

Cite this: *Chem. Sci.*, 2024, 15, 1177

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 21st October 2023  
Accepted 15th December 2023

DOI: 10.1039/d3sc05618j

rsc.li/chemical-science

## Organocatalytic activation of hydrogen peroxide: towards green and sustainable oxidations

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The advent of organocatalysis provided an additional option in every researcher's arsenal, towards the development of elegant and sustainable protocols for various organic transformations. Oxidation reactions are considered to be key in organic synthesis since oxygenated functionalities appear in many natural products. Hydrogen peroxide is categorized as a green oxidant, since its only by-product is water, offering novel opportunities for the development of green and sustainable protocols. In this review article, we intend to present recent developments in the field of the organocatalytic activation of hydrogen peroxide, providing useful insight into the applied oxidative protocols. At the same time, we will present some interesting mechanistic studies, providing information on the oxygen transfer processes.

### Introduction

The majority of organic molecules contain oxygen functionalities. These molecules find excellent applications in agrochemicals, materials science, petrochemistry and medicinal chemistry since many of these compounds exhibit pharmaceutical properties. For this reason, there is a high demand for

synthetic protocols, targeting the oxidation of organic molecules. Alkanes, alkenes, alcohols, ketones, sulfides, *etc.* are considered as valuable precursors for the manufacture of a variety of functionalized derivatives, which serve as important building blocks in organic synthesis.<sup>1</sup>

Since 2000, organocatalysis, the use of small organic molecules as catalysts, has brought a revolution in modern organic synthetic chemistry. In 2021, the Nobel Prize in Chemistry was awarded to David W. C. MacMillan<sup>2</sup> and Benjamin List,<sup>3</sup> who pioneered the field of asymmetric organocatalysis. This revolution led many scientists, both in industry and academia, to explore eco-friendly procedures, replacing metal-based catalysts

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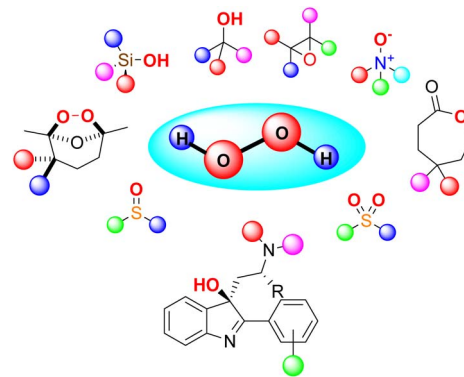
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with small organic molecules that have a lower environmental impact. Thus, a plethora of organocatalytic protocols have been reported in the literature, aiming at organic transformations that were previously underexplored. Oxidative procedures were mostly investigated and many organocatalytic protocols were developed targeting the epoxidation of alkenes, the oxidation of sulfides into sulfoxides, the direct C–H functionalization of alkanes, *etc.* Aiming at the development of sustainable protocols that are characterized by lower environmental impact, reduced costs of reagents, as well as high applicability and broad scope of substrates, the use of the oxidant is key to fulfil the above-mentioned parameters. In the context of this review, we will discuss the use of the environmentally benign oxidant, hydrogen peroxide. Hydrogen peroxide is the simplest form of peroxides and was first identified and isolated by Luis Jaques Thenard, in 1818.<sup>4</sup> Hydrogen peroxide (and its derivatives, such as the urea hydrogen peroxide complex) is considered as a green oxidant, since its only by-product is water.<sup>5</sup> Hydrogen peroxide is mainly available in aqueous solutions, which are safer in storage, operation and transportation. In many cases, when the reagents are sensitive to moisture, ethereal hydrogen peroxide can be used, although it is not storable and must be used with great care. It is easy to handle, and this feature makes hydrogen peroxide the oxidant of choice in the pharmaceutical industry. However, its key limiting factor is the lack of reactivity to promote an oxidation reaction and thus an *in situ* or a beforehand activation is required. For many years, this was mainly achieved *via* metal catalysis.<sup>6</sup> In many cases, its complex with urea appears to be more reactive, since urea activates hydrogen peroxide through hydrogen bonding. Nowadays, many efforts are targeting the activation of hydrogen peroxide using small organic molecules. In this review article, we intend to highlight

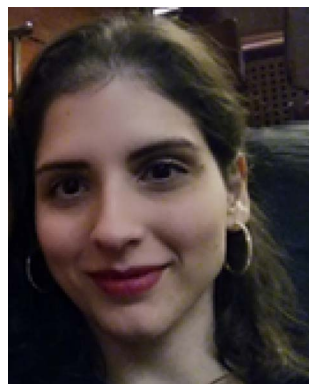


Scheme 1 Applications of hydrogen peroxide in oxidative organic transformations.

the different approaches that have been followed to activate hydrogen peroxide towards racemic and asymmetric epoxidations, C–H hydroxylation, Baeyer–Villiger oxidation, *etc.* (Scheme 1). Also, some remarkable fundamental mechanistic studies will be mentioned in due course. The authors believe that such information will provide greater insights into the organocatalytic activation of hydrogen peroxide and this will be the stepping stone for the rational design of more efficient and sustainable protocols in the future.

## Organocatalytic activation of hydrogen peroxide by activated carbonyls

The uprise of organocatalysis prompted many researchers to search for small organic molecules that might act as potential catalysts to promote various organic transformations. The use



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Organic Chemistry in the Department of Chemistry of the National and Kapodistrian University of Athens, Greece and promoted to Assistant Professor (2016) and Associate Professor (2020). He was also elected a Chemistry Europe Fellow in 2022 (Class 2020–2021). His research interests lie in asymmetric organocatalysis, photocatalysis and green methodologies for oxidation reactions and their application in the synthesis of pharmaceuticals, bioactive molecules and high-added value chemicals.



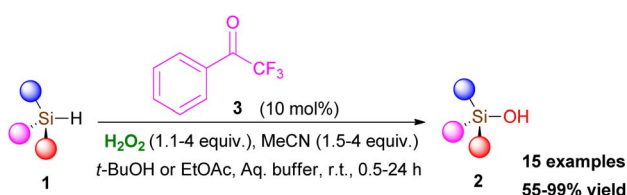
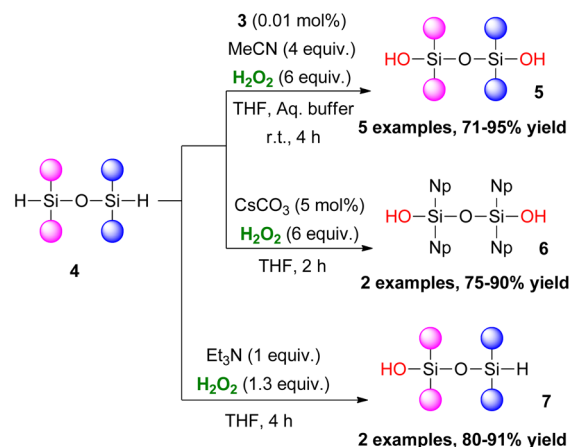
## Perspective

of small organic molecules offers unlimited advantages in organic synthesis. Especially, in the pharmaceutical industry, the replacement of expensive metal catalysts by organic molecules that can be easily removed from the reaction mixture and in many cases may be reused, firstly offers a greener alternative and secondly reduces the overall cost of the process. Some extremely useful classes of molecules of great interest in organocatalysis are ketones and aldehydes. Pioneers in this field were the research groups of Denmark,<sup>7</sup> Yang<sup>8</sup> and Shi,<sup>9</sup> who provided useful results for the basic application of ketones as catalysts in oxidation protocols.

## Heteroatom oxidations with hydrogen peroxide

In 2013, Kokotos and coworkers, captivated by the above-mentioned elegant contributions in the field, envisaged that an activated ketone might activate hydrogen peroxide to form an intermediate, capable of inducing an oxidation reaction. Thus, they introduced the first organocatalytic oxidation protocol for the conversion of silanes **1** to silanols **2**, an organic transformation with significant importance in the pharmaceutical industry, materials science and organic synthesis (Scheme 2).<sup>10</sup> The authors tested a variety of commercially-available carbonyl derivatives and concluded that 2,2,2-trifluoroacetophenone (**3**) acts efficiently as the organocatalyst, activating hydrogen peroxide. It must be pointed out that acetonitrile plays a crucial role in the reaction output, since in its absence, the reaction does not take place. A series of optimization experiments illustrated that 10 mol% of **3**, in the presence of 1.1 equiv. of hydrogen peroxide and 1.5 equiv. of acetonitrile led to quantitative formation of the desired product after 24 h. Increasing the equiv. of both hydrogen peroxide and acetonitrile (up to 4 equiv.) led to a significant reduction in the reaction time. A vast variety of symmetrical and non-symmetrical alkyl silanes was tested, leading to the corresponding silanols in good to excellent yields (Scheme 2). The oxidation of silanes bearing a double or a triple bond proved to be problematic. To circumvent this issue, the authors altered the reaction medium to ethyl acetate, leading to the desired products in good to excellent yields. Furthermore, the great advantage of this organocatalytic protocol appears to be its application to aryl silanes, where the Tamao-Fleming oxidation pathway does not take place.

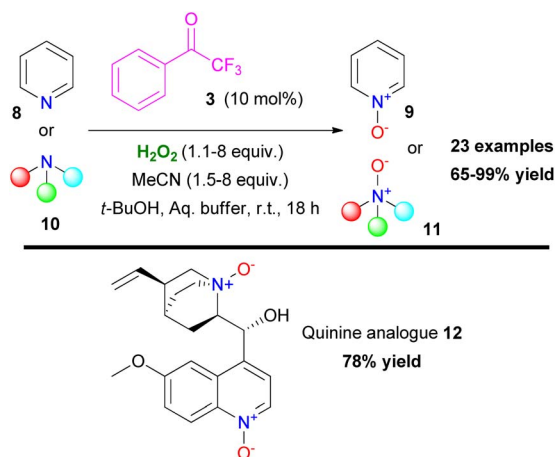
In 2019, Franz and coworkers studied the oxidative hydrolysis of hydrido-siloxanes **4** to siloxanols **5-7** using H<sub>2</sub>O<sub>2</sub> (Scheme 3).<sup>11</sup> They discovered that an extremely low catalyst loading of **3** (0.01 mol%) under basic conditions was able to promote the formation 1,3-disiloxanediols **5**. The authors

Scheme 2 Organocatalytic oxidation of silanes **1** to silanols **2**.

Scheme 3 Hydrolysis of hydrido-siloxanes to siloxanols.

performed several control experiments, reporting that basic conditions in the absence of **3** also promoted the reaction. Tetra-aryl 1,3-dihydro-disiloxanes **6** showed excellent chemoselectivity when CsCO<sub>3</sub> was used as the base. Interestingly, 1 equiv. of Et<sub>3</sub>N allowed an unprecedented chemoselective hydrolysis of **4** to **7**. Regrettably, Tamao-Fleming oxidation persisted in all the above cases in phenyl-containing substrates. Further study on this matter, revealed that while *ortho*-substitution suppresses the effect, an electron-withdrawing group diminishes that suppression.

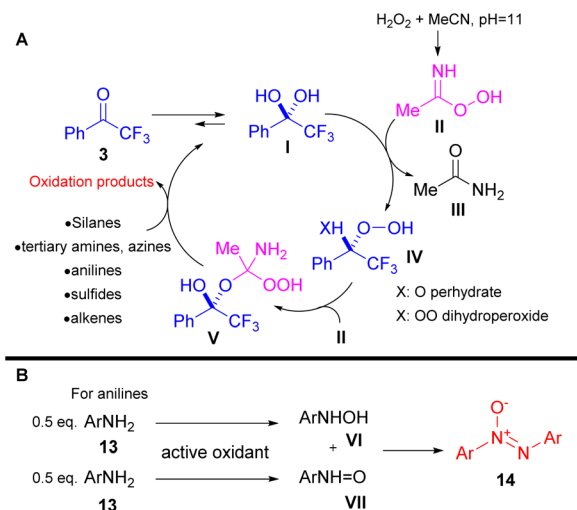
Based on their previous findings, Kokotos and coworkers expanded their work on heteroatom oxidation, utilizing azines or tertiary amines, providing access to *N*-oxides in excellent yields (Scheme 4).<sup>12</sup> The developed protocol combines short reaction times and quantitative formation of the corresponding *N*-oxides (**9** or **11**) under mild reaction conditions. A variety of substrates was tested, proving the excellent functional group tolerance of the organocatalytic protocol. The authors employed the organocatalytic protocol for the synthesis of compound **12**, derived from quinine, in high yield (78%) (Scheme 4). It must be

Scheme 4 Organocatalytic oxidation of tertiary amines or azines to the corresponding *N*-oxides.

mentioned though that secondary or primary amines were not tested, probably due to oxidative decomposition pathways that prevail on this occasion.

A few years later, the authors implemented their organocatalytic protocol towards the oxidation of anilines.<sup>13</sup> In their attempt to probe the reaction mechanism, they noticed the formation of azoxy compounds **14**, instead of the desired nitro derivatives **15** (Scheme 5). Even upon increasing the equiv. of hydrogen peroxide, the reaction rate for the synthesis of nitro compounds remained low.<sup>13</sup> This can be attributed to the slow conversion of the formed nitroso compound to the nitro derivative. As a result, the hydroxylamine intermediate **VI** undergoes a condensation reaction with the nitroso intermediate **VII**, delivering the azoxy compound as depicted in Scheme 6B. In the absence of the organocatalyst, the reaction output was different.<sup>13</sup> In this case, the use of 6.5 equiv. of hydrogen peroxide boosted the reaction towards the formation of the corresponding nitro derivative **15** (Scheme 5). Substituted anilines bearing either electron-withdrawing or electron-donating substituents were successfully applied to the organocatalytic protocol. On the other hand, 2-aminopyridine favoured the corresponding *N*-oxide. Under the catalyst-free conditions, the corresponding nitro compounds were formed in good to excellent yields. Interestingly, in this case, 2-aminopyridine was selectively converted to the nitro derivative in good yield. It is worth mentioning that naphthylamines and aliphatic amines were not viable under both reaction conditions. In order to elucidate the reaction mechanism, the authors performed a series of HRMS studies, identifying the possible intermediates that are involved in the oxidation procedure.

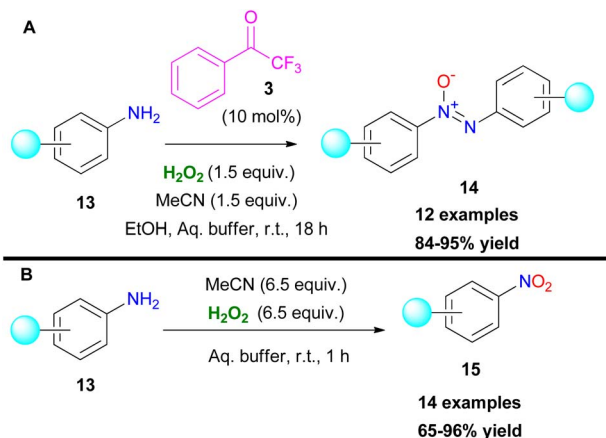
In their contributions, Kokotos and coworkers performed a series of mechanistic studies to elucidate the oxidation pathways and to identify the active oxidant species that are generated. The developed oxidative protocols are based on the equilibrium between the keto form (**3**) and the hydrate form **I** of the catalyst (Scheme 6A). In the presence of acetonitrile, Payne's intermediate **II** (ref. <sup>14</sup>) is formed through acetonitrile's interaction with hydrogen peroxide at the appropriate pH (pH = 11). The latter interacts with hydrate form **I**, shifting the equilibrium



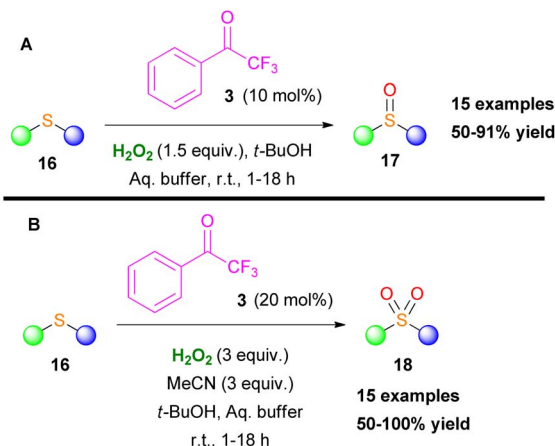
Scheme 6 Proposed catalytic pathway of 2,2,2-trifluoroacetophenone towards novel oxidation transformations. (B) Proposed pathway for the formation of azoxy compounds.

to **I**, generating either the perhydrate **IV** (X = O) or dihydroperoxide **IV** (X = OO) intermediate (Scheme 6A). Based on HRMS studies performed by the authors, intermediate **IV** undergoes addition to Payne's intermediate, generating the active oxidant **V**, which is responsible for the oxidative organic transformations (Scheme 6A).<sup>10,12,13</sup>

In the same vein, Kokotos and coworkers developed two oxidation protocols for the selective oxidation of sulfides either to sulfoxides or sulfones.<sup>15</sup> Both families of compounds display a salient pharmaceutical profile and find many applications in medicinal chemistry and agriculture (Scheme 7).<sup>15</sup> Acetonitrile plays a key role in the reaction output, since in its presence the overoxidized sulfone derivative is being formed. Based on mechanistic studies, the authors concluded that a perhydrate intermediate **IV** (X = O) from the perfluoroketone **3** is the active oxidant for the formation of sulfoxides, since Payne's intermediate<sup>14</sup> was not detected (Scheme 6A).<sup>15</sup>



Scheme 5 Oxidation of anilines towards (A) azoxy compounds, (B) nitro compounds.



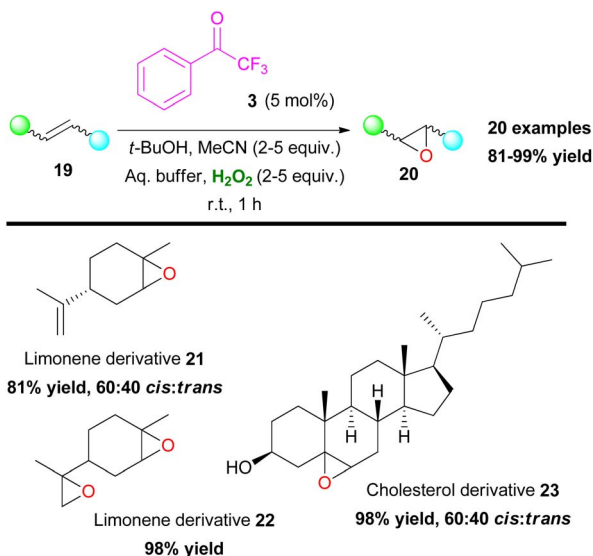
Scheme 7 Selective oxidation of sulfides to (A) sulfoxides and (B) sulfones.



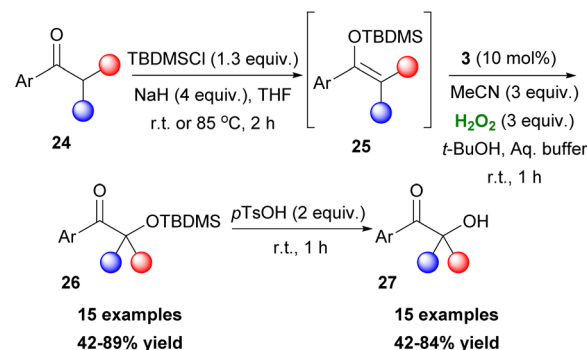
## Hydrogen peroxide-mediated epoxidation reactions

Another organic transformation with significant importance in organic synthesis is the formation of epoxides. The most common approach for the synthesis of epoxides is the epoxidation of unactivated olefins. This organic reaction has been well-studied by many research groups worldwide and there have been numerous contributions in the literature.<sup>16</sup> Sharpless,<sup>17</sup> Katsuki,<sup>18</sup> Jacobsen<sup>19</sup> and others pioneered the field, adding novel metal-based approaches towards oxirane synthesis. Furthermore, Denmark,<sup>7</sup> Yang<sup>8</sup> and Shi<sup>9</sup> introduced dioxirane derivatives as the active oxidants in the first organocatalytic approaches in this area. Having established an organocatalytic approach in a series of organic transformations, Kokotos and coworkers expanded their strategy in investigating the use of 2,2,2-trifluoroacetophenone (**3**) towards the epoxidation reaction of unactivated alkenes (Scheme 8).<sup>20</sup> The authors employed an extremely low catalyst loading (up to 5 mol%) of ketone **3**, which was found to be capable of promoting with ease the selective epoxidation of various mono-, di- and trisubstituted alkenes and known natural compounds, such as limonene (**21** and **22**) or cholesterol (**23**) in excellent yields (up to 99%) combining short reaction times (Scheme 8). This was a major improvement, compared to the state of the art at that time. The authors based on NMR experiments evaluated a similar mechanistic pathway, to the one presented in Scheme 6A, where intermediate **V** is acknowledged as the active oxidant species.<sup>20</sup>

2,2,2-Trifluoroacetophenone **3** found an excellent application as the organocatalyst, by the Kokotos group, for the *in situ* oxidation of TBDMS-protected enols **25** to form TBDMS-protected **26** and free  $\alpha$ -hydroxy ketones **27**, upon treatment with an acid (Scheme 9).<sup>21</sup> This method follows a similar concept proposed by Rubbotom.<sup>22</sup> Aryl-methyl ketones, regardless of substitution in the aryl group, can yield both products successfully. Moreover, a substrate bearing a phenol scaffold showed a preference for the deprotection of the alcohol. This protocol can generate both secondary and tertiary alcohols at slightly reduced yields.

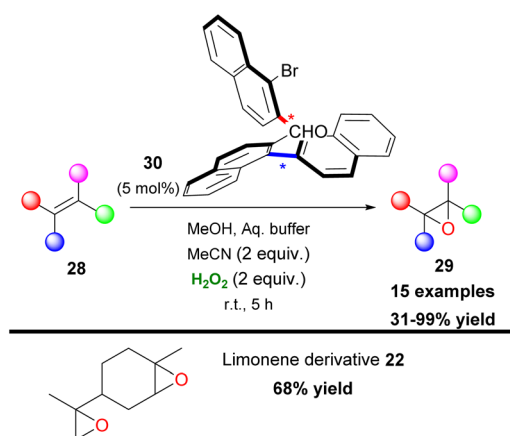


Scheme 8 Novel epoxidation protocol by Kokotos.

Scheme 9 Synthesis of TBDMS-protected and free  $\alpha$ -hydroxy ketones.

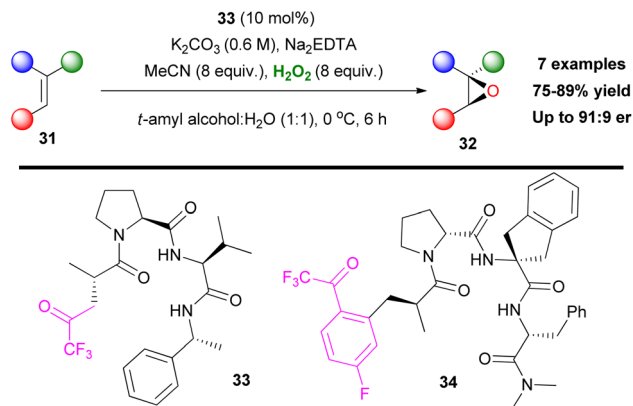
Inspired by Kokotos' work on organocatalytic alkene epoxidation, Tyablikov and coworkers developed a heterogenous catalyst, where the 2,2,2-trifluoroacetophenone moiety of **3** was embedded in SBA-15 mesoporous silica, in their effort to prepare a catalyst that can be easily recycled.<sup>23</sup> Furthermore, two different research groups<sup>24,25</sup> sought to harness this protocol, for large-scale reactions. Employing continuous-flow reactor apparatus, Zheng and coworkers improved mass and heat transfer rates.<sup>24</sup> After a thorough optimization of each reaction parameter, a fast and high yielding method was established. Chen and Xu<sup>25</sup> utilized a microreaction continuous flow system that also provided high selectivity and yield of styrene oxide in shorter times, even when the amount of oxidant was reduced.

In an attempt to provide an asymmetric variant that failed and seeking other potential carbonyl-based molecules that might activate hydrogen peroxide, Kokotos, Sparr and coworkers, in 2021, developed an epoxidation protocol, introducing for the first time an aldehyde-catalysed epoxidation (Scheme 10).<sup>26</sup> A good substrate scope was tested, providing an efficient sustainable protocol for the epoxidation of unactivated alkenes. Usually, in this type of reaction introduced by Mukaiyama<sup>27</sup> in 1991, an overstoichiometric amount of aldehyde is required and the active intermediate is a matter under discussion.<sup>28</sup> However, the authors performed a series of HRMS mechanistic studies and proved that atropisomeric aldehyde



Scheme 10 First aldehyde-catalysed epoxidation protocol.





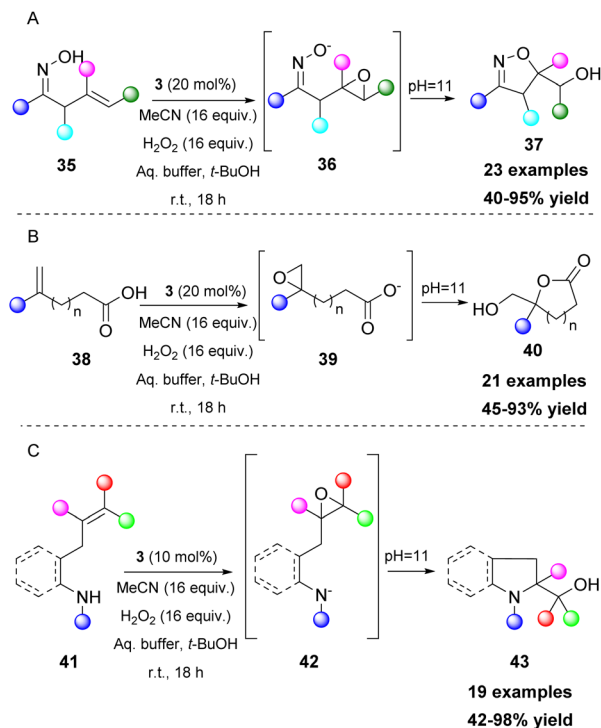
Scheme 11 Miller's perfluoroketone-embedded peptide catalysts, enantioselective epoxidation reaction with peptide catalyst **33**.

**30**, forms a dioxirane, which acts as the active oxidant. These findings are of great importance as it is indicated that aldehydes can serve as possible activators of hydrogen peroxide towards oxidative transformations even in sub-stoichiometric amounts. Unfortunately, the atropisomeric aldehyde proved to have no impact on the enantioselectivity of the epoxidation protocol.

Asymmetric epoxidation has always been of great interest for organic synthesis, since its introduction. Inspired by Shi's contributions in this field,<sup>9</sup> Miller and coworkers envisaged that a ketone moiety, embedded in a peptide, might induce enantioselectivity towards alkene epoxidation.<sup>29</sup> For this reason, they prepared a series of peptides, decorated by the 2,2,2-trifluoromethylcarbonyl moiety (Scheme 11). Based on their initial idea, in the presence of hydrogen peroxide, a dioxirane should be formed. The peptide core can form an enantioselective transition state inducing asymmetry. Several alkenes were tested, affording the corresponding epoxides in good to excellent enantioselectivity.<sup>29</sup> Under the optimized reaction conditions, trisubstituted epoxides were prepared in high enantioselectivity, while in disubstituted substrates selectivity dropped to modest (Scheme 11). Because of their innate chirality, peptide-based catalysts induce asymmetric induction. Exploiting this feature, Miller and coworkers, two years later, developed phenylalanine-based trifluoromethyl ketones as potential oxidation catalysts.<sup>30</sup> In the case of catalyst **34**, under the same reaction conditions, even though it was able to epoxidize less reactive olefins, such as *N*-(3-(prop-1-en-2-yl)phenyl)acetamide, the observed enantioselectivity was poor. This verifies indeed the fact that, even though high yielding epoxidation procedures are within reach, asymmetric induction is always a challenge.

### One-pot transformations

Epoxides are versatile intermediates and due to their ring strain, they are susceptible to ring opening reactions and other transformations. Kokotos and coworkers, having developed a series of organic transformations using 2,2,2-trifluoroacetophenone (**3**) as a potent catalyst, expanded its use towards one-pot transformations. A strategically placed functional group next to the formed epoxide was able to perform an intramolecular cyclization reaction, leading to the formation of

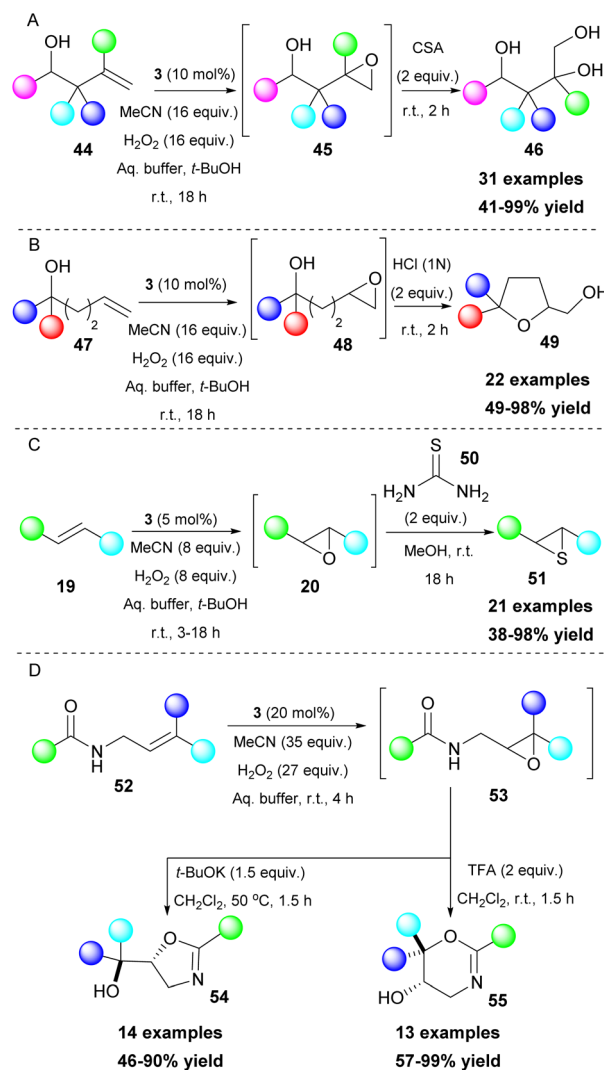


Scheme 12 Versatile one-pot transformations from functionalized epoxides to (A) isoxazolines, (B) lactones, (C) indolines and pyrrolidines.

various substrates, such as dihydrobenzofurans,<sup>31</sup> isoxazolines,<sup>32</sup> lactones,<sup>33</sup> indolines and pyrrolidines (Scheme 12).<sup>34</sup> In these cases, the aqueous buffer solution also provides the appropriate pH for the *in situ* deprotonation of the OH, N-OH, COOH and NH groups, enhancing their nucleophilicity and facilitating the ring opening of the epoxide (Scheme 12). To achieve the synthesis of pyrrolidines and indolines, protection of the nitrogen atom was vital to enhance the acidity of the free proton. Among all the substituents on the nitrogen atom, the mesyl group afforded the best results. Nevertheless, in some cases, a strong base (*i.e.*  $t$ -BuOK) was required (Scheme 12C).<sup>34</sup>

Tuning the reaction conditions and applying a variety of reagents provide access to various classes of molecules. Poly-alcohols<sup>35</sup> or polysubstituted tetrahydrofurans<sup>36</sup> can be accessed by the addition of a strong acid (Scheme 13A and B), while in a more recent development, thiiranes can also be obtained, using thiourea **50** as the thiolating reagent (Scheme 13C).<sup>37</sup> Interestingly, when substituted allylamides **52** were employed, the resulting epoxide **53** led to different cyclization products, depending on the additive that was used. In the presence of  $t$ -BuOK, a 5-*exo-tet* cyclization occurred, leading to the formation of oxazolines **54**. On the contrary, in an acidic environment (TFA), a 6-*endo-trig* cyclization afforded dihydrooxazines **55** (Scheme 13D).<sup>38</sup> An interesting feature is that allylamines show excellent chemoselectivity under the reaction conditions.<sup>38</sup> This unique feature enabled the application of a Meisenheimer rearrangement step towards *O*-allylhydroxylamines **58** (Scheme 14). It needs to be highlighted that aromatic or conjugated aromatic allylic amines **56** allowed an additional rearrangement step (Scheme 14).<sup>39</sup>





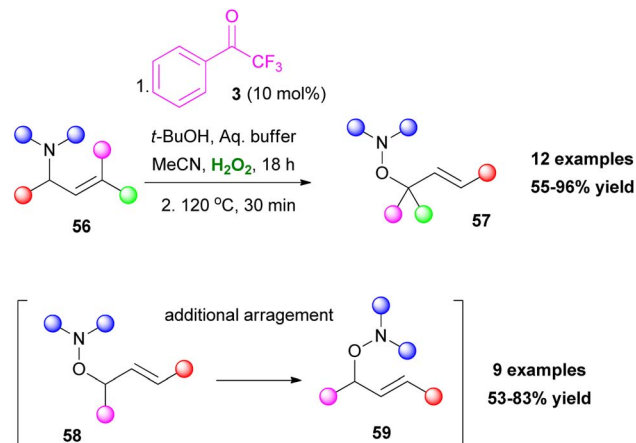
Scheme 13 One-pot transformations employing an additional step leading to (A) polyalcohols, (B) substituted tetrahydrofurans, (C) thioamides, (D) oxazolines and dihydrooxazines.

In this field, in 2014, Hilinski and coworkers proposed an elegant protocol for the C–H hydroxylation of alkenes, using hydrogen peroxide and a catalytic amount of ketone.<sup>40</sup> In the same line with Kokotos' observations, the authors reported an organocatalytic protocol providing access to a variety of alcohols **62** (Scheme 15). Despite this elegant approach, the over-stoichiometric use of hydrogen peroxide posed significant difficulties, such as the formation of overoxidized ketone or ester by-products.

## Organocatalytic activation of hydrogen peroxide with peptide-embedded carboxylic acids for asymmetric oxidation

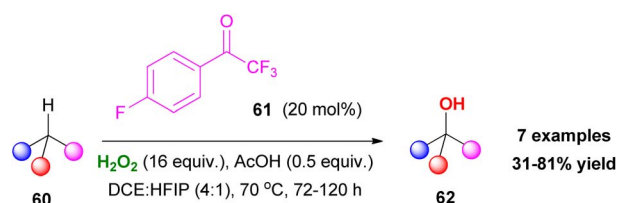
### Asymmetric epoxidation derived from catalyst–substrate interactions

As mentioned previously, the asymmetric epoxidation of alkenes is considered as a valuable tool in organic synthesis.



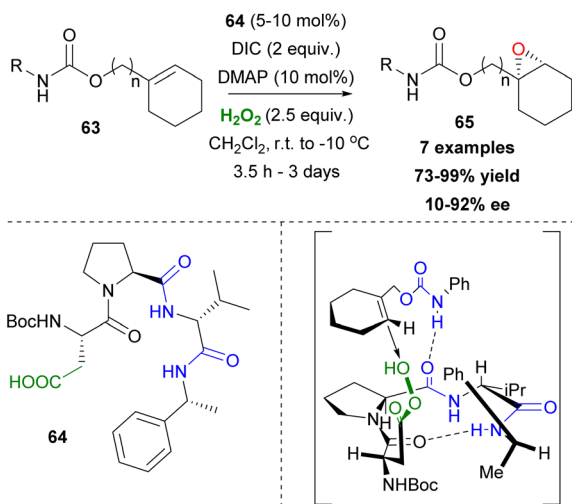
Scheme 14 Oxidation of tertiary allylic amines followed by a [2,3]-Meisenheimer rearrangement (additional arrangement for aromatic or conjugated aromatic allylic amines).

Miller and coworkers reported a series of contributions utilizing peptide-based carboxylic acids for the activation of hydrogen peroxide.<sup>41</sup> Previous work in this field,<sup>42</sup> led the authors to investigate a similar approach, utilizing the carboxylic residues in amino acids and peptides as potential catalysts.<sup>43</sup> Knowing that peracids are famous epoxidizing agents, the authors envisioned that Asp- or Glu-based peptides that have free carboxylic groups in their structure could serve as catalysts in asymmetric epoxidation through the formation of the peracid intermediate (Scheme 16). Eventually, the Asp-based catalyst **64** in the presence of hydrogen peroxide, following a peracid activation pathway, afforded the desired epoxide **65** (R = Bn) in good yield and enantioselectivity (Scheme 16). The substitution of the nitrogen atom of the carbamate moiety and its position regarding the double bond appears to be key factors to the resulting enantioselectivity. This is reasonable, considering the appropriate transition state, based mainly on the formation of hydrogen bonding that is capable of inducing an enantioselective approach of hydrogen peroxide onto the double bond of the alkene (Scheme 16). Miller's group exploited the carbodiimide strategy that is usually used in peptide synthesis to activate hydrogen peroxide.<sup>43</sup> Diisopropylcarbodiimide (DIC) enhances the electrophilicity of the catalyst, forming intermediate **67** and DMAP accelerates the oxygen atom transfer process, eventually generating the active electrophilic peracid intermediate **68** of the peptide catalyst (Scheme 17). Apart from its role in forming



Scheme 15 Hilinski's chemoselective C–H hydroxylation.

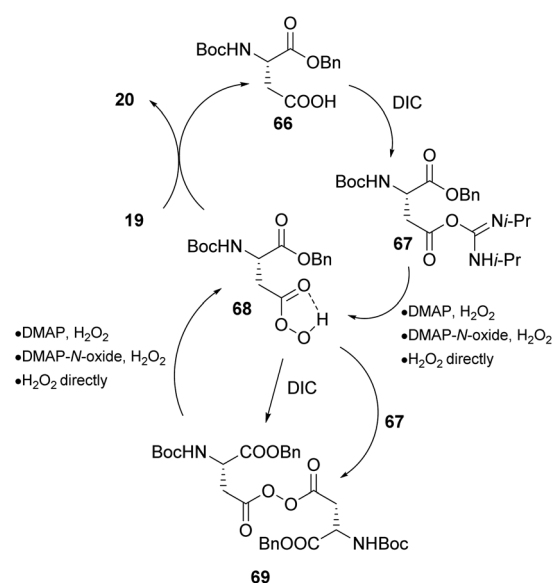




Scheme 16 Miller's asymmetric epoxidation.

intermediate **68**, DMAP also facilitates the perhydrolysis of intermediate **69**, promoting the productivity of the catalytic cycle (Scheme 17). To gain greater insight into the interactions that govern the enantioselectivity of the epoxidation reaction, the authors proceeded with various changes on the catalyst's backbone. Their experiments showcased that H-bonding interactions in the transition state induce enantioselectivity in the corresponding epoxides.<sup>44</sup>

In order to identify the appropriate peptide-based catalyst, Miller and coworkers developed a high-throughput screening strategy. The authors combined split-and-pool synthesis and one-bead-one-compound (OBOC) type libraries<sup>45</sup> to opt for the best catalyst towards the epoxidation of alkenes.<sup>46</sup> Based on this strategy, a number of resin-bound peptide catalysts bearing the Boc-Asp-Pro motif were employed for the selective epoxidation

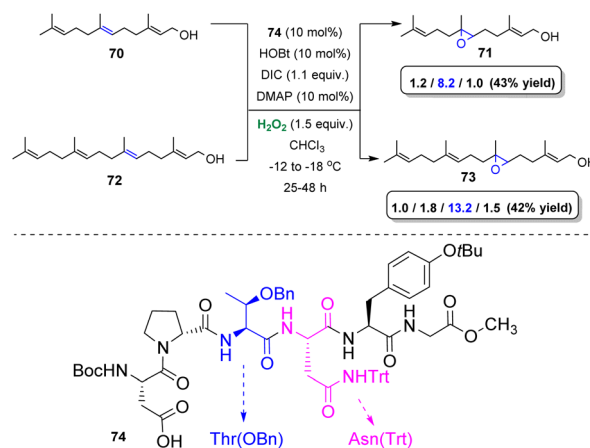
Scheme 17 Proposed mechanism using an Asp catalyst **66** following a peracid moiety **68** generation.

of polyenes, such as farnesol. The selective oxidation of such kind of substrates is considered an extremely challenging task in organic chemistry and it is mainly performed employing enzymatic catalysis.<sup>47</sup> After testing an enormous number of bead-bound peptides, an increased selectivity towards 2,3-epoxyfarnesol and towards 6,7-epoxyfarnesol was reported.<sup>47,48</sup> Ultimately,  $\beta$ -turns along with NH directing groups of Thr(OBn) and Asn(Trt) of catalyst **74** proved to be the directing factors of the observed 6,7-selectivity (Scheme 18). Substituting the hydroxyl-directing group of farnesol (methyl ether) altered the reported selectivity. Interestingly, replacing the bulkier Thr(OBn) amino acid by Ile in the structure of the catalyst **74**, according to the authors makes space for ether-directed epoxidation, providing promising regioselectivities. A few years later, Miller and coworkers based on the same strategy successfully assessed the basis of the 2,3-selectivity.<sup>49</sup> (*Z*)-Allylic alcohols proved to be the best candidates, in terms of yields and enantioselectivity, while the addition of Et<sub>3</sub>N in the reaction mixture, in some cases enhanced the outcome.

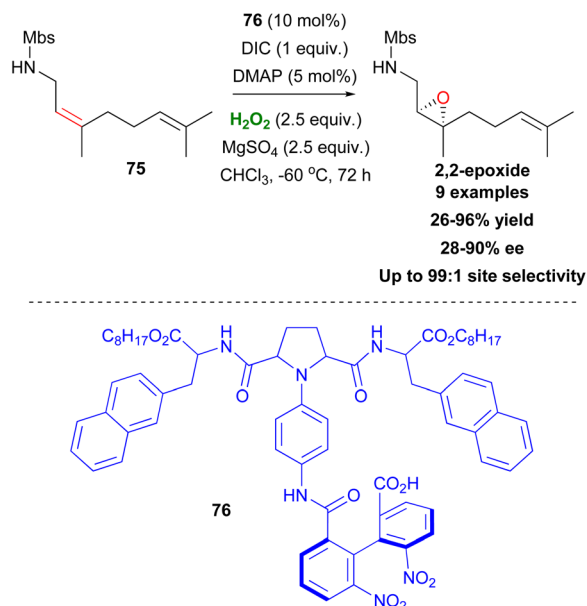
Inspired by Miller's studies, Kawabata proposed catalyst **76**, capable of site-selective asymmetric epoxidation of nerylamine derivatives, favouring the formation of 2,3-epoxides (Scheme 19).<sup>50</sup> According to the authors, site selectivity is controlled by the biphenyl moiety with an amide group of **76** and the pyrrolidine moiety being responsible for the enantioselectivity. Interestingly, substitution of the NHMbs group by *N*MeMbs leads to total inversion of site selectivity, favouring the 6,7-epoxides, instead. Using epoxidation conditions with *m*-CBPA as the oxidant, also led to 6,7-epoxidation. The presence of MgSO<sub>4</sub> as a drying agent was also important, as it removed the excess water produced by H<sub>2</sub>O<sub>2</sub>, which freezes at very low temperatures, leading to reduced yields (Scheme 19).

### Baeyer-Villiger oxidation

The Baeyer-Villiger oxidation is a very useful oxidative organic transformation,<sup>51</sup> which has attracted many research groups worldwide to develop more sustainable and easy-to-execute protocols. In 2008, Miller and coworkers envisaged that the

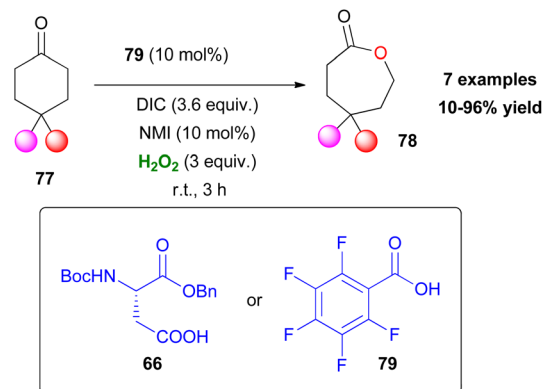
Scheme 18 Site selectivity of catalyst **74** towards 6,7-monoepoxides of farnesol and geranylgeraniol.



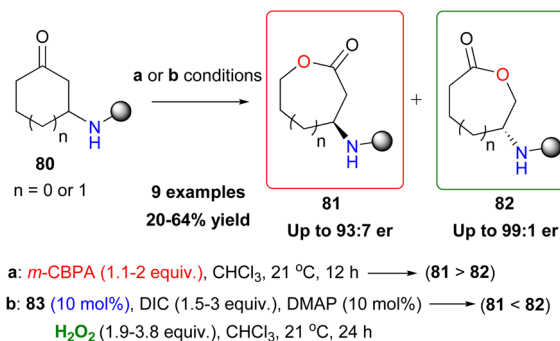


Scheme 19 Site selective asymmetric epoxidation of nerylamine derivatives.

same peracid catalytic route, which was previously reported, could be applied for a Baeyer–Villiger oxidation of ketones using hydrogen peroxide as the oxidant.<sup>52</sup> However, the major drawback in the process is the amount of the inactive diacyl peroxide **69** (Scheme 17), that is formed in the presence of DIC. This was successfully encountered in the epoxidation protocol, utilizing DMAP as the additive to promote its perhydrolysis. In the Baeyer–Villiger oxidation process, this drawback was circumvented by the slow addition of DIC, decreasing the formation of **69**. To avoid this, the authors envisaged that a more acidic catalyst such as pentafluorobenzoic acid **79** ( $\text{p}K_{\text{a}} = 1.74$  compared to catalyst **66**  $\text{p}K_{\text{a}} = 4.4$ ) will solve this issue as the formation of the lactone was attained in higher yields (Scheme 20). Even though asymmetric induction was not achieved at the time, the authors implied its possibility by testing catalyst **64**. Following their research, Miller and coworkers investigated the use of a peptide-based catalyst to achieve a more rigid transition state, inducing regio- and enantioselectivity. Applying their high throughput screening strategy, the authors turned their attention to catalyst **83** (Scheme 21).<sup>53</sup> Compared to *m*-CBPA, the selected peptide catalyst **83** showed increased affinity, towards the disfavoured reverse oxidation product (**81** vs. **82**) as depicted in Scheme 21. Even though the measured total yield was mostly mediocre in most substrates, the regioselectivity and enantioselectivity of reverse product **82** were favourable. According to the authors, these can be attributed mainly to the Pro groups in *i* + 1 and *i* + 3 positions of the catalyst and of course to the NH functional group attached to the substrate's structure, likely leading to H-bonding directing interactions. Further analysis regarding the conformations that catalyst **83** can exhibit in solution on its own or in the presence of the substrate or its respective favoured lactone product revealed a much more complex reason behind its catalytic behaviour. The importance



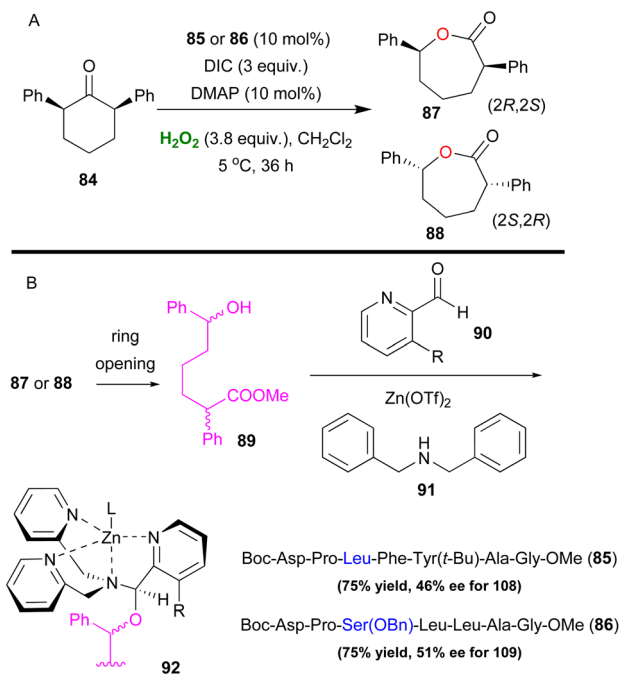
Scheme 20 Initial Baeyer–Villiger oxidation by Miller.



Scheme 21 Enantioselective and regioselective Baeyer–Villiger oxidation of functionalized ketones.

of *D*-Lys in the *i* + 2 position, regarding this behaviour, was also highlighted.<sup>54</sup> Substrates deprived of these directing groups are a special challenge in asymmetric induction, therefore this “uncharted” area was further explored by Miller, Anslyn and coworkers.<sup>55</sup> Screening a library of catalysts, which was composed solely of *L*-amino acids, the authors concluded that the use of two catalysts, one with a Leu in the *i* + 2 position (**85**) and one with a Ser(OBn) in the *i* + 2 position (**86**) favoured a different enantiomer formation, which was validated by HPLC and circular dichroism (CD) assays (Scheme 22A).<sup>56</sup> The latter method, which was on par with HPLC results, allowed not only for the rapid catalyst evaluation but also the analysis of the enantiomeric excess of alcohols, derived from the ring opening of the parent lactone products, which serve as ligands to zinc complex **92**, exhibiting characteristic Cotton effects<sup>56</sup> (Scheme





Scheme 22 (A) Unfunctionalized ketone enantioselective Baeyer–Villiger oxidation. (B) Analysis of absolute stereochemistry and enantioselectivity from the Zn-complex with CD arrays.

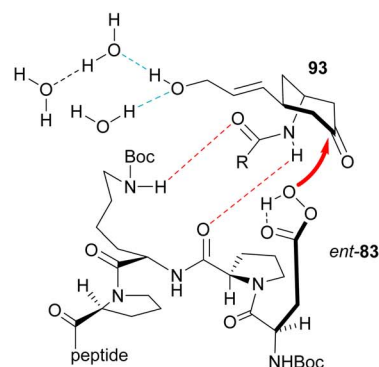
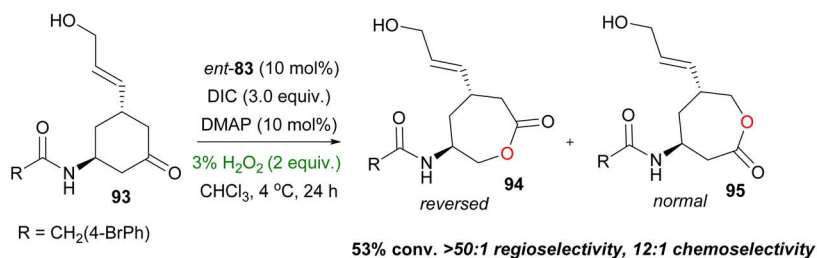
22B). The two peptide-based catalysts were found to induce an enantioselective Baeyer–Villiger oxidation. Catalysts containing Leu in the *i* + 2 position favoured the 2*R*,6*S*-lactone derivative

(87), while the 2*S*,6*R*-lactone derivative (88) was favoured in the presence of the Ser(OBn) catalyst. In both cases, it is believed thus, to proceed *via* a peptide-Criegee intermediate (Scheme 22B).

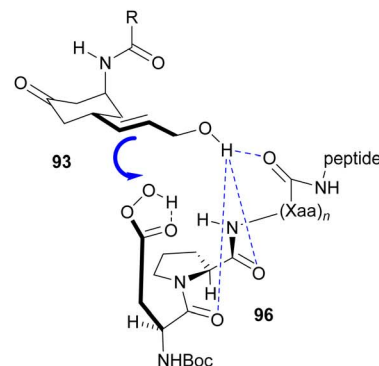
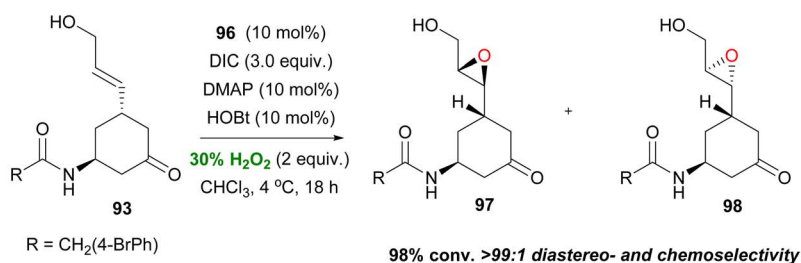
### Baeyer–Villiger oxidation vs. epoxidation reaction

In general, the most difficult task in organic chemistry is chemoselectivity. Biocatalysis, mainly, offers the opportunity to tune the chemical reactivity of the functional groups that appear in a molecule. In 2016, Miller and coworkers in a ground-breaking contribution synthesised bifunctional substrates that are susceptible to both Baeyer–Villiger and epoxidation and can exhibit orthogonal reactivity, depending on the peptide catalyst used.<sup>57</sup> The embedded aspartyl peracid moiety can serve as a nucleophilic or electrophilic oxidant and peptides **96** and **83** already showed their catalytic activity in directed epoxidation of allylic alcohols<sup>47</sup> and Baeyer–Villiger oxidation of functionalized ketones,<sup>53</sup> respectively (Scheme 23). When **96** was used in the presence of a free hydroxyl group, excellent regio- and diastereoselectivity can be obtained for the corresponding epoxide, with only traces of other undesired oxidation products (Scheme 23). While using catalyst **83**, the epoxidation product prevailed over the Baeyer–Villiger oxidation product and this was attributed to the stereochemical mismatch between **83** and substrate **93**. This speculation proved to be right since the use of *ent*-**83** afforded the desired chemoselectivity (Scheme 23). Further investigation of the reaction conditions led the authors to the conclusion that increasing the ratio of water, compared to H<sub>2</sub>O<sub>2</sub>, enhanced the

#### A. Amido Directed Nucleophilic Bayer Villiger Oxidation

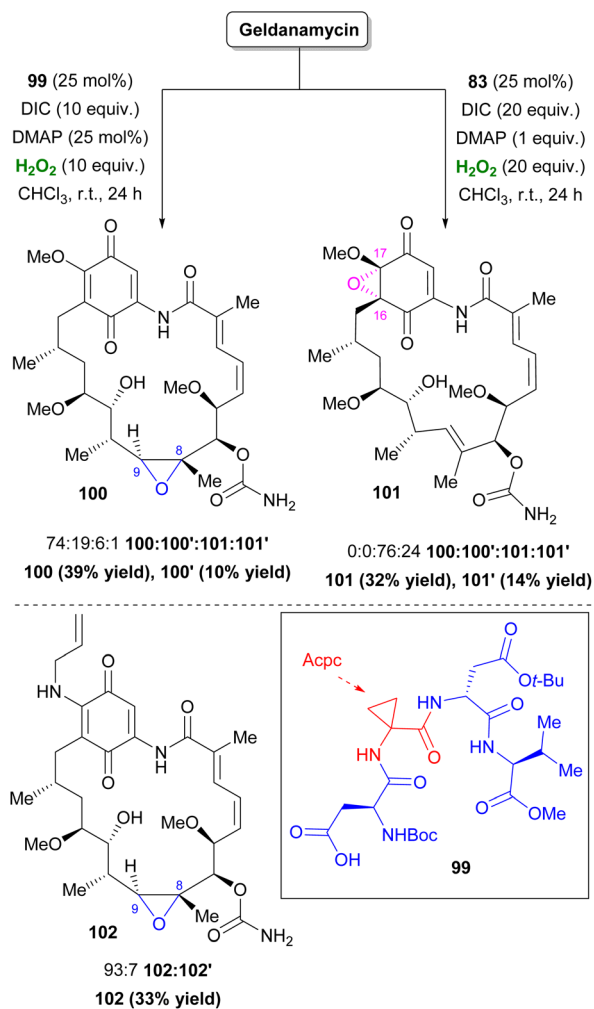


#### B. Alcohol Directed Electrophilic Epoxidation

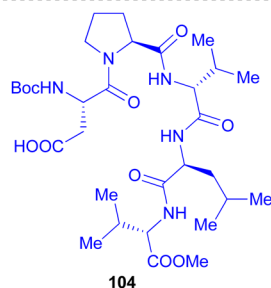
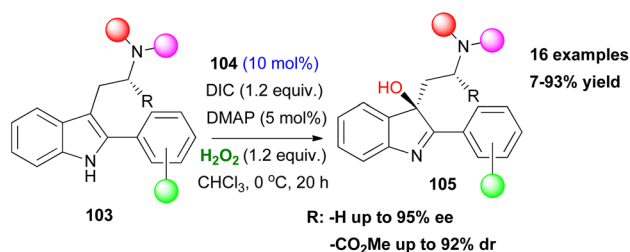


Scheme 23 Catalyst dependent chemoselective oxidations of bifunctional substrates using (A) *ent*-**83** or (B) **96**.





Scheme 24 Geldanamycin's chemoselective epoxidation.



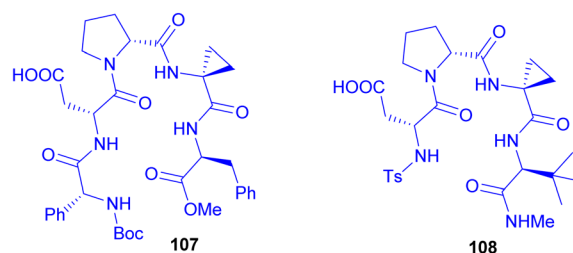
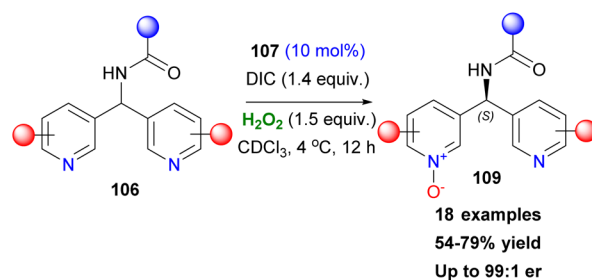
Scheme 25 Asymmetric oxidation of indoles to 3-hydroxyindolenines.

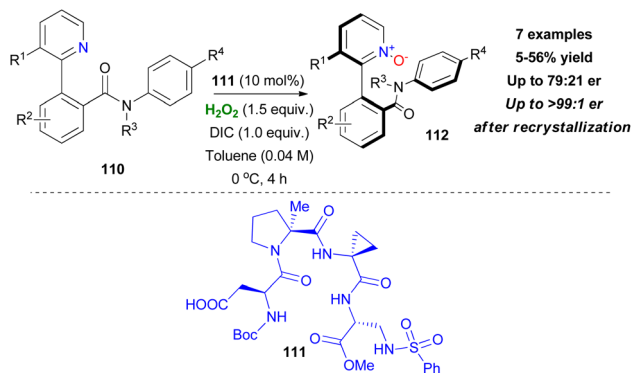
Baeyer–Villiger oxidation pathway on the free hydroxyl group substrate. Indeed, at the cost of reducing the yield (50–58%), water anchors the hydroxyl group with competing H-bonding, allowing the desired outcome (Scheme 23).

In 2020, Miller and co-workers incorporating their Asp-based peptide method, found two catalysts for the selective oxidation of Geldanamycin, a compound that inhibits the function of Hsp90 protein.<sup>58</sup> Catalyst **99** was selective towards 8,9-epoxide **100**, suggesting that  $\beta$ -turn conformation allowed interaction of the carbamate in C7 with the  $i + 1$  Acpc group of **99**. On the other hand, catalyst **83**, which previously showed potential in nucleophilic Bayer–Villiger oxidation, favored an unprecedented quinone epoxidation in the 16,17-position (**101**) (Scheme 24).<sup>59</sup> A truncated study revealed that, in this case, Asp–Pro is mainly responsible for this outcome. In contrast, this was not repeated with simpler quinones. Tanespimycin or 17-AAG, an improved Geldanamycin analogue, exhibited similar behavior using catalyst **99**, providing **102** with elevated selectivity (Scheme 24).

### Applications of the Asp–peracid oxidation

After the successful application of Asp peptide-based catalysts in oxidation protocols, such as the asymmetric epoxidation and Baeyer–Villiger oxidation, Miller and coworkers attempted to expand the general affinity of the aspartyl peracid route in other oxidative transformations. Their first attempt was focused on the selective oxidation of indoles, which is considered important, due to the existence of the indole moiety in a variety of natural products. In 2011, in collaboration with Movassaghi, they investigated indole oxidation under the already known reaction conditions.<sup>60</sup> After screening the peptide catalyst used, not only diastereoselective oxidation of tryptophan-based indoles **103** was at hand, but also enantiomeric induction of achiral scaffolds was introduced (Scheme 25). Interestingly, the presence of other free indole or NH-groups in the structure did not dampen the pre-established chemoselectivity, excluding the

Scheme 26 Desymmetrisation of bis(pyridines) by *N*-oxidation.

Scheme 27 Stabilisation of the atropisomeric axis by *N*-oxidation.

need for protecting groups. Seeking more potential candidates that might undergo an oxidative transformation, Miller and coworkers studied the oxidation of a series of substituted pyridine scaffolds.<sup>61</sup> Desymmetrisation of bis(pyridines), with a H-bonding group strategically placed in a pro-stereogenic center was achieved by peptide-based catalyst **107**, after catalyst screening employing the OBOC method (Scheme 26).<sup>61</sup> It needs to be clarified that these molecules can function as co-catalysts as depicted in Scheme 26, rendering the use of DMAP unnecessary. Substitution at the 6,6'-position of the substrates proved vital for inducing excellent enantioselectivity. To showcase the advantages offered by this protocol, the authors performed several derivatization experiments, highlighting the utility of the formed *N*-oxides **109**. Furthermore, application in scaffolds resembling medicines, like Loratadine or Varenicline, exhibited promising results in terms of generality of the current method. In the same vein, Miller and coworkers expand their protocol proposing a chemoselective *N*-oxidation that leads to asymmetric induction in pyridyl sulfoximines employing catalyst **108**.<sup>62</sup>

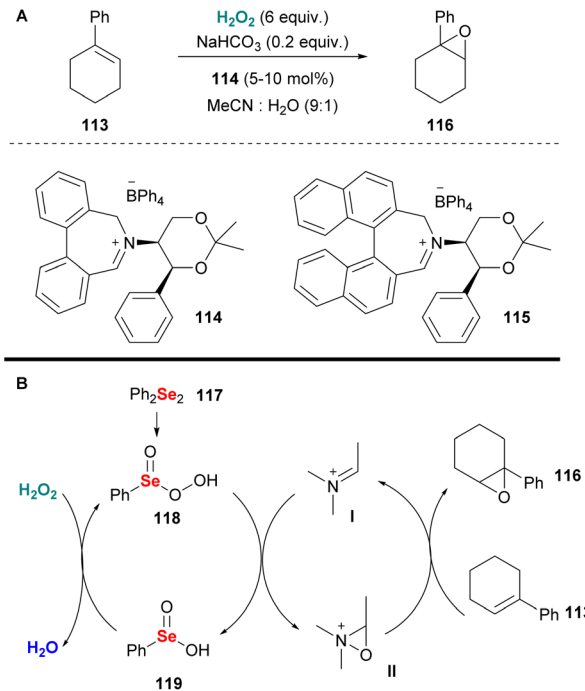
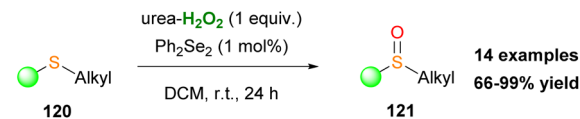
The most recent work of Miller's group focuses on stabilisation of stereogenic axis centres *via* *N*-oxidation with catalyst **111** (Scheme 27).<sup>63</sup> Trisubstituted biaryl scaffolds with substitution in the 3-position of the pyridine moiety prevented the unwanted racemization, which occurs by rotation of the axis, to some extent.

The proton of the amide group was necessary in terms of selectivity for catalyst–substrate interactions, however at the risk of racemization. Even though the reaction conditions were optimized for enantiomeric excess and atropisomeric stability, an inevitable protonation of the pyridine moiety by various potential proton sources in the reaction mixture seemed to influence the reaction outcome eventually. However, recrystallization of the final product provided enantiomeric enrichment (Scheme 27).<sup>63</sup>

## Organocatalytic activation of hydrogen peroxide with iminium salts

### Applications of iminium salts in organic oxidations

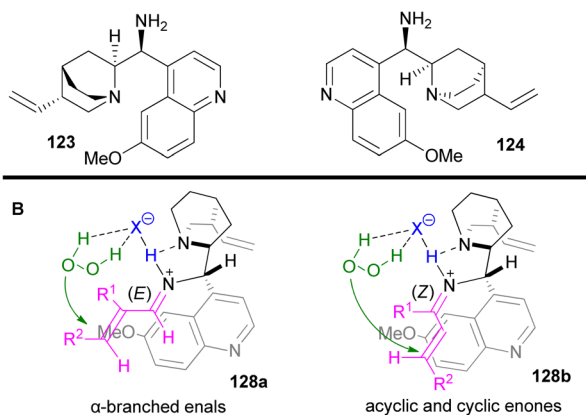
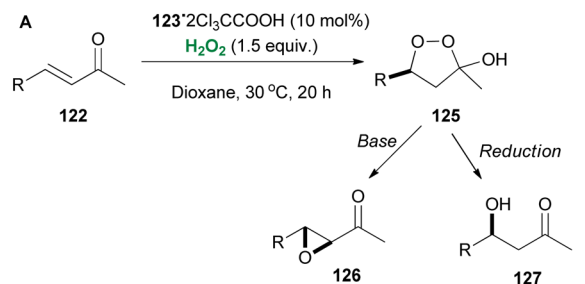
Since 1976, when Lusinchi first reported the use of iminium salts as potential organocatalysts in asymmetric epoxidations,<sup>64</sup>

Scheme 28 (A) Olefin epoxidation employing catalyst **114**. (B) Catalytic cycle with the use of diselenide **117** as the co-catalyst.

Scheme 29 Sulfide oxidation protocol by Page and coworkers.

many researchers introduced a plethora of iminium salt catalysts. Page and coworkers were among the first to introduce a series of iminium salt catalysts, based on the tetrahydroisoquinoline scaffold decorated with a chiral substituent on the nitrogen atom.<sup>65</sup> Having successfully employed these novel organocatalysts in alkene epoxidation, employing Oxone as the oxidant, the authors investigated the use of other potential oxidants, aiming at high enantioselectivity. Therefore, hydrogen peroxide was employed as an alternative eco-friendly oxidant. The authors opted for sodium bicarbonate as the optimum base to promote the epoxidation of 1-phenylacetylene, minimizing the background reaction (Scheme 28A). Additionally, they examined the effect of the reaction parameters (temperature, co-solvent, base *etc.*) and reported a plausible double mechanistic scenario, where the base might act either as a base or a peroxidophore, providing a useful guide for future attempts. Unfortunately, this elegant organocatalytic protocol suffers from low enantioselectivity and only 1-phenylcyclohexene was tested. To address this drawback and increase the enantioselectivity of the epoxidation process the authors, inspired by Santoro's and Du Bois' work<sup>66</sup> exploited diphenyl diselenide **117** as the co-catalyst.<sup>67</sup> This novel oxidation system generates benzeneperseleninic acid **118**, which oxidises iminium salt **I**,



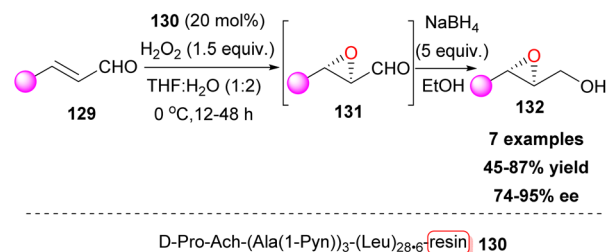


Scheme 30 (A) Peroxide formation and its applications. (B) Proposed transition states from List and coworkers.

facilitating the enantioselective oxygen transfer as depicted in Scheme 28B. With these reaction conditions, Page and coworkers achieved higher enantioselectivities, increasing the reaction rate.<sup>67</sup>

Following their research in oxidative protocols, employing hydrogen peroxide as the oxidant, Page and coworkers applied Du Bois' reaction conditions<sup>66b</sup> towards sulfide oxidation.<sup>68</sup> This contribution provides easy access to sulfoxides **121**, avoiding the formation of sulfone (Scheme 29). Nevertheless, this protocol cannot be used, when sulfide's substituents are decorated with a double bond.

Iminium catalysis has been employed not only towards the hydrogen peroxide activation but also towards the substrate activation, inducing an oxidation reaction. Ground-breaking contributions by Jorgensen<sup>69</sup> and MacMillan<sup>70</sup> introduced this feature as a powerful strategy for the enantioselective epoxidation of  $\alpha,\beta$ -unsaturated carbonyl compounds. Many researchers employed this strategy in oxidation reactions.<sup>71</sup> In 2008, pioneering the field of enantioselective catalysis,<sup>72</sup> List and coworkers developed an elegant asymmetric hydroperoxidation protocol of  $\alpha,\beta$ -unsaturated ketones **122**, employing Cinchona alkaloid derivatives **123** or **124** as the catalysts (Scheme 30).<sup>73</sup> In this contribution, the authors reported easy access to enantiopure peroxyhemiacetals **125**, intermediates of great importance in natural product synthesis, using hydrogen peroxide as the oxidant. These versatile intermediates provided easy access to enantiopure epoxides **126** or alcohols **127**, upon workup. In this contribution, the main problem faced by the authors appeared to be the substrate scope, since aromatic and trisubstituted enones proved to be unreactive (Scheme 30).

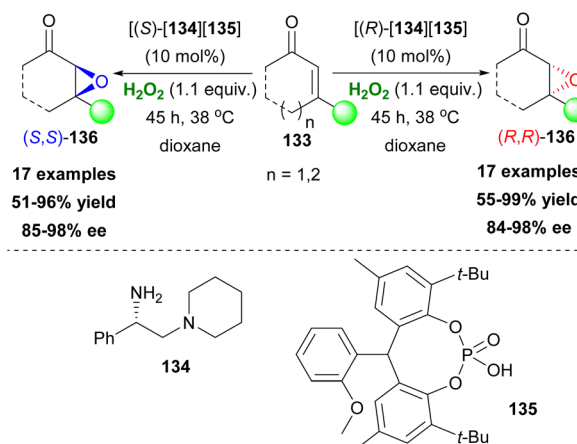


Scheme 31 Resin-bound peptide catalyst for asymmetric epoxidation of  $\alpha,\beta$ -unsaturated cinnamaldehydes.

In a later study, the same group managed to expand the substrate scope even more with some alterations in the reaction conditions, thus including acyclic enones, cyclic enones and  $\alpha$ -branched enals. Through extensive research, the authors also proposed possible transition states (**128a** and **128b**) that explain the observed stereoselectivities (Scheme 30B).<sup>74</sup>

Knowing that asymmetric induction in aqueous media is more challenging compared to organic solvents, Kudo and coworkers envisaged a resin-bound peptide that provided a hydrophobic microenvironment.<sup>75</sup> To this end, peptide catalysts with a resin-supported poly-Leu chain, that adopt an  $\alpha$ -helix structure, were tested in search of novel catalytic sequences for the enantioselective epoxidation of  $\alpha,\beta$ -unsaturated cinnamaldehydes **129**, which were subjected to reduction afterwards. After a thorough screening, peptide catalyst **130** emerged, capable of three reuses without loss of enantioselectivity (Scheme 31). Other cinnamaldehydes and some aliphatic aldehydes also yielded high stereo- and enantioselectivities.

After a novel study proposed by List,<sup>76</sup> combining iminium and Brønsted acid catalysis for the nucleophilic epoxidation of  $\alpha,\beta$ -unsaturated ketones, Schröder and coworkers<sup>77</sup> tested a series of chiral diamines and flexible phosphoric acids in search of a new counteranion pair for this reaction (Scheme 32). Diamine **134** and phosphoric acid **135** proved to be an excellent pair in ether-like solvents, with dioxane being the optimum,



Scheme 32 Phosphoric acid and diamine synergistic effect in the asymmetric epoxidation of enones.

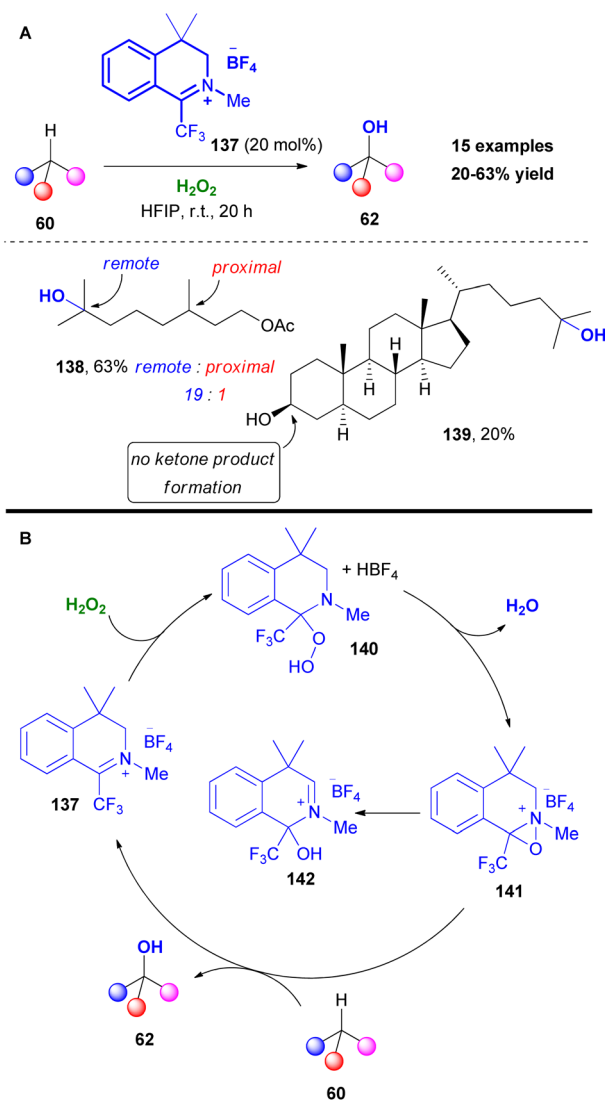


since its low dielectric constant and its miscibility with  $\text{H}_2\text{O}_2$  facilitated high enantioselectivity and yield, respectively. More in-depth investigation revealed that these ion-paired catalysts behave as one stereoisomer making their antipode counterpart accessible, and therefore employing one “stereoisomer” each time led to stereochemical control of the final product **136** (Scheme 32). The substrate scope was extended to cyclic and some acyclic enones with excellent enantioselectivities. Eventually, this robust catalytic system was successfully expanded to other asymmetric transformations in the same work.

### Applications of iminium salts in the C–H hydroxylation reaction

Another challenging task, which attracted the researchers' interest, is the chemoselective C–H bond hydroxylation. The increased number of contributions in the literature, including numerous late-stage functionalizations of complex molecules, pointed out the importance of this useful transformation. Based on the reaction output and inspired by Du Bois' work,<sup>66b</sup> Hilinski and coworkers, investigated the use of oxaziridinium salts in C–H hydroxylation reactions.<sup>78</sup> Initially, the authors unsuccessfully used Page's catalyst,<sup>79</sup> in the presence of hydrogen peroxide as the oxidant (Scheme 33). Slight modification in the catalyst's core afforded promising results. It must be mentioned that the catalytic activity of **137** was enhanced in the presence of a *gem*-dimethyl substitution at the benzylic position, which prevented the possibility of aromatization and *N*-methyl substitution. Furthermore, the use of HFIP was essential, since it is known to activate hydrogen peroxide. The authors reported higher selectivity for hydroxylation of 3° C–H bonds that are remote to an electron-withdrawing group, compared to what is known in the literature. This effect can be attributed to the solvent effect, since HFIP has the ability to deactivate potential reactive sites *via* hydrogen bonding. Testing their protocol in a series of substrates, the authors noticed that C–H hydroxylation took place in the presence of a primary or secondary alcohol.

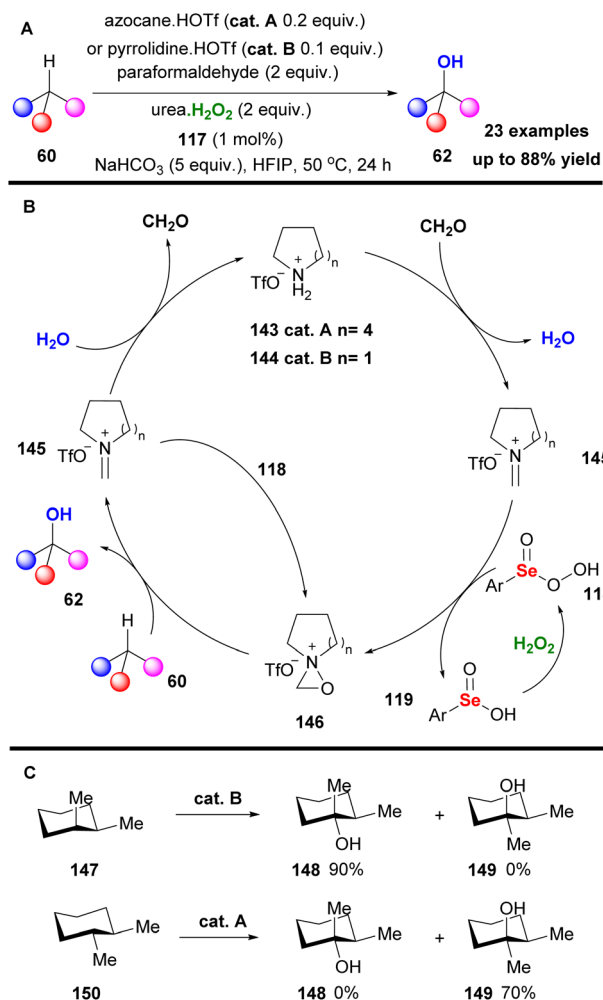
Contrary to what is stated in the literature, this protocol promoted the hydroxylation of unactivated secondary C–H bonds, minimizing the overoxidation pathway (Scheme 33A). To probe the reaction mechanism, Hilinski and coworkers conducted NMR studies, verifying the formation of oxaziridinium salt **141**, proposing the mechanism depicted in Scheme 33B. Initially, addition of hydrogen peroxide onto catalyst **137** liberates fluoboric acid, forming intermediate **140**. The acidic environment promotes the formation of the oxaziridinium salt **141**, which reacted with substrate **60**, delivering the desired product. Following their continuous interest in C–H hydroxylation reactions, Hilinski and coworkers acknowledging the advantages offered by iminium ion catalysis, envisaged the *in situ* generation of an oxaziridinium salt, combining a secondary amine, a ketone or aldehyde and an oxidant.<sup>80</sup> This concept was elegantly employed by Yang and coworkers in epoxidation reactions.<sup>81</sup> The authors performed a series of optimisation experiments identifying azocane triflate salt and para-formaldehyde as the starting material for the imine synthesis,



Scheme 33 (A) C–H hydroxylation by Hilinski and coworkers. (B) Catalytic cycle of C–H hydroxylation.

1,2-bis(3,5-bis(trifluoromethyl)phenyl)diselane **117** as the peroxide promoter and urea- $\text{H}_2\text{O}_2$  as the oxidant (Scheme 34A). With these conditions in hand, excellent chemoselectivity and site selectivity were acquired, along with high yields. In many cases, including rigid substrates, pyrrolidine triflate salt **144** afforded the highest yield. This protocol was successfully tested in a vast substrate scope, affording excellent results in remote chemoselectivity. Furthermore, it was found to be effective in late-stage functionalization and was successfully tested in a gram scale reaction. According to the proposed mechanism, the *in situ* formed iminium salt reacts with the perselenic acid **118** to deliver oxaziridinium salt **146** (Scheme 34B). Then, the active oxidant performs the C–H hydroxylation. Since the hydroxylation reaction of **60** is governed by the formation rate of intermediate **145**, the size of the secondary amine is believed to play a prominent role in the reaction mechanism (Scheme 34B). Furthermore, the authors investigated the stereospecificity of the reaction. For this reason, *cis*- and *trans*-1,2-

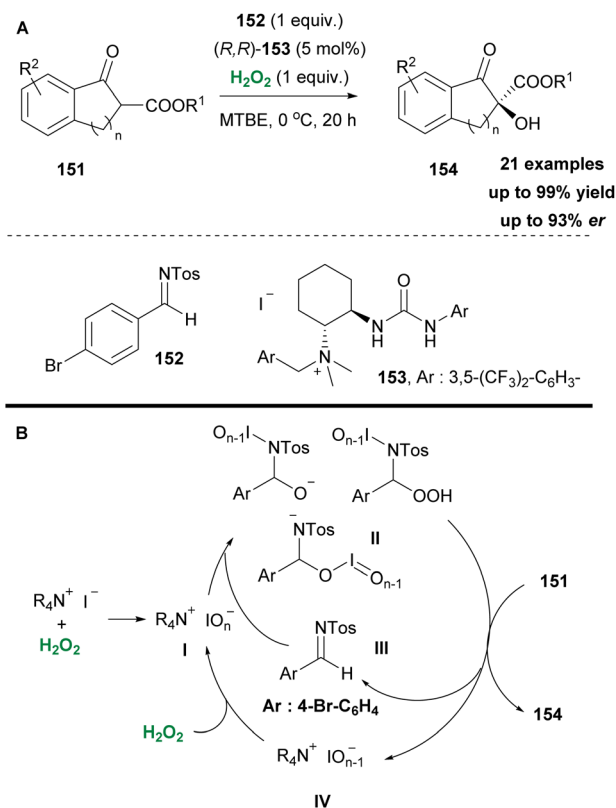




Scheme 34 (A) C–H hydroxylation employing the *in situ* generated iminium salt **145**. (B) Studies on the retention of stereochemistry. (C) Hydroxylation of cyclohexanes.

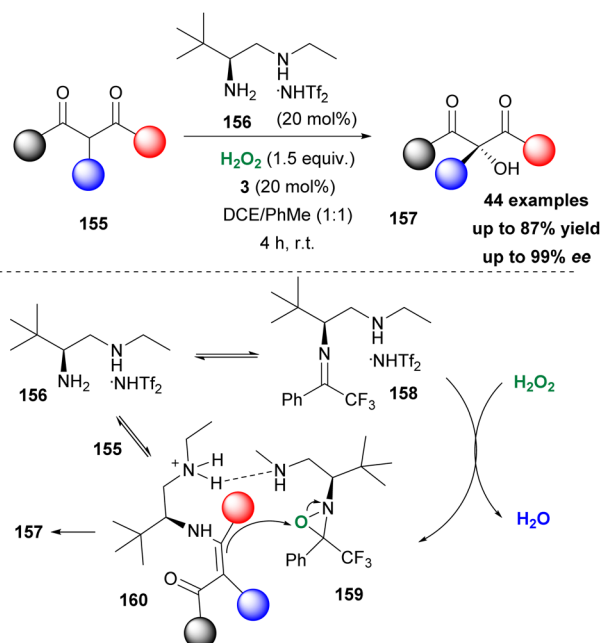
dimethylcyclohexane were employed, showing complete retention of stereochemistry (Scheme 34C).

In the same vein, Waser and coworkers few years earlier based on their previous work,<sup>82</sup> enriched by Ooi's contributions to asymmetric oxaziridine synthesis,<sup>83</sup> envisioned a straightforward asymmetric  $\alpha$ -hydroxylation of  $\beta$ -ketoesters *via* an *in situ* generation of oxaziridine (Scheme 35A).<sup>84</sup> A series of investigations to obtain the optimum reaction conditions revealed the crucial role of the counter anion, which proved to be responsible for the hydrogen peroxide activation, instead of the formation of an oxaziridine intermediate. This was elegantly reported in the past by Ishihara and coworkers.<sup>85</sup> Based on previous reports in the literature, in their mechanistic scenario the authors supported the formation of iodine hypervalent species **I**, upon interaction of hydrogen peroxide with ammonium iodide (Scheme 35B). This species reacts with imine **152** to form an unknown oxidant partner **II**, which actually promotes asymmetric hydroxylation (Scheme 35). It is supported by the authors that hypervalent species **II**, apart from their role in reacting with the imine **152**, also behave as the base to



Scheme 35 (A) C–H hydroxylation protocol by Waser and coworkers. (B) Catalytic cycle.

deprotonate  $\beta$ -ketoesters **151**. Based on their finding, iodide is necessary as the oxidizable counter-anion, since bromide afforded mediocre results. A good substrate scope was evaluated



Scheme 36 Dual amine/ketone organocatalytic activation of hydrogen peroxide.

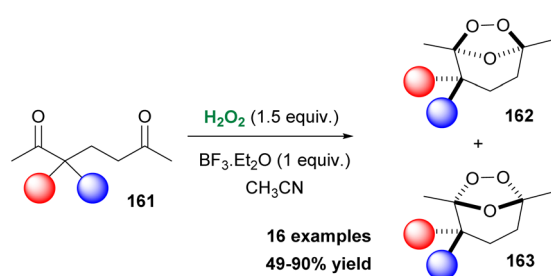


with excellent results. Nevertheless, regarding the realistic mechanistic approach, more experiments should be performed.

Recently, Zhang, Luo and coworkers reported a dual amine-ketone cooperative catalysis for the asymmetric  $\alpha$ -hydroxylation of keto-compounds (Scheme 36).<sup>86</sup> Screening a number of primary-secondary diamines, the authors opted for amine **156** as the optimum partner for ketone **3** to afford an excellent organocatalytic system. Hydrogen peroxide was identified as the oxidant of choice. A vast variety of substrates was tested affording the desired hydroxylated derivatives in good to excellent yields with high enantioselectivities. Not only  $\beta$ -keto-esters but also  $\beta$ -keto-amides afforded excellent results. The authors performed several mechanistic studies (DFT calculations and HRMS experiments) to probe a plausible mechanistic pathway. In their proposal, amine reacts in the acidic environment (induced by  $\text{NHTf}_2$ ) to form iminium salt **158**. The latter in the presence of hydrogen peroxide forms oxaziridinium salt **159**, which transfers an oxygen atom to enamine **160** to deliver the desired product. As depicted in Scheme 36, amine **156** has a dual role, as it forms the active oxidant and at the same time forms enamine **160**, upon reaction with **155**, facilitating the oxidation reaction.

### Use of hydrogen peroxide to form endoperoxides and their applications in oxidation reactions

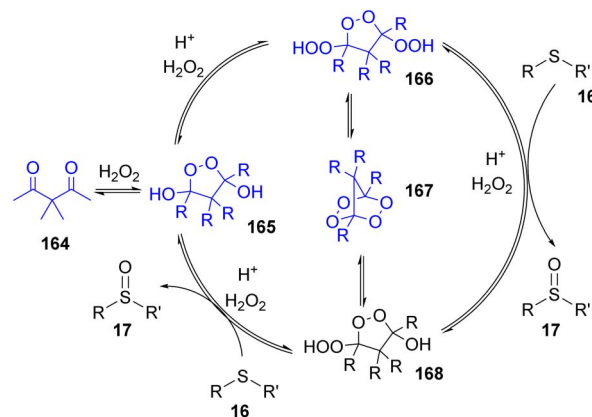
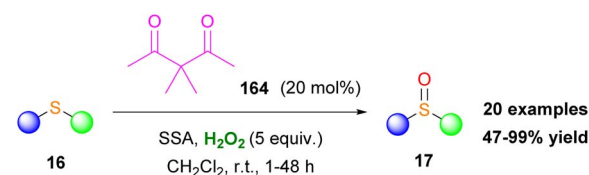
Over the past decade, many researchers acknowledged the great importance of endoperoxides in modern synthetic chemistry, as well as in medicinal chemistry. Organic peroxides are found in many natural products and compounds of medicinal interest, exhibiting anticancer, antimalarial and antiviral activity. In 2015, a naturally-occurring product, Artemisinin, was recognized by the Nobel Prize in Medicine as an antimalarial agent.<sup>87</sup> Furthermore, peroxides derived from ketones find excellent application as radical initiators in polymer production.<sup>88</sup> As a consequence, many synthetic approaches have been reported, providing access to various classes of peroxides. Additionally, in the past years, many efforts have been made, targeting also the synthesis of azaperoxides. In 2018, Alabugin, Terent'ev and coworkers reported an excellent study on ozonide synthesis from 1,5-diketones, employing hydrogen peroxide as the oxidant.<sup>89</sup> The major advantage of this study, compared to what already existed in the literature, is the one-step formation of ozonides without the formation of other peroxides or even oxidized by-products. To probe the optimal reaction conditions,



Scheme 37 Ozonide synthesis.

the authors employed diketone **161** as the model substrate (Scheme 37). Hydrogen peroxide was found to be the reagent of choice, while  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  as the catalyst (0.5 equiv.) provided the highest yield of products (95%), along with a modest selectivity towards **162**. This oxidative protocol exhibited high functional group tolerance. A variety of 1,5-diketones decorated with electron-withdrawing or electron-donating groups afforded ozonides in good to excellent yields (Scheme 37). It must be mentioned that compounds bearing a double or a triple bond remained intact and the authors did not mention the formation of by-products, derived from epoxidation reactions or other oxidative pathways. The authors performed a series of computational studies to probe the thermodynamic stability of the product. The efficient stability of the formed ozonides under several reaction conditions might find excellent application as potential protecting groups.<sup>89</sup>

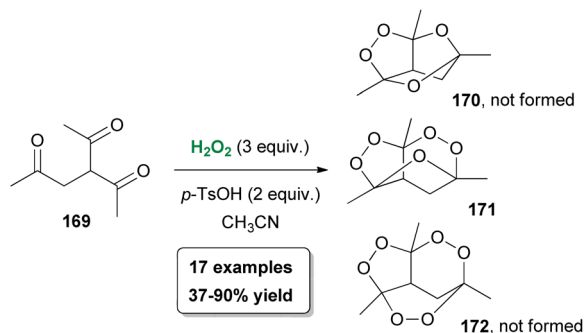
In a more recent study, Tomkinson and coworkers employed peroxides to achieve organocatalytic sulfoxidation.<sup>90</sup> Specifically, the authors examined a series of diketones, like **164**, as catalysts, along with silica-sulfuric acid (SSA) as an effective recyclable co-catalyst (Scheme 38). The presence of  $\alpha$ -hydrogens, between the two carbonyls, reduces their electrophilicity and therefore renders the catalyst less effective. A variety of sulfides **16** were applied to this protocol. Electron-rich sulfides required faster reaction times, while sulfides with bulky groups required longer reaction times. Oxidizable and acid sensitive groups remained intact. The proposed catalytic cycle in Scheme 38 involves the formation of three important peroxides (**165**, **166** and **167**) in equilibrium, confirmed by single X-ray analysis. X-ray analysis demonstrated the *trans*-relationship of the exocyclic oxygen substituents in the intermediates **165** and **166**. The active species is peroxide **166**, which can oxidize two different



Scheme 38 Tomkinson's sulfoxidation and proposed mechanistic scenario.



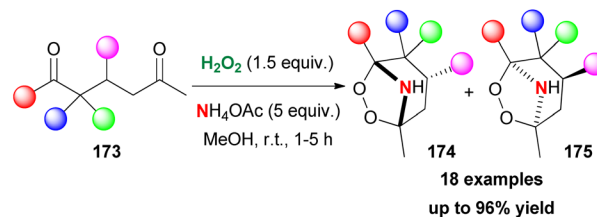


Scheme 39 Oxidation of substituted triketones **169**.

molecules of sulfide, leading to peroxide **168** and eventually returning to **165** (Scheme 38).

A few years later, following their interest in peroxide chemistry, Alabugin, Terent'ev and coworkers reported the use of hydrogen peroxide towards the synthesis of oxygen-rich tricyclic heterocycles.<sup>91</sup> Based on their previous findings, the authors exploited triketones **169**, which are considered flexible precursors, as the starting materials providing theoretical access to oxygen-rich structures **170–172** (Scheme 39). For this purpose,  $\beta,\gamma'$ -triketones **169** were used, due to their capability of forming more easily a peroxide bridge. A series of optimization experiments provided the optimum conditions, where *p*-TsOH·H<sub>2</sub>O was identified as the appropriate Lewis acid. Under the optimal reaction conditions, bis-peroxide derivative **171** was obtained in high yield as the sole product, while neither the monoperoxide **170** nor the tris-peroxide analogue **172** was formed. In the presence of a substituent at the  $\alpha$ -position, along with the formation of the bis-peroxide derivative, the formation of the monoperoxide **170** also took place. In their effort to broaden the scope of the peroxidation protocol, the authors proved that in the presence of excess hydrogen peroxide, monoperoxides can be converted into bis-peroxide analogues. Despite the complexity of the structure, the bis-peroxide derivatives were found to be stable. Computational and mechanistic studies provided a plausible mechanism for this oxidative process.<sup>91</sup>

Having developed a series of contributions towards the synthesis of organic peroxides, Alabugin and Terent'ev turned their attention to implementing their protocols in the synthesis of azaperoxides, a family of compounds whose synthesis was unexplored at the time.<sup>92</sup> For this purpose, 1,5-diketones as the starting materials, hydrogen peroxide and a nitrogen group source were employed. Contrary to their previous studies, in this case, the presence of a Lewis acid was not necessary. 1,5-Diketone **173**, in the presence of hydrogen peroxide and 22% aqueous NH<sub>3</sub> in MeOH, led to the formation of two azaozonides **174** (kinetically controlled product) and **175** (thermodynamically controlled product) as shown in Scheme 40. Ammonium acetate was opted as the nitrogen source. A variety of substrates was tested with excellent results. But, the presence of an ester group led to the formation of a dihydropyridine ring, due to the enolization that takes place initially. The authors performed experiments, excluding the possible formation of azaozonides



Scheme 40 Synthesis of azaozonides.

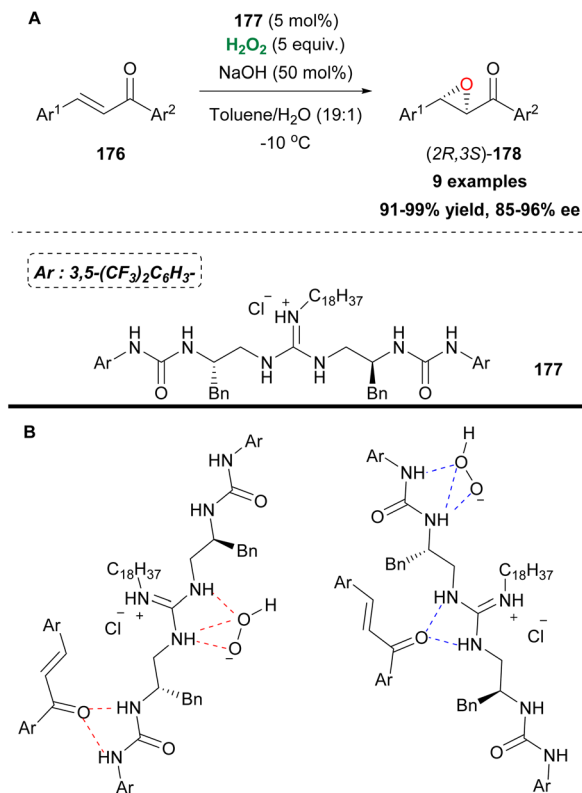
from the reaction of the ammonium salt with the ozonides. Based on computational studies, the authors proposed a mechanistic scenario involving initial addition of the NH<sub>2</sub> group to the carbonyl group. A series of condensation steps led to the formation of the desired product. With these results in hand, they also investigated the access to more complex molecules. Employing  $\beta,\beta'$ -triketones as the starting materials, the authors reported a protocol *en route* to bridged tricyclic azaperoxides.<sup>93</sup> Despite the structural complexity, the formed products showed excellent stability. The main mechanistic proposal involves the addition of hydrogen peroxide and the formation of peroxy-hemiacetals or peroxy-hemiaminals.

#### Activation of hydrogen peroxide by various organic molecules

Since hydrogen peroxide is considered as a green oxidant, many researchers turned their attention to alternative ways for its activation. For this purpose, a vast variety of organic molecules has been employed, targeting the activation of hydrogen peroxide. Julia, Colonna and coworkers pioneered the field reporting a series of publications employing poly-amino acids, activating chalcones *via* hydrogen bond formation promoting asymmetric epoxidation.<sup>94</sup> In the context of this review, we will not discuss the activation of hydrogen peroxide employing pyrazinium flavinium salts or artificial flavin systems, since these two categories are already discussed in an elegant review article by Cibulka.<sup>95</sup>

Small organic molecules can activate hydrogen peroxide *via* the formation of hydrogen bonds, enhancing its electrophilic nature. Guanidine-based catalysts have been explored in asymmetric epoxidations presenting mediocre results. Nagasawa and coworkers designed a bifunctional catalyst, combining the guanidine motif with a urea functional group (Scheme 41). Since urea is known to activate hydrogen peroxide and based on the ability of both functional groups, attached to the catalyst, to interact with either hydrogen peroxide or chalcones *via* hydrogen bonding, they developed an elegant protocol for the asymmetric epoxidation of 1,3-diarylenones **176** (Scheme 41A and B).<sup>96</sup> The authors identified compound **177**, decorated with a long alkyl chain on the guanidine group, to improve the catalytic activity in a biphasic system, as the catalyst of choice (Scheme 41A). The 3,5-bistrifluoromethyl groups attached to the phenyl group proved to have a positive impact, regarding the enantioselectivity of the oxidation process. Additionally, the catalyst can be easily reused without any significant loss of the catalytic activity. A variety of substituted chalcones were tested, affording excellent yields and high

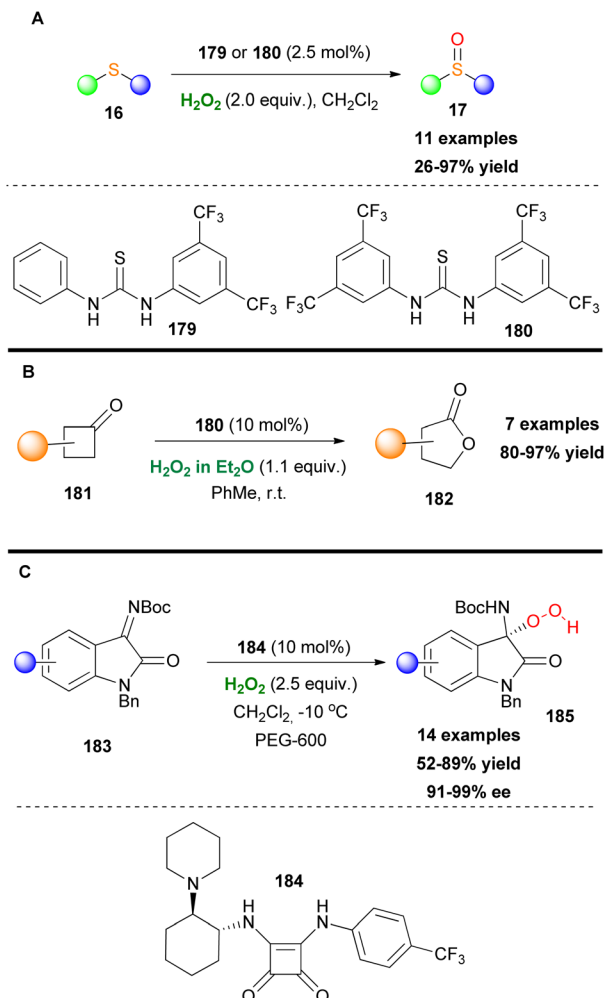




Scheme 41 (A) Epoxidation employing bifunctional catalyst **177**. (B) Hydrogen bond formation leading to the desired product.

enantioselectivities. Recently, another bifunctional urea catalyst was introduced for the synthesis of chiral glycidic ester derivatives, with a quinidine scaffold, providing high yields and enantioselectivities, due to its bulky *t*-butyl group.<sup>97</sup>

In the same line with Nagasawa, Cai and coworkers designed recyclable thiourea organocatalysts, decorated with 3,5-bis-fluoromethyl groups, and employed them towards the chemoselective oxidation of sulfides (Scheme 42A).<sup>98</sup> The novel thiourea-based catalysts demonstrated excellent functional group tolerance and were reused up to five times without any significant loss of reactivity. Another interesting use of thiourea-based catalysts was reported by Kotsuki and coworkers, in 2012.<sup>99</sup> Based on hydrogen bond formation between the thiourea-based catalyst, hydrogen peroxide and the cyclobutanone scaffold, the authors developed a novel efficient Baeyer–Villiger oxidation protocol of cyclobutanones **181**. Despite this elegant procedure which is taking place under mild reaction conditions the authors did not study the possible enantioselective pathway (Scheme 42B). Another well-known class of compounds with excellent catalytic activities are squaramides. The nitrogen-substituted cyclobutenodione core resembles the active center of the urea catalyst. Liu and Li used an acid–base bifunctional chiral squaramide **184** as the chiral organocatalyst to enhance the nucleophilicity of H<sub>2</sub>O<sub>2</sub> (Scheme 42C).<sup>100</sup> Initially, these hydroperoxide products were unstable in the reaction mixture and prone to dimerization. The authors speculated that a crowding environment of hydrogen bonding



Scheme 42 (A) Sulfide oxidation induced by thiourea-based catalysts. (B) Baeyer–Villiger oxidation of cyclobutanones. (C) Organocatalytic activation of hydrogen peroxide by squaramides.

provided by an additive could stabilize and facilitate their isolation. Polyethylene glycols (PEGs) specifically PEG-600 served that purpose. A study of the substrate scope showed great tolerance of this method when various functional groups were present on the aryl ring and replacement of the Boc group with the 1-adamantylloxycarbonyl group (Adoc). Noteworthy is the first enantioselective 1,2-hydroperoxidation of isatin-derived ketimines **183**.

Another category of organic molecules that can easily activate hydrogen peroxides through hydrogen bond formation is perfluorinated alcohols. The strong electron-withdrawing properties of the fluorine atom, combined with the ability of the hydroxyl group to form hydrogen bonds lead to an electrophilic activation of hydrogen peroxide. Based on this idea, Neumann and coworkers exploited 2,2,2-trifluoroethanol (TFE) and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) to promote the epoxidation of alkenes.<sup>101</sup> A series of cycloalkenes and terminal alkenes were tested, affording the corresponding epoxides in good to excellent yields. In the case of a tetrasubstituted alkene, the epoxidation proceeded sufficiently, but due to the acidic



conditions, ring opening followed by pinacol metathesis led to the formation of a ketone by-product. This protocol was furthermore applied successfully, towards the sulfide oxidation. 1,1,1,3,3,3-Hexafluoroisopropanol (HFIP) was also used by Bonnet-Delpon and coworkers to activate urea-hydrogen peroxide *via* hydrogen bonding in a catalytic epoxidation reaction.<sup>102</sup> The major concern derived from the use of perfluorinated solvents is their high toxicity. This problem led many scientists to find ways to reduce their use. Towards this direction, Berkessel and coworkers designed a series of dendritic fluorinated catalysts, aiming at reducing the amount of the solvent, and maintaining the local concentration of the fluoroalcohol in order to promote the oxidation reaction.<sup>103</sup> The authors prepared two hyperbranched polyglycerol-based HFIP derivatives, where the active fluoroalcohol group was determined to be 2.9 and 3.0 mmol per gram of catalyst. Both catalysts promoted the epoxidation reaction sufficiently using only 20 mol%. Open chain alkenes afforded moderate yields. The main advantage, derived from the use of those catalysts, appeared to be their potential recovery for multiple uses. Additionally, the authors employed the catalyst in the oxidation of thioanisole to the corresponding sulfoxide without the formation of sulfone. Despite this interesting finding, the scope of sulfides remained unexplored.

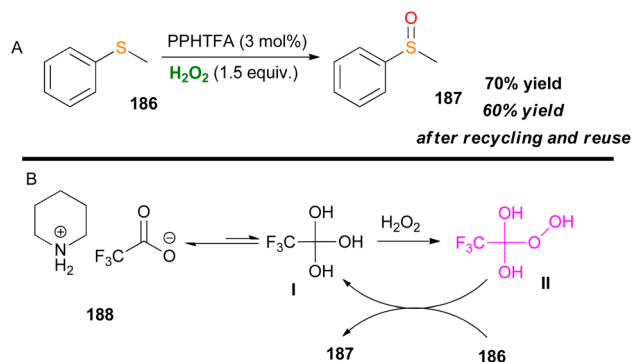
An interesting approach is the use of piperidinium trifluoroacetate (PPHTFA) ionic liquid as a catalytic activator of H<sub>2</sub>O<sub>2</sub> for the selective oxidation of thioanisole **186**, from Alnezhad and coworkers (Scheme 43).<sup>104</sup> After a series of mechanistic experiments, the proposed active species was a trifluoro hydroperoxy species **II** (Scheme 43B). Recycling and reuse of the ionic liquid gave a desirable outcome with total chemoselectivity to sulfoxide **187**. Higher temperatures gave room for overoxidation, which was also verified by DFT calculations.

A well-known family of compounds that are able to form hydrogen bonds and likewise might serve as potential activators of hydrogen peroxide are chiral phosphoric acids. Ding and coworkers were the first to introduce their use in an enantioselective Baeyer–Villiger oxidation in excellent yield and high enantioselectivity contrary to what was reported in the literature.<sup>105</sup> In their effort to optimize their preliminary results, they tested a variety of BINOL- and octahydroBINOL-derivatives to

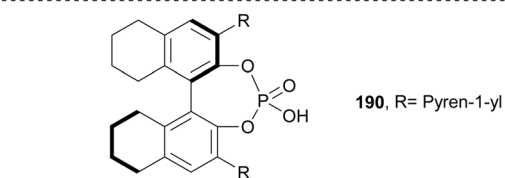
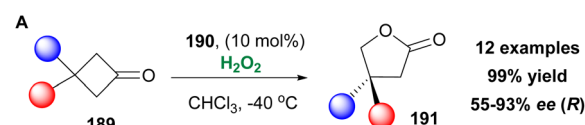
achieve higher enantioselectivities (Scheme 44). Chiral phosphoric acid **190** afforded the highest enantioselectivity, along with the highest yield. It must be mentioned that when the catalyst was washed with 4 N HCl and water prior to use, its catalytic activity was enhanced. The authors examined the good scope of 3,3-bissubstituted cyclobutanones **189**, which afforded the corresponding lactones **191** in excellent yields and up to 93% ee (Scheme 44).<sup>106</sup> The authors managed to showcase the capability of Brønsted acids to induce an asymmetric Baeyer–Villiger oxidation, though without providing any mechanistic details at the time. Two years later, the authors revisited the mechanism of the Baeyer–Villiger oxidation of 3-substituted cyclobutanones **189** and performed a series of mechanistic studies.<sup>107</sup> Their major conclusion derived from these studies was that the chiral phosphoric acid is capable of activating both the substrate, by increasing its electrophilicity, and hydrogen peroxide, by increasing its nucleophilicity, through the formation of hydrogen bonds (Scheme 44B).

Having established an elegant oxidation protocol, they expanded its use in a variety of bicyclic and tricyclic cyclobutanone derivatives, providing access to the synthesis of complex ester derivatives.<sup>108</sup> These ground-breaking contributions by Ding and coworkers found excellent application in the synthesis of prostaglandins. Inspired by Ding's work, Chen, Peng and coworkers employed the asymmetric organocatalytic Baeyer–Villiger oxidation to synthesize a generic lactone intermediate, which served as a versatile building block for the synthesis of prostaglandin derivatives in high enantiomeric purity.<sup>109</sup>

Another useful application of chiral phosphoric acids was reported by List and coworkers.<sup>110</sup> Acknowledging the great importance of chiral sulfoxides, they successfully utilize chiral phosphoric acid **192** in a highly enantioselective oxidative protocol, converting sulfides **16** into the corresponding sulfoxides **17** (Scheme 45A).<sup>110</sup> It is worth mentioning that the use of



Scheme 43 (A) Activation of H<sub>2</sub>O<sub>2</sub> by an ionic liquid catalyst. (B) Proposed reaction mechanism.



Scheme 44 (A) Baeyer–Villiger oxidation employing catalyst **190** by Ding and coworkers. (B) Proposed transition state.



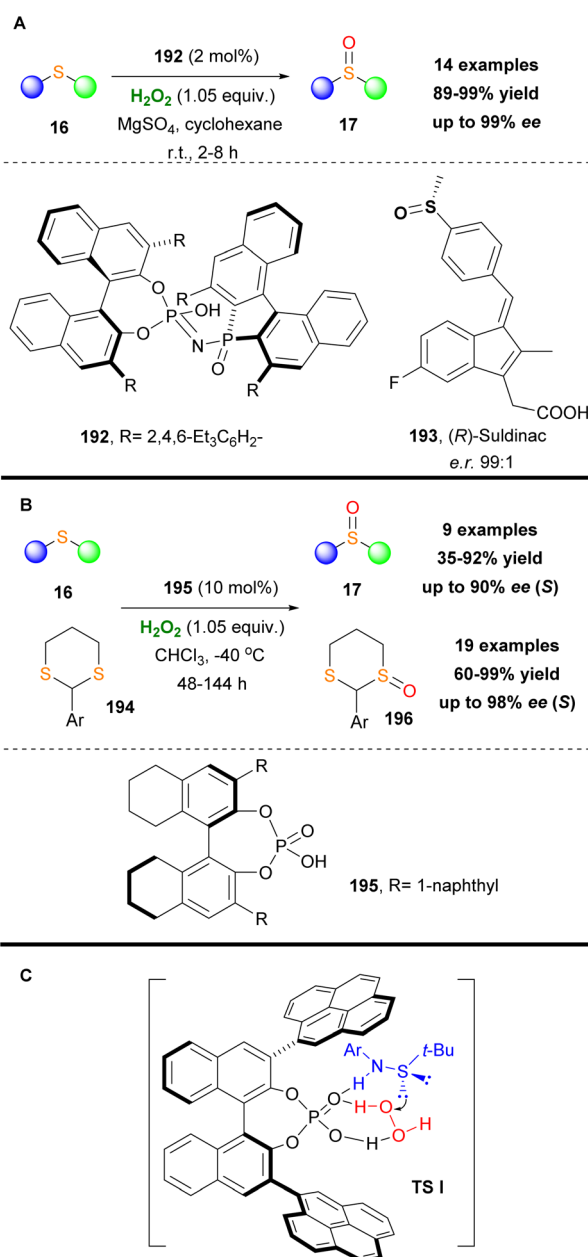
MgSO<sub>4</sub> to remove water from the reaction mixture led to significantly shortened reaction times. The enantioselective protocol was successfully applied to a variety of sulfides displaying excellent functional group tolerance. Additionally, it must be mentioned that the overoxidized sulfone byproduct was detected in low yields. The authors tested their enantioselective protocol in real-life applications synthesizing successfully, on a 4 g scale, in high yields and enantioselectivity the nonsteroidal anti-inflammatory drug Sulindac **193** (Scheme 45A).

Almost at the same period, Wang and coworkers reported a similar protocol, where chiral phosphoric acid **195** was found to be the optimum catalyst. In their contribution, the authors

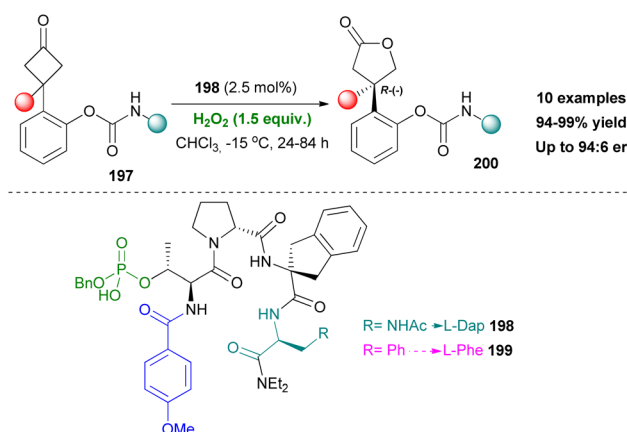
enriched the substrate scope, where apart from the use of sulfides, they applied their methodology towards the oxidation of 1,3-dithianes. Despite the fact that the oxidative protocol suffered from prolonged reaction times (up to 144 h), it was characterized by high yields and high enantioselectivities (Scheme 45B).<sup>111</sup>

Seeking more sulfur-containing molecules that can be easily oxidized, Tang and coworkers, in 2019, reported the asymmetric oxidation of sulfenamides, employing hydrogen peroxide as the oxidant.<sup>112</sup> The corresponding chiral sulfonamides are useful intermediates, leading to the synthesis of chiral sulfoxides and sulfenamides in high yields. The mechanistic scenario involves the formation of the transition state as depicted in Scheme 45C, where based on the formation of hydrogen bonding, the oxidation proceeds in high enantioselectivity. Similar to List's approach, also in this study, the use of MgSO<sub>4</sub> was an essential feature, since its dehydration activity does not allow water to destroy hydrogen bonding that is formed in the transition state.

In 2019, Miller's group established a new asymmetric Baeyer-Villiger oxidation method.<sup>113</sup> This time, however, the active group of the proposed peptide catalyst would be a pThr moiety instead of an Asp, introducing a different functionalisation for peptide catalysts. The authors began their investigation using unfunctionalized cyclobutanones, while screening various pThr-embedded peptides adopting  $\beta$ -turns. Initially, enantiomeric excess was not observed. Believing that the absence of an H-directing group in the substrate was behind this problem, carbamate functionality was once again added. This turned out to be half the solution to the problem, since the decision to incorporate L-Dap, as a side chain director in the *i* + 3 position, had a dramatic effect. Moreover, meddling on the *N*-terminus part, led to introduction of the electron-rich *p*-MeO-benzamide group, thus creating the optimal peptide catalyst **198** (Scheme 46). Catalyst **198** provided high enantioselectivity and yields, on *ortho*-carbamate substrates **197**. An interesting stereodivergence was observed when the position of the carbamate group of the substrate changed to *meta*- and *para*-. While the *ortho*-position provided the (*R*)-(-) absolute configuration, the other two favored the (*S*)-(+ configuration, which was

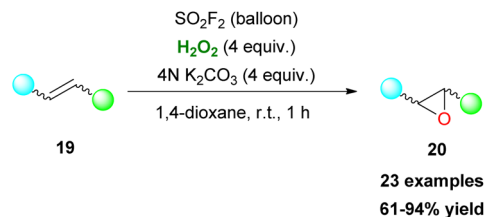
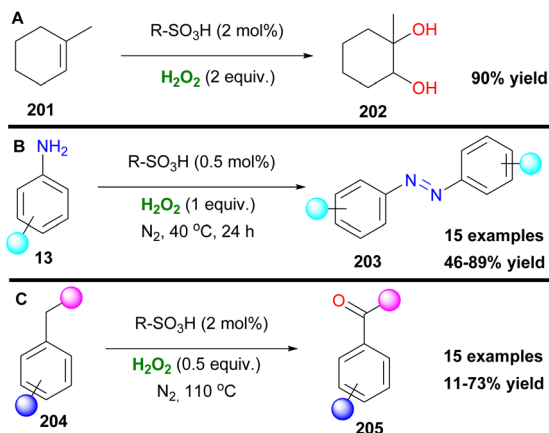


Scheme 45 (A) Sulfide oxidation by List and coworkers. (B) Sulfide and dithiane oxidation using catalyst **195**. (C) Oxidation transition state.



Scheme 46 pThr-embedded peptide catalysts for asymmetric Baeyer-Villiger oxidation.

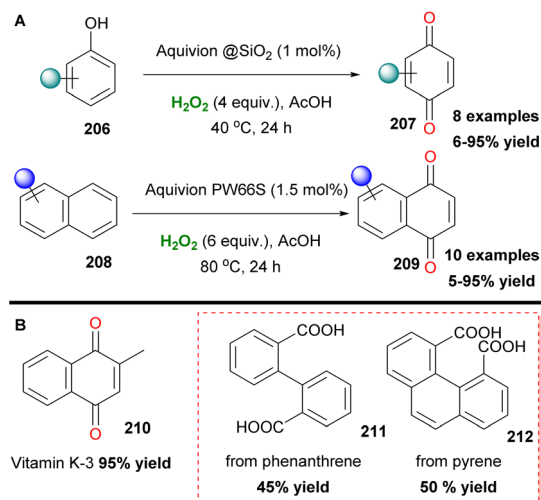


Scheme 47 SO<sub>2</sub>F<sub>2</sub>-mediated epoxidation of double bonds.

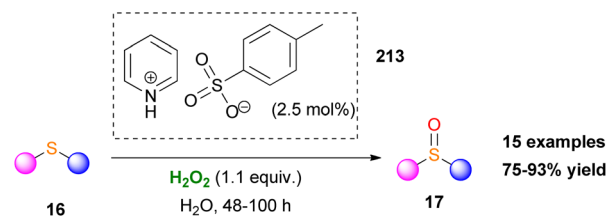
Scheme 48 Various oxidative transformations with sulfonic acids. (A) Dihydroxylation. (B) Synthesis of azobenzenes. (C) Oxidation to ketones.

validated by X-ray analysis. Noteworthy is the fact that changing the *i* + 3 position to Phe led to inversion of the absolute configuration in *meta*- and *para*-analogues ((*R*)-(-)). The authors concluded that while both **198** and **199** have the same conformation, **198** permits H-bonding interaction and **199** engages in steric repulsive interactions. This can very well mean that this protocol is mainly substrate-oriented, rather than catalyst-oriented.

Organosulfonic peracids, a family of unstable but potent oxidants, can be formed *in situ* from H<sub>2</sub>O<sub>2</sub> as depicted by Schulz and Kim for epoxidation reactions.<sup>114</sup> However, harsh reaction conditions and expensive or explosive reagents were required in these cases. In an effort to address these issues, Yan, Lin and coworkers proposed the use of the SO<sub>2</sub>F<sub>2</sub>/K<sub>2</sub>CO<sub>3</sub>/H<sub>2</sub>O<sub>2</sub> system for a cheap and mild activation of hydrogen peroxide.<sup>115</sup> This method works well in a variety of double bonds and has the potential for upscaling (Scheme 47). In the past few years, Maggi and coworkers have been interested in the use of various silica-supported sulfonic acid catalysts for mild oxidative transformations (Scheme 48) such as dihydroxylation of 1-methylcyclohexene **201** to diol **202** (Scheme 48A),<sup>116</sup> dimerization of anilines **13** to azobenzenes **203** (Scheme 48B)<sup>117</sup> and selective Csp<sup>3</sup> oxidation of benzylic methylenes **204** to aryl carbonyls **205** (Scheme 48C),<sup>118</sup> under neat reaction conditions, thus minimizing waste production. In their latest work, however, the authors employed a catalyst derived from Aquivinion, a commercially available polymer with sulfonic groups in side



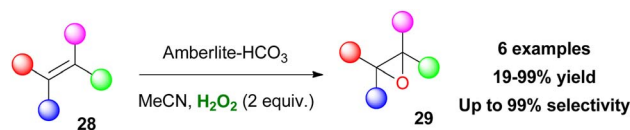
Scheme 49 (A) Dearomatization of phenols and polycyclic arenes and (B) selected examples.



Scheme 50 Air stable pyridinium salt catalyst for sulfoxidation.

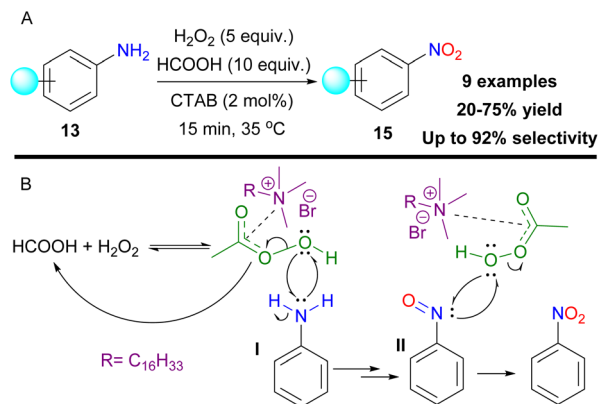
chains of a perfluorinated scaffold. The presence of a polar, water-soluble solvent was imperative for the effective dearomatization of phenols **206** to quinones **207** (Scheme 49A).<sup>119</sup> In order to incorporate naphthalenes **208** and some polycyclic arenes in this method, re-optimisation of the reaction conditions led to an unsupported polymeric sulfonic acid as the catalyst and an increase of the oxidant and temperature (Scheme 49A). Vitamin K<sub>3</sub> **210** was successfully retrieved almost quantitatively from 2-methylnaphthalene (Scheme 49B). Moreover, electron-poor substrates were not suitable in any case, while phenanthrene and pyrene were oxidatively cleaved giving **211** and **212**, respectively (Scheme 49B).

In another study, sulfonic acids have been applied as counteranions in metal-free ammonium and pyridinium salts.<sup>120</sup> Employing catalyst **213**, various aromatic and aliphatic sulfides were selectively oxidized to sulfoxides in high yields. However, long reaction times were needed and any attempt to induce



Scheme 51 Application of quaternary ammonium bicarbonate catalysts in olefin epoxidation.





Scheme 52 (A) Aniline oxidation by *in situ* generated performic acid and (B) proposed reaction mechanism.

enantioselectivity was fruitless (Scheme 50). Quaternary ammonium bicarbonate catalysts have also been utilised for epoxidation reactions. Mielby and Kegnæs applied an easily accessible and recyclable heterogenous Amberlite-bicarbonate catalyst that provided promising epoxidation yields and selectivities (Scheme 51).<sup>121</sup> It was suggested that epoxidation possibly occurs by a peroxycarboximidic acid intermediate, since acetamide was detected as a by-product, along with a bicarbonate-activation of  $\text{H}_2\text{O}_2$  as Yao and Richardson proposed.<sup>122</sup>

In an effort to selectively oxidize anilines **13** to nitro compounds **15**, Birada and colleagues used formic acid and hydrogen peroxide to generate performic acid as the active oxidant (Scheme 52A).<sup>123</sup> To maintain the desired selectivity, the authors used cetyltrimethylammonium bromide (CTAB), a cationic surfactant, that stabilizes aniline **I** and the nitroso intermediate **II**, by inducing radical pathways (Scheme 52B) and short reaction times. 4-Nitro and halogen-substituted anilines could not maintain desirable selectivity. The authors also concluded that the aromatic ring is mandatory to activate the oxidation.

## Conclusions

The progress in the field of organocatalysis achieved from 2000 until today has been one of the major landmarks in organic chemistry and offered unique opportunities to researchers in academia and industry. The use of small organic molecules that can activate either the substrate or the reagents, promoting fundamental organic transformations was highly appreciated. Organocatalysis offers an alternative and more sustainable approach, replacing metal-based catalysts, developing environmentally benign procedures, and reducing the overall cost of the synthetic route. Since hydrogen peroxide and its derivatives are considered as green oxidants, organocatalysis found excellent application in oxidative organic transformation. From the literature illustrated in this review, asymmetric epoxidation, Baeyer–Villiger oxidation, oxidation of sulfides, amines, silanes *etc.* were thoroughly investigated by the use of a variety of organocatalysts, which were able to activate hydrogen peroxide.

In particular the field of peptide-based catalysts provides numerous different approaches in the area of asymmetric oxidation and will continue to do so in the future. Few examples of C–H activation–oxidation have been reported, but this field remained unexplored. We strongly believe that this field is still promising and future efforts will target the induction of enantioselectivity. The rational design of the catalysts offered the possibility of asymmetric induction. The oxidation of double bonds was thoroughly investigated, applying a variety of organocatalysts. Despite the plethora of contributions in the literature, there is still space for novel organocatalytic (asymmetric) epoxidation of unfunctionalized alkenes. Furthermore, there are applications, where the organocatalysts are embedded in a solid support, providing the opportunity of its reuse or recycling. Overall, the area of organocatalysed oxidation with green oxidants, like hydrogen peroxide, is demonstrating rapid progress in both quantitative and qualitative respects. The future for the development of organocatalytic protocols activating hydrogen peroxide seems to be bright.

## Author contributions

E. T. P., P. L. G. and I. T. prepared the first draft of the manuscript and C. G. K. performed the final editing. The manuscript was written through contributions of all authors.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

The authors gratefully acknowledge the Hellenic Foundation for Research and Innovation (HFRI) for financial support through a grant, which is financed by 1st Call for H.F.R.I. Research Projects to Support Faculty Members & Researchers and the procurement of high-cost research equipment grant (grant number 655).

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