

## 1

## An Introduction to Organic Transformations in Water

Nissy Ann Harry<sup>1</sup> and Gopinathan Anilkumar<sup>2,3</sup>

<sup>1</sup>Catholicate College, Postgraduate and Research Department of Chemistry, Pathanamthitta, Kerala 689645, India

<sup>2</sup>Mahatma Gandhi University, School of Chemical Sciences, Priyadarsini Hills PO, Kottayam, Kerala 686560, India

<sup>3</sup>Mahatma Gandhi University, Institute for Integrated programs and Research in Basic Sciences (IIRBS), Priyadarsini Hills PO, Kottayam, Kerala 686560, India

### 1.1 The Emergence of Water as a Solvent in Organic Chemistry

A world without the plethora of goods produced by industrial organic synthesis is inconceivable in terms of societal welfare. Environmental concerns have been raising their head since the 1940s, coinciding with the expansion of industrial activity [1]. Merely a tiny percentage of the earth's resources are transformed into the intended goods by chemical processes, producing copious amounts of toxic elements and pollutants.

Solvents comprise a significant portion of the total mass needed in a chemical process; therefore, selecting the right one is crucial. Water is the greenest solvent readily accessible and has the least negative environmental effects. The reaction solvent utilized by nature is water. It is an inexhaustible naturally occurring, non-flammable, and abundant solvent. Other intriguing properties of water are the extensive hydrogen bonding, the pH of water can be changed, salts or surfactants can be added to provide salting-in or salting-out effects, and co-solvent or biphasic reaction systems can be used [2].

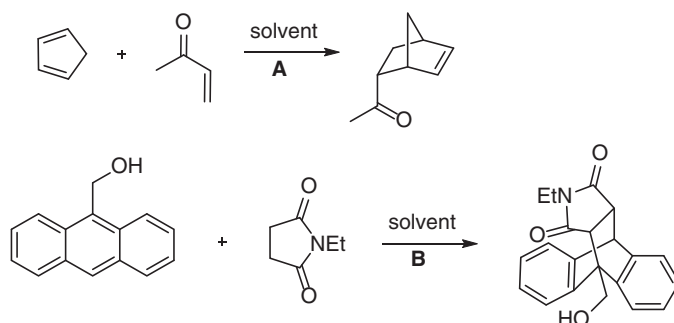
In 1828, Wohler's urea synthesis was the first organic reaction to employ water as a solvent [3]. The synthesis of indigo by Baeyer and Drewsen in 1882 may be the first instance of real organic synthesis. A sodium hydroxide solution was added to a suspension of *o*-nitrobenzaldehyde in aqueous acetone during their synthesis. The distinctive blue color of indigo appeared instantly, and the product eventually precipitated. But later on, water was practically eliminated from reactions as a result of the development of organometallic chemistry. The availability of conventional solvents for several processes has improved due to advancements in the petrochemical industry. Also, there was a fallacy, "*Corpora non agunt nisi fluida (or liquida) seu*

*Organic Transformations in Water: Principles and Applications*, First Edition.

Edited by Gopinathan Anilkumar, Nissy Ann Harry, and Sankuviruthiyil M. Ujwaldev.

© 2025 WILEY-VCH GmbH. Published 2025 by WILEY-VCH GmbH.

*soluta*” (“The substances do not react unless fluid or if dissolved”) [4]. This state of concern persisted until Breslow’s groundbreaking study in 1980 demonstrated how adding water could accelerate the Diels–Alder process (Scheme 1.1) [5]. Here, water continued to be the most effective medium. Furthermore, even faster rates were produced by the salting-out effect of LiCl, which further reduced the solubility of organic partners in water. In addition, the presence of guanidinium chloride acted to decrease hydrophobic interactions, which resulted in slower reactions. This eliminated the possibility that the dissolution of organic reactants was necessary.

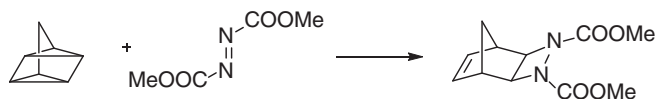


Solvents	A Rate constants $k_2 \times 10^5$	B Rate constants $k_2 \times 10^5$
Water	4400 ± 70	22600 ± 700
Water/ $\beta$ -cyclodextrin	10900	13800
Water/LiCl	10800	Not determined
Water/ $C(NH_2^+)_3Cl^-$	4300	Not determined
Acetonitrile	Not determined	107 ± 8
Methanol	75.5	344 ± 25
Isooctane	5.94 ± 0.3	796 ± 71

**Scheme 1.1** Acceleration of reaction rate by on-water protocol.

With the release of some masterworks by the Sharpless (Scheme 1.2) and Breslow groups, water has gained popularity as a reaction medium [6, 7]. Sharpless called these water-enhanced reactions between water-insoluble reactants “on-water reactions.”

Butler, Coyne, and Fokin defined water-based reactions [8]. If the transition state occurs in bulk water and the substrate solubility is more than  $0.01 \text{ mol l}^{-1}$ , the reaction is said to occur “in water”. Substrates that have a solubility of less than  $10^{-5} \text{ mol l}^{-1}$  in water and a transition state that takes place on the organic side of the interface are considered to be “on-water” conditions. Lastly, both reaction types are likely to happen simultaneously for reactants with intermediate solubilities [9]. In a most recent review, Kitanosono and Kobayashi suggested classifying all



Solvent	Concentration (M)	T (°C)	Time	Yield (%)
Neat	4.53	0	2 h	0
Neat	4.53	23	48 h	85
Toluene	1	80	24 h	74
On-water	4.53	0	1.5 h	93
On-water	4.53	23	10 min	82

**Scheme 1.2** Comparison of the reactivity of quadricyclane with dimethyl azodicarboxylate in different solvents.

reactions that employ water as the reaction media as “in water,” regardless of the usage of catalysts [10]. Recently, several reports, reviews, and chapters were published showing the importance of water as a green organic solvent [11, 12]. However, the water as a reaction medium is less focused on books [13]. Water is now exclusively employed as a green solvent in several organic transformations, such as cross-coupling reactions, C–H activations, multicomponent reactions [14–16].

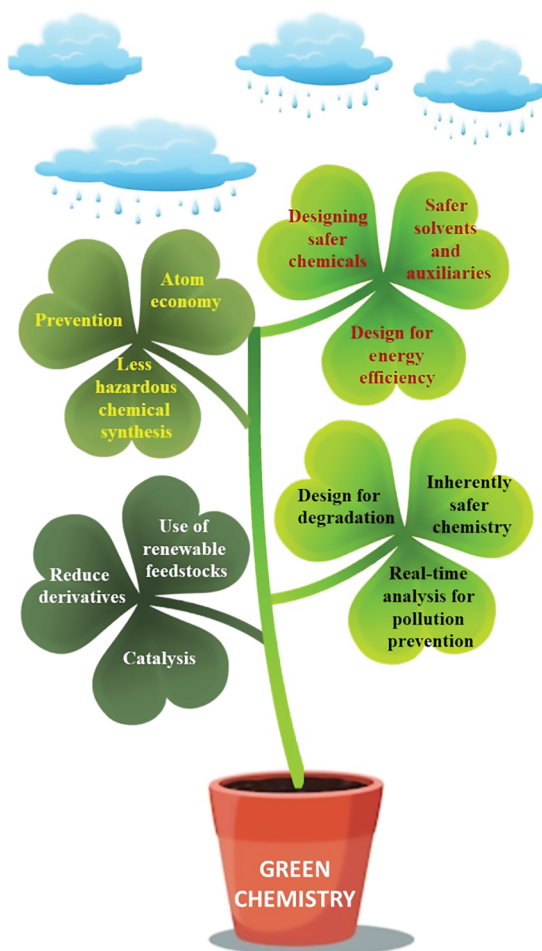
## 1.2 Green Chemistry and Water

Green chemistry, established about two decades ago, has drawn much attention [17]. The design of chemical processes and products to minimize or eliminate the usage or production of hazardous compounds is referred to as “green chemistry,” or sustainable chemistry [18]. The choice of green solvents to reduce toxicity and pollution is a significant step toward implementing the twelve principles of green chemistry. Solvents make up between 50% and 80% of the mass in a chemical process. Solvents are an important factor that significantly influence the total toxicity profile of a chemical process.

They typically raise the most concerns regarding process safety issues because of their volatility, flammability, and potential for explosion under specific circumstances [19]. Green alternatives include solventless systems, supercritical fluids (SCF), green solvents like water, and, more recently, ionic liquids.

Among the 12 principles of green chemistry, the use of water as a solvent always increases the greenness and sometimes the efficiency of the reaction (Figure 1.1) [20].

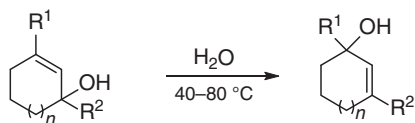
*Prevention of waste* in a reaction is crucial for sustainable development. According to estimates, solvents make up over 60% of the mass of chemicals in the pharmaceutical and chemical sectors. Reuse of solvents is still rare, and the majority of these solvents are incinerated after use to recover energy, which has a significant negative influence on the environment and waste output [21]. Furthermore, burning



**Figure 1.1** Diagrammatic representation of green chemistry principles.

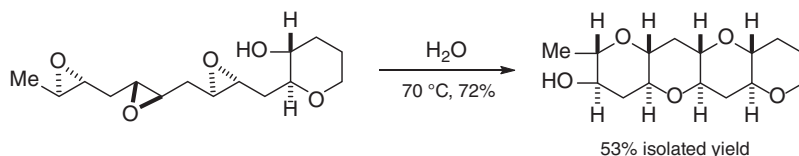
organic solvents produces  $\text{CO}_2$ , which is largely attributed to the waste output and, to a lesser extent, to climate change. The E factor, positive material identification (PMI), and other typical green chemistry metrics used in reactions conducted in organic solvents are frequently taken into consideration in quantitative studies of waste quantity production [22].

Synthetic methods should be designed in such a way that all reactants that participate in the reaction are included in the final product. Hot-water-promoted, *atom economic* 1,3-rearrangements of cyclic allylic alcohols were reported (Scheme 1.3) [23]. Upon raising the temperature, the  $\text{pK}_w$  of water increases, indicating a greater abundance of the strong base  $\text{OH}^-$  and strong acid  $\text{H}_3\text{O}^+$  compared to  $25^\circ\text{C}$ . Raising the temperature also lowers the dielectric constant of water, improving its suitability as a solvent for organic molecules. In contrast to high-temperature water under pressure, hot water (between  $60$  and  $100^\circ\text{C}$ ) is more readily available in both natural and laboratory settings.



**Scheme 1.3** 1,3-Rearrangement of cyclic alcohols promoted by hot water.

The effective use of water as a solvent paves the way toward *less hazardous chemical synthesis*. The development of tandem and cascade reaction techniques, which combine as many reactions as feasible to yield the end product in a single operation, is crucial to the creation of greener synthetics. Jamison and coworker synthesized the essential component of the “ladder” polyether marine natural product through a biomimetic cascade cyclization in neutral water (Scheme 1.4) [24].



**Scheme 1.4** Synthesis of polyether marine natural product in water.

Along with the advent of green chemistry concepts, the phrase “green solvent” was also created and several studies on the *use of safer solvents and auxiliaries* arose. To identify green solvents at an early stage, Capello et al. employed the EHS (E: Environment, H: Health, and S: Safety) assessment approach to rate standard organic and novel solvents (Table 1.1). The approach ranks solvents according to an EHS value between zero and nine using nine effect categories for a solvent, including flammability, risk of explosion, decomposition, and toxicity. An elevated EHS value denotes an elevated danger linked to the solvent. The EHS values of a few chosen solvents

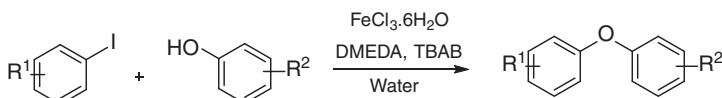
**Table 1.1** Selected EHS values of solvents.

Solvent	EHS
Acetone	3.1
Dimethylether	3.9
Methanol	2.7
Acetonitrile	4.5
Ethanol	2.6
THF	3.9
Cyclohexane	4.0
Water	0

Source: Adapted from Capello et al. [25].

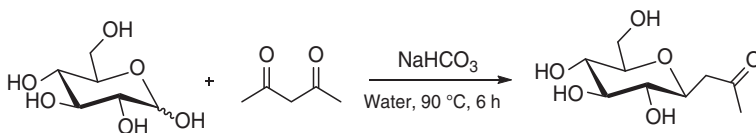
used in chemical synthesis are displayed in (Table 1.1) [25]. Water has an EHS value of 0 and is the safest solvent.

Anilkumar and coworkers reported the first iron-catalyzed coupling of aryl iodides with phenols in water as a solvent [26]. Diaryl ethers are produced in good-to-exceptional yields using a 1,2-dimethylethylenediamine (DMEDA) catalytic system and inexpensive and easily accessible  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  in this synthesis (Scheme 1.5). Compatibility of this reaction with a broad variety of functional groups further demonstrated its efficiency. Furthermore, the process is made easier because this conversion is done in the presence of air. Therefore, the process offers a simple, affordable, and environmentally responsible method of obtaining diaryl ethers.



**Scheme 1.5** Synthesis of diaryl ethers in water using iron catalysis.

*Reducing derivatives* is a key step to achieving green chemistry goals. The total synthesis efficiency is increased by the removal of laborious protection-deprotection procedures for specific acidic-hydrogen-containing functional groups when water is used as a solvent. The ability to use water-soluble hydroxyl groups directly without protection or deprotection is a significant benefit of reactions in water. This characteristic is helpful in the chemistry of carbohydrates, where protection and deprotection are frequently used [27]. For example, C-glycosides are potential enzyme inhibitors commonly used in total synthesis. The traditional protocols involve the addition of nucleophiles to a protected sugar while it is anhydrous. Water is now used as a solvent in an effective protocol that eliminates the need for laborious protection and deprotection processes (Scheme 1.6). Using commercially available D-glucose and pentane-2,4-dione as starting materials, a one-step synthesis of 38  $\beta$ -C glycosidic ketone from an aqueous  $\text{NaHCO}_3$  solution in nearly quantifiable quantities was achieved [28].

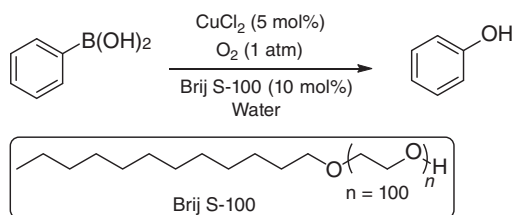


**Scheme 1.6** Single-step synthesis of  $\beta$ -C glycosidic ketone in water.

*Catalysis* via “in water” and “on-water” processes are known approaches [29]. Surfactants and the spontaneous development of micellar aqueous media, however, offer a more widely applicable and practical way to deal with the limited solubility of organic reagents and metal catalysts in water [30]. The hydrophobic effect in water forms aggregates that function as nanoreactors [31]. Higher local concentrations

with rate enhancement and particular solvation effects result from this, which favorably influences the chemo-, regio-, and stereo-selectivity of the final product [32].

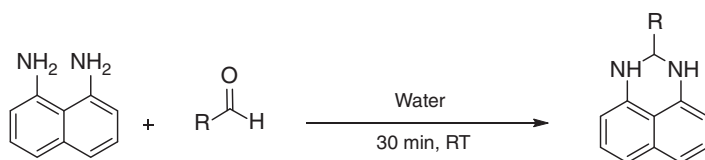
Amphiphilic surfactant Brij S-100 was employed for oxidative hydroxylation of aromatic boronic acids to phenols using  $\text{CuCl}_2$  as a catalyst in water without the need for bases or ligands (Scheme 1.7) [33]. The reaction proceeded smoothly with several electron-withdrawing and electron-donating boronic acids to afford the corresponding phenols in moderate-to-excellent yields.



**Scheme 1.7** Oxidative hydroxylation of aromatic boronic acids to phenols.

*The use of renewable feedstock* like bio-based compounds over fossil-based chemicals marks another step toward green chemistry. Research teams have just lately begun to look into the use of biosurfactants in traditional micellar catalysis reactions, such as Pd-catalyzed cross-couplings. High biodegradability and biological synthesis from renewable feedstocks are the two greatest advantages of biosurfactants; these two key benefits will further encourage the use of biosurfactants in micellar catalysis [34].

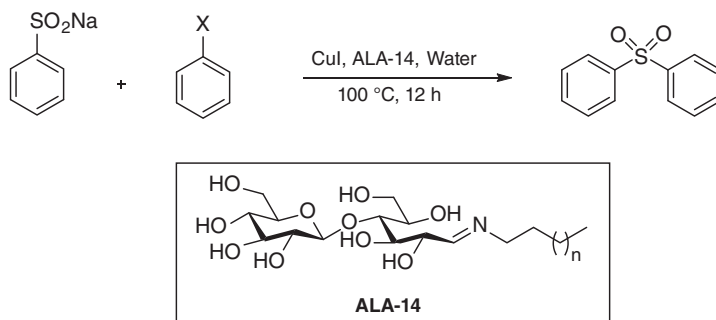
*Design for energy efficiency* is a significant step toward green chemistry [35]. The synthesis of 2-substituted 2,3-dihydro-1*H*-perimidines on water using a unique, environmentally friendly, and energy-efficient protocol was reported by Anilkumar and coworkers [36]. Using a catalyst-free on-water technique at room temperature, 1,8-diaminonaphthalene is reacted with various aldehydes to produce the 2,3-dihydro-1*H*-perimidine product in 30 minutes with moderate-to-good yields (Scheme 1.8). A multigram scale reaction is also carried out to guarantee the reaction's scalability.



**Scheme 1.8** Energy-efficient synthesis of perimidines in water.

*Designing for degradation* and *designing safer chemicals* that are biodegradable or less harmful to the environment is of utmost importance [37, 38]. Petrochemical compounds are the primary source of surfactants used by the chemical industry. As a result, traditional neutral or anionic surfactants do not meet these criteria. In this

sense, emerging designer surfactants mark a significant shift since all newly suggested amphiphilic molecules consist of bio-based units, at least in the hydrophobic portion. For use in the Ullmann type C–S coupling reaction in water mediated by copper salt, an intriguing new surfactant bearing a sugar unit for metal catalysis in water was described (Scheme 1.9). It connects a lactose hydrophilic unit to an aliphatic alkyl chain forming the alkyl lactosamine ALA-14, which is readily synthesized and naturally degradable [39].



**Scheme 1.9** Ullmann C–S coupling using ALA14 in aqueous solution.

Reactions in water thus naturally contribute to *inherently safer chemistry for accident prevention* regarding common dangers, such as fires, explosions, or toxicity on release, in contrast to extensively used catalytic processes in organic solvent systems [40].

*Real-time analysis for pollution prevention*, in-process monitoring and control before the creation of hazardous chemicals, and analytical methods must be further developed [41]. For reactions carried out in water, such analysis can identify catalyst poisoning, changes in process pH or temperature before a reaction spirals out of control, and other harmful events before a significant catastrophe happens.

### 1.3 Conclusion

The development of organic reactions in water has received tremendous attention from chemists over the past two decades, and this topic is seeing a significant expansion in study. Lipophilic substrates react in hydrophobic pockets that are generated in water. These pockets serve as reaction vessels that mimic the chemistry found in nature and give us a clear path forward for further research in this field. Employing surfactants in micellar conditions – in which the micelle functions as a nano-reactor is another simple way to do catalysis in water. The use of water as a solvent for organic transformations has the potential to significantly advance the fields of chemistry, the chemical industry, and environmental preservation. Putting its regulation into action is one of its biggest obstacles. It takes a lot of work to properly screen reaction conditions to facilitate the reactions in water. In



the approaching decades, water as a solvent will remain intriguing and beneficial as there will be a lot more reports released in this area. A greater emphasis on large-scale application should be placed on research. More lenient legislation, faster technology transfers between academia and governments, and tax breaks for businesses using such green standards in the workplace are all necessary to enable the adoption of these technologies in the business sector.

## References

- 1 Ritter, S.K. (2001). *Chem. Eng. News* 79: 27–37.
- 2 Li, C.J. and Anastas, P.T. (2012). *Chem. Soc. Rev.* 41: 1413–1414.
- 3 Wöhler, F. (1828). *Annalen der Physik und Chemie* 88: 253–256.
- 4 “The substances do not react unless fluid or if dissolved”, quoted by Aristotle (384–322 BCE).
- 5 Rideout, D.C. and Breslow, R. (1980). *J. Am. Chem. Soc.* 102: 7816–7817.
- 6 Narayan, S., Muldoon, J., Finn, M.G. et al. (2005). *Angew. Chem. Int. Ed.* 44: 3275–3579.
- 7 Breslow, R. (2004). *Acc. Chem. Res.* 37: 471–478.
- 8 (a) Butler, R.N. and Coyne, A.G. (2010). *Chem. Rev.* 110: 6302–6337. (b) Chanda, A. and Fokin, V.V. (2009). *Chem. Rev.* 109: 725–748.
- 9 (a) Butler, R.N. and Coyne, A.G. (2016). *Org. Biomol. Chem.* 14: 9945–9960. (b) Cortes-Clerget, M., Yu, J., Kincaid, J.R.A. et al. (2021). *Chem. Sci.* 12: 4237–4266.
- 10 Kitanosono, T. and Kobayashi, S. (2020). *Chem. –Eur. J.* 26: 9408–9429.
- 11 (a) Harry, N.A., Radhika, S., Neetha, M., and Anilkumar, G. (2019). *Chemistry Select* 4: 12337–12355. (b) Fabris, F., Illner, M., Repke, J.-U. et al. (2023). *Molecules* 28: 4809–4845. (c) Sachdeva, H. and Khaturia, S. (2017). *Biorg. Org. Chem.* 1: 239–243. (d) Kitanosono, T., Masuda, K., Xu, P., and Kobayashi, S. (2018). *Chem. Rev.* 118: 679–746. (e) Li, C.J. and Chen, L. (2006). *Chem. Soc. Rev.* 35: 68–82.
- 12 Harry, N.A., Rohit, K.R., and Anilkumar, G. (2021). *Green Organic Reactions* (ed. G. Anilkumar and S. Saranya), 33–49. Springer.
- 13 (a) Lindstrom, U.M. (ed.) (2007). *Organic Reactions in Water: Principles, Strategies and Applications*. Wiley-Blackwell. (b) Li, C.-J. and Chan, T.-H. (ed.) (2006). *Comprehensive Organic Reactions in Aqueous Media*. John Wiley & Sons. (c) Grieco, P.A. (ed.) (1998). *Organic Synthesis in Water*. Springer.
- 14 Dong, D.-Q., Yang, H., Zhou, M.-Y. et al. (2023). *Curr. Opin. Green Sustain. Chem.* 40: 100778.
- 15 Dalton, T., Faber, T., and Glorius, F. (2021). *ACS Cent. Sci.* 7: 245–261.
- 16 Paprocki, D., Madej, A., Koszelewski, D. et al. (2018). *Front. Chem.* 6: 502–523.
- 17 Anastas, P.T. and Warner, J.C. (ed.) (1988). *Green Chemistry – Theory and Practice*. New York: Oxford University Press.
- 18 Anastas, P. and Eghbali, N. (2010). *Chem. Soc. Rev.* 39: 301–312.

- 19 Earle, M.J., Seddon, K.R., Adams, C.J., and Roberts, G. (1998). *Chem. Commun.* 2097–2098.
- 20 Zhou, F., Hearne, Z., and Li, C.-J. (2019). *Curr. Opin. Green Sustain. Chem.* 18: 118–123.
- 21 Sheldon, R.A., Bode, M.L., and Akakios, S.G. (2022). *Curr. Opin. Green Sustain. Chem.* 33: 100569–100575.
- 22 (a) Benison, C.H. and Payne, P.R. (2022). *Curr. Res. Green Sustain. Chem.* 5: 100229–100234. (b) Gonzalez, C. and Lund, C. (2022). *Curr. Opin. Green Sustain. Chem.* 33: 100564.
- 23 Li, P.-F., Wang, H.-L., and Qu, J. (2014). *J. Org. Chem.* 79: 3955–3962.
- 24 Vilotijevic, I. and Jamison, T.F. (2007). *Science* 317: 1189–1192.
- 25 Capello, C., Fischer, U., and Hungerbühler, K. (2007). *Green Chem.* 9: 927–934.
- 26 Sindhu, K.S., Ujwaldev, S.M., Krishnan, K.K., and Anilkumar, G. (2017). *J. Catal.* 348: 146–150.
- 27 Guo, J. and Ye, X.-S. (2010). *Molecules* 15: 7235–7265.
- 28 Rodrigues, F., Canac, Y., and Lubineau, A. (2000). *Chem. Commun.* 2049–2050.
- 29 Harry, N.A., Shilpa, T., Ujwaldev, S.M., and Anilkumar, G. (2021). *J. Heterocyclic Chem.* 58: 375–381.
- 30 Cortes-Clerget, M., Kincaid, J.R.A., Akporji, N., and Lipshutz, B.H. (2022). *Supramolecular Catalysis* (ed. P.W.N.M. van Leeuwen and M. Raynal), 467–487. New York: Wiley.
- 31 Strukul, G., Fabris, F., and Scarso, A. (2022). *Supramolecular Catalysis: New Directions and Developments*, Chapter 31 (ed. P.W.N.M. van Leeuwen and M. Raynal), 451–466. New York: Wiley.
- 32 Scarso, A. and Strukul, G. (2019). *Green Synthetic Processes and Procedures* (ed. R. Ballini), 268–288. London: Royal Society of Chemistry.
- 33 Inamoto, K., Nozawa, K., Yonemoto, M., and Kondo, Y. (2011). *Chem. Commun.* 47: 11775–11777.
- 34 Adamik, R., Herczegh, A.R., Varga, I. et al. (2023). *Green Chem.* 25: 3462–3468.
- 35 Quadrelli, E.A. (2016). *Green Chem.* 18: 328–330.
- 36 Harry, N.A., Cherian, R.M., Radhika, S., and Anilkumar, G. (2019). *Tetrahedron Lett.* 60: 150946–150950.
- 37 Cucciniello, R. and Anastas, P.T. (2021). *Curr. Opin. Green Sustain. Chem.* 31: 100528.
- 38 DeVito, S.C. (2016). *Green Chem.* 18: 4332–4347.
- 39 Ge, X., Zhang, S., Chen, X. et al. (2019). *Green Chem.* 21: 2771–2776.
- 40 Khan, F.I. and Abbasi, S.A. (1998). *J. Loss. Prev. Process Ind.* 11: 361–372.
- 41 Wang, J. (2002). *Acc. Chem. Res.* 35: 811–816.