Synthesis of polymer-supported Zn(II) as a novel and green nanocatalyst for promoting click reactions and using design of experiment for optimization of reaction conditions

Mansoureh Daraiea, Majid M. Heravi, and Negin Sarmasti

ABSTRACT
A novel, highly stable and green ZnCl₂ nanoparticles (NPs) of modified poly(styrene-co-maleic anhydride) (SMA) was prepared by a simple procedure and was used to investigate the efficiency of the Click reaction. In this regard, SMA was modified with 3-aminopyridine to obtain the corresponding poly(styrene-co-maleimide) (SMI). ZnCl₂ was immobilized onto SMI as NPs. The obtained Zn(II)-SMI nanocatalyst was characterized using various techniques including FTIR, energy-dispersive X-ray spectroscopy, scanning electron microscope image, thermogravimetric analysis and inductively coupled plasma. The catalytic activity of aforementioned NPs was successfully tested in the regioselective synthesis of 1,4-disubstituted 1,2,3-triazole. On the other hand, the design of experiment was used as a systematic method to optimize the reaction condition. Programming shows that the optimum reaction temperature and amount of catalyst are 96°C and 0.05 g, respectively.

1. Introduction
Although natural secondary metabolites exhibit different pharmaceutical activities, drug discovery development based on them is not impressive because extraction of these compounds from their natural sources is sluggish and cost-effective, while the final yield is low. However, high-output and valuable screening relating to the combinatorial chemistry have been revolutionized within the past two decades in terms of drug discovery, creation of the target molecules is still dependent on the chemical reaction for the construction of the new molecular scaffold and investigation of their medicinal properties in a living organism.¹

1,2,3-Triazoles belong to an important class of heterocycles with diverse industrial applications as corrosion inhibitors, agrochemicals, dyes, photo stabilizers and optical brighteners.²⁴ Also, a large numbers of oligosaccharides, peptides and natural products include triazole in their structure providing unique biological properties such as antitumor, antimicrobial, anti-HIV and anticonvulsant activities.⁵⁶ Some substituted triazole derivatives have been successfully employed as cleaving agent of deoxyribose nucleic acid and potassium channel activators. In particular, in the recent decade, many organic compounds containing triazole were useful as clinical and commercial drugs such as indole-amine 2,3-dioxygenase inhibitors,⁷ antiviral drugs,⁸ antibiotics⁹ and histone deacetylase inhibitors (Fig. 1)¹⁰

A regioselective synthesis of 1,4-disubstituted 1,2,3-triazole compounds is practicable by the use of metal catalyzed Huisgen cycloaddition reaction.¹¹ Literature survey shows...
many articles focusing on the application of Copper (I) and Copper (I) immobilized substrates,\textsuperscript{[12–14]} as catalyst in Click reaction. While according to the publication of Sharma et al.,\textsuperscript{[15]} Zinc may also catalyze such reactions.

ZnCl$_2$ is known as an effective Lewis acid, catalyst, promoting several organic transformations because it is biodegradable, nontoxic, easily available and cost effective. High hygroscopic properties of ZnCl$_2$ make it difficult to select ZnCl$_2$ as a catalyst in water sensitive reactions.\textsuperscript{[16]}

Recently, some of the industrial chemical reactions are based on the heterogeneous catalytic processes.\textsuperscript{[17]} Heterogeneous catalysts provide various advantages compared to the homogeneous ones which are the simple separation and purification of the products and recyclability of the catalyst.\textsuperscript{[18]} Some heterogeneous catalysts are prepared through anchoring homogeneous catalyst either on the surface of a substrate or onto the pore of a porous material; these types of catalysts include a multitude of catalytic sites, are characterized difficult at great expense while understanding their mechanistic behavior is almost impossible.\textsuperscript{[19]}

Nowadays, various polymers are employed as versatile supports for the immobilization of different catalysts.\textsuperscript{[20]} The first report for the synthesis and application of polymers as support appeared in chemical literature in 1963 when R.B. Merrifield Nobel Prize laureate in 1984, suggested the synthesis of polypeptides through attaching a chain of growing amino acid to polystyrene as an insoluble based substrate.\textsuperscript{[21]}

Most of insoluble polymers as support can be easily separated from reaction mixture and reused; besides, they have superb process ability and surface qualities. Thus, they can be utilized as catalyst supports for heterogenization of an appropriate homogeneous catalysts meeting the criteria required for an ideal catalyst in different chemical transformations.\textsuperscript{[22]} In addition, the surface of polymers can be functionalized with organic acids or bases, chemically in order to diminish problems caused for the chemical transformations. Thus, such polymers are considered as chemicals meeting the principles defined for green chemistry.\textsuperscript{[23]}

Generally, Lewis acid catalysts generate threats such as toxicity, potential hazard in handling, discarding difficulties due to acidic wastes and problems for the isolation of the products. To circumvent these problems, Lewis acids are frequently immobilized in an appropriate inorganic supports.\textsuperscript{[24–26]} These heterogeneous supported catalysts show significant important values for environmental regulation, deriving toward “Green Chemistry. The supports also frequently increase the effectiveness of Lewis acids as catalysts.\textsuperscript{[27,28]}

The loaded Zinc (II) on solid supports, as catalyst, overcomes the disadvantages of homogenous Zinc (II) salts. These heterogenized catalysts have attracted considerable attention of organic chemists. Since nanocatalysts containing metal ions increases the sustainability and effectiveness of the reaction compared to the conventional catalysis, they become interesting catalysts among chemists. Such nanoparticles (NPs) have high surface area, high activity under the mild conditions and excellent efficiency so that at the same time providing the favorable features of both homogeneous and heterogeneous catalysts.\textsuperscript{[29–31]}

In the course of our studies on the modification and use of heterogeneous catalyst in organic transformations,\textsuperscript{[32–41]} and in continuation of our interest in synthesis of biologically heterocyclic systems via MCR,\textsuperscript{[42–48]} herein, for the first time, we have developed the synthesis of a new polymer-supported ZnCl$_2$ NP catalyst (Scheme 1).

We wish to report polymer-supported ZnCl$_2$ NPs as an effective heterogeneous catalyst in the regioselective synthesis of some 1,2,3-triazoles possessing various pharmaceutical activities.
of biologically important 1,4-disubstituted-1H-1,2,3-triazoles via the Huisgen 1,3-dipolar cycloaddition (Scheme 2).

2. Experimental

2.1. Materials and methods

\(N, N\)-dimethylformamide (DMF) and triethylamine (TEA) were distilled before use, other reagents were used as received from Aldrich and Merck with high-grade quality. The general formula of poly(styrene-co-maleic anhydride) (SMA) which was obtained from KARABOND, is \([C_8H_8]_{0.6} [C_4H_2O_3]_{0.4} \) with \(M_n (\text{g/mol}) = 86,666\), \(M_w = 82,000\) and \(M_w/M_n = 2.1\).

Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. \(^1\)HNMR, \(^{13}\)CNMR spectra were recorded on a Bruker spectrometer at 250 MHz, respectively, using TMS as an internal standard (DMSO-d\(_6\) solution). IR spectra were recorded from KBr disk on the FT-IR Bruker Tensor 27. Zink content was measured on a Varian Vistapro analyzer by inductively coupled plasma (ICP). The scanning electron micrographs were recorded using a MIRA 3 TESCAN instrument.

2.1.1. Preparation of poly(styrene-co-maleimide)

The method published by Lee and Ahn\(^{[48]}\) was employed for the preparation of poly(styrene-co-maleimide) (SMI) catalyst. In this regard, SMA (1.00 g) was suspended in 10 mL dry DMF and 3-aminopyridine (1.54 g, 16 mmol) was then added to it. The mixture was stirred for about 3.5 h at 35 °C under N\(_2\) atmosphere. Then after, TEA (0.3 mL, 2 mmol), anhydrous sodium acetate (0.33 g, 4 mmol) and acetic anhydride (99%, 0.6 mL, 6 mmol) were added to the stirring reaction mixture (Scheme 1). Subsequently, it was refluxed at 70 °C for 4 h, and then was cooled to ambient temperature. To extract the product, the crude reaction mixture was slowly mixed with 300 mL dry methanol and correspondingly the light yellow polymer was precipitated. It was filtered, washed well with methanol and dried at 70 °C.

2.2. Preparation of polymer-supported catalyst

Dry Zinc(II) chloride (0.175 mg, 1.2 mmol) dissolved in ethanol (2 mL) was added to DMF (10 mL) to provide ZnCl\(_2\) NPs. Next, SMI (1.00 g) was added to it, and the mixture was carefully mixed under reflux condition for 5 h. Then, it was filtered off and the obtained crude solid, Zn(II)-SMI (4), was purified through washing with ethanol and subsequently dried in an oven at 60 °C (Scheme 1). The scanning electron microscope (SEM) image of Zn(II)-SMI was captured to analyze its surface morphology, and energy dispersive spectroscopy analysis of X-rays (EDX) technique was employed to detect the elements presence in the structure of Zn(II)-SMI catalyst. Moreover, The ICP analysis was used to determine the Zn content in Zn(II)-SMI which was obtained as 7.61% w/w. The Zn concentration was also assessed from the atomic emission (213.856 nm).

2.3. General procedure for the synthesis of triazoles

In a two-necked round-bottom flask, the Zn(II)-SMI catalyst (0.05 g), \(\alpha\)-haloketones or alkyl halide (1 mmol), alkynye (1 mmol) and sodium azide (0.07 g, 1.1 mmol) was added to 10 mL water as solvent. This mixture was refluxed for an appropriate time. The reaction progress was traced by TLC technique as the mobile phase included n-hexane and ethylacetate in a ratio of 7 to 3, respectively. Next, the mixture was cooled off and the crude product was filtered, dissolved in hot ethanol and the catalyst was separated using filtration. The crystalized product was obtained from evaporated ethanol at room temperature. The separated Zn(II)-SMI nanocatalyst was recovered after washing with hot EtOH, and reused for six cycles without appreciable loss of activity.
3. Results and discussion

Previously, the efficiency of ZnCl₂ as catalyst has been proved in organic reactions,[13] however, its recovery from the reaction mixture is impossible. Herein, by introducing ZnCl₂ NPs onto a stable polymer (SMA), a recoverable ZnCl₂-based catalyst (Zn(II)-SMI) is obtained. Scheme 1 is a schematic representation of Zn(II)-SMI preparation. Initially, modification of SMA (1) surface with 3-aminopyridine (2) was successfully carried out according to the method published before.[49] This method has been improved by employing ultrasonic irradiation in the work-up step giving the finer particles. The Zn(II)-SMI catalyst was analyzed and characterized using different techniques including SEM image (for investigating the surface morphology), EDX (for the elemental analysis), FT-IR (to characterize the presence of organic functional groups in the polymer structure), 1H NMR (to determine the polymer structure) and ICP analysis (to assess the Zn content).

3.1. Characterization of the SMI

The absorption bands in the FT-IR spectra confirmed the conversion of maleic anhydride moiety to maleimide in the structure of SMI polymer. After modification of SMA with 3-aminopyridine, a new imide absorption band is appeared at 1714–1781 cm⁻¹, while the absorption band for amino groups at 3300–3400 cm⁻¹ is completely removed (Fig. 2). This proves the successful treatment of SMA with 3-aminopyridine.[47]

1H NMR spectrum of the polymer is shown in Fig. 3. The presence of peaks related to the aromatic C–H of the pyridine moiety around 7.96 ppm, and also the absence of N–H peaks belongs to the amino group confirms the introduction 3-aminopyridine in the SMI structure giving the amide groups.

3.2. Characterization of the catalyst

SEM image, EDAX and ICP analysis are the only applicable techniques for the characterization of Zn(II)-SMI because it is insoluble in all common organic solvents. The SEM image of the Zn(II)-SMI (Fig. 4) represents the homogeneous immobilization of Zn(II) on the SMI surface. The average particles’ size of Zn(II) NPs is about 30–60 nm.

To investigate the surface morphology and particle size of the catalyst, TEM analysis was carried out for as-prepared catalyst (Fig. 5). As can be seen, the ZnNPs were homogeneously dispersed on the surface of Zn(II)-SMI.
The Zn(II)-SMI catalyst was also studied using EDX analysis (Fig. 6). The presence of Zn and Cl atoms establishes the coordination of ZnCl₂.

The thermal stability of Zn(II)-SMI was investigated using thermogravimetric analysis (TGA) (Fig. 7). The thermogram curve of Zn(II)-SMI shows two weight loss steps. A weight loss in 115°C is corresponding to the loss physically adsorbed solvent. Thermal decomposition at 270–330°C can also be attributed to the thermal decomposition of organic compound.

ICP analysis determined the Zn content in the polymer structure as 7.61% w/w.

The advantages of this method are facile preparation and modification of the polymer support, simple characterization, no need to pre-activation of Zn(II)-SMI to use as catalyst and recoverability of the catalyst for at least six cycles.

### 3.3. Click reaction using Zn(II)-SMI nanocatalyst

The successful preparation of Zn(II)-SMI confirmed by characterization methods encouraged us to use it as catalyst in click reactions for developing the synthesis of 1,4-disubstituted-1H-1,2,3-triazoles. To confirm the function of the zinc catalyst in the reaction, we compared the performance of zinc catalyst in the structure of SMI with copper in the same structure. The results are given in the Table 1.

### 3.4. Effect of solvent on the reaction

First, to investigate the effect of solvents on the reaction output, namely yield and time, the reaction of α-haloketones/alkyl halide, alkyne and sodium azide was selected as a representative reaction. The Zn(II)-SMI was used as the nanocatalyst and the reaction was carried out in various solvents, namely, chloroform, acetonitrile, ethanol, water. Results show that usage of solvent increases the reaction time to achieve to a specific reaction yield. In the other hand, the reaction in water is more efficient than in the other solvent. The results of investigated experiments are given in the Table 2.

### 3.5. Experimental design

In brief, the Central Composite Design (CCD) as an experimental design methodology was used to design the
CCD is one of the response surface methods which provide the suitable experimental point which must be done. In our prototype reaction, the amount of catalyst ($X_1$) and temperature ($X_2$) were chosen as the two main factors that should be changed to find the optimum reaction yield ($Y$). These variables ($X_1$ and $X_2$) were coded to three levels of $+1$, $0$ and $1$. To investigate curvature in response, three replicate at center point were imposed, if there is one. The levels of the $X_1$ and $X_2$ and the corresponding response values (reaction yield) are given in Table 3. Analysis of variance (ANOVA) shows that a quadratic model is the best model that fits to the experimental

experimental.\cite{50,51}
The coefficient of determination ($R^2$) for the yield is 0.9777, which represents the degree to which laboratory data and model results match (Table 5). The $p$-values show that the model results are not due to chance. The smaller the $p$-value, the more the significant term.

Table 4. Analysis of variance for the response surface quadratic model of the time.

| Source         | $p$-val. prob. > $F$ |
|----------------|----------------------|
| Model (yield)  | <0.0001              |
| $X_1$          | <0.0001              |
| $X_2$          | <0.0001              |
| $X_1X_2$       | 0.0009               |
| $X_1^2$        | 0.0003               |
| $X_2^2$        | 0.0003               |
| $R^2$          | 0.9994               |
| Predicted $R^2$| 0.9963               |
| Lack of fit    | 0.1242               |

Table 5. Analysis of variance for the response surface quadratic model of the yield.

| Source         | $p$-val. prob. > $F$ |
|----------------|----------------------|
| Model (yield)  | <0.0001              |
| $X_1$          | <0.0001              |
| $X_2$          | <0.0001              |
| $X_1X_2$       | 0.5002               |
| $X_1^2$        | 0.0007               |
| $X_2^2$        | 0.1295               |
| $R^2$          | 0.9901               |
| Predicted $R^2$| 0.9792               |
| Lack of fit    | 0.9772               |

Expression (1) shows the relation between prototype reaction yield and time, temperature and the amount of the catalyst:

\[
\text{Yield} = 73.58 + 699.53 X_1 - 7.46 \times 10^{-3} X_2 + 0.35 X_1X_2 \\
- 6875.00 X_1^2 + 5.95 X_2^2 \\
+ 9687.50 X_1^2 + 3.07 X_2^2
\]

Generally, the terms that have minus and plus sign have increasing and decreasing effect on yield, respectively. The absolute magnitude of the coefficient in the equation determines the extent of the effect. Figure 8 shows the three-dimensional and the contour of reaction yield versus temperature and amount of catalyst. As it is seen in Fig. 8, increasing the amount of catalyst and temperature will reduce the reaction time and increase the reaction efficiency.

3.6. Optimization of reaction condition and validation of the model

To find out the optimum value of the temperature and catalyst, the expression (1) together with numerical technique were used. Optimization showed that $X_1$ and $X_2$ should be 0.05 g and 96 °C, respectively. The reaction yield and time in the optimum condition are 97.83%, and 29.62 min, respectively. The predictive power of the model should be evaluated. Accordingly, the prototype reaction carried out at
optimum reaction condition with three replicate. The mean value of the experimental yield together with the predicted yield by the model is given in Table 6. The deviation of experimental reaction yield from predicted value is 0.86%.

In other experiment, the effect of catalyst on the reaction time was evaluated, so that the optimum reaction condition was repeated without catalyst. The result shows that the usage of Zn(II)-SMI is vital to decrease the reaction time (30 min versus >60 min). The obtained second order model (expression (1) is valid only in the experimental temperature and catalyst interval, so that it gives outlier data, if used outside the interval.

3.7. Synthesis of 1,4-disubstituted 1,2,3-triazoles

In the synthesis of 1,2,3-triazole derivatives, using these optimized reaction conditions for the synthesis of a wide variety of substituted triazole derivatives and the obtained results are summarized in Table 8. Thank you for reviewer’s attention, all compounds are known and their melting points with those reported for authentic samples. Some selected spectral data is reported.

3.8. Product characterization data

1-Phenyl-2-(4-phenyl-[1–3]triazol-1-yl)ethanone (7a)
M. P.: 169–170°C. 1H NMR (500 MHz, DMSO): 8 = 8.54 (s, 1 H, CH), 8.12–7.34 (m, 10 H, Ar), 6.28 (s, 2 H, CH2) ppm. IR (KBr): 1701, 1223 cm⁻¹.

2-(4-Phenyl-1H-1,2,3-triazol-1-yl)-1-p-tolyl-ethanone (7 b)
M. P.: 158–160°C. 1H NMR (500 MHz, DMSO): 8 = 8.52 (s, 1 H, CH), 8.00–7.99 (m, 2 H, Ar), 7.88–7.87 (m, 2 H, Ar), 7.47–7.33 (m, 5 H, Ar), 6.21 (s, 2 H, CH2), 2.41 (s, 3 H, CH3) ppm. IR (KBr): 1695 (s), 1232 (s) cm⁻¹.

1-(4-Chlorophenyl)-2-(4-phenyl-1H-1,2,3-triazol-1-yl)ethanone (7c)
M. P.:106–109°C. 1H NMR (500 MHz, DMSO): 8 = 8.52 (s, 1 H, CH), 8.12–7.87 (m, 4 H, Ar), 7.71–7.34 (m, 5 H, Ar), 6.27 (s, 2 H, CH2) ppm. IR (KBr): 1710 (s), 1230 (s) cm⁻¹.

1-(2-Bromophenyl)-2-(4-phenyl-1H-1,2,3-triazol-1-yl)ethanone (7e)
M. P.: 189–190°C. 1H NMR (250 MHz, DMSO): 8 = 8.51 (s, 1 H, CH), 8.03–8.00 (d, 2 H, Ar), 7.88–7.81(t, 3 H, Ar), 7.48–7.42 (t, 2 H, Ar), 7.36–7.30 (t, 2 H, Ar), 6.24 (s, 2 H, CH2) ppm. IR (KBr): 1720, 1216 cm⁻¹.

3.9. Recycles

To investigate the reusability of catalyst, phenacyl bromide, Phenylacetylene and sodium azide were utilized.
as model substrates under optimized reaction condition. After completion of each cycle, the reaction mixture was filtered off and the catalyst was isolated and washed with hot ethanol. As can be observed in Fig. 9, the catalyst could be recycled for 6 runs without a significant loss of activity.

### 4. Conclusions

As summary, in this work a novel polymer-supported Zn(II) based catalyst have been synthesized which was used as an efficient and green catalyst in the click reaction. The catalyst was very efficient and gained triazole derivatives in good to brilliant yields. Moreover, the catalyst was stable under the reaction conditions, catalyzed the reaction with no pre-activation and was recyclable for at least six cycles without significant loss of activity. According to the mentioned advantages, this supported Zn(II) catalyst is strongly recommended as a useful heterogeneous Lewis acid catalyst to catalyze acid-based organic reactions. In addition, the design of experiments was used to find the optimum reaction condition, so that increasing the amount of catalyst and temperature will reduce the reaction time and increase the reaction efficiency.

### Table 8. Synthesis of 1,2,3-triazole derivatives in the presence of Zn(II)-SMI.

| Entry | Phenacyl bromide/alkylhalide | Product | Time (Min) | Yield (%)<sup>a</sup> | M. P. Obs. | M. P. Rep. \[47,52\] |
|-------|-----------------------------|---------|------------|-----------------------|------------|-----------------|
| 1     | 7a                          | 98      | 171–172    | 169–170               |
| 2     | 7b                          | 96      | 158–159    | 158–160               |
| 3     | 7c                          | 95      | 107–110    | 106–109               |
| 4     | 7d                          | 95      | 116–117    | 115–118               |
| 5     | 7e                          | 94      | 189–190    | 189–190               |
| 6     | 7f                          | 92      | 114–115    | 114–116               |
| 7     | 7g                          | 94      | 125–128    | 128–130               |
| 8     | 7g                          | 96      | 126–128    | 128–130               |
| 9     | CH₃I                        | 85      | 123–126    | 125                   |

<sup>a</sup>Yield refer to pure and isolated products.

### Table 9. Comparison of Zn(II)-SMI with other Zn catalysts.

| Entry | Catalyst | Time (h) | Yield (%) | Condition |
|-------|----------|----------|-----------|-----------|
| 1     | Zn/C     | 15       | 63–95%    | DMF, 50 °C \[53\] |
| 2     | Zn(OAc)<sub>2</sub>/ ascorbic acid | 5        | 94        | H₂O, 75 °C, MW. \[54\] |
| 3     | SiO₂@APTES@2HAP-Zn | 2        | 95        | H₂O/tBuOH, 55 °C \[15\] |
| 4     | Zn(II)-SMI | 0.4      | 98        | H₂O, reflux (This work) |
Figure 9. Reusability of Zn(II)-SMI nanocomposite catalyst in the Click reaction.

Funding

M. Daraie and M. M. Heravi are grateful to Alzahra University Research Council for partial financial support.

ORCID

Majid M. Heravi http://orcid.org/0000-0003-2978-1157

References

[1] Sharpless, K. B.; Manetsch, R. In Situ Click Chemistry: A Powerful Means for Lead Discovery. Expert Opin. Drug Discov. 2006, 16, 525. DOI: 10.1517/17460441.1.6.525.

[2] Abd-Elaal, A. A.; Aïad, I.; Shaban, S. M.; Tawfiq, S. M.; Sayed, A. Synthesis and Evaluation of Some Triazole Derivatives as Corrosion Inhibitors and Biocides. J. Surfacet. Deterg. 2014, 17, 483–491. DOI: 10.1007/s11743-013-1547-0.

[3] Duan, T.; Fan, K.; Fu, Y.; Zhong, C.; Chen, X.; Peng, T.; Qin, J. Triphenylamine-Based Organic Dyes Containing a 1,2,3-Triazole Bridge for Dye-Sensitized Solar Cells via a ‘Click’ Reaction. Dyes Pigm. 2012, 94, 28–33. DOI: 10.1016/j.dyepig.2011.11.008.

[4] Abu-Orabi, S. T.; Atfah, M. A.; Jibril, I.; Mari’i, F. M.; Ali, A. A.-S. Dipolar Cycloaddition Reactions of Organic Azides with Some Acetylenic Compounds. J. Heterocycl. Chem. 1989, 26, 1461–1468. DOI: 10.1002/jhet.5570260541.

[5] Tron, G. C.; Pirali, T.; Billington, R. A.; Canonico, P. L.; Sorba, G.; Genazzani, A. A. Click Chemistry Reactions in Medicinal Chemistry: Applications of the 1,3-Dipolar Cycloaddition between Azides and Alkynes. Med. Res. Rev. 2008, 28, 278–308. DOI: 10.1002/med.20107.

[6] Thirumurugan, P.; Matosiuk, D.; Joziwiak, K. Click Chemistry for Drug Development and Diverse Chemical–Biology Applications. Chem. Rev. 2013, 113, 4905–4979. DOI: 10.1021/cr300409f.

[7] Totir, M. A.; Padyatotti, P. S.; Helfand, M. S.; Carey, M. P.; Bonomo, R. A.; Carey, P. R.; Akker, F. Effect of the Inhibitor-Resistant M69V Substitution on the Structures and Populations of trans-Enamine β-Lactamase Intermediate. Biochemistry 2006, 45, 11895–11904. DOI: 10.1021/bi060990m.

[8] Bhat, J.; Zhang, L.; Han, Y.; Wang, C.; Zhang, L. Histone Deacetylase Inhibitors: Potent Anti-Leukemic Agents. CMC 2015, 22, 2065–2074. DOI: 10.2174/092986732266615041694720.

[9] Röhrig, U. F.; Majjigapu, S. R.; Grosdidier, A.; Bron, S.; Stroobant, S.; Pilotte, L.; Colau, D.; Vogel, P.; Eynde, B. J.; Zoete, V.; Michielin, O. Rational Design of 4-Aryl-1,2,3-Triazoles for Indoleamine 2,3-Dioxygenase 1 Inhibition. J. Med. Chem. 2012, 55, 5270–5290. DOI: 10.1021/jm300260v.

[10] El Akri, K.; Bougrin, K.; Balzarini, J.; Faraj, A.; Benhida, R. Efficient Synthesis and In Vitro Cytostatic Activity of 4-Substituted Triazolyl-Nucleosides. Bioorg. Med. Chem. Lett. 2007, 17, 6656–6659. DOI: 10.1016/j.bmcl.2007.08.077.

[11] Heravi, M. M.; Tamimi, M.; Yahyavi, H.; Hosseinejad, T. Huisgen’s Cycloaddition Reactions: A Full Perspective. Curr. Org. Chem. 2016, 20, 1591. DOI: 10.2174/18552782820666151217183010.

[12] Jin, T.; Yan, M.; Yamamoto, Y. Click Chemistry of Alkyn–Azide Cycloaddition Using Nanostructured Copper Catalysts. ChemCatChem 2012, 4, 1217. DOI: 10.1002/cctc.201200193.

[13] Kolb, H. C.; Finn, M. G.; Sharpless, K. B. Click Chemistry: Diverse Chemical Functionality from a Few Good Reactions. Angew. Chem. 2001, 113, 2056–2075.

[14] Tornøe, C. W.; Christensen, C.; Meldal, M. Peptidotriazoles on Solid Phase: [1,2,3]-Triazoles by Regiospecific Copper(i)-Catalyzed 1,3-Dipolar Cycloadditions of Terminal Alkynes to Azides. J. Org. Chem. 2002, 67, 3057–3064. DOI: 10.1021/jo011148i.

[15] Sharma, R. K.; Mishra, M.; Sharma, S.; Dutta, S. Zinc(II) Complex Immobilized on Amine Functionalized Silica Gel: A Novel, Highly Efficient and Recyclable Catalyst for Multicomponent Click Synthesis of 1,4-Disubstituted 1,2,3-Triazoles. J. Coord. Chem. 2016, 69, 1152–1165. DOI: 10.1080/00958972.2016.1165807.

[16] Sun, Q.; Wang, Y.-Q.; Ge, Z.-M.; Cheng, T.-M.; Li, R.-T. A Highly Efficient Solvent-Free Synthesis of Dihydropyrimidinones Catalyzed by Zinc Chloride. Synthesis 2004, 7, 1047. DOI: 10.1055/s-2004-822331.

[17] Armor, J. N. New Catalytic Technology Commercialized in the USA during the 1990s. Appl. Catal. A: Gen. 2001, 222, 407–426. DOI: 10.1016/S0926-860X(01)00846-8.

[18] Rashed, M. N.; Siddiki, S. M. A. H.; Ali, M. A.; Moromi, S. K.; Touchy, A. S.; Kon, K.; Toyao, T.; Shimizu, K.-I. Heterogeneous Catalysts for the Cyclization ofDicarboxylic Acids to Cyclic Anhydrides as Monomers for Bioplastic Production. Green Chem. 2017, 19, 3238–3242. DOI: 10.1039/C7GC00538E.

[19] Kulkab, E. B.; Goren, K.; Portnoy, M. Advantages of Polymer-Supported Multivalent Organocatalysts for the Baylis-Hillman Reaction over Their Soluble Analogues. Pure Appl. Chem. 2014, 86, 1805. DOI: 10.1515/pac-2014-0721.

[20] Lu, J.; Toy, P. H. Organic Polymer Supports for Synthesis and for Reagent and Catalyst Immobilization. Chem. Rev. 2009, 109, 815–838. DOI: 10.1021/cr8004444.

[21] Merrifield, R. B. Solid Phase Peptide Synthesis. I. The Synthesis of a Tetrapeptide. J. Am. Chem. Soc. 1963, 85, 2149–2154. DOI: 10.1021/ja00897a025.
1. Chapter One - Diketene a Privileged Synthon in the Synthesis of Heterocyclic Compounds Part 1: Three- and Four-Membered Heterocycles. 

2. Chapter Two - Diketene as a Privileged Synthon in the Synthesis of Heterocycles Part 1: Four- and Five-Membered Ring Heterocycles.

3. Chapter Three - Paal–Knorr Reaction in the Synthesis of Heterocyclic Compounds. 

4. Chapter Four - Ketenes as Privileged Synthons in the Synthesis of Heterocyclic Compounds Part 3: Six-Membered Heterocycles. 

5. Chapter Five - Recent Advances in Synthesis of Benzo[b]Furans.

6. Chapter Seven - Synthesis of Pyrazolopyranopyrimidines via a One-Pot, Four-Component Reaction in Water.

7. Chapter Eight - Immobilization of Cu Nanoparticles on Activated Carbon.

8. Chapter Nine - Synthesis of Poly(Sterene-co-Maleic Anhydride) and Its Catalytic Application in Regioselective Synthesis of 1,2,3-Triazoles. 

9. Chapter Ten - Synthesis of Novel Pyrazole Based Pyrido[2,3-d]Pyrimidine-Diones in Water: A Green Synthesis.

10. Chapter Eleven - Synthesis of 1,4-Disubstituted 1,2,3-Triazoles.

11. Chapter Twelve - Synthesis of 1,3-Dipolar Cycloaddition of Azides and Aryl Alkynes.

12. Chapter Thirteen - Synthesis of 3-Amino-2-Pyrrolidinone and its Application in Heterocyclic Chemistry.