includes humanitarian aspects, which reveal the more sustainable tomorrow towards which human society is generally striving for.

#### 1.2 Why Green Chemistry?

This issue of environmental protection and sustainable development has been gathering awareness since the late years of the 20th century, initially starting from Rachel Carson's *Silent Spring* which highlighted the detrimental effects caused by the release of pesticides in the environment (Carson et al., 1962). This spark set in motion the development of various policies and practices, such as USA's Pollution Prevention Act in 1990, which emphasized the environmental and economic urge to adopt the policy of pollution prevention instead of end-of-pipeline control (Congress, 1990). It became clear that a paradigm shift was needed in industrial organic synthesis

\*Correspondence to: G. Bosica ([giovanna.bosica@um.edu.mt](mailto:giovanna.bosica@um.edu.mt))

from traditional concepts of reaction efficiency and selectivity, that focus largely on chemical yield, to one that assigns value to raw materials utilisation, elimination of waste and circumventing the use of toxic and/or hazardous substances. More than 50 years later, the general goal has shifted towards the development of a more sustainable future, with the United Nations outlining 17 Sustainable Development Goals in the 2030 Agenda for Sustainable Development. Goal 9 in particular states the need to: “*Build Resilient Infrastructure, Promote Inclusive and Sustainable Industrialisation and Foster Innovation*” (Nations, 2021). This goal directly specifies the need to innovate as it is the main driver which allows understanding and development. However, the means by which innovation is met also has to be sustainable itself (Anastas et al., 2018). One could say that sustainability is our ultimate common goal and green chemistry is a means to achieving it (Sheldon, 2000).

### 1.3 Green metrics—a way to measure the reaction environmental benignity

One very important aspect of Green Chemistry is the use of certain metrics which can quantify how environmentally-benign a given chemical process is and allow comparisons to be made between different methods. The E-factor is one of the most widely used metrics as it quantifies the amount of waste generated relative to the amount of product produced in a chemical process (equation 1) (Sheldon, 2007). The higher the E-factor, the more waste is generated, ergo meaning that in green chemistry the aim is to always keep the E-factor as low as possible. This concept is particularly illuminating in organic synthesis, as the metric that in the past was generally regarded as important was the overall reaction yield, with high yielding reactions implying efficient conversion of the limiting organic substrate. However, the reaction yield does not consider the consumption of excess reagents, organic or inorganic, which end up being wasted at the end of the reaction. Meanwhile, the E-factor does take into account all the waste generated which includes by-products, excess reagents and any chemicals required for work-up and which are ultimately discarded as waste. The E-factor can be lowered only if certain “waste materials” are recycled or repurposed for other uses. This can be put in practice by opting for fully recyclable catalysts and trying to convert by-products into raw materials for other processes. It is also interesting to note that such a case can be made for solvents, which can be mostly recovered using distillation processes in certain circumstances.

Another important measure used in Green Chemistry is the Atom Economy (AE) metric, which can be defined as the proportion of reagent atoms which are incorporated

$$\text{E-Factor} = \frac{\text{Mass of waste (kg)}}{\text{Mass of product (kg)}}$$

**Equation 1:** The Environmental Impact Factor—A green metric which quantifies the amount of waste generated in the production of 1 kilogram of product.

$$\text{Atom Economy} = \frac{\text{RMM}_{\text{product}}}{\sum \text{RMM}_{\text{reagent}}} \times 100$$

RMM = Relative Molecular Mass

**Equation 2:** Atom Economy—A green metric which quantifies the proportion of reagent atoms which are incorporated in the final product.

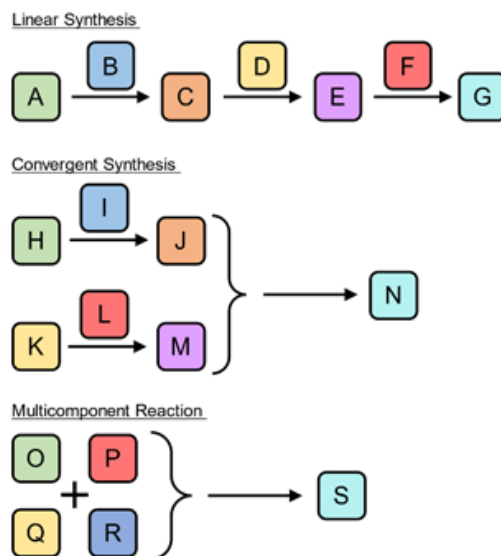
in the final product (equation 2) (Trost, 1991).

The metric quantifies how efficient a reaction is in terms of incorporating raw material atoms into the desired product. A higher atom economy is preferred as it implies a more efficient use of the starting reagents. In truth there are other green metrics which exist apart from the two aforementioned terms. Yet, the ease and simplicity with which the E-factor and AE metrics can be determined, makes them more generally used.

### 1.4 Multicomponent reactions

Multicomponent Reactions (MCRs) can be defined as reactions that combine three or more reagents in the same reaction pot to yield one main product (Zhu et al., 2014). As illustrated in figure 1, these types of reaction are different from typical linear synthetic reactions whereby reagents are added sequentially in to form a final product. Instead, they have a convergent nature whereby different reactions occur in parallel and intermediates combine to form the final product. However, MCRs are more efficient when compared to typical convergent synthesis. Whereas the reactions in a convergent synthetic pathway typically occur under separate conditions, the reaction steps in an MCR occur in the same pot, thus avoiding the need to isolate and purify any synthetic intermediates.

A large number of MCRs have been developed over the years, all furnishing diverse products. This allows MCRs to be powerful tools in modern-day drug discovery, due to ease with which a wide-variety of structurally similar compounds containing privileged scaffolds can be generated (Kalinski et al., 2010). MCR innovation is one of the current developments in these types of reactions. One of the most common techniques employed is the single reactant replacement (SRR) approach, whereby one of the starting reagents is replaced with a different functionality that mimics some of its chemical properties (Ganem, 2009).



**Figure 1:** Schematic representation of linear synthesis, convergent synthesis and multicomponent reactions.

There are also many advantages associated with MCRs in the context of Green Chemistry (Cioc et al., 2014). The “one-pot” nature of these systems greatly reduces the need of auxiliary solvents and chemicals that would be required in the isolation and purification of intermediates. MCRs also typically consist of addition and condensation steps, which have high atom economies. Hence, this implies more efficient use of raw materials and reduced waste generation. The combination of three or more reactants in a single reaction also generates a product with a larger molecular weight (and different functionalities) compared to its precursors and by-products. These factors contribute to differing solubilities and opens up the possibility for purification via recrystallisation rather than chromatography or distillation, which in turn makes use of less solvents and auxiliary chemicals. More so, well-established MCRs typically exhibit a high degree of chemo- and regioselectivity, further reducing the need for derivatising steps and the use of blocking groups.

### 1.5 Solvents in green synthesis

Solvents play important roles in synthetic organic chemistry. Apart from facilitating reaction progression via reagent solvation, the appropriate solvent can also favour certain reaction mechanisms rendering certain synthesis more viable. However, from a Green Chemistry perspective, solvent use can be problematic principally because it results in significant levels of waste generation. Furthermore, since commonly used solvents are volatile, environmental containment is difficult and workers are more exposed during use. In light of this, there has been significant focus on decreasing the hazards and environmental

impact caused by solvents. One general approach involves switching to less harmful solvents whenever possible (Alfonsi et al., 2008). More modern approaches involve using greener solvents. An alternative tactic is actually not using a solvent at all and running the reaction neat (Zangade et al., 2019). This can be done if some of the reagents are liquids under conventional heating conditions, although this technique can also be coupled with the use of alternative energy-transferring mechanisms (Sainath et al., 2019).

### 1.6 Heterogeneous catalysts preferred to homogeneous ones

The use of catalysts over stoichiometric quantities is fundamental in Green Chemistry, with the main aim being to further reduce the waste generated in a reaction (Anastas et al., 2001). A catalyst can be loosely defined as a chemical which participates and speed up a reaction but is ultimately chemically unaltered. This should, in principle, allow the catalyst to be recycled for further runs, thereby further minimizing the waste generated. However, catalyst recycling can be a laborious and energy-intensive process if the catalyst in question is homogeneous in nature, as it would probably require the use of other solvents and materials to isolate and reuse. This is where employing a heterogeneous catalyst becomes advantageous, as it allows the catalyst to be easily separated from the reaction mixture through filtration, which allows for easier catalyst recycling and reaction quenching. The nature of heterogeneous catalysis must also be discussed as the difference between homogeneous and heterogeneous catalysts is not as clear cut as it might seem. This argument applies

especially for catalysts consisting of a catalytic species immobilised onto a heterogeneous support. Sheldon described three main scenarios that can occur (Sheldon et al., 1998):

1. The active species remains bound to its support throughout the duration of the reaction, making the catalysis observed truly heterogeneous or,
2. The active species leaches but does not act as a homogeneous catalyst or,
3. The active species leaches and acts as a homogeneous catalyst.

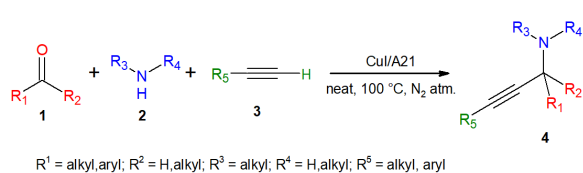
The presence of these three potential scenarios brings about the need for determining whether the catalyst is truly heterogeneous in nature and whether catalytic leaching occurs throughout the course of the reaction. A number of different tests have been developed, which can be used to determine which scenario is present, with one of the most commonly used being the Sheldon hot filtration test, which determines whether the catalyst is truly heterogeneous in nature or not (Crabtree, 2012). A wide variety of heterogeneous catalysts have been employed over the years, either directly as reagents or as supports for active catalysts. These range from clays and zeolites (Varma, 2002) to functionalised polymer resins such as Amberlyst A-15 (Kuchukulla et al., 2019; Yadav et al., 2007) and Amberlyst A-21, naturally-derived supports such as chitosan (Bodhak et al., 2015), metal organic frameworks (MOFs) (Pascanu et al., 2019), and even magnetic nanoparticles (MNPs) (Abu-Dief et al., 2018). Each support has its own advantages and special properties, ranging from increased porosity, stability, functionality, versatility, handling and ease of recovery (particularly in the case of MNPs). But the common theme between all these examples remains the ease with which they can be recycled, which in turn further contributes towards making synthesis more environmentally-benign.

### 1.7 Bosica et al. and research in green synthetic chemistry via MCRs

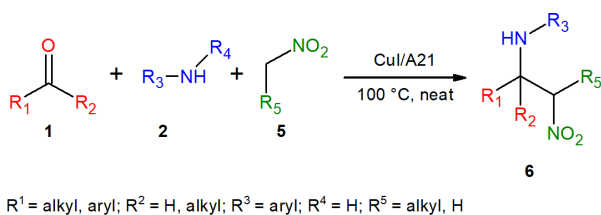
Organic synthesis needs to go hand in hand with the pillars of green chemistry (waste prevention, renewable feedstock, catalysis, alternative solvents, less toxic and safer reaction conditions, energy efficiency, and synthetic efficiency) especially since it plays a critical role in the preparation of functionalized products with special physical, chemical, and biological utilities. Synthetic efficiency is particularly important because it is not only driven by the green chemistry considerations but may also have huge economic benefits. One-pot organic reactions are important methods to achieve high synthetic efficiency. As described in the previous section, there are different tools

that can be employed in order to make a particular synthesis greener. The research group led by Prof. Bosica has recently made a shift towards investigating certain MCRs and improving on existing protocols by modification of the substrates, hence expanding their versatility and making them more environmentally friendly via the use of heterogeneous catalysts and either solventless conditions or green solvents. The work focuses on applying green chemistry principles in the development and improvement of one-pot multicomponent reactions. Over a variety of projects, the group is applying the idea of single reactant replacement (SRR) which involves the replacement of one of the reactants by a related one which may or may not have a similar role in the overall mechanism of the reaction. As a general approach, a number of heterogeneous catalysts are screened on a model reaction, followed by a reaction optimisation whereby the most ideal conditions are determined by altering certain reaction conditions such as catalytic quantities, reaction temperature and solvents. The model reaction is also studied extensively by using GC analysis in order to understand the mechanism by which it is proceeding. The robustness of the developed procedure is then assessed by systematically altering the starting reagents to expand the scope of the reaction protocol. A number of green metrics are also calculated to quantify how "green" the reaction is, whilst recycling tests are carried out in order to determine to what extent the catalyst can be re-used after recovery. Scheme 1 shows one of the earliest MCRs tackled by this group i.e. the synthesis of propargylamines via the A<sup>3</sup> coupling reaction (Bosica et al., 2015), as well as its similar counterpart, the KA<sup>2</sup> coupling reaction (Bosica et al., 2017). Whilst the reaction itself had already been previously reported, the novelty in the developed protocol was the application of copper(I) iodide supported on Amberlyst A-21; a heterogeneous catalyst with both Lewis acidic and basic properties. In both cases, the reaction was also carried out under solventless conditions, further reducing the use of solvent in the overall process. In both studies a plethora of products were obtained in excellent yields and in relatively short reaction times. Furthermore, under the developed protocol, the reaction showed a high Atom Economy of 95%, a low E-factor of 0.3, and appreciable catalyst recyclability potential (catalyst could be reused in six consecutive trials in case of the A<sup>3</sup> and for four times in case of the KA<sup>2</sup> coupling).

This CuI/A21 catalyst was also applied in another MCR investigated, namely the nitro-Mannich reaction (scheme 2) (Bosica et al., 2018b). In order to arrive at this reaction, the SRR approach was applied, with the nitroalkane replacing the ketone owing to its similar chemical reactivities i.e. the presence of acidic  $\alpha$ -hydrogens.



**Scheme 1:** Synthesis of propargylamines via the A<sup>3</sup> or KA<sup>2</sup> coupling reaction in which substrate 1 is an aldehyde or a ketone respectively.



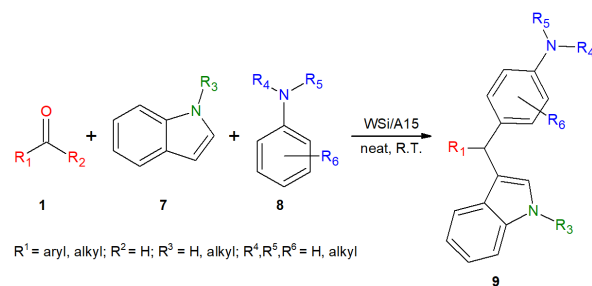
**Scheme 2:** Synthesis of  $\beta$ -nitroamines via the nitro-Mannich reaction.

Thus, the scope was to investigate a less well-known MCR and optimize it under heterogeneous catalysis and solventless conditions.

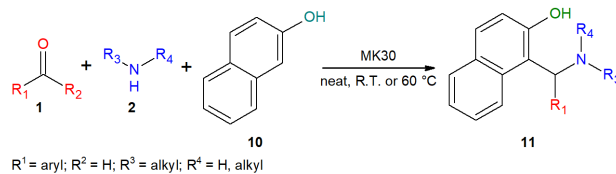
Once again, the recyclability and stability of the catalyst indicated consistent performance with a reduction of only 10% of the original yield over eight cycles and the loss of only 1% (by mass) of copper content. The green metrics results of this reaction were also highly praised with a high atom economy of 93% and a low E-factor of 1.26. Furthermore, the reaction showed a broad scope of reactants and the group was able to synthesize over twenty-five novel products in moderate to high yields.

Another example of investigating an MCR variant is shown in [scheme 3](#), whereby a green protocol was developed for a modified aza-Friedel-Craft reaction (Bosica et al., 2017). Noteworthy, in an unprecedented approach, three types of anilines (primary, secondary and tertiary) all were reacted successfully with the other two components of the reaction, ergo indoles and aldehydes to generate 3-substituted indoles. Solventless conditions were likewise employed, and the reactions proceeded under ambient conditions, making them energy efficient. Similar to the above studies, the catalyst used, silicotungstic (WSi) acid immobilised on Amberlyst A-15 beads, was heterogeneous in nature.

The protocol developed was especially renowned because for the first time it was reported that primary anilines gave excellent yields under neat conditions with a heterogeneous catalyst. More importantly, while pre-



**Scheme 3:** Modified aza-Friedel-Crafts reaction employing primary, secondary and tertiary anilines (9)



**Scheme 4:** The Betti synthesis reaction catalysed by MK30 clay in neat conditions.

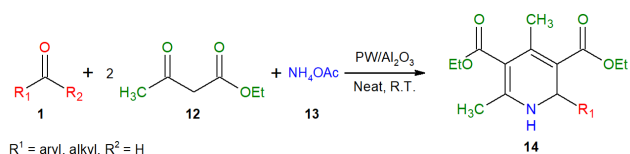
vious publications highlighted alternative product formation when utilising tertiary amines, in this study, all the reactions involving primary, secondary, and tertiary anilines proceeded regio-selectively. Lastly, the catalyst was fully and easily recoverable (due to its physical spherical nature) and recyclable up to 5 times with the yield only decreasing by 10%.

[Scheme 4](#) shows a modified Betti synthesis which was optimised under heterogeneous catalysis and solventless conditions (Bosica et al., 2018a). In this case, the ammonia reagent present in the original Betti reaction was replaced with a secondary amine instead. An acidic clay catalyst, Montmorillonite K-30, was employed.

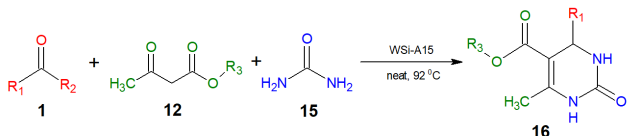
The resulting E-factor and atom economy were 3.92 and 94% respectively. As part of the study, the library of products obtained from the scope of reaction were tested for pharmacological applications. Impressively, a number of products manifested anti-proliferative activity prompting further research of the respective Betti bases as privileged scaffolds in tryptophan mimetics in blocking the solute carrier transporter SLC6A14 (Puerta et al., 2019).

More recently, a modified version of the Hantzsch synthesis was optimised under green conditions ([scheme 5](#)) (Bosica et al., 2020). Whilst the classical Hantzsch reaction tends to furnish 1,4-dihydropyridine products, the use of certain conditions was noted to result in the formation of the 1,2-dihydropyridine regioisomers as the main product instead. Indeed, this variation was investigated, with phosphotungstic acid (PW) immobilised on alumina





**Scheme 5:** Modified Hantzsch synthesis resulting in the formation of 1,2-dihydropyridine derivatives (14)



**Scheme 6:** The Biginelli synthesis catalysed by silicotungstic acid supported on Amberlyst 15

in solventless conditions at room temperature proving to be the ideal catalyst and conditions.

Silicotungstic acid, a heteropoly acid structurally similar to phosphotungstic acid, was supported on Amberlyst-15 beads and used successfully as a heterogeneous catalyst for the Biginelli reaction under solventless conditions (scheme 6). The three-component Biginelli reaction involves the combination of an aldehyde, a  $\beta$ -ketoester and urea to produce 3,4-dihydropyrimidin-2(1H)-ones, also known as DHPMs. The synthesis of these products is highly important due to their myriad of medicinal properties, amongst them acting as calcium channel blockers and antihypertensive and anti-inflammatory agents.

The catalyst was fully recoverable and reusable for up to five runs and the heterogeneity of the reaction was confirmed by carrying out a hot filtration test (Bosica et al., 2021). Again, a high atom economy of 87% and a low E-factor of 0.95 highlighted the greenness of the procedure.

## 2 Conclusion

Green chemistry emerged in the 1990s to address the increasing number of health and environmental issues caused by hazardous chemicals and materials. Their toxicity was either not considered or undervalued and sometimes even just simply ignored. The use and development of MCRs in the future must not be underestimated as they represent a truly viable solution for more sustainable synthesis. The general approach taken by Prof. Bosica research group is to optimize certain less-investigated variations of known MCRs or to develop new ones whilst always aiming for environmentally-benign conditions. At the heart of the strategy, the best heterogeneous catalyst for the reactions is identified on the basis of recyclabil-

ity, cost, yield of the product and rate of reaction. The catalysts can be either found commercially as Montmorillonite clay or synthesised in the lab as in the case of Amberlyst-21-immobilised copper(I) iodide. Therefore, a particular emphasis is being placed on the use of heterogeneous catalysts due to their recyclable nature, with the advantages of being easily separated from reaction mixtures, having high catalytic activity, not requiring hydrolytic workup and solvent extraction, and last but not least being easier to handle and causing less risk to human beings.

## 3 Acknowledgements

The authors thank the University of Malta and the ENDEAVOUR Scholarship Scheme (Malta) part-financed by the European Union—European Social Fund (ESF) under Operational Programme II—Cohesion Policy 2014-2020, “Investing in human capital to create more opportunities and promote the well-being of society” for financial and technical support.

## References

- Abu-Dief, A. M. & Abdel-Fatah, S. M. (2018). Development and functionalization of magnetic nanoparticles as powerful and green catalysts for organic synthesis. *Beni-Suef University Journal of Basic and Applied Sciences*, 7(1), 55–67.
- Alfonsi, K., Colberg, J., Dunn, P. J., Fevig, T., Jennings, S., Johnson, T. A. & Perry, D. A. (2008). Green chemistry tools to influence a medicinal chemistry and research chemistry based organisation. *Green Chemistry*, 10(1), 31–36.
- Anastas, P. T. & Eghbali, N. (2010). Green chemistry: Principles and practice. *Chem. Soc. Rev.*, 39, 301–312.
- Anastas, P. T., Kirchhoff, M. M. & Williamson, T. C. (2001). Catalysis as a foundational pillar of green chemistry. *Applied Catalysis A: General*, 221(1–2), 3–13.
- Anastas, P. T. & Warner, J. C. (1998). *Green chemistry: Theory and practice*. Oxford University Press.
- Anastas, P. T. & Zimmerman, J. B. (2018). The United Nations sustainability goals: How can sustainable chemistry contribute? *Current Opinion in Green and Sustainable Chemistry*, 13, 150–153.
- Anastas, P. T. & Zimmerman, J. B. (2019). The periodic table of the elements of green sustainable chemistry. *Green Chem*, 21(24), 6545–6566.
- Bodhak, C., Kundu, A. & Pramanik, A. (2015). An efficient and recyclable chitosan supported copper(II) heterogeneous catalyst for C–N cross coup-

- ling between aryl halides and aliphatic diamines. *Tetrahedron Letters*, 56(2), 419–424.
- Bosica, G. & Abdilla, R. (2017). The KA<sup>2</sup> coupling reaction under green, solventless, heterogeneous catalysis. *Journal of Molecular Catalysis A: Chemical*, 426, 542–549.
- Bosica, G., Abdilla, R. & Demanuele, K. (2018a). Revisiting the Betti synthesis: Using a cheap, readily available, recyclable clay catalyst under solventless conditions. *European Journal of Organic Chemistry*, 2018(44), 6127–6133.
- Bosica, G., Cachia, F., De Nittis, R. & Mariotti, N. (2021). Efficient one-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones via a three-component Biginelli reaction. *Molecules (Basel, Switzerland)*, 26, 12.
- Bosica, G., Demanuele, K., Padrón, J. M. & Puerta, A. (2020). One-pot multicomponent green Hantzsch synthesis of 1,2-dihydropyridine derivatives with antiproliferative activity. *Beilstein Journal of Organic Chemistry*, 16(1), 2862–2869.
- Bosica, G. & Gabarretta, J. (2015). Unprecedented one-pot multicomponent synthesis of propargylamines using Amberlyst A-21 supported CuI under solvent-free conditions. *RSC Advances*, 5(57), 46074–46087.
- Bosica, G. & Zammit, R. (2018b). One-pot multicomponent nitro-Mannich reaction using a heterogeneous catalyst under solvent-free conditions. *PeerJ*, 6(e5065).
- Carson, R. & Darling, L. (1962). *Silent spring*. Houghton Mifflin Co.
- Cioc, R. C., Ruijter, E. & Orru, R. V. A. (2014). Multicomponent reactions: Advanced tools for sustainable organic synthesis. *Green Chemistry*, 16(6), 2958–2975.
- Congress, U. (1990). Pollution prevention act of 1990. *Public law (10th ed)*.
- Crabtree, R. H. (2012). Resolving heterogeneity problems and impurity artifacts in operationally homogeneous transition metal catalysts. *Chemical Reviews*, 112(3), 1536–1554.
- Ganem, B. (2009). Strategies for innovation in multicomponent reaction design. *Accounts of Chemical Research*, 42(3), 463–472.
- Kalinski, C., Umkehrer, M., Weber, L., Kolb, J., Burdack, C. & Ross, G. (2010). On the industrial applications of MCRs: Molecular diversity in drug discovery and generic drug synthesis. *Molecular Diversity*, 14(3), 513–522.
- Kuchukulla, R. R., Li, F., He, Z., Zhou, L. & Zeng, Q. (2019). A recyclable Amberlyst-15-catalysed three-component reaction in water to synthesize diarylmethyl sulfones. *Green Chemistry*, 21(21), 5808–5812.
- Linhorst, J. A. (2010). An overview: Origins and development of green chemistry. *Foundations of chemistry*, 12(1), 55–68.
- Nations, U. (2021). The 17 goals - sustainable development.
- Pascanu, V., Miera, G., G., A., Inge & Martin-Matute, B. (2019). Metal-organic frameworks as catalysts for organic synthesis: A critical perspective. *Journal of the American Chemical Society*, 141(18), 7223–7234.
- Puerta, A., Galán, A. R., Abdilla, R., Demanuele, K., Fernandes, M. X., Bosica, G. & Padron, J. M. (2019). Naphthol-derived Betti bases as potential SLC6A14 blockers. *Journal of Molecular and Clinical Medicine*, 2(2), 35–40.
- Sainath, Z. & Pravinkumar, P. (2019). A review on solvent-free methods in organic synthesis. *Current Organic Chemistry*, 23(21), 2295–2318.
- Sheldon, R. A. (2000). Atom utilization, E factors and the catalytic solution. *Comptes Rendus de l'Academie des Science – Series IIC - Chemistry*, 3(7), 541–551.
- Sheldon, R. A. (2007). The E factor: Fifteen years on. *Green Chemistry*, 9(12), 1273–1283.
- Sheldon, R. A., Wallau, M., Arends, I. & Schuchardt, U. (1998). Heterogeneous catalysts for liquid-phase oxidations: Philosophers' stones or trojan horses. *Accounts of Chemical Research*, 31(8), 485–493.
- Trost, B. M. (1991). The atom economy—a search for synthetic efficiency. *Science*, 254, 1471–1477.
- Varma, R. (2002). Clay and clay-supported reagents in organic synthesis. *Tetra*, 58, 1235–1255.
- Yadav, J. S., Reddy, B. V. S., Gupta, M. K., Prathap, I. & Pandey, S. K. (2007). Amberlyst A-21: An efficient, cost-effective and recyclable catalyst for the synthesis of substituted 4H-chromenes. *Catalysis Communications*, 8(12), 2208–2211.
- Zangade, S. & Patil, P. (2019). A review on solvent-free methods in organic synthesis. *Current Organic Chemistry*, 23, 2295–2318.
- Zhu, J., Wang, Q. & Wang, M. (2014). *Multicomponent reactions in organic synthesis*. John Wiley & Sons.