

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/236081119>

# ChemInform Abstract: Benign by Design: Catalyst-Free In-Water, On-Water Green Chemical Methodologies in Organic Synthesis

ARTICLE *in* CHEMICAL SOCIETY REVIEWS · MARCH 2013

Impact Factor: 33.38 · DOI: 10.1039/c3cs60025d · Source: PubMed

CITATIONS

100

READS

363

## 5 AUTHORS, INCLUDING:



**Dr. Manoj B. GAWANDE**

Palacký University of Olomouc

85 PUBLICATIONS 1,319 CITATIONS

SEE PROFILE



**Vasco D. B. Bonifacio**

University of Lisbon

48 PUBLICATIONS 479 CITATIONS

SEE PROFILE



**Rafael Luque**

University of Cordoba (Spain)

307 PUBLICATIONS 5,826 CITATIONS

SEE PROFILE



**Rajender S Varma**

United States Environmental Protection Ag...

538 PUBLICATIONS 14,893 CITATIONS

SEE PROFILE

## REVIEW ARTICLE

# Benign by design: catalyst-free in-water, on-water green chemical methodologies in organic synthesis

Cite this: *Chem. Soc. Rev.*, 2013, **42**, 5522

Manoj B. Gawande,<sup>\*a</sup> Vasco D. B. Bonifácio,<sup>\*a</sup> Rafael Luque,<sup>b</sup> Paula S. Branco<sup>a</sup> and Rajender S. Varma<sup>\*c</sup>

Catalyst-free reactions developed during the last decade and the latest developments in this emerging field are summarized with a focus on catalyst-free reactions in-water and on-water. Various named reactions, multi-component reactions and the synthesis of heterocyclic compounds are discussed including the use of various energy input systems such as microwave- and ultrasound irradiation, among others. Organic chemists and the practitioners of this art both in academia and industry hopefully will continue to design benign methodologies for organic synthesis in aqueous media under catalyst-free conditions by using alternative energy inputs based on fundamental principles.

Received 25th January 2013

DOI: 10.1039/c3cs60025d

[www.rsc.org/csr](http://www.rsc.org/csr)

<sup>a</sup> REQUIMTE, Departamento de Química, Faculdade de Ciências e Tecnologia, Universidade Nova de Lisboa, 2829-516 Caparica, Portugal.

E-mail: [m.gawande@fct.unl.pt](mailto:m.gawande@fct.unl.pt), [vbb@fct.unl.pt](mailto:vbb@fct.unl.pt); Fax: +351 21 2948550;

Tel: +351 96 4223243, +351 21 2948300

<sup>b</sup> Departamento de Química Orgánica, Universidad de Córdoba, Edif. Marie Curie, Ctra Nnal IVa, Km 396, 14014 Córdoba, Spain

<sup>c</sup> Sustainable Technology Division, National Risk Management Research Laboratory, US Environmental Protection Agency, MS 443, 26 West Martin Luther King Drive, Cincinnati, Ohio 45268, USA. E-mail: [Varma.Rajender@epamail.epa.gov](mailto:Varma.Rajender@epamail.epa.gov)

## 1. Introduction

The field of organic synthesis has recently experienced numerous innovative scientific breakthroughs accompanied by improved and efficient synthetic protocols that avoid the use of toxic reagents. Rather than being a discipline itself, Green chemistry encompasses a series of considerations in the design of



Manoj B. Gawande

Dr. Manoj B. Gawande was born in India at Sawali Buldana, Maharashtra, India. He received his PhD degree in Chemistry in 2008 from the Department of Chemistry, Institute of Chemical Technology, (Formerly UDCT) Matunga, Mumbai, Maharashtra, India, under the supervision of Prof. R. V. Jayaram. He has investigated various mixed metal oxides and organic reagents and their applications in organic synthesis. In 2009, he moved to

South Korea, Department of Molecular/Nuclear Medicine, School of Medicine, Kyungpook National University, Republic of Korea, where he worked on the synthesis of azamacrocycles and its applications in medicinal chemistry with Prof. J. Yoo. Presently, he is working with Prof. Paula Branco at Department of Chemistry, Faculdade de Ciências e Tecnologia, UNL, Lisbon, Portugal. His research interests are greener raw materials, synthesis of nanomaterials and their applications in organic reactions. He has published over 35 scientific research articles, including reviews, patents and articles.



Vasco D. B. Bonifácio

Vasco D. B. Bonifácio was born in Luanda, Angola, in 1973. He received a BS degree in Chemical Engineering in 1995 from ISEL and an MS degree in Applied Chemistry in 1997 from FCT/UNL. After receiving his PhD in Chemistry (Organic Chemistry) in 2006, under the supervision of Prof. S. Prabhakar and Prof. Ana M. Lobo (FCT/UNL), he was a postdoctoral fellow in Scherf's group (Wuppertal, Germany). In 2008, he was appointed Assistant

Researcher of the MIT Portugal Program (Bioengineering Systems Focus Area) and moved to Ana Aguiar-Ricardo's Lab where he started working on supercritical CO<sub>2</sub>-assisted polymerizations. In 2012 he was a visiting researcher at MIT (Boston, USA) in the Hammond's Lab, developing dendrimer-based gene nanocarriers. His main interests are Nanomedicine (polymer therapeutics) and Molecular Electronics (chemical and biochemical sensors). Currently, his research is focused on the synthesis of complex 3D polymer architectures using clean technologies.

environmentally benign protocols comprising subjects such as energy consumption, atom efficiency, and sustainability of chemical processes. A major point in the design of greener

and more sustainable processes relates to the efficiency of the process, which has to take into account several parameters including energy, material consumption (preferably use of bio-renewable resources), man-power (automation), and reactor usage (e.g. flow *versus* batch reactions).



**Rafael Luque**

*Prof. Rafael Luque (PhD 2005, Universidad de Cordoba, Spain) has gained significant experience in biomass and waste valorisation practises of materials, fuels, and chemicals over the past 10 years after spending a 3-year postdoctoral placement in the Green Chemistry Centre of Excellence at the University of York. He has worked extensively in the areas of (nano)materials science, heterogeneous catalysis, biofuels, and green chemical*

*methods. Since 2009, he has been Ramon y Cajal Fellow at UCO. He has published over 140 research articles, filed 3 patent applications and edited 5 books as well as making numerous contributions to book chapters and giving invited, guest and keynote lectures worldwide. Prof. Luque is also a member of the Editorial Advisory Board of several journals, including Chemical Society Reviews, and has recently been awarded the Marie Curie Prize from Instituto Andaluz de Quimica Fina in Spain (2011) and the Green Talents award from the Federal Ministry of Education and Research in Germany (2011).*

Concepts such as “atom-economy”<sup>1</sup> and efforts towards minimization of auxiliary chemicals (which include protection-deprotection sequences and use of volatile organic solvents) form the pillars of material efficiency in chemical production. In chemical reactions, solvents play a very important role in extractions, reactants solubility, washing, and separation of final products. For the past two decades, scientists have devoted a great deal of research effort to replace toxic and harmful solvents by more environmentally benign alternatives.<sup>2</sup> Polyethylene glycol (PEG),<sup>3</sup> ionic liquids,<sup>4</sup> supercritical carbon dioxide (scCO<sub>2</sub>),<sup>5</sup> and water<sup>6</sup> are among the most widely explored greener alternatives in recent years.

Together with solvents, the design of more environmentally sound and low impact protocols by using a range of alternative synthetic methods has become an important practice in organic synthesis.<sup>7–11</sup> The use of magnetically separable nanomaterials,<sup>12–19</sup> ionic liquids,<sup>20–27</sup> scCO<sub>2</sub>,<sup>28–30</sup> solvent-free reactions,<sup>31–48</sup> microwave-assisted synthesis,<sup>33,36,49–57</sup> and reactions in aqueous media<sup>58–70</sup> highlights the key developments in designing greener protocols with improved efficiency.

In recent years, biodegradable glycerol has been used in more than 2000 established procedures as an important starting material in the drug, food, beverage, chemicals and synthetic raw materials industries. The major applications



**Paula S. Branco**

*Paula Sérgio Branco was born in 1963 in Angola and grew up in Portugal. After a licenciateship in Chemistry at Faculdade de Ciências, UL, she joined Faculdade de Ciências e Tecnologia, UNL, in 1987 as a Teaching Assistant where she got her PhD in Chemistry, specialty Organic Chemistry, in 1992 on the synthesis of heterocyclic compounds, under the supervision of Prof. Sundareshan Prabhakar. Since 1992 she has*

*been an Assistant Professor and the main subject of her lectures is organic chemistry. Her research interests focus mainly on organic chemistry involving the development of new methods for the synthesis of heterocycles alongside with the study on chemical reactions mechanisms.*



**Rajender S. Varma**

*Prof. Rajender S. Varma was born in India (PhD, Delhi University 1976). After postdoctoral research at Robert Robinson Laboratories, Liverpool, UK, he was a faculty member at Baylor College of Medicine and Sam Houston State University prior to joining Sustainable Technology Division at US Environmental Protection Agency in 1999. He has over 40 years of research experience in management of multi-disciplinary technical programs.*

*He is extensively involved in broader aspects of chemistry that include synthesis and chemical modification of biologically active molecules, environmental sciences, development of environmentally benign synthetic methods using alternate energy input and efficient technologies for greener remediation of contaminated sites. Lately, he has focused on greener approaches to assembly of nanomaterials and sustainable applications of magnetically retrievable nano-catalysts in benign media. He is a member of the editorial advisory board of several international journals and has published over 360 scientific papers and has been awarded 12 US Patents.*

are in toiletries, sweeteners, softening agents, cosmetics, surface coatings, and paints, among other products, and especially in important organic transformations.<sup>71</sup>

Deep eutectic solvents (DESs) are mixtures of solid ammonium salt and a hydrogen bond donor and have low melting point (often below room temperature), low vapor pressure, high thermal stability, and are commonly water-soluble.<sup>72</sup> In general, DESs are synthesized from low-cost starting raw materials, typically by mixing ethylammonium chloride or choline chloride (ChCl) with an organic hydrogen-bond donor *e.g.* acetamide, urea, malonic acid, *etc.* DESs have the advantage of being, in general, non-toxic and biodegradable as compared to ionic liquids; they have been successfully used for the synthesis of greener raw materials.<sup>73</sup>

In view of these parameters, research endeavors directed towards catalyst-free, solvent-free, and aqueous-mediated reactions have been the subject of numerous studies in recent years.<sup>34,74–80</sup> These investigations have highlighted certain limitations and drawbacks of the aforementioned protocols, such as insolubility of reactants, longer reaction times, lower yields, limited selectivity, *etc.* The limitations can be circumvented by means of ingenious “chemical tricks” such as mixing reactants in water or mixtures of solvents *viz.* water : ethanol,<sup>81</sup> the use of surfactant in aqueous media,<sup>82,83</sup> or reactions at elevated temperatures. Unconventional techniques including mechanochemical (grinding), microwave and ultrasound irradiation as well as more recently introduced flow chemistry have been explored as useful tools to improve the green credentials of organic synthetic protocols.

Conventionally, catalysts (homogeneous and/or heterogeneous) or reagents along with organic solvents (harmful, toxic, or environmental benign solvents) are usually applied in classic organic reactions to achieve targeted products. Avoiding the use of catalyst and harmful/toxic solvents in organic reactions is a highly challenging task. In organic chemistry, the ideal synthesis should be a combination of a number of environmental, health, safety, and economic targets (Fig. 1), which obviously requires a rational design of the target process based on fundamental understanding to

address several green chemistry principles in a comprehensive manner.

In general water is considered a “green solvent” for organic reactions; though, chemical reactions performed “*in-* or “*on-water*” are not generally considered as greener reactions and often do not meet the requirements of ideal green processes.<sup>84</sup> The aim of this work is to provide a comprehensive overview of the most promising, alternative greener methodologies that can be employed in organic synthesis with the purpose of designing safer, more benign as well as low environmental impact processes, which can lead to improved efficiencies for industrial applications. This review highlights catalyst-free reactions in aqueous media (*in-water* and *on-water*) and in supercritical fluids.

## 2. Organic reactions in aqueous media

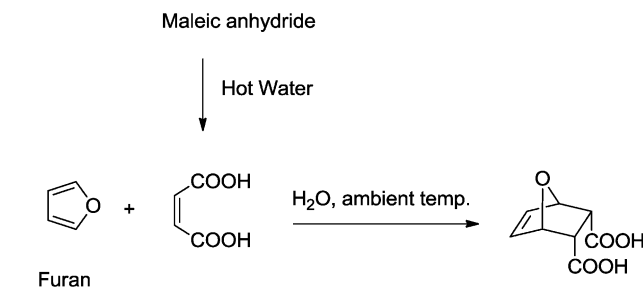
Prior to the pioneering work in the early 1980s, the use of water as solvent for the Diels–Alder reaction was limited, although the very first known example was reported by Diels and Alder in 1931 for the cycloaddition reaction of furan and maleic anhydride;<sup>85</sup> this cycloaddition was performed by the addition of furan to a solution of maleic anhydride in water.

With vigorous shaking, the oily diene eventually dissolved and a crystalline adduct ensued, which was identified as diacid (Scheme 1); this is the expected product after hydrolysis, if the reaction had occurred *via* maleic anhydride.

The use of water as a solvent in organic chemistry was revisited in the 1980s by Breslow,<sup>86,87</sup> who showed that hydrophobic effects could strongly enhance the rate of several organic reactions. Previously, the limited solubility of the reactants in water was the main reason that restricted the use of aqueous media in chemical reactions. Notably, in the exploration of new “green” procedures, high temperature water (HTW) was found to be useful in synthetic organic conversions.<sup>88,89</sup> Under near-critical and supercritical conditions water behaves as a “pseudo-organic solvent”<sup>90</sup> because its dielectric constant decreases substantially; the solvating power toward organic molecules becomes comparable with that of ethanol or acetone at room temperature, and acid or base-catalyzed reactions typically require less catalyst and often proceed rapidly.<sup>90–95</sup> Considering the importance of environmentally friendly protocols in organic chemistry, the applications of aqueous



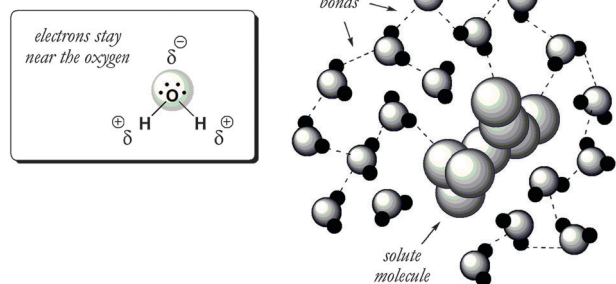
Fig. 1 The ideal synthesis.



Scheme 1 Reaction of maleic anhydride and furan in water under vigorous shaking.



## water as a solvent



**Fig. 2** Chemical structure of water and its physical interactions with solute molecules.

chemistry protocols have attracted significant interest in synthetic processes.<sup>96–100</sup> Water is the solvent of choice not only from an environmental standpoint but also from an economic point of view since it is cheap, non-flammable, and abundantly available.<sup>101–104</sup> Compared with common organic solvents, the unique and unusual physical properties such as high specific heat, high surface tension, high dielectric constant, large cohesive energy density and chemical properties (ability to form hydrogen bonds and amphoteric nature) of water can in principle influence positively the reactivity and selectivity of chemical reactions (Fig. 2).<sup>105–107</sup>

The main advantages of using water are based on:

- Its flexibility to form strong hydrogen bonds that give it a significant surface tension (three times that of liquid ammonia) – which could facilitate the aggregation of reactants.
- Its ability to form weak non-covalent bonds with other compounds.
- Its ability to engage in electron transport reactions as exemplified by many biological and synthetic reactions.<sup>108</sup>

### 2.1. Drawbacks of water as solvent or promoter

In spite of the described interesting properties of water as solvent for chemical processes, water has several associated issues. Most importantly, the solubility of organic reactants is the main drawback in aqueous processes, which generally leads to immiscible and/or biphasic reaction mixtures. Several ways to solve this issue have been proposed by using surfactant combined phases, mixing with co-solvents, heating the reaction mixture, or grinding the reactants. However, the use of aqueous media in organic reactions can have some disadvantages. Some of reactants and products can decompose upon heating of the aqueous reaction mixture, while in other cases water sensitive reactants are simply not compatible or are unable to react in the presence of water. In the case of heterogeneously catalyzed protocols, aqueous phases require stable and water tolerant catalysts which need to be designed to work under these conditions.<sup>109</sup> Formation of unwanted side products is also a major drawback of the utilization of water in organic synthesis. However, some of these issues have been addressed and solved by designing protocols based on the use of microwaves, ultrasound or pressure reactors, and using other benign (co)solvents. Very recently, water-promoted

reactions were classified by Butler and Coyne as *in-water* or *on-water* reactions, according to the associated experimental conditions.<sup>84</sup>

### 2.2. Catalyst-free *on-water* organic reactions

Water is considered a green solvent for various chemical and biological reactions. It is well understood that reactants should be soluble in solvents for the successful performance of reactions. This concept completely changed with the earlier research work on Diels–Alder reactions, the first reports on the use of water as solvent.<sup>86</sup> Subsequently, the advancements in studying the existence of hydrophobic effect in organic synthesis are mainly responsible for the emerging interest in water as a solvent.<sup>110</sup>

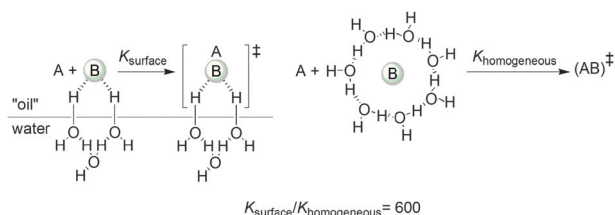
Recently, this concept was revisited by Sharpless and co-workers with some representative reactions where water insoluble reactants are converted to products in high yields; the reaction mixture is usually stirred vigorously in water for a short period.<sup>111</sup> The representative examples included cyclo-additions, such as classic Diels–Alder reactions, as well as nucleophilic ring-opening of epoxides and aromatic Claisen rearrangements. Since the reactants were insoluble in water, the reactions were described as being *on-water*. Due to the aforementioned versatile and unique properties of water, rates and selectivities of pericyclic reactions under *on-water* conditions can be improved, as well as in a series of related organic transformations in the presence and/or absence of catalysts.<sup>86,112–118</sup>

Recently, Chanda and Fokin *et al.* have reviewed the organic “on-water” reactions,<sup>119</sup> where they highlighted heterogeneous reactions for several important reactions such as Diels–Alder, Passerini and Ugi, 1,3-dipolar cycloadditions and Claisen rearrangements.

Keeping in mind the aim and objectives of this review, we will focus on catalyst-free *on-water* organic transformations. *On-water* reactions refer to the remarkable phenomenon of substantial rate accelerations, when insoluble reactants are stirred in aqueous suspensions. The water surface itself has been proposed as a catalyst in such reactions, but the exact prospective of “on effects” is currently unknown.

Jung and Marcus proposed a kinetic model<sup>120</sup> and compared the rate of the reaction for neat, surface and aqueous homogeneous reactions with experimental data. According to their theory, the free OH groups in the case of *on-water* catalysis are better promoters of organic reactions when compared to “*in-water* conditions,” but additional validation of the reaction mechanisms with experimental data is required.

As an example, the reaction of dimethyl azodicarboxylate (DMAD) could be accelerated by a factor of 1000 under *on-water* as compared to *in-water* conditions.<sup>111</sup> A summary of these molecular interpretations is depicted in Fig. 3 and a range of selected examples of these acceleration effects will be highlighted in subsequent sections. According to the Jung and Marcus model, to apprehend the on-water chemistry it is essential to understand the singular pathway that occurs at the water–oil phase boundary where hydrogen-bonding



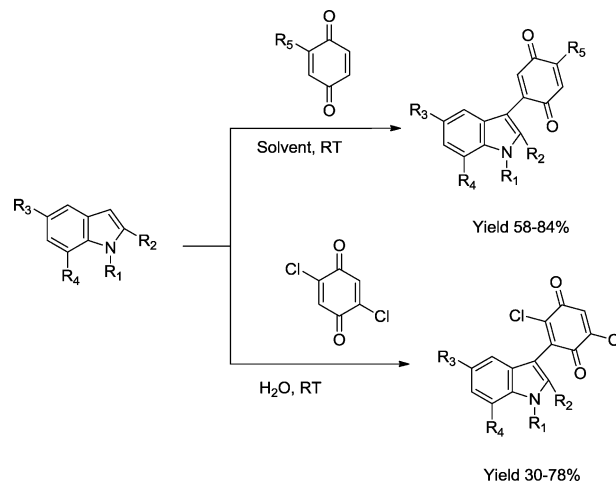
**Fig. 3** On-water catalysis in comparison with surface and aqueous homogeneous conditions (adapted from ref. 120).

interactions that utilize free OH groups of interfacial water molecules are facilitated.

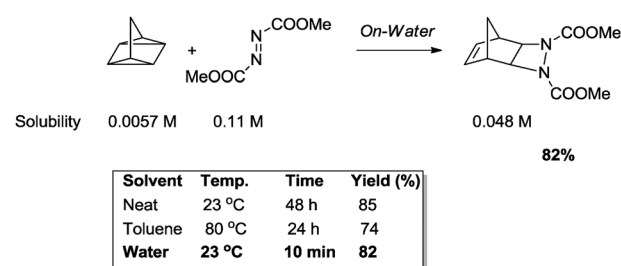
**2.2.1. Coupling reactions.** Carbon–carbon bond formation reactions are fundamental in organic chemistry and a large number of catalysts have been used for the C–C coupling reactions.<sup>121,122</sup> The reaction of indole with 1,4-benzoquinones has been widely studied, since its derivatives including bis(indolyl) quinones are biologically significant.<sup>123</sup> This coupling reaction is generally catalyzed by Brønsted (HCl, H<sub>2</sub>SO<sub>4</sub> and CH<sub>3</sub>CO<sub>2</sub>H)<sup>124,125</sup> and Lewis acids [InBr<sub>3</sub> and Bi(OTf)<sub>3</sub>]<sup>126,127</sup> in organic solvents. On similar lines, Pirrung *et al.* have synthesized bis(indolyl)-1,4-benzoquinone using Zn(OTf)<sub>2</sub> as catalyst in refluxing THF for 26 h, followed by oxidation<sup>128</sup> or by a coupling reaction with Pd<sub>II</sub>/Cu(OAc)<sub>2</sub> and Hg reagents.<sup>129</sup>

Contrarily to traditional methods, Li and Wang *et al.* reported an *on-water* catalyst-free direct coupling of indole derivatives with 1,4-benzoquinones without any additives or co-solvent.<sup>130</sup> Under these *on-water* catalyst-free (OWCF) conditions, reactants were insoluble in aqueous media but a remarkable increase in rates of reaction was found to efficiently furnish a range of bis(indolyl)-1,4-quinones in good yields. Controlled experiments were carried out for reactions involving 2-methylindole and 1,4-benzoquinone. The reactions were performed in various solvents at room temperature for 10 h without any reagents or catalysts. Reactions performed using organic solvents (*e.g.* dichloromethane, toluene, acetonitrile, THF and ethanol) and under solvent-free conditions gave very low yields of coupling products. In the case of solvent mixtures (THF and ethanol with water), yields were slightly better. A variety of quinones and indoles in aqueous medium could be efficiently converted to the corresponding products in average to excellent yields (30–84%) (Scheme 2). In the case of the reactions between 1-methyl indole, 5-methyl indole, and 5-methoxy indole with 2,5-dichloro,1,4-benzoquinone, the formation of mono and bis-coupling products was observed. Further extension of this simple and highly efficient catalyst-free coupling protocol led to the formation of homo-bis(indolyl) quinones and cross-bis(indolyl) quinones in 68–90% and 72–92% yields respectively.

**2.2.2. Cycloaddition reactions.** Sharpless and co-workers reported the synthesis of 1,2-diazetidines from quadricyclane by cycloadditions with azodicarboxylates;<sup>111</sup> these reactions are traditionally carried out in toluene or benzene at 80 °C, for 24 h or longer.<sup>131</sup> In contrast, when a mixture of dimethyl azodicarboxylate (DMAD) and quadricyclane was stirred vigorously *on-water*,



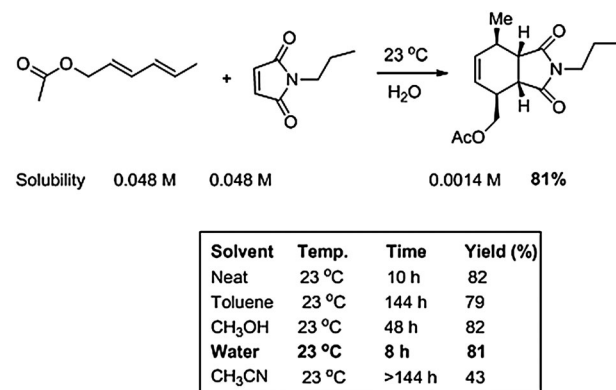
**Scheme 2** Catalyst-free coupling of quinones with indoles *on-water*.



**Scheme 3** Catalyst-free cycloaddition of quadricyclane with dimethyl azodicarboxylate *on-water*.

the corresponding products were obtained in 82% yield after 10 min of reaction. Under solvent-free conditions the reaction required 2 days for completion, as compared to a 74% yield after 24 h using toluene as solvent (Scheme 3). Quadricyclane reactions are also promoted under high pressure conditions which are the closest analogy to *on-water* reactions.

The cycloaddition of *trans,trans*-2,4-hexadienyl acetate and *N*-propylmaleimide<sup>111</sup> under various conditions is depicted in Scheme 4. Protic solvents (methanol) were found to be better solvents with respect to their nonprotic counterparts, and the



**Scheme 4** Catalyst-free cycloaddition of *trans,trans*-2,4-hexadienyl acetate and *N*-propylmaleimide *on-water*.

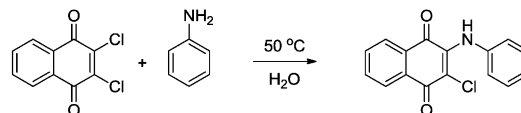
reaction *on-water* (heterogeneous phase or aqueous suspension) showed considerable rate acceleration as compared to that obtained using various organic solvents.

Other organic reactions such as the *Ene* reaction of cyclohexene with bis(trichloroethyl) azodicarboxylate, nucleophilic opening of an epoxide and aromatic Claisen rearrangements showed promising *on-water* results. The original discovery that Diels–Alder cycloadditions can be accelerated under aqueous conditions has prompted extensive exploration of these cycloaddition reactions in water.<sup>86,132–136</sup>

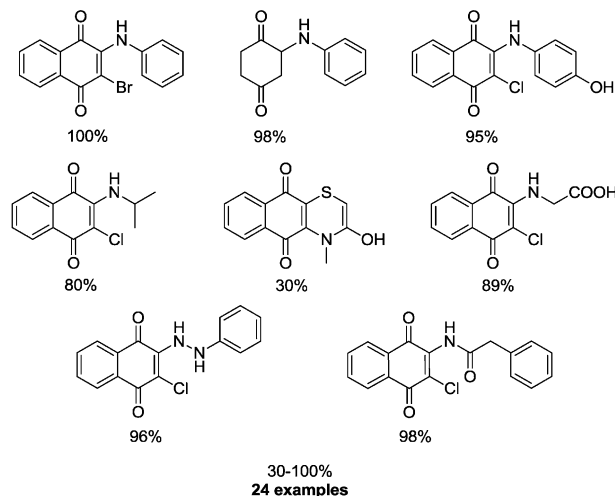
Hetero-Diels–Alder cycloadditions of ketones with dienes can be promoted by catalysis or under pressure conditions.<sup>137</sup> However, the solvent effect on these cycloadditions was untapped until the work of Rawal and Huang, who demonstrated that hetero-Diels–Alder cycloadditions of butadiene derivatives with simple unactivated ketones are accelerated by protic polar solvents but are relatively unaffected by polar aprotic solvents.<sup>138</sup> In addition, Mloston<sup>139</sup> and Brandi<sup>140</sup> have also made major contributions for cycloaddition reactions.

Huisgen cycloaddition, also known as 1,3-dipolar cycloaddition, is a broadly utilized pericyclic reaction in synthetic organic chemistry<sup>141</sup> and often used in the synthesis of five-membered rings from the reaction between a 1,3-dipole and a dipolarophile. Huisgen cycloaddition of the insoluble yellow solid, phthalazinium dicyanomethanide, occurred readily in vigorously stirred aqueous suspensions when the solid dipolarophile had a solubility *ca.*  $>10^{-3}$  M. As depicted in Scheme 5, a range of insoluble solid *N*-aryl maleimides worked well and the corresponding cycloaddition adducts were obtained in excellent yields (91–96%). These reactions occurred due to the hydrophobic effect, which accelerates the reaction of sparingly soluble reactants and immediately expels the more soluble cycloadducts with larger organic surface areas from the medium as soon as they are formed. In line with *on-water* promoted reactions, Butler and co-workers reported the reactions of solid reactants *on-water* (aqueous suspensions).<sup>142</sup>

**2.2.3. Nucleophilic substitution and addition reactions.** Tandon *et al.* reported<sup>143</sup> *on-water* nucleophilic substitution and addition reactions of 1,4-quinones; reaction of 2,3-dichloro-1,4-naphthoquinone with aniline was carried out *on-water* at 50 °C to afford the corresponding product in quantitative yield and was compared with known protocols, which were carried out in benzene,<sup>144</sup> MeOH and EtOH.<sup>145</sup> The *on-water* reaction was found to be more efficient when compared to those performed under conventional conditions (Scheme 6). A variety of aromatic amines,



Solvent	Temp. (°C)	Time (h)	Yield (%)
Benzene	50–60	0.5	81
MeOH	–	–	73
EtOH	RT	1	90
<b>Water</b>	<b>RT</b>	<b>0.83</b>	<b>100</b>
Water	50	0.25	100

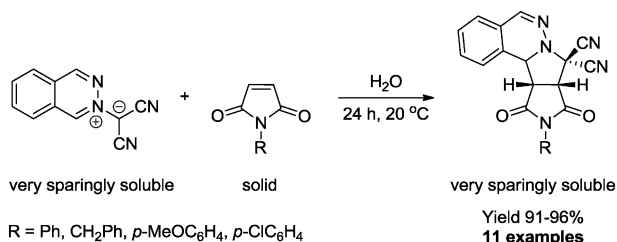


**Scheme 6** Catalyst-free nucleophilic substitutions and addition reactions *on-water*.

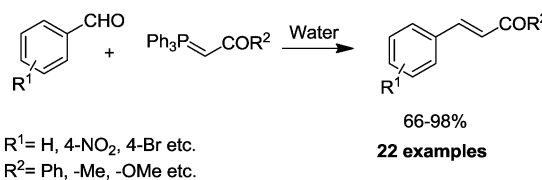
primary aliphatic amines, aminoacids, esters of aminoacids, heterocyclic amines, hydrazines, amides, and thiols underwent nucleophilic substitution and addition reactions.

A clear homogenous mixture is not necessary requisite for the reaction *on-water* even if the reactants are solids, indicating that solubility is not a deciding factor under such conditions. The rate of acceleration and selectivity of these *on-water* reactions obtained *via* the interaction of nonpolar or hydrophobic regions of reactants are of major importance.<sup>146</sup> This protocol, which was reported to be highly successful *on-water* without any catalyst/promoter, is a good alternative for conventional procedures.<sup>147,148</sup>

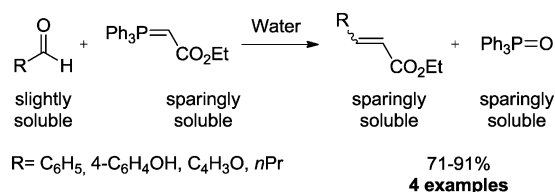
**2.2.4. Wittig reaction.** The Wittig reaction<sup>149,150</sup> is an important reaction in organic synthesis as it generates double bonds with a high level of stereoselectivity.<sup>151</sup> M. Bergdahl and co-workers reported Wittig reaction exemplified by various aromatic aldehydes and stabilized ylides in water and other solvents (Scheme 7);<sup>152</sup> water was found to be the most efficient



**Scheme 5** Catalyst-free 1,3-dipolar cycloadditions *on-water*.



**Scheme 7** Catalyst-free Wittig reactions of aromatic aldehydes and stabilized ylides *on-water*.



**Scheme 8** Catalyst-free Wittig reaction of aldehydes and phosphorous ylides *on-water*.

medium in terms of yield and selectivity of products when compared to methanol, benzene and dichloromethane. It was observed that the solubility in water is not an important factor to achieve good chemical yields and *E/Z*-ratios as shown in the successful Wittig reactions of heterocyclic, aliphatic and protected aldehydes.

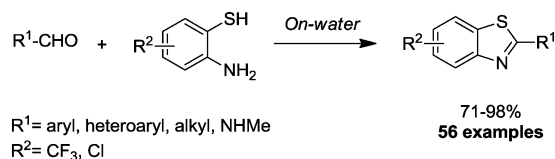
Bergdahl *et al.* further extended this work with reaction of aldehydes with stabilized ylides for the synthesis of  $\alpha,\beta$ -unsaturated esters, mixing aldehydes,  $\alpha$ -bromoesters, and triphenylphosphine in aqueous NaHCO<sub>3</sub>.<sup>66</sup>

Tiwari and Kumar reported the *on-water* Wittig reaction of insoluble aromatic and aliphatic aldehydes with phosphorus ylides at 25 °C (Scheme 8).<sup>153</sup> They found that alkali metal salts (LiCl and NaCl) decreased the rate of reaction. However, the rate of the reaction was measurable, when the same salts were utilized at 65 °C, and guanidinium chloride (anti-hydrophobic salt) decreased the rate of reactions in neat water.

In heterogeneous medium, at 25 °C, smaller particle sizes of the ylide increase the rate of reaction and a plausible reason could be the existence of an interfacial mechanism. The effect of the added salt (LiCl and NaCl) to *on-water* reactions is different in comparison to homogeneous aqueous reactions. The effect of high salt concentrations could be due to a restriction on the availability of free OH groups at the phase boundary so that they are able to reduce the *trans*-phase *H*-bond catalysis (more at 25 °C than for the more loosely structured water at 65 °C).

**2.2.5. Condensation reactions.** Chakraborti and co-workers reported the *on-water* synthesis of 2-aryl/heteroaryl/styryl benzothiazoles and 2-alkyl/aryl alkyl benzothiazolines<sup>154</sup> (Scheme 9).

A variety of aldehydes such as alkyl, aryl, and heteroaryl reacted with 2-amino thiophenol under *on-water* conditions to give the corresponding condensation products. The reaction is chemoselective without thia-Michael addition, *O*-dealkylation/debenzoylation, reduction of the nitro or the  $\alpha,\beta$ -unsaturated carbonyl groups, and substitution of the halogen atom or the nitro group.



**Scheme 9** Catalyst-free condensation of aldehydes with 2-amino thiophenol *on-water*.

*On-water* Knoevenagel condensations of 2-thiobarbituric acid and *N,N*-dimethylbarbituric acid with aromatic and hetero-aromatic aldehydes under catalyst-free conditions have also been explored.<sup>155</sup>

### 3. Catalyst-free reactions *in-water*

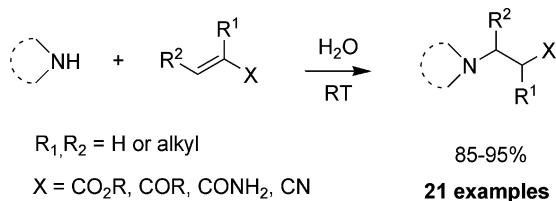
Water can be a better medium to perform catalyst-free organic reactions. Currently, organic reactions that are carried out in water are classified as *on-water* or *in-water*, depending on the solubility of reactants. According to Breslow, *in-water*, the organic molecules are forced to form aggregates in order to decrease the exposed organic surface area.<sup>87</sup> Due to these aggregates, holes are formed in the cluster structure of liquid water and the bulk water molecules surround or hydrate the aggregates.<sup>84</sup> In the final layer of the hydration shell, as the bulk water molecules approach the surface of small aggregates their H-bond links run laterally along the hydrophobic surface.<sup>156</sup> This effect is known as the “*Breslow hydrophobic effect*”. With large hydrophobic surfaces some dangling hydrogen bond (OH-free) groups are orientated toward the barrier to maximize the packing density of the molecule.<sup>157,158</sup> In the last few decades *in-water* reactions have been studied in detail,<sup>110,159–165</sup> the main characteristics being: (a) hydrophobicity, which speeds up reactions; (b) hydrogen bonding, with impact on reactants and transition states which may or may not favor the hydrophobic effect; and (c) water polarity, which may again increase or decrease the reaction rates. In this section, we describe some catalyst-free, organic reactions performed in aqueous media.

#### 3.1. Addition reactions

Addition reactions play a lead role in organic synthesis, due to their importance in the preparation of key pharmaceutical intermediates and other compounds.<sup>166–172</sup> The scope of this type of reaction is largely untapped from the green chemistry point of view. Consequently, Michael addition, Baylis–Hillman and other addition reactions performed in aqueous media are focus of attention in this section.

**3.1.1. Michael-type reactions.** The aza-Michael addition is an important reaction for the synthesis of valuable structural scaffolds,<sup>173,174</sup> and one of the best alternatives to Mannich reactions for the synthesis of  $\beta$ -amino carbonyl compounds (often catalyzed by Lewis or Brønsted acids). However, these methodologies have suffered from disadvantages including leaching of metals and harsh reaction conditions. The development of novel, facile and environmentally friendly protocols for the aza-Michael addition is highly desirable. Ranu *et al.* demonstrated the addition of amines to conjugated alkenes in aqueous media at room temperature without any catalyst or additives.<sup>175</sup> The reaction is clean and high yielding; the rates of the reaction are faster (20–50 min) when performed in aqueous media (*in-water* reactions) as compared to already existing protocols in which organic solvents were utilized with catalysts.





**Scheme 10** Catalyst-free aza-Michael reaction in aqueous media.

An aza-Michael reaction using amines and Michael acceptors is shown in Scheme 10; the main drawback of the reaction is the lack of reactivity of aromatic amines under these conditions.

Marini and co-workers have synthesized aziridines by an aza-Michael initiated ring-closure reaction (aza-MIRC) *via* tandem Michael-intramolecular nucleophilic substitution. The substituted aziridines, from vinyl selenones and primary amines, amino alcohols, or diamines,<sup>176</sup> (Scheme 11) were obtained in good to excellent yields both in toluene (40–99%) and *in-water* (61–99%) conditions.

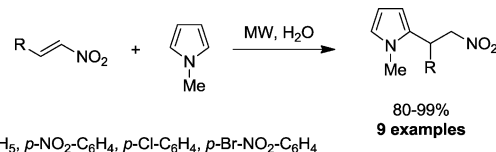
Diastereoisomeric aziridines were synthesized from chiral amines under aqueous media in short reaction times.

Soriente *et al.* described the addition of pyrroles and indoles to nitroalkenes under catalyst-free conditions in aqueous media.<sup>177</sup> A variety of pyrroles, indoles, or nitroalkenes rapidly afforded the corresponding adducts in excellent yields (Scheme 12).

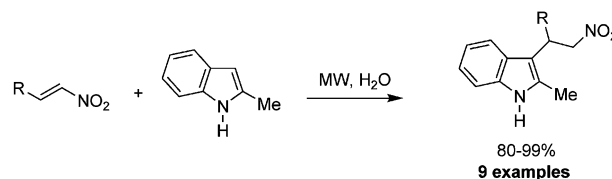
This greener protocol was extended to the nitro-Michael addition of nitroalkenes and a variety of substituted indoles (Scheme 13). The corresponding adducts were obtained in good to excellent yields (80–99%).

The advantage of this general protocol is that it can be applied to a variety of pyrroles and indoles in the synthesis of natural products bearing these moieties.

Indoles and their derivatives (*e.g.* hapalindole alkaloids, which exhibit significant antibacterial and antimycotic activity) and other indole alkaloids such as uleine, aspidospermidine, ibophyllidine, and numerous tryptamine derivatives are associated with important biological activities.<sup>178</sup> Therefore, the synthesis of indole derivatives in aqueous media is highly desirable. The reaction of indoles with several  $\beta$ -nitrostyrenes in aqueous media under catalyst-free conditions was investigated by Yao *et al.* (Scheme 14).<sup>179</sup>



**Scheme 12** Catalyst-free nitro-Michael addition of 1-methyl-pyrrole to nitroalkenes under microwave irradiation in aqueous media.



**Scheme 13** Catalyst-free nitro-Michael addition of substituted indoles in aqueous media.

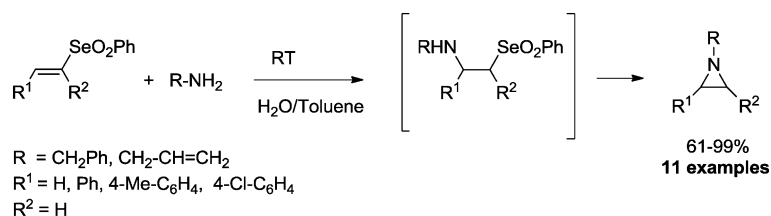
Mishra *et al.* reported a water promoted, catalyst-free synthesis of 3-mercapto- or 3-dithiocarbamoyl-2-deoxycarbohydrate derivatives by the conjugate addition of thiols or dithiocarbamates to glycal-derived  $\alpha, \beta$ -unsaturated carbonyl compounds (Scheme 15).<sup>180–182</sup>

Ziyaei-Halimehjani *et al.* have described a water-promoted catalyst-free Michael addition of thioacetic and thiobenzoic acids to activated olefins.<sup>183</sup>

**3.1.2. Mukaiyama-aldol reactions.** Rosa and Soriente reported the uncatalyzed addition between Rawal's diene (1-dimethylamino-3-silyloxy-1,3-butadiene) and various carbonyl compounds using water as solvent.<sup>184</sup> The corresponding Mukaiyama-type aldol adducts were obtained in moderate to excellent yields (44–93%) (Scheme 16).

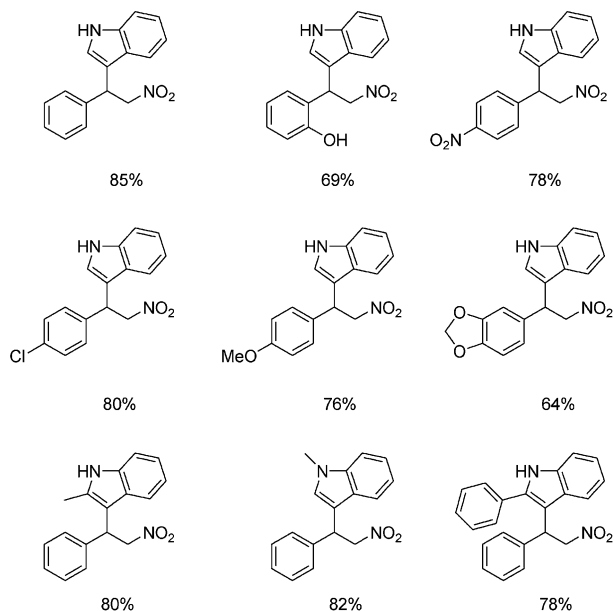
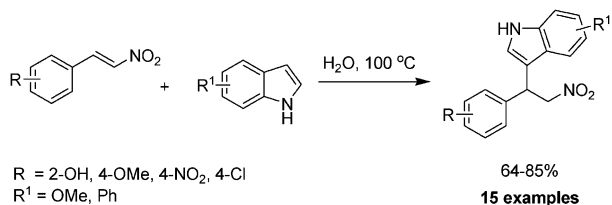
The reaction also worked well with aromatic aldehydes bearing either electron-donating or electron-withdrawing groups, although the conversion observed with these latter groups was lower. The process was investigated for pyruvate esters (Scheme 17) and the corresponding Mukaiyama-type adducts were obtained in very good yields (85–91%).

In terms of mechanism, water plays a major role in addition-type reactions by activating the oxygen of the carbonyl compound (**B**) through hydrogen bonding. The Rawal's diene (**A**) reacts with the carbonyl carbon to form a new C–C bond *via* a Mukaiyama-aldol reaction pathway to yield the target product (**C**) (Scheme 18).

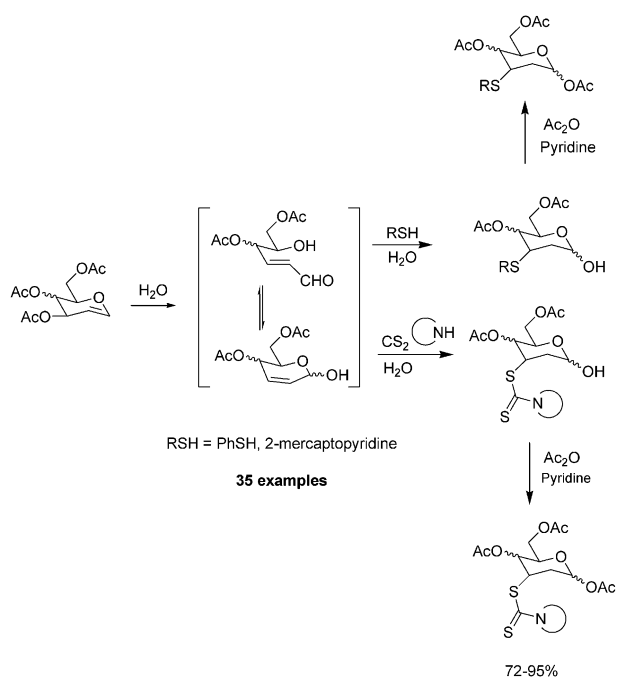


For Water 61-99%, 11 examples  
 For Toluene 40-99%, 18 examples

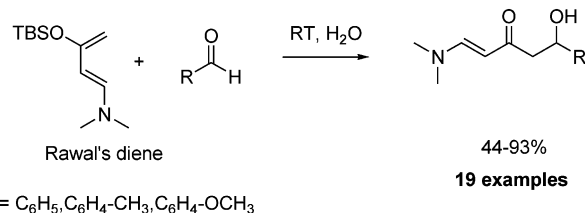
**Scheme 11** Catalyst-free synthesis of aziridines from vinyl selenones and primary amines *in-water*.



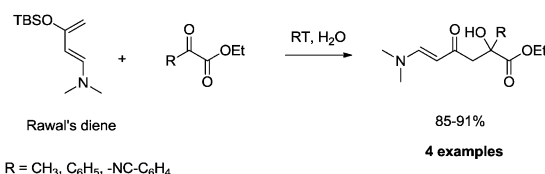
**Scheme 14** Catalyst-free reaction of indoles with  $\beta$ -nitrostyrenes in aqueous media.



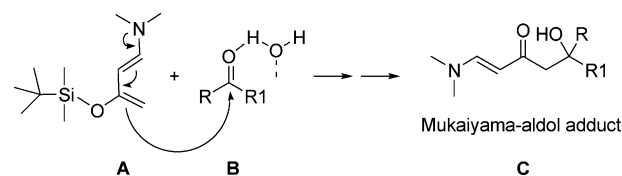
**Scheme 15** Catalyst-free addition of thiols or dithiocarbamates to glycal-derived  $\alpha,\beta$ -unsaturated carbonyl compounds *in-water*.



**Scheme 16** Catalyst-free additions of Rawal's diene to aldehydes *in-water*.



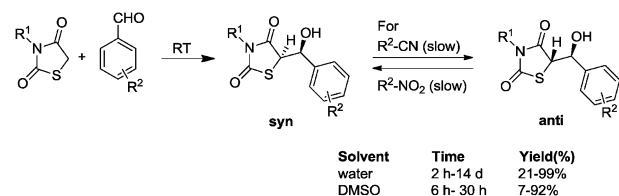
**Scheme 17** Catalyst-free Mukaiyama aldol reactions with Rawal's diene and pyruvate esters in aqueous media.



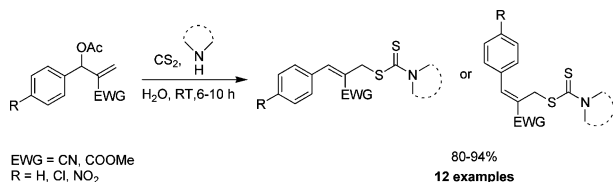
**Scheme 18** Reaction mechanism for the water-promoted addition of Rawal's diene (A) to a compound (B).

**3.1.3. Aldol reaction of thiazolidinediones.** Stereoselective aldol reactions are one of the most important tools for the carbon-carbon bond formation in organic synthesis.<sup>156,185,186</sup> In recent years, considerable attention has been directed towards development of benign protocols for aldol reactions. The thiazolidinediones, however, have never been used as nucleophilic donors in aldol reactions.<sup>187</sup> This may be attributed to the formation of the dehydration products<sup>188,189</sup> even under mild reaction conditions. Thiazolidinedione and their derivatives are pharmaceutically important frameworks and potential chemotherapeutic agents in medicinal chemistry.<sup>189-191</sup>

Dash *et al.* investigated the reactivity of aromatic aldehydes using thiazolidinediones as aldol donors *on-water* and in DMSO, in the absence of catalysts, to prepare the corresponding  $\beta$ -hydroxy carbonyl compounds.<sup>192</sup> The *p*-cyano and *p*-nitro substituted aldol products undergo a *syn/anti* isomerization *via on-water* diastereoselectivity control. The water molecules play a noteworthy role in stabilizing the *syn* aldol products of pyridine and thiazole containing aldehydes (Scheme 19).



**Scheme 19** Catalyst-free aldol reaction of thiazolidinediones.



**Scheme 20** Catalyst-free one-pot synthesis of allyl dithiocarbamates in aqueous media.

Thiazolidinedione derivatives usually undergo *syn* selective aldol reactions, except in the case of *p*-cyano benzaldehyde, which gives only the *anti* aldol product after 6 days. This uncatalyzed protocol exemplifies a rare example<sup>190,193</sup> of an aldol reaction using thiazolidinediones as pronucleophiles.

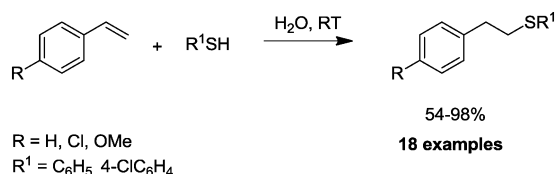
**3.1.4. Nucleophilic displacement ( $S_N2'$ ) on Baylis–Hillman adducts.** The Baylis–Hillman (BH) reaction is an important carbon–carbon coupling reaction in organic synthesis and pharmaceutical chemistry. The synthesized adducts *via* BH reactions have many applications as resourceful building blocks of many bioactive compounds and/or versatile synthetic intermediates.<sup>194–196</sup>

Yadav and co-workers have reported the stereoselective synthesis of (*E*)- and (*Z*)-allyl dithiocarbamates from acetates of BH adducts under catalyst-free conditions *via* one-pot three-component coupling reactions of carbon disulfide and amines in aqueous media.<sup>197</sup> The corresponding functionalized allyl dithiocarbamates were obtained in high yields (80–94%) (Scheme 20). The reaction pathway involves the nucleophilic displacement ( $S_N2'$ ) of BH acetates by the dithiocarbamate anions using water as a solvent and a promoter, thus avoiding the use of catalysts and toxic solvents.

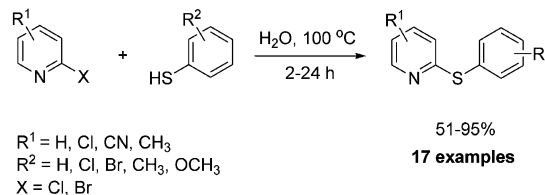
**3.1.5. Other addition reactions.** Movassagh *et al.* reported a simple and efficient catalyst-free protocol for the anti-Markovnikov addition of thiols to styrenes at room temperature (Scheme 21),<sup>198</sup> yielding the corresponding adducts in good to excellent yields (54–98%). Interestingly, the use of other solvents, including MeOH,  $CHCl_3$ , THF, and *n*-hexane, or performing the reaction under solvent-free conditions provided lower yields to those obtained in aqueous media.

In similar approaches, Chakraborti *et al.*<sup>199</sup> and Saidi *et al.*<sup>200</sup> reported the conjugate addition of thiols, and amines and carbon disulfide, respectively, to  $\alpha,\beta$ -unsaturated carbonyl compounds, under water promoted catalyst-free one-pot reactions.

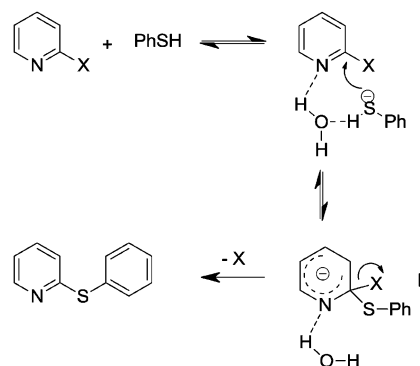
Pyridines and their derivatives are the most important heterocycles among biologically active compounds.<sup>201</sup> In general, 2-thiopyridines derivatives are useful starting materials in the synthesis of valuable building blocks<sup>202</sup> and thioethers are prepared using metal catalysts, bases and polar solvents.<sup>203–206</sup>



**Scheme 21** Catalyst-free anti-Markovnikov addition of thiols to styrenes in aqueous media.



**Scheme 22** Catalyst-free synthesis of biaryl sulfides in aqueous media.



**Scheme 23** Possible mechanism for the biaryl sulfides formation using water as a promoter.

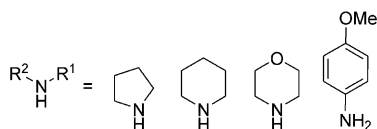
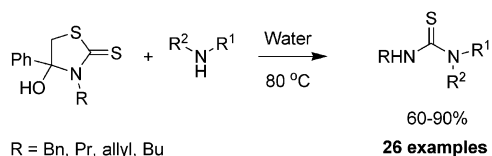
Sreedhar and co-workers studied the synthesis of biaryl sulfides in aqueous media under catalyst/base free conditions.<sup>207</sup> The biaryl sulfides were obtained in good to excellent yields (51–95%) from a range of heteroaryl halides and thiols *via* a  $S_NAr$  reaction (Scheme 22); the mechanism is depicted in Scheme 23.

Water exhibits an amphiphilic catalytic effect by cooperative hydrogen bond formation with the nitrogen atom of the halopyridine and the SH hydrogen of thiophenol (I). After conjugation, the nucleophile adds to the substrate to generate a 1 : 1 ( $\sigma$ )-adduct (II), which upon removal of the leaving group affords the  $S_NAr$  product. The present protocol is cost effective, environmentally sound, and catalyst-free.

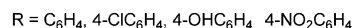
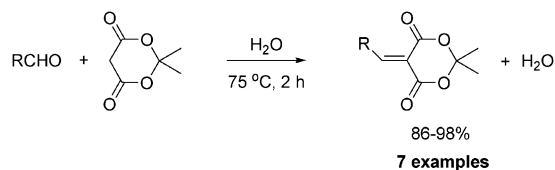
Thiourea and derivatives are important building blocks in the synthesis of heterocyclic scaffolds.<sup>208–210</sup> Traditionally, substituted thioureas have been synthesized by the condensation of amines (primary and secondary) with thiophosgene,<sup>211</sup> or isothiocyanate,<sup>212</sup> and reaction of amines with carbon disulfide,<sup>213,214</sup> among others.<sup>215,216</sup> Sun and co-workers established the synthesis of substituted thiourea derivatives under catalyst-free conditions in aqueous media<sup>217</sup> *via* the reaction of thiazolidine-2-thiones with various amines (Scheme 24); a variety of unsymmetrical and symmetrical thioureas were obtained in good to excellent yields (60–90%). The protocol offers numerous advantages including a catalyst-free approach, a broad applicability, and simple operation, while providing a greener alternative to conventional routes.

### 3.2. Knoevenagel condensation reactions

The Knoevenagel condensation is a nucleophilic addition of an active methylene to a carbonyl group followed by dehydration.<sup>43,218</sup>



**Scheme 24** Catalyst-free synthesis of substituted thioureas in aqueous media.

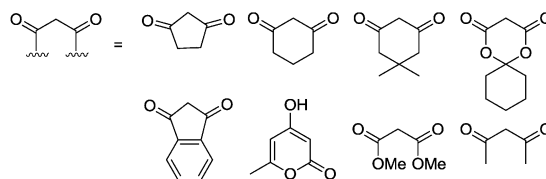
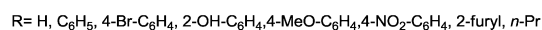
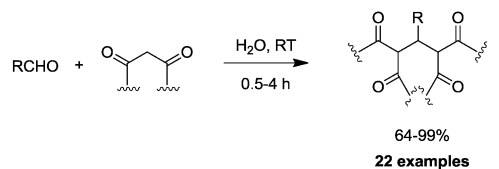


**Scheme 25** Catalyst-free Knoevenagel condensation of Meldrum's acid and aldehydes in aqueous media.

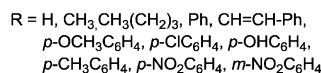
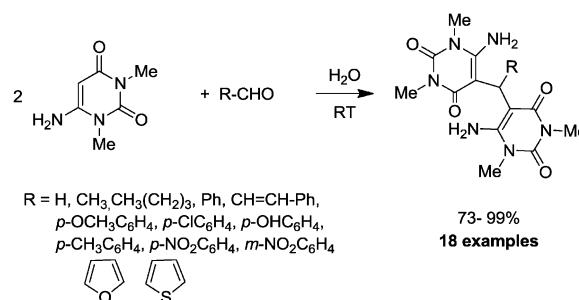
Traditionally, catalysts such as alkali metal hydroxides (*e.g.* NaOH and KOH), pyridine, and piperidine are often used, although some related solid base catalysts have been reported.<sup>219</sup> Condensation adducts such as arylidine derivatives synthesized by Knoevenagel condensation of Meldrum's acid and aromatic aldehydes are widely used as starting materials.<sup>220</sup> These adducts are key intermediates for addition reactions and for the synthesis of heterocyclic compounds with potential pharmacological activity.<sup>221</sup> Bigi *et al.* have reported a catalyst-free Knoevenagel condensation of Meldrum's acid with various aldehydes in aqueous media.<sup>222</sup> The corresponding arylidine derivatives were obtained in excellent yields (86–98%). The protocol was also amenable to a variety of aldehydes including aromatic, heteroaromatic, and hindered aliphatic aldehydes, which worked well under the investigated reaction conditions (Scheme 25).

Yu and co-workers reported an uncatalyzed tandem Knoevenagel condensation and Michael addition in aqueous media.<sup>223</sup> The corresponding tetraketones were obtained in good to excellent yields (64–99%) from the reaction of cyclic or acyclic 1,3-diketones and different types of aldehydes (Scheme 26).

The reaction protocol is very simple, efficient, and environmentally benign. In a typical reaction, an homogeneous system is formed when benzaldehyde and 1,3-cyclohexanedione are mixed in aqueous media. Interestingly, the product formed upon completion of the reaction crashes out of the solution and can be easily isolated by simple filtration followed by washing with water. This procedure completely avoids the traditional use of organic solvents or co-solvents, and catalysts. In another example, Thakur *et al.* have reported a facile and simple condensation of 6-amino-1,3-dimethyluracil with aldehydes (aromatic, aliphatic, and heterocyclic) to synthesize aryl/alkyl/heteroaryl substituted bis(6-amino-1,3-dimethyluracil-5-yl)methanes



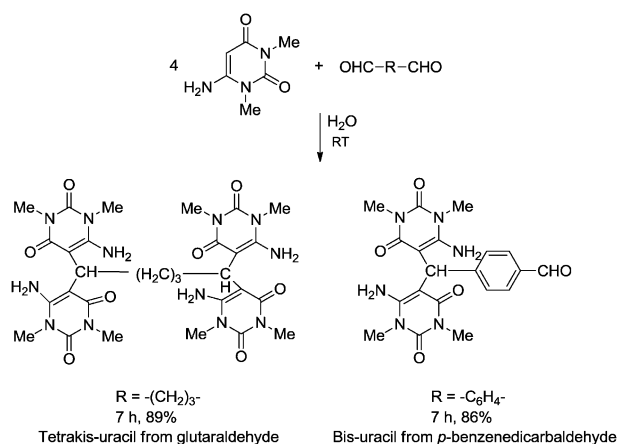
**Scheme 26** Catalyst-free synthesis of tetraketones in aqueous media.



**Scheme 27** Catalyst-free synthesis of bis-uracil derivatives in aqueous media.

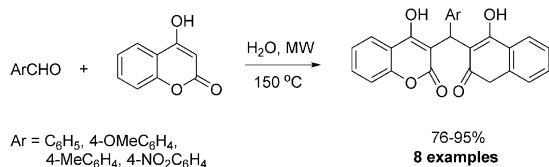
in aqueous media at room temperature (Scheme 27).<sup>224</sup> Bis-uracil derivatives, which have versatile biological and pharmacological activities,<sup>225–228</sup> were obtained in good to excellent yields (73–99%) in 0.25 to 10 h.

The scope and limitations of this reaction were investigated through the reaction of 6-amino-1,3-dimethyluracil with dicarb-aldehyde. The aliphatic dicarb-aldehyde, *viz.* glutaraldehyde, was converted into a tetrakis-uracil adduct, but aromatic dicarb-aldehydes (*e.g.* *p*-benzenedicarb-aldehyde) provided bis-uracil adducts (Scheme 28).



**Scheme 28** Catalyst-free synthesis of uracil derivatives in aqueous media.



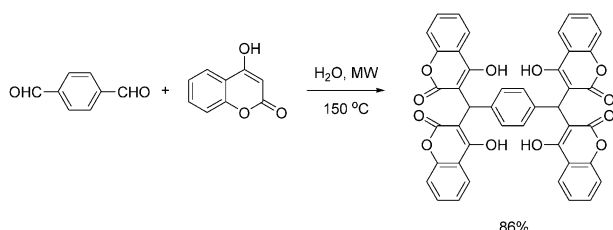


**Scheme 29** Catalyst-free synthesis of  $\alpha,\alpha$ -bis(4-hydroxycoumarin-3-yl)toluene in aqueous media.

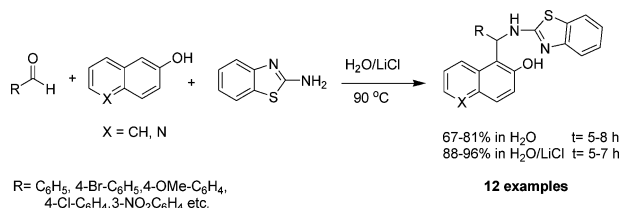
The bis-uracil and tetrakis-uracil derivatives were obtained by simple filtration, avoiding the use of organic solvents.

Zhou *et al.* reported the catalyst-free synthesis of  $\alpha,\alpha$ -bis(4-hydroxycoumarin-3-yl)toluene in aqueous media under MW irradiation.<sup>229a</sup> The adducts were obtained in high yields (76–94%) and in a short reaction time (Scheme 29) for all the aldehydes investigated.

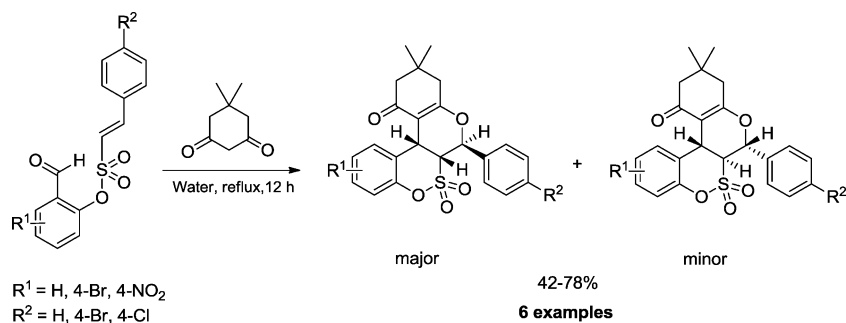
The reaction scope was extended to the synthesis of 1,4( $\alpha,\alpha',\alpha'',\alpha'''$ )-tetra(4-hydroxycoumarin-3-yl)toluene from the reaction between 1,4-benzenedialdehyde and 4 molecules of 4-hydroxycoumarin (Scheme 30) and appears to be a cost effective, simple, and environmentally friendly protocol.



**Scheme 30** Catalyst-free synthesis of 1,4-( $\alpha,\alpha',\alpha'',\alpha'''$ )-tetra(4-hydroxycoumarin-3-yl)toluene in aqueous media.



**Scheme 31** Catalyst-free synthesis of 2'-aminobenzothiazolomethyl naphthols or 5-(2'-aminobenzothiazolomethyl)-6-hydroxyquinolines in aqueous media.



**Scheme 32** Catalyst-free synthesis of hexahydro-chromene-annulated benzo- $\delta$ -sultones in aqueous media.

Shaabani and co-workers have reported the synthesis of 2'-aminobenzothiazolomethyl naphthols or 5-(2'-aminobenzothiazolomethyl)-6-hydroxyquinolines *via* one-pot three-component condensation reaction in aqueous media with or without LiCl (Scheme 31).<sup>229b</sup>

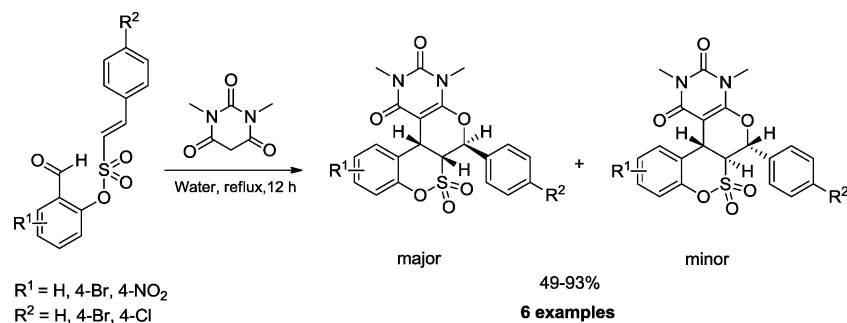
In a typical experiment, an aldehyde, 2-aminobenzothiazole, and 2-naphthol or 6-hydroxyquinoline were reacted together in aqueous media at 90 °C to give the corresponding products in good to excellent yields (67–81% for aqueous media, 88–96% for LiCl in aqueous media). The products were isolated by simple filtration, washing with water, and purified *via* recrystallization from acetone.

The domino-Knoevenagel-hetero-Diels–Alder reaction introduced by Tietze is well known for its powerful sequential transformation.<sup>230,231</sup> The reactions can be used for the construction of annulated dihydropyrans and for the synthesis of numerous natural products.<sup>232–234</sup> Previous reports describe catalysis by some Lewis acids and amine-based catalysts.<sup>235–238</sup> Ghandi and co-workers have reported a one-pot synthetic approach for the preparation of benzo- $\delta$ -sultones bearing hexahydro-chromene and tetrahydro-pyrano[2,3- $\delta$ ]pyrimidine derivatives in aqueous media.<sup>239</sup> A variety of 2-formyl-4-phenyl-(*E*)-2-phenylethenesulfonates were synthesized and underwent a one-pot domino-Knoevenagel-hetero-Diels–Alder reaction, respectively, with Meldrum's acid and *N,N*-dimethylbarbituric acid *in-water* (Schemes 32 and 33).

2-Formyl-4-phenyl-(*E*)-2-phenylethenesulfonates react with Meldrum's acid under aqueous media to deliver the corresponding adducts as mixtures of diastereoisomers in fair to good yields (42–78%). Similarly, the reaction with *N,N*-dimethylbarbituric acid *in-water* gave the corresponding products in fair to excellent yields (46–93%). The starting materials, 2-formyl-4-phenyl-(*E*)-2-phenylethenesulfonates, were prepared by simple condensation of 2-hydroxybenzaldehyde and (*E*)-2-phenylethene-sulfonyl chloride in acetone under basic conditions.

The present protocol opens the door for the synthesis of other important pharmaceutical intermediates *via* a domino-Knoevenagel-hetero-Diels–Alder reaction using water as a solvent. The beauty of this reaction relies on its simplicity, short reaction times, and avoidance of numerous sequential steps.

Coumarins, chromones, and their derivatives are important components of natural products and organic synthesis.



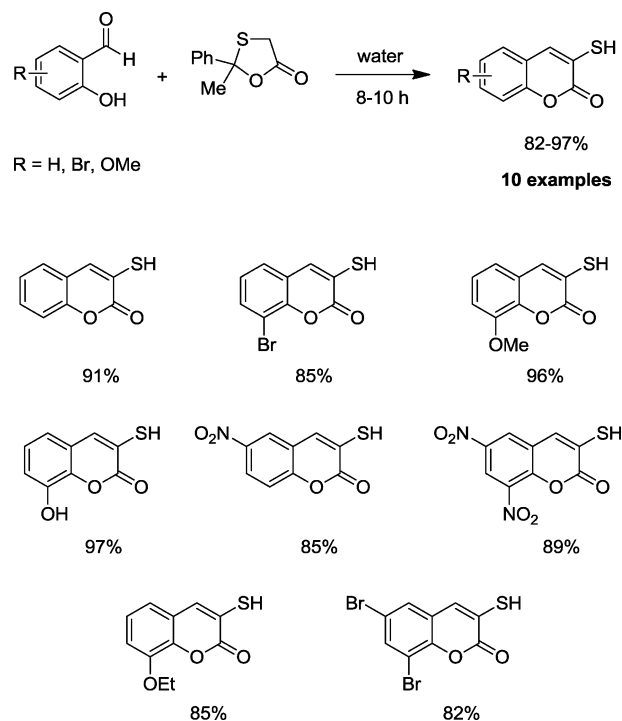
**Scheme 33** Catalyst-free synthesis of tetrahydro-pyrano[2,3-d]pyrimidine-annulated benzo- $\delta$ -sultones in aqueous media.

They have been widely utilized in the preparation of fragrances, pharmaceuticals, cosmetics, agrochemicals, optical brightening agents, and tunable dye lasers; many biological activities such as antihelminthic, hypnotic, insecticidal, and anticoagulant have been associated with these compounds.<sup>240–242</sup>

Coumarins and their derivatives are synthesized by a Pechmann condensation, using Lewis or protic acid catalysts. In recent years, heterogeneous catalysts have played an important role in the synthesis of coumarins.<sup>243–246</sup> However, these protocols have many drawbacks including the use of expensive catalysts and hazardous solvents. Moghaddam and co-workers have synthesized pentacyclic thiochromone-annulated thiopyranocoumarin and its derivatives *via* domino-Knoevenagel-hetero-Diels–Alder reaction of 4-hydroxy dithiocoumarin and *O*-acrylated salicylaldehyde derivatives under catalyst-free conditions in aqueous media.<sup>247</sup> The products are formed in good yields (60–90%) with high regio- and stereoselectivity (Scheme 34).

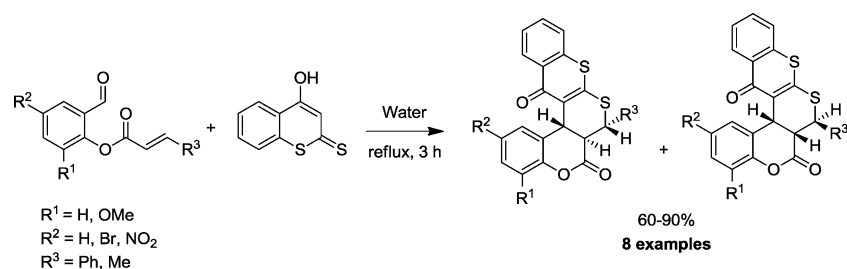
The *O*-acrylated salicylaldehyde derivatives were prepared from the corresponding substituted salicylaldehydes and (*E*)-acryloyl chloride derivatives (cinnamoyl chloride, crotonoyl chloride, and acryloyl chloride) using  $\text{K}_2\text{CO}_3$  in dry acetone with high yields (75–95%) and excellent purity of products at room temperature. This protocol is very efficient for the greener synthesis of novel heteropolycyclic compounds by the domino-Knoevenagel-hetero-Diel–Alder reaction of *O*-acrylated salicylaldehydes with 4-hydroxy dithiocoumarin in aqueous medium.

Yadav *et al.* reported the synthesis of 3-mercaptocoumarins *via* mercaptoacetylation cyclisation *in-water* under mild conditions. The as-synthesized 3-mercaptocoumarins were obtained in good to excellent yields (82–97%)<sup>248</sup> by a convenient, efficient and high yielding procedure (Scheme 35).

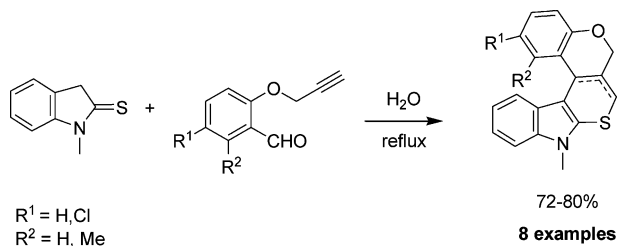


**Scheme 35** Catalyst-free synthesis of 3-mercaptocoumarins in aqueous media.

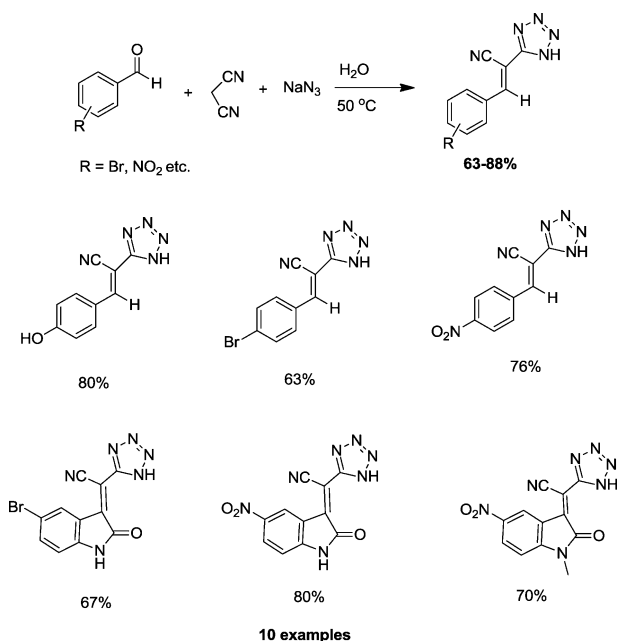
Majumdar and co-workers investigated the domino-Knoevenagel-hetero-Diels–Alder reactions in aqueous medium.<sup>249</sup> The *O*-propargylated salicylaldehyde and 1-methylindoline-2-thione were treated in aqueous medium for the synthesis of hitherto unreported indole-annulated pentacyclic heterocycles containing oxygen,



**Scheme 34** Catalyst-free domino-Knoevenagel-hetero-Diels–Alder reactions in aqueous media.



**Scheme 36** Catalyst-free domino-Knoevenagel-hetero-Diels-Alder reaction in aqueous media.



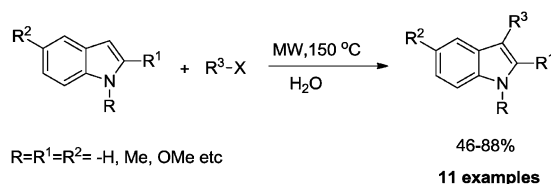
**Scheme 37** Catalyst-free multi-component domino-Knoevenagel condensation and 1,3 polar cycloaddition reaction in aqueous media.

nitrogen, and sulfur (Scheme 36). The desired polycyclic heterocycles were obtained in high yields (72–80%). This efficient and regioselective methodology can be useful for the synthesis of important heterocyclic compounds obtained from *O*-propargylated salicylaldehyde and corresponding coumarin derivatives.

Bazgir and Dabiri *et al.* reported the multi-component domino Knoevenagel condensation and 1,3 polar cycloaddition reaction of carbonyl compounds, malononitrile and sodium azide; corresponding 5-substituted-tetrazoles were obtained in good to excellent yields in water under mild reaction conditions (63–88%, Scheme 37).<sup>250</sup> These products were scarcely obtained in non-polar solvents such as benzene and toluene, and even polar solvents such as methanol and ethanol also gave poor yields. In addition, carbonyl compounds such as ninhydrin reacted with malononitrile and sodium azide to yield the corresponding products in water.

### 3.3. Friedel–Crafts type alkylation reaction

The Friedel–Crafts alkylation reaction was originally reported in 1877 by Charles Friedel and James Mason Crafts when they



**Scheme 38** Catalyst-free Friedel–Crafts C-alkylation reaction of indoles in aqueous media.

isolated amyl benzene from the reaction between amyl chloride and  $\text{AlCl}_3$  in benzene. Since its invention, Friedel–Crafts alkylations has remained a primary method for the alkylation of arenes and heteroarenes. Several types of Lewis ( $\text{BF}_3$ ,  $\text{BeCl}_2$ ,  $\text{TiCl}_4$ ,  $\text{SbCl}_5$  or  $\text{SnCl}_4$ ) and Brønsted-acids (sulfuric acid, hydrofluoric acid), as well as superacid catalysts ( $\text{HF}$ ,  $\text{SbF}_5$  and  $\text{HSO}_3\text{F}$ ,  $\text{SbF}_5$ ) have been widely explored in the Friedel–Crafts alkylation, together with many heterogeneous solid acid catalysts.<sup>42,251</sup>

Considering the significance of the Friedel–Crafts type reactions in organic chemistry, there is an urgent need for the development of environmentally and economically benign protocols using solventless and catalyst-free protocols (as well as reactions under flow conditions) would be highly desirable.

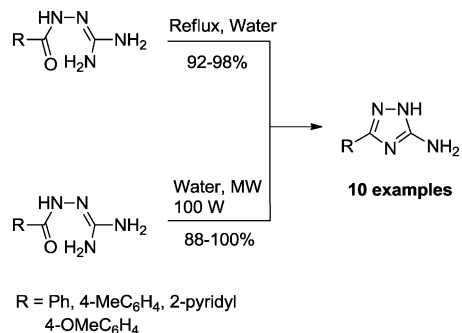
De Rosa *et al.* reported the catalyst-free Friedel–Crafts C-alkylation reaction of indoles in aqueous media;<sup>252</sup> a variety of functionalized indoles has been prepared in moderate to good yields (Scheme 38). The combination of superheated aqueous media and microwave irradiation offers significant advantages over the conventional methods. Friedel–Crafts C-alkylation of indoles with benzyl bromide under microwave irradiation is clean and proceeds with increased regioselectivity; although an *N*-alkylation product was detected in the crude mixture in small amounts, the C-alkylation occurred with high selectivity at position 3 of the indole.

The present protocol validates the prospective benefits of the reaction resulting from the combination of microwaves (MW) and superheated water, and it could be a convenient synthetic way to get functionalized indoles eluding the use of reagents/catalysts and organic solvents.

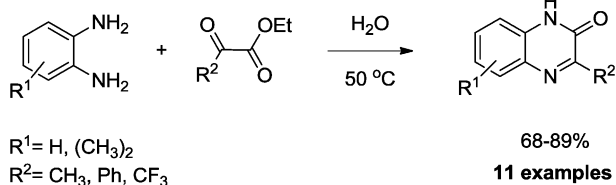
### 3.4. Synthesis of heterocyclic compounds

The synthesis, functionalization, and applications of heterocycle compounds are growing and attracting attention from the scientific community.<sup>253–257</sup> Among them, triazole derivatives<sup>258</sup> and substituted quinoxalinones<sup>259–261</sup> are actively investigated in medicinal chemistry; their preparation usually requires high temperatures<sup>262,263</sup> and/or strong bases,<sup>264</sup> with tedious workup and low yields.

**3.4.1. Synthesis of triazoles.** Dolzhenko *et al.* have reported the catalyst-free synthesis of 3(5)-amino-5(3)-(het)aryl-1,2,4-triazoles in aqueous media<sup>265</sup> in excellent yields (88–100%) *via* the cyclocondensation of amidoguanidines under conventional heating (92–98%) and MW irradiation conditions (88–100%) (Scheme 39). The tautomeric forms were analyzed using NMR spectroscopy and X-ray crystallography; triazoles were obtained exclusively in 1*H*-forms, without any traces of the corresponding 4*H*-forms.



**Scheme 39** Catalyst-free synthesis of 3(5)-amino-5(3)-(hetero)aryl-1,2,4-triazoles in aqueous media.

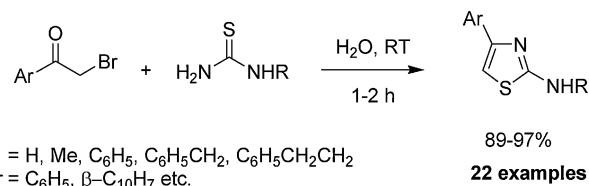


**Scheme 40** Catalyst-free synthesis of 3-substituted quinoxalinones in aqueous media.

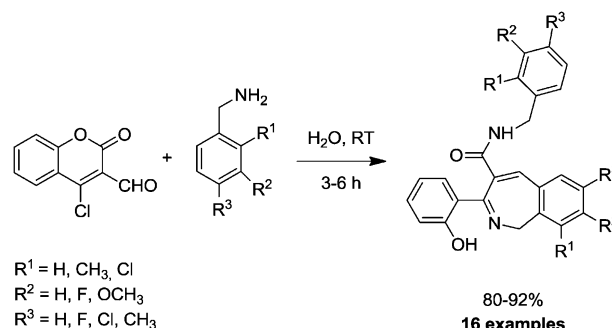
**3.4.2. Synthesis of quinoxalinones.** The Hinsberg reaction<sup>266</sup> is a practical method to obtain 3-substituted quinoxalin-2(1H)-one derivatives, a class of nitrogen-containing compounds;<sup>267</sup> many syntheses of substituted derivatives have been reported.<sup>268–271</sup> Nageswar and co-workers demonstrated that 3-substituted quinoxalinone derivatives can be obtained in quantitative yields and short reaction times from substituted benzene-1,2-diamine and  $\alpha$ -keto esters, at 50 °C in aqueous media under catalyst-free conditions<sup>272</sup> (Scheme 40). This simple and facile protocol possesses advantages over existing methods in terms of waste minimization, compound isolation, and environmental friendly operation.

**3.4.3. Synthesis of thiazoles.** The thiazole moiety, particularly 2-aminothiazole, is an important scaffold in medicinal chemistry. Numerous compounds having this framework are present in bioactive molecules and are currently under study for the development of drugs for treatment of inflammations,<sup>273</sup> allergies,<sup>274</sup> hypertension,<sup>275</sup> and schizophrenia<sup>276</sup> among others.<sup>277</sup> Recently, many improved protocols have been reported for the synthesis of thiazoles using catalysts, including  $\text{NaHSO}_4$ ,<sup>278</sup> and ammonium-12-molybdophosphate (AMP),<sup>279</sup> and reaction conditions such as MW irradiation in ethanol,<sup>280,281</sup>  $\beta$ -cyclodextrin in water,<sup>258</sup> and iodine.<sup>282</sup> However, some protocols still suffer from drawbacks related to the use of harsh reaction conditions, complex product isolation procedures, and the use of hazardous organic solvents.

Potewar and Srinivasan recently reported the uncatalyzed synthesis of substituted 2-aminothiazoles in aqueous media in short reaction time (1–2 h) and in good to excellent yields (89–97%) from substituted phenacyl bromide and thiourea derivatives (Scheme 41).<sup>283</sup>



**Scheme 41** Catalyst-free synthesis of substituted 2-aminothiazoles in aqueous media.



**Scheme 42** Catalyst-free synthesis of 2-benzazepines in aqueous media.

**3.4.4. Synthesis of benzazepines.** Benzoannulated nitrogen heterocyclic derivatives show wide ranges of biological activities; specifically, benzodiazepines, thiazepines, or oxazepines have become very popular targets in combinatorial synthesis.<sup>284–286</sup> Comparatively, much less attention has been paid to 2-benzazepine derivatives, which possess a similar structure and are present in natural and synthetic bioactive products;<sup>287</sup> there are few reports on the synthesis of benzodiazepine derivatives.<sup>288,289</sup> These reported protocols suffer some disadvantages including the use of palladium as catalyst combined with environmentally detrimental organic solvents.

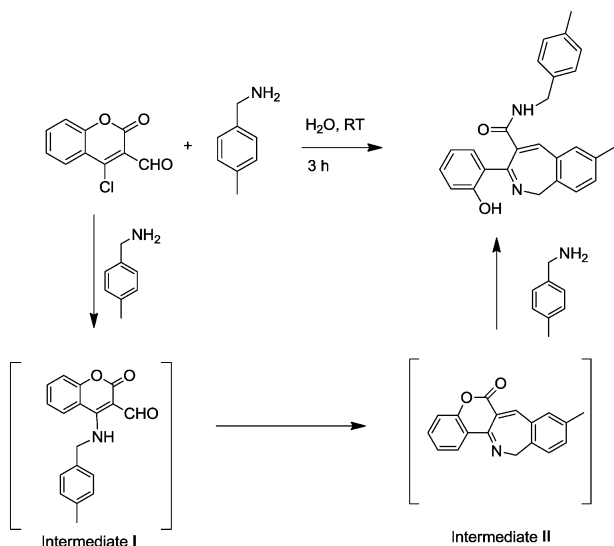
Kumar and co-workers reported the synthesis of 2-benzazepine derivatives in good to excellent yields (80–92%) in short reaction times in aqueous media and at room temperature under catalyst-free conditions (Scheme 42).<sup>290</sup>

A possible mechanism for the synthesis of 2-benzazepines is depicted in Scheme 43 and was supported by isolation of the intermediates **I** and **II** when the reactions were conducted in water with equivalent amounts of *p*-methylbenzyl amine and 4-chloro-3-formylcoumarin. Intermediate **I** was obtained after 20 min and further reaction for 90 min provided the cyclic intermediate **II**. Both intermediates were isolated and well characterized by spectroscopic techniques and this general, efficient, and environment friendly protocol has potential for further development and can be adapted to related synthetic targets.

### 3.5. Multicomponent reactions

Multicomponent reactions (MCRs) can use up to seven starting components and very often produce higher product yields than the classical chemistry approach.<sup>291</sup> An important example is the Biginelli reaction, one of the most important one-pot three-component reactions, in which aldehydes, urea/thiourea,

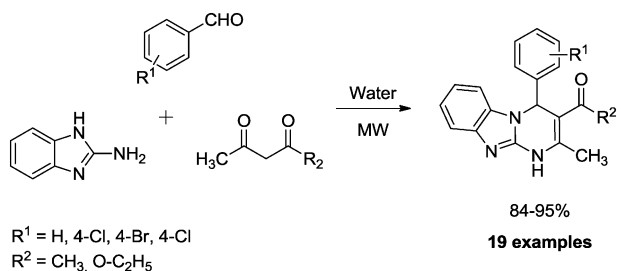




**Scheme 43** Proposed reaction mechanism for the synthesis of 2-benzazepines.

and open-chain dicarbonyl compounds, under catalytic conditions, react to yield a 3,4-dihydropyrimidin-2(1*H*)-one unit.<sup>292</sup>

**3.5.1. Synthesis of dihydropyrimidinones.** The Italian chemist, Pietro Biginelli, in 1893, first synthesized dihydropyrimidinones (DHPMs) through a MCR.<sup>293</sup> These compounds were found to be valuable intermediates in combinatorial synthesis;<sup>294,295</sup>



**Scheme 44** Catalyst-free synthesis of benzo[4,5]imidazo[1,2-a]pyrimidine derivatives in aqueous media under microwave irradiation.

targets include derivatives of marine alkaloids containing a dihydropyridine (DHP) core unit, which possess excellent biological activities (antiviral, antibacterial, and anti-inflammatory).<sup>296–298</sup> Traditionally, the Biginelli reaction has been catalyzed under basic or acidic medium,<sup>208,299,300</sup> though recently there have been various reports on the use of heterogeneous catalysts which are able to provide excellent yields.<sup>301–303</sup>

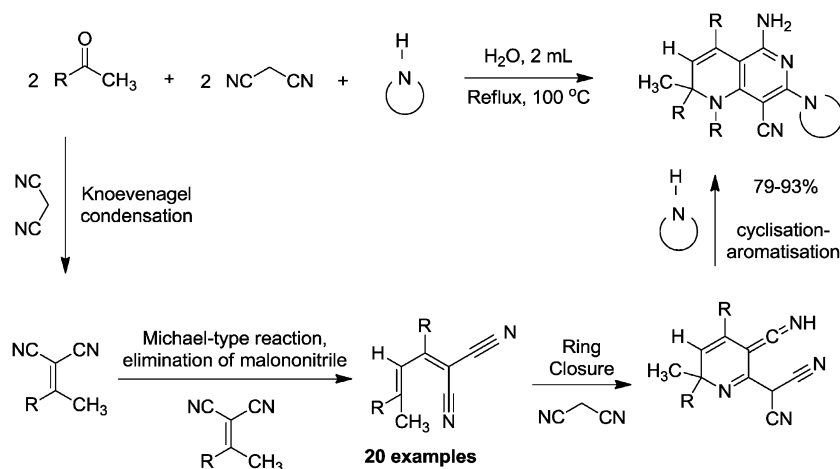
Tu and co-workers have investigated the catalyst-free and water-promoted one-pot three-component reaction of aldehydes,  $\beta$ -dicarbonyl compounds, and 2-aminobenzimidazole under MW irradiation<sup>304</sup> (Scheme 44). The corresponding DHMP derivatives were obtained in excellent yields (84–95%).

**3.5.2. Synthesis of naphthyridines.** Mukhopadhyay *et al.* reported the first one-pot pseudo-five-component synthesis of 1,2-dihydro[1,6]naphthyridines from methyl ketones, amines, and malononitrile under catalyst-free conditions in aqueous media (Scheme 45)<sup>305</sup> in good to excellent yields (79–93%); various electron-rich ketones (4-methoxy acetophenone) successfully reacted under these conditions (Scheme 46).

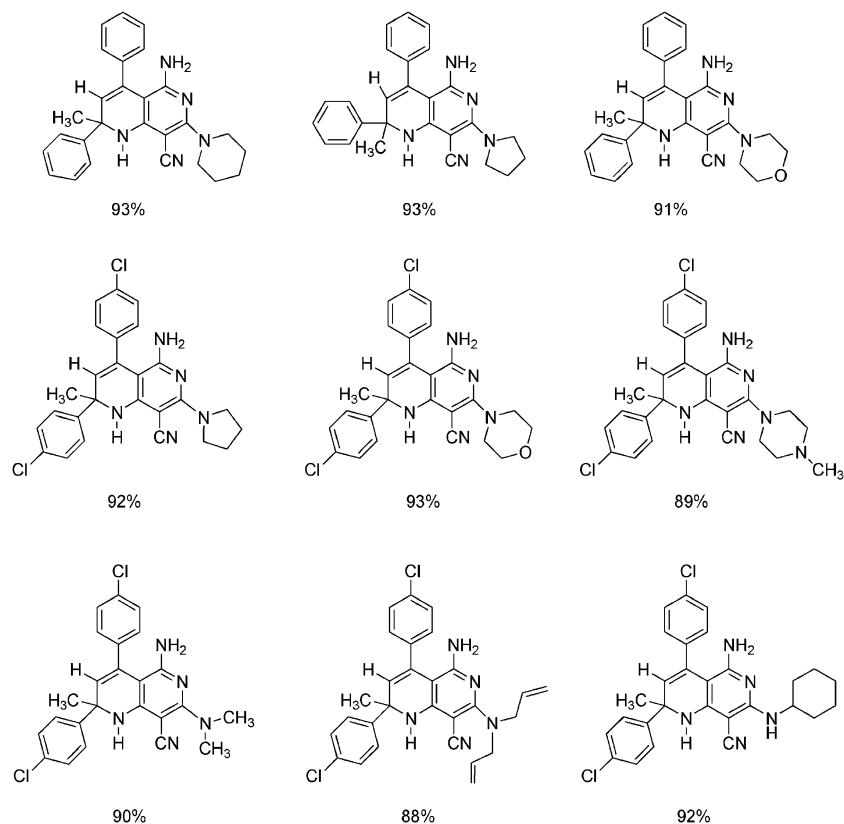
These functionalized [1,6]-naphthyridines and their benzo-heterofused analogues are found in many products of marine origin and possess biological activities, including antiproliferative,<sup>306</sup> HIV-1 integrase inhibition,<sup>307</sup> allosteric inhibition of Akt1 and Akt2<sup>308</sup> and selective antagonistic activity for 5-HT4 receptors.<sup>309</sup>

Traditionally, the synthesis of naphthyridines was carried out either using expensive catalysts<sup>310–312</sup> or multistep syntheses,<sup>313</sup> but these greener protocols can offer a useful alternative to synthetically important organic compounds. Indeed, the synthesis of 1,2-dihydro[1,6]naphthyridine and its derivatives using the aforementioned methodology avoids the use of expensive catalysts, toxic organic solvents, and anhydrous conditions.

4-Aryl-1,4-dihydropyridine (1,4-DHP) derivatives are useful drugs for the treatment of cardiovascular disorders<sup>314</sup> and play an important role in several classes of calcium channel blockers.<sup>315</sup> 1,4-DHP derivatives are generally prepared by using catalytic conditions,<sup>316,317</sup> and the use of MW-assisted and catalyst-free aqueous mediated reactions can be interesting alternative protocols to be considered.



**Scheme 45** Catalyst-free one-pot pseudo-five-component synthesis of 1,2-dihydro[1,6]naphthyridines in aqueous media.



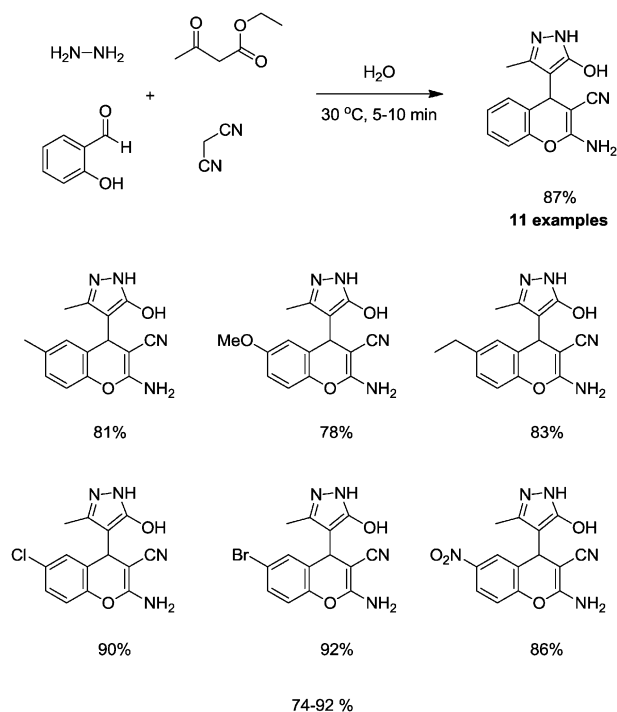
**Scheme 46** Catalyst-free synthesis of 1,2-dihydro[1,6]naphthyridines in aqueous media.

**3.5.3. Synthesis of pyrazolones.** Pyrazolones and their derivatives are important moieties in various pharmaceutical and chemical syntheses and have broad scope in biological activities such as antipyretics and analgesics;<sup>318,319</sup> their synthesis is normally conducted using acid catalysts and expensive reagents.<sup>320–322</sup>

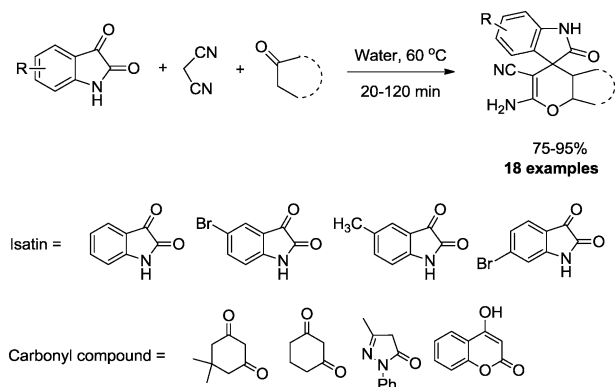
Vasuki and Kumaravel investigated the uncatalyzed synthesis of a combinatorial library of 2-amino-4-(5-hydroxy-3-methyl-1H-pyrazol-4-yl)-4H-chromene-3-carbonitrile derivatives *via* a four component reaction between hydrazine hydrate, ethyl acetoacetate, 2-hydroxybenzaldehydes, and malononitrile *in-water* at room temperature (Scheme 47);<sup>323</sup> this multicomponent catalyst-free protocol in aqueous media is highly atom economic with ethanol and water being the only byproduct of the reaction.

**3.5.4. Synthesis of spirooxindoles.** Spirooxindole and their derivatives represent an important class of biological active<sup>324–327</sup> heterocycles present in a large number of bioactive natural products, such as coerulecine, horsifiline, welwitindolinone A, spirotryprostatin A, elacomine, alstonisine, and surugatoxin. The derivatives of isopteropodine have medicinal applications in modulating the function of muscarinic serotonin receptors.<sup>328</sup> Generally, the synthesis of spirooxindoles is conducted by employing both acidic and basic catalysts and toxic solvents.<sup>329–333</sup>

As an alternative to these conventional protocols, Zhao *et al.* reported a catalyst-free, one-pot, three-component reaction for



**Scheme 47** Catalyst-free multicomponent synthesis of 4-pyrazolyl-4H-chromenes in aqueous media.

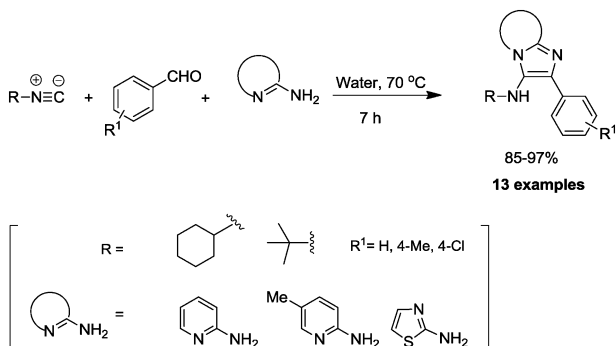


**Scheme 48** Catalyst-free synthesis of spirooxindole derivatives in aqueous media.

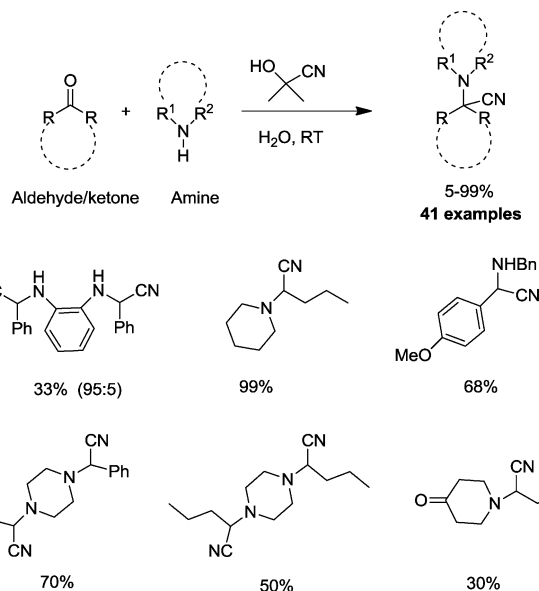
the synthesis of spirooxindole derivatives in aqueous media.<sup>334</sup> Structurally diverse spirooxindole derivatives were synthesized in excellent yields (75–95%) and in short reaction times for the reaction between isatins, malononitrile, and carbonyl compounds (Scheme 48) in an efficient, facile, cost effective, and environmentally benign manner.

**3.5.5. Synthesis of thiazoles.** The synthesis of 2-aminothiazoles in aqueous media avoids the use of polar and toxic organic solvents such as dimethyl formamide (DMF), dioxane, or methanol and also avoids any catalyst or additives. Adib *et al.* have synthesized imidazo[1,2-*a*]pyridines and imidazo[2,1-*b*][1,3]thiazoles in aqueous media in good to excellent yields (85–97%);<sup>335</sup> the desired products were obtained from the reaction between 2-aminopyridines or 2-aminothiazoles, aldehydes, and isocyanides (Scheme 49).

**3.5.6. Synthesis of  $\alpha$ -amino nitriles.** The Strecker reaction is commonly used in the preparation of  $\alpha$ -aminonitriles,<sup>336</sup> important raw materials for the synthesis of natural and non-natural  $\alpha$ -amino acids.<sup>337</sup> The classical Strecker reaction involves a three-component reaction between a carbonyl compound, ammonia, and cyanide, and is generally performed in water.<sup>338,339</sup> Galletti and Giacomini *et al.* synthesized  $\alpha$ -amino nitriles *via* a general one-pot, three-component Strecker reaction of an amine, a carbonyl compound, and acetone cyanohydrin in water<sup>340</sup> (Scheme 50). Most of the reactions proceeded very



**Scheme 49** Catalyst-free synthesis of imidazo[1,2-*a*]pyridines and imidazo[2,1-*b*][1,3]thiazoles in aqueous media.



**Scheme 50** Catalyst-free synthesis of  $\alpha$ -amino nitriles *via* a multicomponent Strecker reaction in aqueous media.

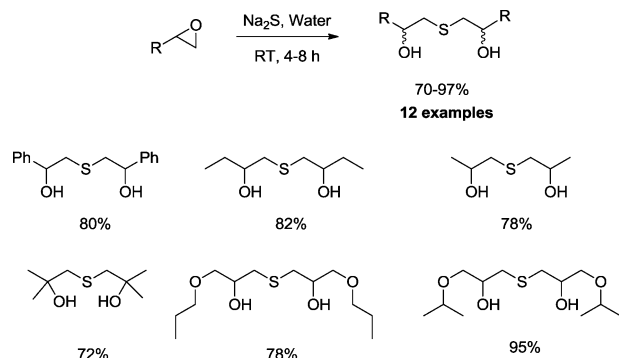
efficiently at room temperature with high selectivity and afforded pure  $\alpha$ -amino nitriles that separated directly from the water phase.

### 3.6. Ring-opening reaction of epoxides

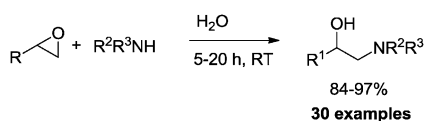
The ring opening of epoxides in aqueous media is a widely studied reaction;<sup>341</sup> epoxides and their derivatives are important starting materials and efficient intermediates in chemical synthesis due to their versatile chemical properties and reactivity with an extensive range of nucleophiles.<sup>342–345</sup> They have extensive applications in natural products,<sup>346,347</sup> medicinal,<sup>320,321,348,349</sup> and polymer chemistry.<sup>350</sup> Often various catalysts/reagents such as supported catalysts, oxides, and some complexes are reported for the ring-opening of epoxides. However, the catalyst-free and aqueous mediated ring-opening reactions remain largely untapped,<sup>351–356</sup> with few exceptions.<sup>357–359</sup>

Azizi and Saidi have reported water as a greener solvent for the ring-opening reaction of epoxides with  $Na_2S$  at room temperature.<sup>360</sup> The substituted bis(hydroxyethyl) thioethers were obtained in good to excellent yields (70–97%) (Scheme 51). Water was found to be the most efficient solvent among others ( $CH_2Cl_2$ ,  $CH_3CN$ , diethyl ether), or under solvent-free conditions, in terms of yields.

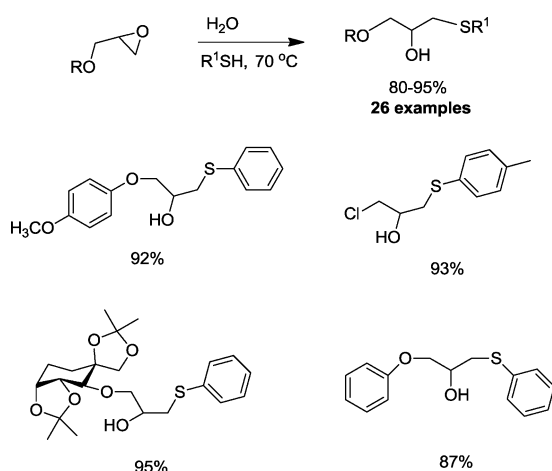
Enantiomerically pure  $\beta$ -amino alcohols play an increasingly important role as medicinal drug intermediates, chiral auxiliaries, and chiral substrates and have been also employed as catalysts. The reports on the synthesis of  $\beta$ -amino alcohols, by direct aminolysis of epoxides with excess amines or from reduction of  $\alpha$ -amino acids, make use of promoters and catalysts. Therefore, the design of more environmentally friendly protocols is warranted. Aqueous media was the optimal choice of Saidi and co-workers for the ring-opening of aliphatic epoxides with amines to obtain the corresponding  $\beta$ -amino alcohols



**Scheme 51** Catalyst-free ring-opening of epoxides with  $\text{Na}_2\text{S}$  in aqueous media.



**Scheme 52** Catalyst-free chemoselective ring-opening of epoxides with amines in aqueous media.



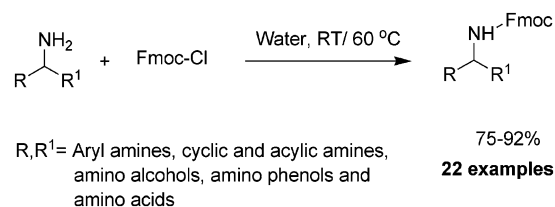
**Scheme 53** Catalyst-free regioselective thiolysis of epoxides in aqueous media.

in good to excellent yield (84–97%), in aqueous media (Scheme 52).<sup>361</sup>

Misra *et al.* performed regioselective thiolysis of epoxides with a variety of thiols in water without any catalyst or promoters.<sup>362</sup> The corresponding  $\beta$ -hydroxy sulfides are important intermediates for the synthesis of several molecules of biological importance and natural products. In a typical experimental procedure, epoxides were simply stirred with thiols at 70 °C for an appropriate time and the  $\beta$ -hydroxy sulfides obtained in good to excellent yields (Scheme 53).

### 3.7. Protection and deprotection reactions

Synthetic processes for the manufacture of pharmaceutical drug intermediates, fine chemicals or for organic synthesis frequently require a protection step to minimize potential side



**Scheme 54** Catalyst-free Fmoc protection of amines and amino acids in aqueous media.

reactions and the formation of unwanted products.<sup>363</sup> A protection step is invariably followed by eventual deprotection of the functional group to achieve the target compound. In view of these facts, protection and deprotection reactions can be considered as one of the most important synthetic strategies in spite of the fact that they do not fit into the green chemical processes. Acids, as well some basic catalysts, are used in the presence of an organic solvent for these type of chemistries.<sup>364</sup> Due to a growing environmental awareness, there is an urgent need for alternative options,<sup>365</sup> although only handful of cases have been reported in aqueous media.

Gawande and Branco have reported a novel and environmentally benign 9-fluorenylmethoxycarbonyl (Fmoc) protection of a variety of aliphatic and aromatic amines, amino acids, amino alcohols, and amino phenols in aqueous media under mild and catalyst-free conditions (Scheme 54);<sup>366</sup> the corresponding Fmoc protected products are obtained in good to excellent yields (75–92%).

The efficiency of Fmoc protection of aniline was compared to other known methods (Table 1), which clearly indicates that the catalyst-free Fmoc protection of aniline in aqueous media is a relatively efficient, clean, and green process (Table 1, entry 5). Water as a solvent can provide polar and other interactions needed to stabilize the transition state without causing a reduction in the rate of reaction due to solvent dilution.<sup>175,367</sup>

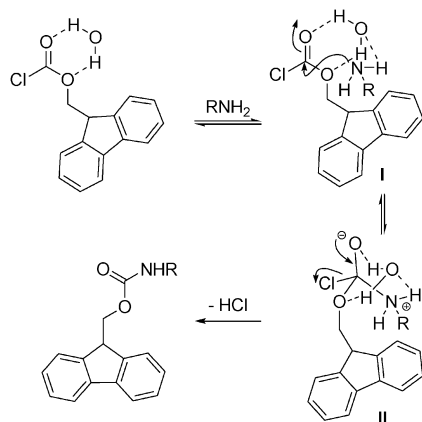
Hydrogen bond formation between water and the oxygen atoms of chloroformate causes an enhancement of the electrophilicity of the carbonyl group, making it more susceptible to nucleophilic attack. The oxygen atom of water, in turn, forms a hydrogen bond with the hydrogen atom of the amine and increases the electron density at the nitrogen atom (Scheme 55, structure **I** and **II**). The dual activation role of water through cooperative hydrogen bond formation accounts for the results observed during the catalyst-free Fmoc protection of amines.

A range of protective groups has been developed in the past few years, along with various methodologies for their removal.

**Table 1** Comparison of *N*-(9-fluorenylmethoxycarbonyl)aniline synthesis with reported methods

Entry	Solvent and conditions	Time (h)	Yield (%)	<i>E</i> -factor	Mass intensity
1	PhMe, 70 °C <sup>368</sup>	5	78	14.34	16.81
2	$\text{CH}_2\text{Cl}_2$ , RT <sup>369</sup>	24	68	527.54	666.00
3	PhH, RT or PhNCO, reflux <sup>370</sup>	1	94	0.5	4.6
4	THF–pyridine, 23 °C <sup>371</sup>	7	90	14.2	150.56
5	$\text{H}_2\text{O}$ , no catalyst, 60 °C	2	90	5.05	6.35





**Scheme 55** Proposed mechanism for Fmoc protection of amines in aqueous media.

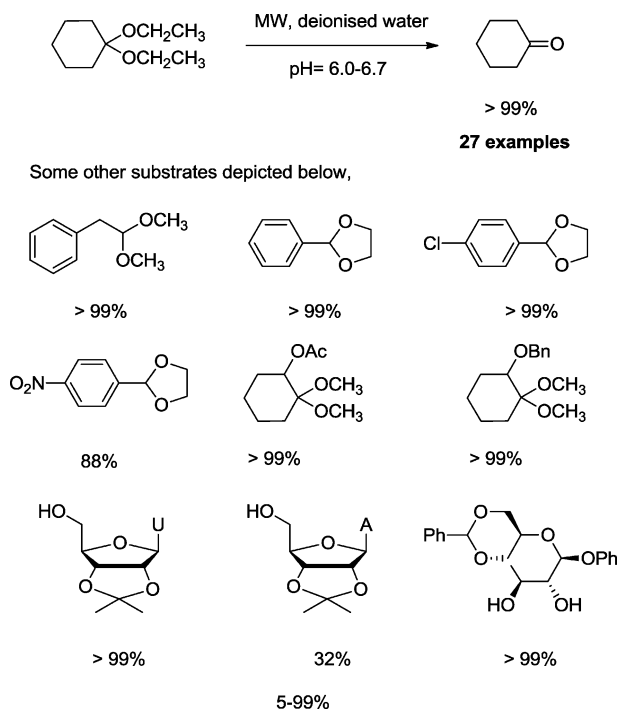
For example, *tert*-butoxycarbonyl (Boc) is frequently used as protecting group for amines in peptide chemistry. In general, Boc deprotection requires highly acidic conditions ( $\text{CF}_3\text{CO}_2\text{H}$ ,  $\text{HCl}$ ,  $\text{HNO}_3$ , and  $\text{H}_2\text{SO}_4$ ) and/or the use of Lewis acids [e.g.  $\text{ZnBr}_2$ ,  $\text{BiCl}_3$ ,  $\text{Ce}(\text{NH}_4)_2(\text{NO}_3)_6$ ]. Jia *et al.* reported N-Boc deprotection of amines under catalyst-free conditions in aqueous media.<sup>372a</sup> The corresponding amines were obtained in good to excellent yields (81–100%) in aqueous media at 150 °C without any additional reagents. Without using any acid/base for the deprotection of Boc protected amines and an aqueous media, this protocol is environment friendly and amenable to large scale adaption in industry.

Acetal and ketal functionalities are present among the vast majority of perfumes and pharmaceutical intermediates in organic synthesis and are often used to protect the carbonyl group during complex synthetic pathways; a variety of methods have been developed for their deprotection. Procopio and co-workers have recently devised a promising strategy to achieve the cleavage of acetals and ketals in catalysts-free and aqueous media under MW irradiation.<sup>372b</sup> In a typical experimental procedure, cyclohexanone diethyl ketal is treated with deionized water in a Teflon vessel at 80 °C for 15 min under MW irradiation to yield the corresponding cyclohexanone (Scheme 56). A variety of substrates (some examples shown in Scheme 56) were employed under these conditions, which avoids the use of catalysts or organic solvents.

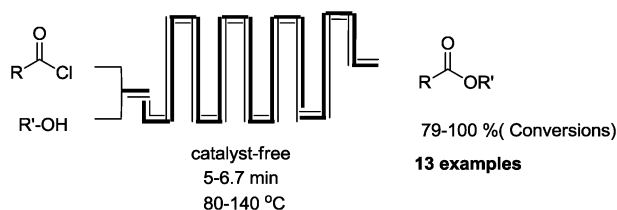
Esterification with acid chlorides is a well-known reaction and is used extensively for the protection of hydroxyl groups.<sup>373</sup> Usually, this reaction is accomplished in the presence of catalyst/reagents. Among the base catalysts used for this reaction, the most common are pyridine,  $\text{Et}_3\text{N}$  and 4-dimethylaminopyridine.<sup>373,374</sup>

Stevens and co-workers reported a catalyst-free continuous flow procedure for the condensation of acid chlorides and alcohols.<sup>375</sup> A variety of esters were obtained in excellent conversions under catalyst-free conditions starting from the corresponding acid chlorides and alcohols in very short reaction times (Scheme 57).

The reaction is performed under neat conditions for liquid reagents, but requires a solvent for solid reagents in order to



**Scheme 56** Catalyst-free deprotection of acetals in aqueous media under MW irradiation.



**Scheme 57** Catalyst-free condensation of acid chlorides and alcohols using continuous flow.

prevent clogging of the microreactor. Since no catalyst is needed, the purification of the reaction mixture is very clean. The scale-up of the reaction to a microreactor with an internal volume of 13.8 mL makes possible the production of  $2.2 \text{ g min}^{-1}$  of ester with an isolated yield of 98% and recovery of the  $\text{HCl}$  formed, which makes this industrially relevant protocol.

## 4. Catalyst-free reactions in supercritical fluids

### 4.1. Near-critical and supercritical water

The use of high temperature water (HTP) or water under supercritical conditions (374 °C, 22.1 MPa) has been actively explored as an environmentally benign medium for organic chemical reactions.<sup>376–379</sup> The replacement of conventional solvents by water, near and above the critical point, has a dramatic effect on the reproducibility, selectivity, and yield of many reactions. Since its physicochemical properties can be finely “tuned” with pressure and temperature, a versatile

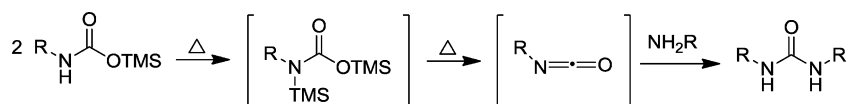
medium is achieved, where water can simultaneously and efficiently play the role of solvent, reactant, and catalyst. Due to lower dielectric constant and hydrogen bonds HTW water behaves like many organic solvents.<sup>380</sup> Under HTW conditions ( $150\text{ }^{\circ}\text{C} < T < 370\text{ }^{\circ}\text{C}$ ,  $0.4 < p < 22\text{ MPa}$ ) water can release the dissociated ions, that may act as catalysts or promoters for the reaction. Consequently, HTW is a suitable alternative to catalysts in some acid- and base-catalyzed reactions.<sup>381</sup> Moreover, current research using HTW or SCW uses both mini-autoclaves and continuous-flow reactors, which can be easily scalable.

Polyorganosiloxanes were successfully synthesized by Ogawa *et al.*<sup>382</sup> using a catalyst-free reaction under HTW conditions (0.9–10 MPa, 200–300  $^{\circ}\text{C}$ ). The hydrolysis and polycondensation of alkoxyasilanes (tetraethoxysilane, TEOS; tetramethoxysilane, TMOS; methyltrimethoxysilane, MTMS; phenyltrimethoxysilane, PTMS and methylphenyldimethoxysilane, MPDMS) generates methanol as a byproduct. The molecular weight of

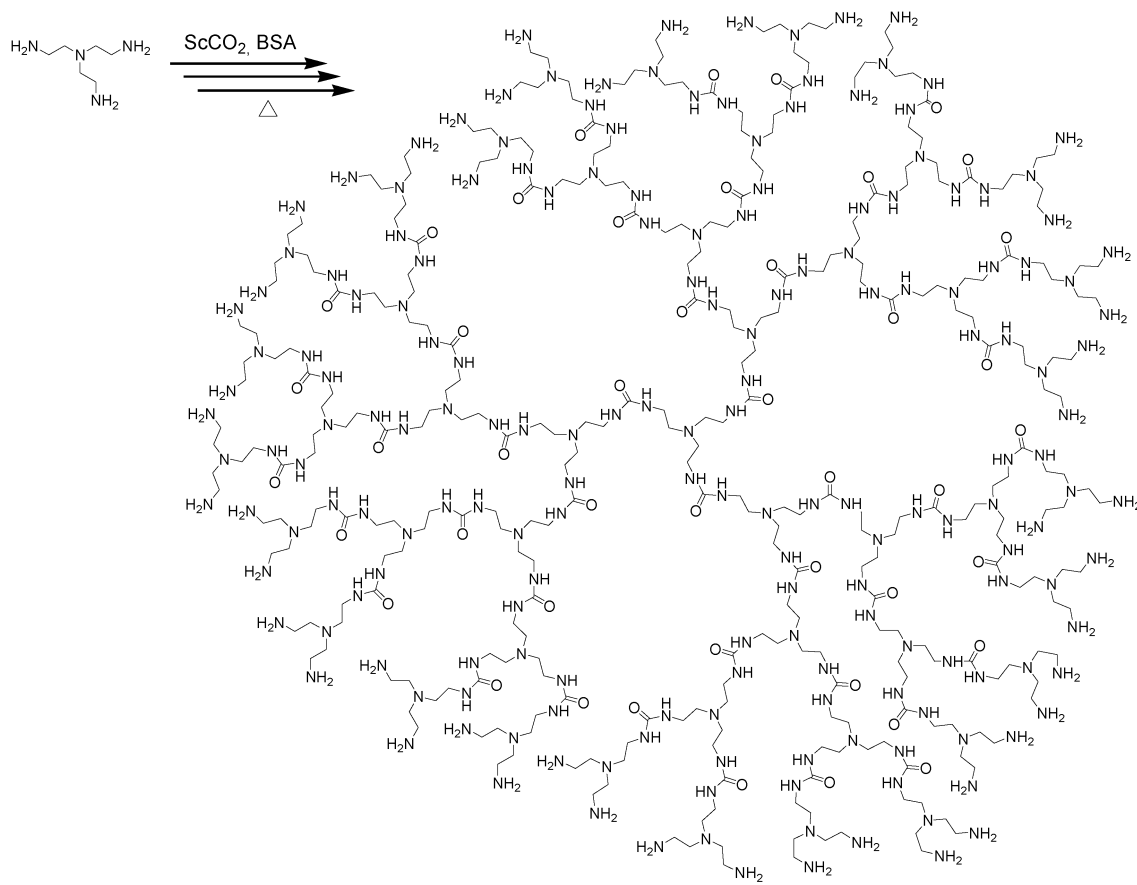
poly(phenylsilsesquioxane) (PPSQ) can be tuned by controlling the methanol concentration in the reactor using narrow tubing (trapping of methanol shifts the equilibration to the product-side). The salient features of this new process are the absence of contamination from volatile organic compounds in the final product and the elimination of the neutralization process invariably required by conventional solution-based synthesis. The authors studied in detail the hydrolysis and subsequent polycondensation of phenyltrimethoxysilane to gain insights into the reaction mechanism.<sup>383</sup>

#### 4.2. Supercritical carbon dioxide

Although carbon dioxide has been used as a reagent in the synthesis of many useful organic compounds, the reported reactions are almost exclusively made under catalytic conditions.<sup>385</sup> The potential of  $\text{scCO}_2$  as an alternative solvent for organic chemical reaction has been successfully demonstrated in

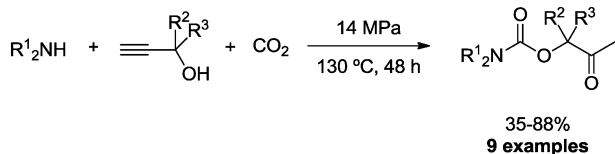


**Scheme 58** Proposed mechanism for the synthesis of ureas in supercritical carbon dioxide.



**PURE-G4**

**Scheme 59** Synthesis of PURE-type dendrimers in supercritical carbon dioxide.



**Scheme 60** Synthesis of  $\beta$ -oxopropylcarbamates in supercritical carbon dioxide.

the last decade.<sup>384,385</sup> The use of  $\text{scCO}_2$  offers many advantages over conventional solvents:  $\text{CO}_2$  is nontoxic, non-flammable, inexpensive, and readily available in high purity from a variety of sources. Since it is a gas at normal pressure, by simply reducing the pressure of the system, it is possible to easily separate the solvent from the products, leading to highly pure chemicals. In the past decade, Poliakov *et al.* have studied important and interesting applications of supercritical carbon dioxide ( $\text{scCO}_2$ ) under environmentally benign conditions.<sup>386-390</sup>

The reaction of amines with  $\text{CO}_2$ , which is usually viewed as an undesirable side reaction, can be exploited beneficially when used as a  $\text{scCO}_2$  medium since  $\text{CO}_2$  could be used not only as solvent but also as a reagent (C1 feedstock). Fuchter and co-workers<sup>391</sup> reported the synthesis of *O*-silylcarbamates from the corresponding silylamines in  $\text{scCO}_2$ . The authors demonstrated that  $\text{CO}_2$  is able to insert into the N-Si bond of *N*-silylamines by simple heating. *O*-silylcarbamates are obtained in quantitative yield and are synthetically useful intermediates in the synthesis of symmetrical and unsymmetrical ureas. A plausible mechanism for urea formation is shown in Scheme 58. It was found that both electron-deficient and electron-rich *N*-silylanilines gave the corresponding ureas in moderate to good yields.

A similar approach was very recently reported<sup>392</sup> for the synthesis of PURE-type dendrimers, a novel class of polyurea biocompatible, biodegradable, and intrinsically blue fluorescent dendrimers constructed by a divergent iterative synthetic approach. The reaction involves a simple one-pot procedure starting from a readily available amine and bis(trimethylsilyl)-acetamide (BSA), using  $\text{CO}_2$  as solvent and reagent, where the dendrimer generations are controlled in a step-by-step fashion, leading to well-defined 3D architectures (Scheme 59).

The reactivity of carbon dioxide towards alcohols and amines was investigated by Qi and Jiang,<sup>393</sup> by reacting propargylic alcohols with secondary amines in  $\text{scCO}_2$  (14 MPa, 130 °C) for 48 h;  $\beta$ -oxopropylcarbamates were isolated in moderate to high yields (35–88%) (Scheme 60).

More recently Xu and coworkers<sup>394</sup> found that under similar reaction conditions, but using primary amines, the reaction goes further and oxazolidinones are obtained in good yields (65–87%).

## 5. Conclusions and future prospects

Synthetic organic protocols using greener and more efficient methodologies are crucial for the development of more sustainable processes. This article highlights the importance of water-promoted catalyst-free methodologies in organic synthesis, with the inclusion of a comprehensive range of examples and

chemistries that illustrate the significant strides made in this research area over the past few years. Major developments in the field have focused on solving typical issues of organic reactions including insolubility of reagents/products, long reaction times, low yields and selectivity issues in non-conventional solvents or in the absence of catalysts.

First, research endeavors related to in-water-promoted reactions have attracted a staggering degree of attention in recent years. Its combination with alternate energy input, such as microwave and ultrasound irradiation, offers a promising environmentally benign option with many advantages compared to conventional protocols. Several examples and chemistries highlighting these advantages have been summarized in this review, which hopefully will introduce young academics and scientists starting in the field to this fascinating area of aqueous-organic synthesis. In addition, water-promoted organic reactions, under catalyst-free conditions, also comprise an important part of this report, with a wide range of reactions that can be promoted using various alternative and low-impact environmental technologies including sonication. Supercritical fluids have been considered as an appealing alternative to develop catalyst-free processes, with some promising examples reported under subcritical water conditions. Although this area has been relatively less explored compared to other reported technologies, applications using supercritical carbon dioxide are highly desirable and may take the lead in coming years as the field is rapidly expanding and the technology may become cost-competitive. In the light of these premises, further developments of benign by design methodologies are expected in the coming decade and authors believe this review will inspire and stimulate scientists and researchers across the globe to develop yet more innovative, cost-efficient, and sustainable strategies that can address all green chemistry principles in a comprehensive manner, utilizing bio-renewable resources.

## List of abbreviations

AMP	ammonium-12-molybdophosphate
aza-MIRC	aza-Michael initiated ring-closure reaction
BH	Baylis-Hillman
BSA	bis(trimethylsilyl)acetamide
DHPMs	dihydropyrimidinones
DHP	dihydropyridine
DMAD	dimethyl azodicarboxylate
DMF	dimethyl formamide
DESS	deep eutectic solvents
Fmoc	9-fluorenylmethoxycarbonyl
HTW	high temperature water
MPDMS	methylphenyldimethoxysilane
MTMS	methyltrimethoxysilane
MCRs	multicomponent reactions
PTMS	phenyltrimethoxysilane
PPSQ	poly(phenylsilsesquioxane)
PEG	polyethylene glycol
$\text{scCO}_2$	supercritical carbon dioxide
TEOS	tetraethoxysilane
TMOS	tetramethoxysilane

## Acknowledgements

This work has been supported by *Fundação para a Ciência e a Tecnologia* through grant PEst-C/EQB/LA0006/2011. Manoj B. Gawande thanks the PRAXIS program for the award of research fellowship SFRH/BPD/64934/2009.

## References

- 1 B. M. Trost, *Acc. Chem. Res.*, 2002, **35**, 695–705.
- 2 R. A. Sheldon, *Green Chem.*, 2005, **7**, 267–278.
- 3 J. Chen, S. K. Spear, J. G. Huddleston and R. D. Rogers, *Green Chem.*, 2005, **7**, 64–82.
- 4 T. Welton and P. J. Smith, *Adv. Organomet. Chem.*, 2004, **51**, 251–284.
- 5 P. G. Jessop, in *Carbon Dioxide Utilization for Global Sustainability*, ed. S. E. Park, J. S. Chang and K. W. Lee, 2004, vol. 153, pp. 355–362.
- 6 C. J. Li, *Chem. Rev.*, 2005, **105**, 3095–3165.
- 7 R. Sheldon, *Nature*, 1999, **399**, 33–33.
- 8 W. Leitner, *Science*, 1999, **284**, 1780–1781.
- 9 M. Tobiszewski, A. Mechlinska and J. Namiesnik, *Chem. Soc. Rev.*, 2010, **39**, 2869–2878.
- 10 A. M. Balu, B. Baruwati, E. Serrano, J. Cot, J. Garcia-Martinez, R. S. Varma and R. Luque, *Green Chem.*, 2011, **13**, 2750–2758.
- 11 M. B. Gawande, R. K. Pandey and R. V. Jayaram, *Catal. Sci. Technol.*, 2012, **2**, 1113–1125.
- 12 R. B. N. Baig and R. S. Varma, *Chem. Commun.*, 2013, **49**, 752–770.
- 13 R. B. Nasir Baig and R. S. Varma, *Green Chem.*, 2013, **15**, 398–417.
- 14 M. B. Gawande, P. S. Branco and R. S. Varma, *Chem. Soc. Rev.*, 2013, DOI: 10.1039/c3cs35480f.
- 15 V. Polshettiwar, M. N. Nadagouda and R. S. Varma, *Aust. J. Chem.*, 2009, **62**, 16–26.
- 16 V. Polshettiwar and R. S. Varma, *Green Chem.*, 2010, **12**, 743–754.
- 17 V. Polshettiwar, R. Luque, A. Fihri, H. B. Zhu, M. Bouhrara and J. M. Bassett, *Chem. Rev.*, 2011, **111**, 3036–3075.
- 18 M. B. Gawande, A. Rath, I. D. Nogueira, C. A. A. Ghumman, N. Bundaleski, O. M. N. D. Teodoro and P. S. Branco, *ChemPlusChem*, 2012, **77**, 865–871.
- 19 M. B. Gawande, A. K. Rath, P. S. Branco, I. D. Nogueira, A. Velhinho, J. J. Shrikhande, U. U. Indulkar, R. V. Jayaram, C. A. A. Ghumman, N. Bundaleski and O. M. N. D. Teodoro, *Chem.-Eur. J.*, 2012, **18**, 12628–12632.
- 20 C. C. K. Keh, V. V. Namboodiri, R. S. Varma and C. J. Li, *Tetrahedron Lett.*, 2002, **43**, 4993–4996.
- 21 Z. G. Li, C. M. Wei, L. Chen, R. S. Varma and C. J. Li, *Tetrahedron Lett.*, 2004, **45**, 2443–2446.
- 22 V. V. Namboodiri and R. S. Varma, *Org. Lett.*, 2002, **4**, 3161–3163.
- 23 V. V. Namboodiri and R. S. Varma, *Tetrahedron Lett.*, 2002, **43**, 5381–5383.
- 24 K. S. Ya, V. V. Namboodiri, R. S. Varma and P. G. Smirniotis, *J. Catal.*, 2004, **222**, 511–519.
- 25 X. F. Yang, M. W. Wang, R. S. Varma and C. J. Li, *Org. Lett.*, 2003, **5**, 657–660.
- 26 X. F. Yang, M. W. Wang, R. S. Varma and C. J. Li, *J. Mol. Catal. A: Chem.*, 2004, **214**, 147–154.
- 27 S. Toma, M. Meciarova and R. Sebesta, *Eur. J. Org. Chem.*, 2009, 321–327.
- 28 T. Seki and M. Onaka, *J. Mol. Catal. A: Chem.*, 2007, **263**, 115–120.
- 29 M. McCarthy, H. Stemmer and W. Leitner, *Green Chem.*, 2002, **4**, 501–504.
- 30 L. K. Yeung, C. T. Lee, K. P. Johnston and R. M. Crooks, *Chem. Commun.*, 2001, 2290–2291.
- 31 D. Kumar, V. S. Rao and R. S. Varma, *Tetrahedron Lett.*, 2006, **47**, 4197–4199.
- 32 V. Polshettiwar and R. S. Varma, *Tetrahedron Lett.*, 2008, **49**, 2661–2664.
- 33 R. S. Varma, *Green Chem.*, 1999, **1**, 43–55.
- 34 M. Jeselnik, R. S. Varma, S. Polanc and M. Kocivar, *Chem. Commun.*, 2001, 1716–1717.
- 35 T. Patonay, R. S. Varma, A. Vass, A. Levai and J. Dudas, *Tetrahedron Lett.*, 2001, **42**, 1403–1406.
- 36 R. S. Varma, *Pure Appl. Chem.*, 2001, **73**, 193–198.
- 37 R. S. Varma and D. Kumar, *Org. Lett.*, 1999, **1**, 697–700.
- 38 R. S. Varma, K. P. Naicker and P. J. Liesen, *Tetrahedron Lett.*, 1998, **39**, 8437–8440.
- 39 G. Guillena, M. D. Hita, C. Najera and S. F. Viozquez, *J. Org. Chem.*, 2008, **73**, 5933–5943.
- 40 R. S. Varma and D. Kumar, *Tetrahedron Lett.*, 1999, **40**, 7665–7669.
- 41 R. S. Varma and V. V. Namboodiri, *Chem. Commun.*, 2001, 643–644.
- 42 M. B. Gawande, S. S. Deshpande, S. U. Sonavane and R. V. Jayaram, *J. Mol. Catal. A: Chem.*, 2005, **241**, 151–155.
- 43 M. B. Gawande and R. V. Jayaram, *Catal. Commun.*, 2006, **7**, 931–935.
- 44 M. B. Gawande, V. Polshettiwar, R. S. Varma and R. V. Jayaram, *Tetrahedron Lett.*, 2007, **48**, 8170–8173.
- 45 M. Bandini, R. Luque, V. Budarin and D. J. Macquarrie, *Tetrahedron*, 2005, **61**, 9860–9868.
- 46 R. Luque and D. J. Macquarrie, *Org. Biomol. Chem.*, 2009, **7**, 1627–1632.
- 47 M. B. Gawande, S. N. Shelke, P. S. Branco, A. Rath and R. K. Pandey, *Appl. Organomet. Chem.*, 2012, **26**, 395–400.
- 48 U. U. Indulkar, S. R. Kale, M. B. Gawande and R. V. Jayaram, *Tetrahedron Lett.*, 2012, **53**, 3857–3860.
- 49 M. J. Gracia, J. M. Campelo, E. Losada, R. Luque, J. M. Marinas and A. A. Romero, *Org. Biomol. Chem.*, 2009, **7**, 4821–4824.
- 50 S. Alesi, F. Di Maria, M. Melucci, D. J. Macquarrie, R. Luque and G. Barbarella, *Green Chem.*, 2008, **10**, 517–523.
- 51 C. Gonzalez-Arellano, J. M. Campelo, D. J. Macquarrie, J. M. Marinas, A. A. Romero and R. Luque, *ChemSusChem*, 2008, **1**, 746–750.



- 52 T. D. Conesa, J. M. Campelo, J. H. Clark, R. Luque, D. J. Macquarrie and A. A. Romero, *Green Chem.*, 2007, **9**, 1109–1113.
- 53 R. S. Varma, *J. Heterocycl. Chem.*, 1999, **36**, 1565–1571.
- 54 V. Polshettiwar and R. S. Varma, *Acc. Chem. Res.*, 2008, **41**, 629–639.
- 55 V. V. Namboodiri and R. S. Varma, *Green Chem.*, 2001, **3**, 146–148.
- 56 Y. H. Ju and R. S. Varma, *Org. Lett.*, 2005, **7**, 2409–2411.
- 57 Y. J. Kim and R. S. Varma, *Tetrahedron Lett.*, 2005, **46**, 7447–7449.
- 58 Y. H. Ju, D. Kumar and R. S. Varma, *J. Org. Chem.*, 2006, **71**, 6697–6700.
- 59 V. Polshettiwar and R. S. Varma, *Tetrahedron Lett.*, 2007, **48**, 8735–8738.
- 60 V. Polshettiwar and R. S. Varma, *Tetrahedron Lett.*, 2007, **48**, 7343–7346.
- 61 V. Polshettiwar and R. S. Varma, *J. Org. Chem.*, 2007, **72**, 7420–7422.
- 62 V. Polshettiwar and R. S. Varma, *J. Org. Chem.*, 2008, **73**, 7417–7419.
- 63 D. Kumar, N. M. Kumar, G. Patel, S. Gupta and R. S. Varma, *Tetrahedron Lett.*, 2011, **52**, 1983–1986.
- 64 L. Chen and C. J. Li, *Adv. Synth. Catal.*, 2006, **348**, 1459–1484.
- 65 K. M. Dawood, *Tetrahedron*, 2007, **63**, 9642–9651.
- 66 A. El-Batta, C. C. Jiang, W. Zhao, R. Anness, A. L. Cooksy and M. Bergdahl, *J. Org. Chem.*, 2007, **72**, 5244–5259.
- 67 J. C. Serrano-Ruiz, R. Luque and A. Sepulveda-Escribano, *Chem. Soc. Rev.*, 2011, **40**, 5266–5281.
- 68 F. Rajabi, S. Naserian, A. Primo and R. Luque, *Adv. Synth. Catal.*, 2011, **353**, 2060–2066.
- 69 D. Sinou, *Modern Solvents in Organic Synthesis*, 1999, vol. 206, pp. 41–59.
- 70 A. R. Katritzky, D. A. Nichols, M. Siskin, R. Murugan and M. Balasubramanian, *Chem. Rev.*, 2001, **101**, 837–892.
- 71 A. E. Diaz-Alvarez, J. Francos, B. Lastra-Barreira, P. Crochet and V. Cadierno, *Chem. Commun.*, 2011, **47**, 6208–6227.
- 72 A. P. Abbott, D. Boothby, G. Capper, D. L. Davies and R. K. Rasheed, *J. Am. Chem. Soc.*, 2004, **126**, 9142–9147.
- 73 Z.-H. Zhang, X.-N. Zhang, L.-P. Mo, Y.-X. Li and F.-P. Ma, *Green Chem.*, 2012, **14**, 1502–1506.
- 74 X. J. Mu, M. Y. Lei, L. P. Zou and W. Zhang, *Tetrahedron Lett.*, 2006, **47**, 1125–1127.
- 75 J. F. Zhang, Z. W. Cui, F. Wang, Y. Wang, Z. W. Miao and R. Y. Chen, *Green Chem.*, 2007, **9**, 1341–1345.
- 76 J. L. Zhao, L. Liu, H. B. Zhang, Y. C. Wu, D. Wang and Y. J. Chen, *Synlett*, 2006, 96–100.
- 77 M. Y. Wu, K. Li, N. Wang, T. He and X. Q. Yu, *Synthesis*, 2011, 1831–1839.
- 78 G. Palmisano, S. Tagliapietra, A. Barge, A. Binello, L. Boffa and G. Cravotto, *Synlett*, 2007, 2041–2044.
- 79 M. I. Uddin, K. Nakano, Y. Ichikawa and H. Kotsuki, *Synlett*, 2008, 1402–1406.
- 80 N. Azizi, B. Pourhasan, F. Aryanassab and M. R. Saidi, *Synlett*, 2007, 1239–1242.
- 81 R. Luque and J. H. Clark, *Catal. Commun.*, 2010, **11**, 928–931.
- 82 J. J. Shrikhande, M. B. Gawande and R. V. Jayaram, *Tetrahedron Lett.*, 2008, **49**, 4799–4803.
- 83 J. J. Shrikhande, M. B. Gawande and R. V. Jayaram, *Catal. Commun.*, 2008, **9**, 1010–1016.
- 84 R. N. Butler and A. G. Coyne, *Chem. Rev.*, 2010, **110**, 6302–6337.
- 85 O. Diels and K. Alder, *Ann. Chem.*, 1931, **490**, 243–247.
- 86 D. C. Rideout and R. Breslow, *J. Am. Chem. Soc.*, 1980, **102**, 7816–7817.
- 87 R. Breslow, *Acc. Chem. Res.*, 1991, **24**, 159–164.
- 88 J. Y. An, L. Bagnell, T. Cablewski, C. R. Strauss and R. W. Trainor, *J. Org. Chem.*, 1997, **62**, 2505–2511.
- 89 C. R. Strauss and R. W. Trainor, *Aust. J. Chem.*, 1998, **51**, 703–705.
- 90 C. R. Strauss and R. W. Trainor, *Aust. J. Chem.*, 1995, **48**, 1665–1692.
- 91 C. R. Strauss, *Aust. J. Chem.*, 1999, **52**, 83–96.
- 92 L. Bagnell, T. Cablewski, C. R. Strauss and R. W. Trainor, *J. Org. Chem.*, 1996, **61**, 7355–7359.
- 93 K. D. Raner, C. R. Strauss, R. W. Trainor and J. S. Thorn, *J. Org. Chem.*, 1995, **60**, 2456–2460.
- 94 L. Bagnell, M. Bliese, T. Cablewski, C. R. Strauss and J. Tsanaksidis, *Aust. J. Chem.*, 1997, **50**, 921–925.
- 95 J. M. Kremsner and C. O. Kappe, *Eur. J. Org. Chem.*, 2005, 3672–3679.
- 96 P. A. Grieco, *Organic Synthesis in water*, Blackie Academic and Professional, London, 1998.
- 97 Y. Hirai and Y. Uozumi, *Chem. Commun.*, 2010, **46**, 1103–1105.
- 98 M. M. Savant, A. M. Pansuriya, C. V. Bhuvu, N. Kapuriya, A. S. Patel, V. B. Audichya, P. V. Pipaliya and Y. T. Naliapara, *J. Comb. Chem.*, 2010, **12**, 176–180.
- 99 M. Carril, R. SanMartin, I. Tellitu and E. Dominguez, *Org. Lett.*, 2006, **8**, 1467–1470.
- 100 C. J. Li and L. Chen, *Chem. Soc. Rev.*, 2006, **35**, 68–82.
- 101 P. Tundo, P. Anastas, D. S. Black, J. Breen, T. Collins, S. Memoli, J. Miyamoto, M. Polyakoff and W. Tumas, *Pure Appl. Chem.*, 2000, **72**, 1207–1228.
- 102 K. Manabe, S. Iimura, X. M. Sun and S. Kobayashi, *J. Am. Chem. Soc.*, 2002, **124**, 11971–11978.
- 103 T. Tsukinoki, S. Nagashima, Y. Mitoma and M. Tashiro, *Green Chem.*, 2000, **2**, 117–119.
- 104 F. Bigi, M. L. Conforti, R. Maggi, A. Piccinno and G. Sartori, *Green Chem.*, 2000, **2**, 101–103.
- 105 T. Head-Gordon and G. Hura, *Chem. Rev.*, 2002, **102**, 2651–2669.
- 106 U. M. Lindstrom, *Chem. Rev.*, 2002, **102**, 2751–2771.
- 107 Y. Hayashi, *Angew. Chem., Int. Ed.*, 2006, **45**, 8103–8104.
- 108 J. M. Saveant, *Energy Environ. Sci.*, 2012, **5**, 7718–7731.
- 109 C. X. A. da Silva, V. L. C. Goncalves and C. J. A. Mota, *Green Chem.*, 2009, **11**, 38–41.
- 110 R. Breslow, *Acc. Chem. Res.*, 2004, **37**, 471–478.

- 111 S. Narayan, J. Muldoon, M. G. Finn, V. V. Fokin, H. C. Kolb and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2005, **44**, 3275–3279.
- 112 S. Guizzetti, M. Benaglia, L. Raimondi and G. Celentano, *Org. Lett.*, 2007, **9**, 1247–1250.
- 113 D. Gonzalez-Cruz, D. Tejedor, P. de Armas and F. Garcia-Tellado, *Chem.-Eur. J.*, 2007, **13**, 4823–4832.
- 114 N. Shapiro and A. Vigalok, *Angew. Chem., Int. Ed.*, 2008, **47**, 2849–2852.
- 115 M. C. Pirrung and K. Das Sarma, *J. Am. Chem. Soc.*, 2004, **126**, 444–445.
- 116 J. E. Klijn and J. Engberts, *Nature*, 2005, **435**, 900–900.
- 117 S. Tiwari and A. Kumar, *J. Phys. Chem. A*, 2009, **113**, 13685–13693.
- 118 D. V. Demchuk, M. N. Elinson and G. I. Nikishin, *Mendeleev Commun.*, 2011, **21**, 224–225.
- 119 A. Chanda and V. V. Fokin, *Chem. Rev.*, 2009, **109**, 725–748.
- 120 Y. S. Jung and R. A. Marcus, *J. Am. Chem. Soc.*, 2007, **129**, 5492–5502.
- 121 E. M. Beccalli, G. Broggini, M. Martinelli and S. Sottocornola, *Chem. Rev.*, 2007, **107**, 5318–5365.
- 122 M. Carril, R. SanMartin and E. Dominguez, *Chem. Soc. Rev.*, 2008, **37**, 639–647.
- 123 G. D. Harris, A. Nguyen, H. App, P. Hirth, G. McMahon and C. Tang, *Org. Lett.*, 1999, **1**, 431–433.
- 124 M. C. Pirrung, K. Park and Z. T. Li, *Org. Lett.*, 2001, **3**, 365–367.
- 125 M. C. Pirrung, L. Deng, Z. T. Li and K. Park, *J. Org. Chem.*, 2002, **67**, 8374–8388.
- 126 J. S. Yadav, B. V. S. Reddy and T. Swamy, *Synthesis*, 2004, 106–110.
- 127 J. S. Yadav, B. V. S. Reddy and T. Swamy, *Tetrahedron Lett.*, 2003, **44**, 9121–9124.
- 128 M. C. Pirrung, Y. F. Liu, L. Deng, D. K. Halstead, Z. T. Li, J. F. May, M. Wedel, D. A. Austin and N. J. G. Webster, *J. Am. Chem. Soc.*, 2005, **127**, 4609–4624.
- 129 M. C. Pirrung, K. Fujita and K. Park, *J. Org. Chem.*, 2005, **70**, 2537–2542.
- 130 H. B. Zhang, L. Liu, Y. J. Chen, D. Wang and C. J. Li, *Eur. J. Org. Chem.*, 2006, 869–873.
- 131 N. Rieber, J. Alberts, J. A. Lipsky and D. M. Lemal, *J. Am. Chem. Soc.*, 1969, **91**, 5668–5669.
- 132 R. Breslow, U. Maitra and D. Rideout, *Tetrahedron Lett.*, 1983, **24**, 1901–1904.
- 133 R. Breslow and U. Maitra, *Tetrahedron Lett.*, 1984, **25**, 1239–1240.
- 134 R. Breslow and T. Guo, *J. Am. Chem. Soc.*, 1988, **110**, 5613–5617.
- 135 R. Breslow and C. J. Rizzo, *J. Am. Chem. Soc.*, 1991, **113**, 4340–4341.
- 136 R. Breslow and Z. N. Zhu, *J. Am. Chem. Soc.*, 1995, **117**, 9923–9924.
- 137 F. G. Klarner and F. Wurche, *J. Prakt. Chem.*, 2000, **342**, 609–636.
- 138 Y. Huang and V. H. Rawal, *J. Am. Chem. Soc.*, 2002, **124**, 9662–9663.
- 139 G. Mloston and H. Heimgartner, *Pol. J. Chem.*, 2000, **74**, 1503–1532.
- 140 A. Brandi, S. Cicchi, F. M. Cordero and A. Goti, *Chem. Rev.*, 2003, **103**, 1213–1269.
- 141 R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, 1963, **75**, 742–754.
- 142 R. N. Butler, A. G. Coyne and E. M. Moloney, *Tetrahedron Lett.*, 2007, **48**, 3501–3503.
- 143 V. K. Tandon and H. K. Maurya, *Tetrahedron Lett.*, 2009, **50**, 5896–5902.
- 144 J. C. Lien, L. J. Huang, J. P. Wang, C. M. Teng, K. H. Lee and S. C. Kuo, *Bioorg. Med. Chem.*, 1997, **5**, 2111–2120.
- 145 A. Sarhan, A. M. K. El-Dean and M. I. Abdel-Monem, *Monatsh. Chem.*, 1998, **129**, 205–212.
- 146 D. Dallinger and C. O. Kappe, *Chem. Rev.*, 2007, **107**, 2563–2591.
- 147 V. K. Tandon, H. K. Maurya, A. Tripathi, G. B. ShivaKeshava, P. K. Shukla, P. Srivastava and D. Panda, *Eur. J. Med. Chem.*, 2009, **44**, 1086–1092.
- 148 V. K. Tandon, D. B. Yadav, H. K. Maurya, A. K. Chaturvedi and P. K. Shukla, *Bioorg. Med. Chem.*, 2006, **14**, 6120–6126.
- 149 G. Wittig and G. Geissler, *Ann. Chem.*, 1953, **580**, 44–57.
- 150 G. Wittig and H. Laib, *Ann. Chem.*, 1953, **580**, 57–68.
- 151 B. E. Maryanoff and A. B. Reitz, *Chem. Rev.*, 1989, **89**, 863–927.
- 152 J. Dambacher, W. Zhao, A. El-Batta, R. Anness, C. C. Jiang and M. Bergdahl, *Tetrahedron Lett.*, 2005, **46**, 4473–4477.
- 153 S. Tiwari and A. Kumar, *Chem. Commun.*, 2008, 4445–4447.
- 154 A. K. Chakraborti, S. Rudrawar, K. B. Jadhav, G. Kaur and S. V. Chankeshwara, *Green Chem.*, 2007, **9**, 1335–1340.
- 155 A. Palasz, *Synthesis*, 2010, 4021–4032.
- 156 S. Otto and J. B. F. N. Engberts, *Org. Biomol. Chem.*, 2003, **1**, 2809–2820.
- 157 C. Y. Lee, J. A. McCammon and P. J. Rossky, *J. Chem. Phys.*, 1984, **80**, 4448–4455.
- 158 L. F. Scatena, M. G. Brown and G. L. Richmond, *Science*, 2001, **292**, 908–912.
- 159 R. Breslow, *Marcus Lindstrom*, ed. Blackwell Publishers, Oxford, 2007, pp. 1–28.
- 160 R. Breslow, K. Groves and M. U. Mayer, *Pure Appl. Chem.*, 1998, **70**, 1933–1938.
- 161 R. Breslow, *J. Phys. Org. Chem.*, 2006, **19**, 813–822.
- 162 R. Breslow, R. Connors and H. N. Zhu, *Pure Appl. Chem.*, 1996, **68**, 1527–1533.
- 163 M. R. Biscoe and R. Breslow, *J. Am. Chem. Soc.*, 2003, **125**, 12718–12719.
- 164 R. Breslow, K. Groves and M. U. Mayer, *J. Am. Chem. Soc.*, 2002, **124**, 3622–3635.
- 165 R. Breslow and R. V. Connors, *J. Am. Chem. Soc.*, 1995, **117**, 6601–6602.
- 166 J. M. Concellon, H. Rodriguez-Solla, P. L. Bernad and C. Simal, *J. Org. Chem.*, 2009, **74**, 2452–2459.
- 167 T. K. Ellis, H. Ueki, R. Tiwari and V. A. Soloshonok, *Tetrahedron: Asymmetry*, 2009, **20**, 2629–2634.

- 168 A. Yazici and S. G. Pyne, *Synthesis*, 2009, 513–541.
- 169 R. Manzano, J. M. Andres, M. D. Muruzabal and R. Pedrosa, *Adv. Synth. Catal.*, 2010, **352**, 3364–3372.
- 170 D. A. Yalalov, S. B. Tsogoeva and S. Schmatz, *Adv. Synth. Catal.*, 2006, **348**, 826–832.
- 171 H. C. Huang, K. L. Zhu, W. B. Wu, Z. C. Jin and J. X. Ye, *Chem. Commun.*, 2012, **48**, 461–463.
- 172 Y. M. Li, X. Li, F. Z. Peng, Z. Q. Li, S. T. Wu, Z. W. Sun, H. B. Zhang and Z. H. Shao, *Org. Lett.*, 2011, **13**, 6200–6203.
- 173 L. W. Xu and C. G. Xia, *Eur. J. Org. Chem.*, 2005, 633–639.
- 174 L. W. Xu, C. G. Xia, H. J. Wu, L. Yang, W. Zhou and Y. Zhang, *Chinese J. Org. Chem.*, 2005, **25**, 167–175.
- 175 B. C. Ranu and S. Banerjee, *Tetrahedron Lett.*, 2007, **48**, 141–143.
- 176 S. Sternativo, F. Marini, F. Del Verme, A. Calandriello, L. Testaferri and M. Tiecco, *Tetrahedron*, 2010, **66**, 6851–6857.
- 177 M. De Rosa and A. Soriente, *Tetrahedron*, 2010, **66**, 2981–2986.
- 178 R. E. Moore, C. Cheuk and G. M. L. Patterson, *J. Am. Chem. Soc.*, 1984, **106**, 6456–6457.
- 179 P. M. Habib, V. Kavala, C. W. Kuo and C. F. Yao, *Tetrahedron Lett.*, 2008, **49**, 7005–7007.
- 180 P. K. Mandal, G. H. Maiti and A. K. Misra, *J. Carbohydr. Chem.*, 2008, **27**, 238–257.
- 181 J. Madaj, J. Rak, J. Sokolowski and A. Wisniewski, *J. Org. Chem.*, 1996, **61**, 2988–2994.
- 182 H. H. Baer, L. Siemsen, J. Defaye and K. Burak, *Carbohydr. Res.*, 1984, **134**, 49–61.
- 183 K. Marjani, M. Khalesi, A. Ashouri, A. Jalali and A. Ziyaei-Halimehjani, *Synth. Commun.*, 2011, **41**, 451–458.
- 184 M. De Rosa and A. Soriente, *Tetrahedron*, 2011, **67**, 5949–5955.
- 185 U. M. Lindström, *Chem. Rev.*, 2002, **102**, 2751–2772.
- 186 R. Mahrwald, *Chem. Rev.*, 1999, **99**, 1095–1120.
- 187 J. M. McIntosh and R. K. Leavitt, *Can. J. Chem.-Rev. Can. Chim.*, 1985, **63**, 3313–3316.
- 188 Y.-H. Fan, H. Chen, A. Natarajan, Y. Guo, F. Harbinski, J. Iyasere, W. Christ, H. Aktas and J. A. Halperin, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 2547–2550.
- 189 Y. F. Luo, L. Ma, H. Zheng, L. J. Chen, R. Li, C. M. He, S. Y. Yang, X. Ye, Z. Z. Chen, Z. C. Li, Y. Gao, J. Han, G. He, L. Yang and Y. Q. Wei, *J. Med. Chem.*, 2010, **53**, 273–281.
- 190 F. Yu, H. Hu, X. Gu and J. Ye, *Org. Lett.*, 2012, **14**, 2038–2041.
- 191 A. Verma and S. K. Saraf, *Eur. J. Med. Chem.*, 2008, **43**, 897–905.
- 192 S. Paladhi, A. Chauhan, K. Dhara, A. K. Tiwari and J. Dash, *Green Chem.*, 2012, **14**, 2990–2995.
- 193 G. P. Lu, L. Y. Zeng and C. Cai, *Green Chem.*, 2011, **13**, 998–1003.
- 194 P. Langer, *Angew. Chem., Int. Ed.*, 2000, **39**, 3049–3052.
- 195 T. Kondo and T. Mitsudo, *Chem. Rev.*, 2000, **100**, 3205–3220.
- 196 R. D. Norcross and I. Paterson, *Chem. Rev.*, 1995, **95**, 2041–2114.
- 197 L. D. S. Yadav, R. Patel and V. P. Srivastava, *Tetrahedron Lett.*, 2009, **50**, 1335–1339.
- 198 B. Movassagh and M. Navidi, *Arkivoc*, 2008, 47–53.
- 199 G. L. Khatik, R. Kumar and A. K. Chakraborti, *Org. Lett.*, 2006, **8**, 2432–2436.
- 200 N. Azizi, F. Aryanasab, L. Torkiyan, A. Ziyaei and M. R. Saidi, *J. Org. Chem.*, 2006, **71**, 3634–3635.
- 201 J. A. Lowe, W. M. Qian, S. E. Drozda, R. A. Volkmann, D. Nason, R. B. Nelson, C. Nolan, D. Liston, K. Ward, S. Faraci, K. Verdries, P. Seymour, M. Majchrzak, A. Villalobos and W. F. White, *J. Med. Chem.*, 2004, **47**, 1575–1586.
- 202 V. Perrier, A. C. Wallace, K. Kaneko, J. Safar, S. B. Prusiner and F. E. Cohen, *Proc. Natl. Acad. Sci. U. S. A.*, 2000, **97**, 6073–6078.
- 203 P. S. Herradura, K. A. Pendola and R. K. Guy, *Org. Lett.*, 2000, **2**, 2019–2022.
- 204 F. Y. Kwong and S. L. Buchwald, *Org. Lett.*, 2002, **4**, 3517–3520.
- 205 G. Y. Li, G. Zheng and A. F. Noonan, *J. Org. Chem.*, 2001, **66**, 8677–8681.
- 206 N. Taniguchi and T. Onami, *J. Org. Chem.*, 2004, **69**, 915–920.
- 207 B. Sreedhar, P. S. Reddy and M. A. Reddy, *Synthesis*, 2009, 1732–1738.
- 208 R. Yella, H. Ghosh and B. K. Patel, *Green Chem.*, 2008, **10**, 1307–1312.
- 209 P. C. Kearney, M. Fernandez and J. A. Flygare, *J. Org. Chem.*, 1998, **63**, 196–200.
- 210 M. Kidwai, R. Venkataramanan and B. Dave, *Green Chem.*, 2001, **3**, 278–279.
- 211 S. Sharma, *Synthesis*, 1978, 803–820.
- 212 C. R. Rasmussen, F. J. Villani, L. E. Weaner, B. E. Reynolds, A. R. Hood, L. R. Hecker, S. O. Nortey, A. Hanslin, M. J. Costanzo, E. T. Powell and A. J. Molinari, *Synthesis*, 1988, 456–459.
- 213 J. Bernstein, H. L. Yale, K. Losee, M. Holsing, J. Martins and W. A. Lott, *J. Am. Chem. Soc.*, 1951, **73**, 906–912.
- 214 J. G. Erickson, *J. Org. Chem.*, 1956, **21**, 483–484.
- 215 B. L. Yin, Z. G. Liu, M. J. Yi and J. C. Zhang, *Tetrahedron Lett.*, 2008, **49**, 3687–3690.
- 216 M. R. Maddani and K. R. Prabhu, *J. Org. Chem.*, 2010, **75**, 2327–2332.
- 217 S. F. Gan, J. P. Wan, Y. J. Pan and C. R. Sun, *Mol. Diversity*, 2011, **15**, 809–815.
- 218 S. Ghosh, J. Das and S. Chattopadhyay, *Tetrahedron Lett.*, 2011, **52**, 2869–2872.
- 219 F. Y. Zhang, Y. X. Wang, F. L. Yang, H. Y. Zhang and Y. F. Zhao, *Synth. Commun.*, 2011, **41**, 347–356.
- 220 B. C. Chen, *Heterocycles*, 1991, **32**, 529–597.
- 221 B. Pita, E. Sotelo, M. Suarez, E. Ravina, E. Ochoa, Y. Verdecia, H. Novoa, N. Blaton, C. de Ranter and O. M. Peeters, *Tetrahedron*, 2000, **56**, 2473–2479.
- 222 F. Bigi, S. Carloni, L. Ferrari, R. Maggi, A. Mazzacani and G. Sartori, *Tetrahedron Lett.*, 2001, **42**, 5203–5205.

- 223 J. J. Yu, L. M. Wang, J. Q. Liu, F. L. Guo, Y. Liu and N. Jiao, *Green Chem.*, 2010, **12**, 216–219.
- 224 S. Das and A. J. Thakur, *Eur. J. Org. Chem.*, 2011, 2301–2308.
- 225 T. Lundqvist, S. L. Fisher, G. Kern, R. H. A. Folmer, Y. F. Xue, D. T. Newton, T. A. Keating, R. A. Alm and B. L. M. de Jonge, *Nature*, 2007, **447**, 817–822.
- 226 J. B. Parker, M. A. Bianchet, D. J. Krosky, J. I. Friedman, L. M. Amzel and J. T. Stivers, *Nature*, 2007, **449**, U433–U432.
- 227 A. R. Dinner, G. M. Blackburn and M. Karplus, *Nature*, 2001, **413**, 752–755.
- 228 J. Di Noia and M. S. Neuberger, *Nature*, 2002, **419**, 43–48.
- 229 (a) G. X. Gong, J. F. Zhou, L. T. An, X. L. Duan and S. J. Ji, *Synth. Commun.*, 2009, **39**, 497–505; (b) A. Shaabani, A. Rahmati and E. Farhangi, *Tetrahedron Lett.*, 2007, **48**, 7291–7294.
- 230 L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115–136.
- 231 L. F. Tietze, *J. Heterocycl. Chem.*, 1990, **27**, 47–69.
- 232 J. S. Yadav, B. V. S. Reddy, D. Narsimhaswamy, P. N. Lakshmi, K. Narsimulu, G. Srinivasulu and A. C. Kunwar, *Tetrahedron Lett.*, 2004, **45**, 3493–3497.
- 233 L. F. Tietze and U. Beifuss, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 131–163.
- 234 L. F. Tietze and A. Modi, *Med. Res. Rev.*, 2000, **20**, 304–322.
- 235 M. Kiamehr and F. M. Moghaddam, *Tetrahedron Lett.*, 2009, **50**, 6723–6727.
- 236 M. J. Khoshkholgh, S. Balalaie, H. R. Bijanzadeh and J. H. Gross, *Synlett*, 2009, 55–58.
- 237 Y. R. Lee and T. V. Hung, *Tetrahedron*, 2008, **64**, 7338–7346.
- 238 G. Sabitha, N. Fatima, E. V. Reddy and J. S. Yadav, *Adv. Synth. Catal.*, 2005, **347**, 1353–1355.
- 239 M. Ghandi, E. Mohammadimehr, M. Sadeghzadeh and A. H. Bozcheloei, *Tetrahedron*, 2011, **67**, 8484–8491.
- 240 M. A. Musa, J. S. Cooperwood and M. O. F. Khan, *Curr. Med. Chem.*, 2008, **15**, 2664–2679.
- 241 T. K. Mandal, V. V. Kuznetsov and A. T. Soldatenkov, *Khim. Geterotsikl. Soedin.*, 1994, 1011–1033.
- 242 R. D. H. Murray, *Prog. Chem. Org. Nat. Prod.*, 1991, **58**, 84–316.
- 243 F. Borges, F. Roleira, N. Milhazes, L. Santana and E. Uriarte, *Curr. Med. Chem.*, 2005, **12**, 887–916.
- 244 B. Karami and M. Kiani, *Catal. Commun.*, 2011, **14**, 62–67.
- 245 S. Singhal, S. L. Jain and B. Sain, *Heterocycles*, 2008, **75**, 1205–1211.
- 246 A. Sinhamahapatra, N. Sutradhar, S. Pahari, H. C. Bajaj and A. B. Panda, *Appl. Catal., A*, 2011, **394**, 93–100.
- 247 F. M. Moghaddam, M. Kiamehr, M. R. Khodabakhshi, Z. Mirjafary, S. Fathi and H. Saeidian, *Tetrahedron*, 2010, **66**, 8615–8622.
- 248 L. D. S. Yadav, S. Singh and V. K. Rai, *Green Chem.*, 2009, **11**, 878–882.
- 249 K. C. Majumdar, A. Taher and S. Ponra, *Tetrahedron Lett.*, 2010, **51**, 147–150.
- 250 Z. N. Tisseh, M. Dabiri, M. Nobahar, A. A. Soorki and A. Bazgir, *Tetrahedron*, 2012, **68**, 3351–3356.
- 251 C. C. Price, *Org. React.*, 1946, **3**, 1–82.
- 252 M. De Rosa and A. Soriente, *Eur. J. Org. Chem.*, 2010, 1029–1032.
- 253 M. V. Gil, M. J. Arevalo and O. Lopez, *Synthesis*, 2007, 1589–1620.
- 254 D. S. Pedersen and A. Abell, *Eur. J. Org. Chem.*, 2011, 2399–2411.
- 255 E. A. Shafran, V. A. Bakulev, Y. A. Rozin and Y. M. Shafran, *Chem. Heterocycl. Compd.*, 2008, **44**, 1040–1069.
- 256 M. R. Grimmett and B. Iddon, *Heterocycles*, 1995, **41**, 1525–1574.
- 257 Y. X. Ou, B. R. Chen, J. R. Li, S. Dong, J. J. Li and H. P. Jia, *Heterocycles*, 1994, **38**, 1651–1664.
- 258 V. Ganesh, V. S. Sudhir, T. Kundu and S. Chandrasekaran, *Chem.-Asian J.*, 2011, **6**, 2670–2694.
- 259 A. A. El-Tombary, Y. S. Abdel-Ghany, A. S. F. Belal, S. A. S. El-Dine and F. S. G. Soliman, *Med. Chem. Res.*, 2011, **20**, 865–876.
- 260 D. S. Lawrence, J. E. Copper and C. D. Smith, *J. Med. Chem.*, 2001, **44**, 594–601.
- 261 A. K. Verma, R. R. Jha, V. K. Sankar, T. Aggarwal, R. P. Singh and R. Chandra, *Eur. J. Org. Chem.*, 2011, 6998–7010.
- 262 Y. Naito, F. Akahoshi, S. Takeda, T. Okada, M. Kajii, H. Nishimura, M. Sugiura, C. Fukaya and Y. Kagitani, *J. Med. Chem.*, 1996, **39**, 3019–3029.
- 263 C. A. Lipinski, *J. Med. Chem.*, 1983, **26**, 1–6.
- 264 E. Hoggarth, *J. Chem. Soc.*, 1950, 612–614.
- 265 A. V. Dolzhenko, G. Pastorin and W. K. Chui, *Tetrahedron Lett.*, 2009, **50**, 2124–2128.
- 266 H. Hinsberg, *Liebigs Ann. Chem.*, 1887, **237**, 368–373.
- 267 X. H. Luo, E. Chenard, P. Martens, Y. X. Cheng and M. J. Tomaszewski, *Org. Lett.*, 2010, **12**, 3574–3577.
- 268 R. Ballini, S. Gabrielli and A. Palmieri, *Synlett*, 2009, 965–967.
- 269 H. Suschitzky, B. J. Wakefield and R. A. Whittaker, *J. Chem. Soc., Perkin Trans. 1*, 1975, 401–403.
- 270 P. E. Mahaney, M. B. Webb, F. Ye, J. P. Sabatucci, R. J. Steffan, C. C. Chadwick, D. C. Harnish and E. J. Trybulski, *Bioorg. Med. Chem.*, 2006, **14**, 3455–3466.
- 271 J. Gris, R. Glisoni, L. Fabian, B. Fernandez and A. G. Moglioni, *Tetrahedron Lett.*, 2008, **49**, 1053–1056.
- 272 S. N. Murthy, B. Madhav and Y. V. D. Nageswar, *Helv. Chim. Acta*, 2010, **93**, 1216–1220.
- 273 C. M. Moldovan, O. Oniga, A. Parvu, B. Tiperciuc, P. Verite, A. Pirnau, O. Crisan, M. Bojita and R. Pop, *Eur. J. Med. Chem.*, 2011, **46**, 526–534.
- 274 K. D. Hargrave, F. K. Hess and J. T. Oliver, *J. Med. Chem.*, 1983, **26**, 1158–1163.
- 275 W. C. Patt, H. W. Hamilton, M. D. Taylor, M. J. Ryan, D. G. Taylor, C. J. C. Connolly, A. M. Doherty, S. R. Klutchko, I. Sircar, B. A. Steinbaugh, B. L. Batley, C. A. Painchaud, S. T. Rapundalo, B. M. Michniewicz and S. C. Olson, *J. Med. Chem.*, 1992, **35**, 2562–2572.



- 276 J. C. Jaen, L. D. Wise, B. W. Caprathe, H. Tecle, S. Bergmeier, C. C. Humblet, T. G. Heffner, L. T. Meltzer and T. A. Pugsley, *J. Med. Chem.*, 1990, **33**, 311–317.
- 277 F. W. Bell, A. S. Cantrell, M. Hogberg, S. R. Jaskunas, N. G. Johansson, C. L. Jordan, M. D. Kinnick, P. Lind, J. M. Morin, R. Noreen, B. Oberg, J. A. Palkowitz, C. A. Parrish, P. Pranc, C. Sahlberg, R. J. Ternansky, R. T. Vasileff, L. Vrang, S. J. West, H. Zhang and X. X. Zhou, *J. Med. Chem.*, 1995, **38**, 4929–4936.
- 278 S. Rostamizadeh, R. Aryan, H. R. Ghaieni and A. M. Amani, *Monatsh. Chem.*, 2008, **139**, 1241–1245.
- 279 B. Das, V. S. Reddy and R. Ramu, *J. Mol. Catal. A: Chem.*, 2006, **252**, 235–237.
- 280 G. W. Kabalka and A. R. Mereddy, *Tetrahedron Lett.*, 2006, **47**, 5171–5172.
- 281 M. Narender, M. S. Reddy, R. Sridhar, Y. V. D. Nageswar and K. R. Rao, *Tetrahedron Lett.*, 2005, **46**, 5953–5955.
- 282 H. L. Siddiqui, A. Iqbal, S. Ahmad and G. W. Weaver, *Molecules*, 2006, **11**, 206–211.
- 283 T. M. Potewar, S. A. Ingale and K. V. Srinivasan, *Tetrahedron*, 2008, **64**, 5019–5022.
- 284 S. Brase, C. Gil and K. Knepper, *Bioorg. Med. Chem.*, 2002, **10**, 2415–2437.
- 285 R. E. Dolle, *J. Comb. Chem.*, 2001, **3**, 477–517.
- 286 R. E. Dolle, *J. Comb. Chem.*, 2002, **4**, 369–418.
- 287 D. Tourwe, K. Verschuere, A. Frycia, P. Davis, F. Porreca, V. J. Hruby, G. Toth, H. Jaspers, P. Verheyden and G. VanBinst, *Biopolymers*, 1996, **38**, 1–12.
- 288 E. J. Trybulski, E. Reeder, J. F. Blount, A. Walser and R. I. Fryer, *J. Org. Chem.*, 1982, **47**, 2441–2447.
- 289 J. L. Panayides, R. Pathak, C. B. de Koning and W. A. L. van Otterlo, *Eur. J. Org. Chem.*, 2007, 4953–4961.
- 290 J. V. Prasad, M. Prabhakar, K. Manjulatha, D. Rambabu, K. A. Solomon, G. G. Krishna and K. A. Kumar, *Tetrahedron Lett.*, 2010, **51**, 3109–3111.
- 291 *Multicomponent Reactions*, ed. J. Zhu and H. Bienaym, Wiley-VCH, Weinheim, 2005.
- 292 C. O. Kappe, *Multicomponent Reactions*, Wiley-VCH Verlag GmbH & Co. KGaA, 2005, pp. 95–120.
- 293 P. Biginelli, *Gazz. Chim. Ital.*, 1893, **23**, 360–416.
- 294 G. Sabitha, G. Reddy, K. B. Reddy and J. S. Yadav, *Tetrahedron Lett.*, 2003, **44**, 6497–6499.
- 295 C. O. Kappe, *Tetrahedron*, 1993, **49**, 6937–6963.
- 296 L. E. Overman, M. H. Rabinowitz and P. A. Renhowe, *J. Am. Chem. Soc.*, 1995, **117**, 2657–2658.
- 297 B. B. Snider and Z. P. Shi, *J. Org. Chem.*, 1993, **58**, 3828–3839.
- 298 C. O. Kappe, *Acc. Chem. Res.*, 2000, **33**, 879–888.
- 299 Z. L. Shen, X. P. Xu and S. J. Ji, *J. Org. Chem.*, 2010, **75**, 1162–1167.
- 300 K. Konkala, N. M. Sabbavarapu, R. Katla, N. Y. V. Durga, T. V. K. Reddy, B. Devi and R. B. N. Prasad, *Tetrahedron Lett.*, 2012, **53**, 1968–1973.
- 301 H. S. Chandak, N. P. Lad and P. P. Upare, *Catal. Lett.*, 2009, **131**, 469–473.
- 302 M. Arjun, D. Sridhar, M. A. Chari and M. Sarangapani, *J. Heterocycl. Chem.*, 2009, **46**, 119–123.
- 303 M. B. Gawande, D. M. Nagrik and D. M. Ambhore, *Lett. Org. Chem.*, 2012, **9**, 12–18.
- 304 S. J. Tu, Q. Q. Shao, D. X. Zhou, L. J. Cao, F. Shi and C. M. Li, *J. Heterocycl. Chem.*, 2007, **44**, 1401–1406.
- 305 C. Mukhopadhyay, P. Das and R. J. Butcher, *Org. Lett.*, 2011, **13**, 4664–4667.
- 306 S. Rudys, C. Rios-Luci, E. Perez-Roth, I. Cikotiene and J. M. Padron, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 1504–1506.
- 307 B. A. Johns, J. G. Weatherhead, S. H. Allen, J. B. Thompson, E. P. Garvey, S. A. Foster, J. L. Jeffrey and W. H. Miller, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 1802–1806.
- 308 Y. W. Li, J. Liang, T. Siu, E. Hu, M. A. Rossi, S. F. Barnett, D. Defeo-Jones, R. E. Jones, R. G. Robinson, K. Leander, H. E. Huber, S. Mittal, N. Cosford and P. Prasit, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 834–836.
- 309 B. K. Ghotekar, M. G. Ghagare, R. B. Toche and M. N. Jachak, *Monatsh. Chem.*, 2010, **141**, 169–175.
- 310 Q. Zhang, C. S. Shi, H. R. Zhang and K. K. Wang, *J. Org. Chem.*, 2000, **65**, 7977–7983.
- 311 Y. Zhou, J. A. Porco and J. K. Snyder, *Org. Lett.*, 2007, **9**, 393–396.
- 312 V. J. Colandrea and E. M. Naylor, *Tetrahedron Lett.*, 2000, **41**, 8053–8057.
- 313 S. Vanlaer, A. Voet, C. Gielens, M. De Maeyer and F. Compennolle, *Eur. J. Org. Chem.*, 2009, 643–654.
- 314 F. Bossert, H. Meyer and E. Wehinger, *Angew. Chem., Int. Ed. Engl.*, 1981, **20**, 762–769.
- 315 D. M. Stout and A. I. Meyers, *Chem. Rev.*, 1982, **82**, 223–243.
- 316 X. S. Wang, M. M. Zhang, H. Jiang, D. Q. Shi, S. J. Tu, X. Y. Wei and Z. M. Zong, *Synthesis*, 2006, 4187–4199.
- 317 G. W. Wang and C. B. Miao, *Green Chem.*, 2006, **8**, 1080–1085.
- 318 R. N. Brogden, *Drugs*, 1986, **32**, 60–70.
- 319 N. Uramaru, H. Shigematsu, A. Toda, R. Eyanagi, S. Kitamura and S. Ohta, *J. Med. Chem.*, 2010, **53**, 8727–8733.
- 320 R. E. Sammelson, C. D. Gurusinghe, J. M. Kurth, M. M. Olmstead and M. J. Kurth, *J. Org. Chem.*, 2002, **67**, 876–882.
- 321 P. Gunasekaran, S. Perumal, P. Yogeewari and D. Sriram, *Eur. J. Med. Chem.*, 2011, **46**, 4530–4536.
- 322 Z. G. Yang, Z. Wang, S. Bai, X. H. Liu, L. L. Lin and X. M. Feng, *Org. Lett.*, 2011, **13**, 596–599.
- 323 K. Kumaravel and G. Vasuki, *Green Chem.*, 2009, **11**, 1945–1947.
- 324 S. T. Hilton, T. C. T. Ho, G. Pljevaljcic and K. Jones, *Org. Lett.*, 2000, **2**, 2639–2641.
- 325 C. V. Galliford and K. A. Scheidt, *Angew. Chem., Int. Ed.*, 2007, **46**, 8748–8758.
- 326 M. J. Kornet and A. P. Thio, *J. Med. Chem.*, 1976, **19**, 892–898.
- 327 R. M. Williams and R. J. Cox, *Acc. Chem. Res.*, 2003, **36**, 127–139.



- 328 T. H. Kang, K. Matsumoto, M. Tohda, Y. Murakami, H. Takayama, M. Kitajima, N. Aimi and H. Watanabe, *Eur. J. Pharmacol.*, 2002, **444**, 39–45.
- 329 A. Alizadeh, T. Firuzyar and A. Mikaeili, *Synthesis*, 2010, 3913–3917.
- 330 S. J. Chai, Y. F. Lai, J. C. Xu, H. Zheng, Q. Zhu and P. F. Zhang, *Adv. Synth. Catal.*, 2011, **353**, 371–375.
- 331 A. Dandia, V. Parewa, A. K. Jain and K. S. Rathore, *Green Chem.*, 2011, **13**, 2135–2145.
- 332 G. S. Hari and Y. R. Lee, *Synthesis*, 2010, 453–464.
- 333 Y. L. Li, H. Chen, C. L. Shi, D. Q. Shi and S. J. Ji, *J. Comb. Chem.*, 2010, **12**, 231–237.
- 334 L. Q. Zhao, B. Zhou and Y. Q. Li, *Heteroat. Chem.*, 2011, **22**, 673–677.
- 335 M. Adib, M. Mahdavi, M. A. Noghani and P. Mirzaei, *Tetrahedron Lett.*, 2007, **48**, 7263–7265.
- 336 A. Strecker, *Ann. Chem. Pharm.*, 1850, **75**, 27.
- 337 C. Najera and J. M. Sansano, *Chem. Rev.*, 2007, **107**, 4584–4671.
- 338 B. Ganem, *Acc. Chem. Res.*, 2009, **42**, 463–472.
- 339 A. Domling, *Chem. Rev.*, 2006, **106**, 17–89.
- 340 P. Galletti, M. Pori and D. Giacomini, *Eur. J. Org. Chem.*, 2011, 3896–3903.
- 341 S. Bonollo, D. Lanari, A. Marrocchi and L. Vaccaro, *Curr. Org. Synth.*, 2011, **8**, 319–329.
- 342 R. Balamurugan, R. B. Kothapalli and G. K. Thota, *Eur. J. Org. Chem.*, 2011, 1557–1569.
- 343 L. Han, H. J. Choi, S. J. Choi, B. Y. Liu and D. W. Park, *Green Chem.*, 2011, **13**, 1023–1028.
- 344 G. Hasnaoui-Dijoux, M. M. Elenkov, J. H. L. Spelberg, B. Hauer and D. B. Janssen, *ChemBioChem*, 2008, **9**, 1048–1051.
- 345 F. M. Moghaddam, H. Saeidian, Z. Mirjafary, M. J. Javan, M. M. Farimani and M. Seirafi, *Heteroat. Chem.*, 2009, **20**, 157–163.
- 346 B. Halford, *Chem. Eng. News*, 2007, **85**, 7–7.
- 347 I. Vilotijevic and T. F. Jamison, *Angew. Chem., Int. Ed.*, 2009, **48**, 5250–5281.
- 348 J. S. Bajwa and U. B. Sunay, *J. Labelled Compd. Radiopharm.*, 1997, **39**, 787–790.
- 349 R. I. Kureshy, S. Singh, N. U. H. Khan, S. H. R. Abdi, I. Ahmad, A. Bhatt and R. V. Jasra, *Chirality*, 2005, **17**, 590–594.
- 350 C. Moberg and L. Rakos, *React. Polym.*, 1991, **15**, 25–35.
- 351 S. Bhadra, L. Adak, S. Samanta, A. Islam, M. Mukherjee and B. C. Ranu, *J. Org. Chem.*, 2010, **75**, 8533–8541.
- 352 S. Das and T. Asefa, *ACS Catal.*, 2011, **1**, 502–510.
- 353 A. A. Jafari and Moradgholi, *Synth. Commun.*, 2011, **41**, 594–602.
- 354 B. Pujala, S. Rana and A. K. Chakraborti, *J. Org. Chem.*, 2011, **76**, 8768–8780.
- 355 N. K. Shee, F. A. O. Adekunle, D. Das, M. G. B. Drew and D. Datta, *Inorg. Chim. Acta*, 2011, **375**, 101–105.
- 356 F. Zaccheria, F. Santoro, R. Psaro and N. Ravasio, *Green Chem.*, 2011, **13**, 545–548.
- 357 B. Das, M. Krishnalal, P. Thirupathi and K. Laxminarayana, *Tetrahedron Lett.*, 2007, **48**, 4263–4265.
- 358 B. Das, V. S. Reddy, F. Tehseen and M. Krishnaiah, *Synthesis*, 2007, 666–668.
- 359 A. R. Kiasat and M. Fallah-Mehrjardi, *J. Iran. Chem. Soc.*, 2009, **6**, 542–546.
- 360 N. Azizi, E. Akbari, F. Ebrahimi and M. R. Saidi, *Monatsh. Chem.*, 2010, **141**, 323–326.
- 361 N. Azizi and M. R. Saidi, *Org. Lett.*, 2005, **7**, 3649–3651.
- 362 C. Mukherjee, G. H. Maiti and A. K. Misra, *Arkivoc*, 2008, 46–55.
- 363 A. Isidro-Llobet, M. Alvarez and F. Albericio, *Chem. Rev.*, 2009, **109**, 2455–2504.
- 364 T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley and Sons, New York, 1999.
- 365 S. V. Chankeshwara and A. K. Chakraborti, *Org. Lett.*, 2006, **8**, 3259–3262.
- 366 M. B. Gawande and P. S. Branco, *Green Chem.*, 2011, **13**, 3355–3359.
- 367 X. Y. Zhang and K. N. Houk, *J. Org. Chem.*, 2005, **70**, 9712–9716.
- 368 M. Hutchby, C. E. Houlden, J. G. Ford, S. N. G. Tyler, M. R. Gagne, G. C. Lloyd-Jones and K. I. Booker-Milburn, *Angew. Chem., Int. Ed.*, 2009, **48**, 8721–8724.
- 369 M. Shimizu and M. Sodeoka, *Org. Lett.*, 2007, **9**, 5231–5234.
- 370 L. A. Carpino and G. Y. Han, *J. Org. Chem.*, 1972, **37**, 3404–3409.
- 371 H. Sumiyoshi, T. Shimizu, M. Katoh, Y. Baba and M. Sodeoka, *Org. Lett.*, 2002, **4**, 3923–3926.
- 372 (a) G. Wang, C. J. Li and X. S. Jia, *Tetrahedron Lett.*, 2009, **50**, 1438; (b) A. Procopio, M. Gaspari, M. Nardi, M. Oliverio, A. Tagarelli and G. Sindona, *Tetrahedron Lett.*, 2007, **48**, 8623–8627.
- 373 P. G. M. Wuts and T. W. Greene, *Greene's Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc., 2006, pp. 16–366.
- 374 K. Ishihara, H. Kurihara and H. Yamamoto, *J. Org. Chem.*, 1993, **58**, 3791–3793.
- 375 F. E. A. Van Waes, J. Drabowicz, A. Cukalovic and C. V. Stevens, *Green Chem.*, 2012, **14**, 2776–2779.
- 376 J. Fraga-Dubreuil and M. Poliakoff, *Pure Appl. Chem.*, 2006, **78**, 1971–1982.
- 377 I. A. Ibarra, P. A. Bayliss, E. Perez, S. Yang, A. J. Blake, H. Nowell, D. R. Allan, M. Poliakoff and M. Schroder, *Green Chem.*, 2012, **14**, 117–122.
- 378 V. Lehr, M. Sarlea, L. Ott and H. Vogel, *Catal. Today*, 2007, **121**, 121–129.
- 379 P. E. Savage, *Chem. Rev.*, 1999, **99**, 603–622.
- 380 N. Akiya and P. E. Savage, *Chem. Rev.*, 2002, **102**, 2725–2750.
- 381 Y. Ikushima, K. Hatakedo, O. Sato, T. Yokoyama and M. Arai, *J. Am. Chem. Soc.*, 2000, **122**, 1908–1918.
- 382 T. Ogawa, J. Watanabe and Y. Oshima, *J. Supercrit. Fluids*, 2008, **45**, 80–87.
- 383 T. Ogawa, J. Watanabe and Y. Oshima, *J. Polym. Sci., Polym. Chem. Ed.*, 2009, **47**, 2656–2663.

- 384 P. G. Jessop and W. Leitner, *Chemical Synthesis using Supercritical Fluids*, Wiley-VCH, Weinheim, 1999.
- 385 M. F. Kemmere and T. Meyer, *Supercritical Carbon Dioxide*, Wiley-VCH, Weinheim, 2005.
- 386 A. J. Parrott, R. A. Bourne, G. R. Akien, D. J. Irvine and M. Poliakoff, *Angew. Chem., Int. Ed.*, 2011, **50**, 3788–3792.
- 387 R. A. Bourne, X. Han, A. O. Chapman, N. J. Arrowsmith, H. Kawanami, M. Poliakoff and M. W. George, *Chem. Commun.*, 2008, 4457–4459.
- 388 J. A. Darr and M. Poliakoff, *Chem. Rev.*, 1999, **99**, 495–542.
- 389 X. Han and M. Poliakoff, *Chem. Soc. Rev.*, 2012, **41**, 1428–1436.
- 390 G. R. Akien and M. Poliakoff, *Green Chem.*, 2009, **11**, 1083–1100.
- 391 M. J. Fuchter, C. J. Smith, M. W. S. Tsang, A. Boyer, S. Saubern, J. H. Ryan and A. B. Holmes, *Chem. Commun.*, 2008, 2152–2154.
- 392 R. B. Restani, P. I. Morgado, M. P. Ribeiro, I. J. Correia, A. Aguiar-Ricardo and V. D. B. Bonifácio, *Angew. Chem., Int. Ed.*, 2012, **51**, 5162–5165.
- 393 C. -R. Qi and H.-F. Jiang, *Green Chem.*, 2007, **9**, 1284–1286.
- 394 J. X. Xu, J. W. Zhao and Z. B. Jia, *Chin. Chem. Lett.*, 2011, **22**, 1063–1067.