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Recent developments in stereoselective organocatalytic oxyfunctionalizations

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Abstract:
In this chapter, asymmetric at carbon oxidations using organocatalytic systems reported from 2012 up to 2018 have been illustrated. Asymmetric epoxidations and oxidation of heteroatom-containing molecules were not included. The processes selected encopass alpha-hydroxylation of carbonyl compounds, dihydroxylation and dioxygenation of alkenes, Baeyer-Villiger and oxidative desymmetrization reactions.

Keywords: asymmetric oxidation, organocatalysis, green chemistry
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1 Introduction

The area of asymmetric oxidations is one of the most actively investigated by organic chemists, being, the introduction of "oxygen-containing groups" and changing the oxidation state of functional groups and atoms onto a molecule, fundamental and recurrent transformations [1]. The development of these processes in a stereoselective fashion is often prompted by the need to produce chiral molecules, which are ubiquitous in the industry, e. g. pharmaceuticals, agrochemicals, food products, materials science to cite the most relevant. Over the years, the attention of the synthetic community steadily increased toward the development of environmentally-sustainable and convenient to apply processes of asymmetric oxidation [1]. In this endeavor, an important place is occupied by the organocatalytic oxidative methods, which have two major advantages: (1) use of readily available catalysts, often derived from natural sources, (2) mild and manageable reaction conditions, which overcome product contamination problems, associated to residual metal traces, typical of metal-catalysis [2]. Several methodologies are available to stereoselectively oxyfunctionalize organic molecules by catalytic metal-based systems, whereas the organocatalytic tool can be considered still underdeveloped. The aim of the chapter is to highlight the progress achieved from 2012 to 2018 in fundamental stereoselective at carbon oxidation reactions, where the introduction of oxygen atom(s) onto the molecule has been achieved by using organocatalytic systems. Recent reviews and book chapters reported on organocatalytic asymmetric epoxidation and sulfoxidation reactions [1c, 3], which are amongst the most developed. Accordingly, they will not be included, as well as oxidative coupling and dearomatization reactions. The processes selected encopass α-hydroxylation of carbonyl compounds, dihydroxylation and dioxygenation of alkenes, Baeyer–Villiger (BV) and oxidative desymmetrization reactions.

2 α-Oxygenation of carbonyl compounds

α-Oxygenated carbonyl compounds are a common motif in biologically active natural products or pharmaceuticals. The direct stereoselective α-oxygenation of carbonyl compounds promoted by organocatalysts represents a powerful strategy for the construction of optically active α-oxygenated targets and, in the field of asymmetric organocatalysis, chiral H-bonding catalysts and phase-transfer ion-pairing catalysts are extremely useful.

2.1 α-Hydroxylation

In a pioneering work on the enantioselective hydroxylation of 3-substituted-2-oxindoles with molecular oxygen, the Itoh's group [3] demonstrated that the cinchonidine-derived phase-transfer catalyst **1** accelerated the

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reaction considerably (Figure 1). High chemical yields and moderate to good enantioselectivities were obtained, above all by using 4 equiv of triethyl phosphite as additive to reduce the peroxide intermediate, even though the examples reported were restricted to oxindole.

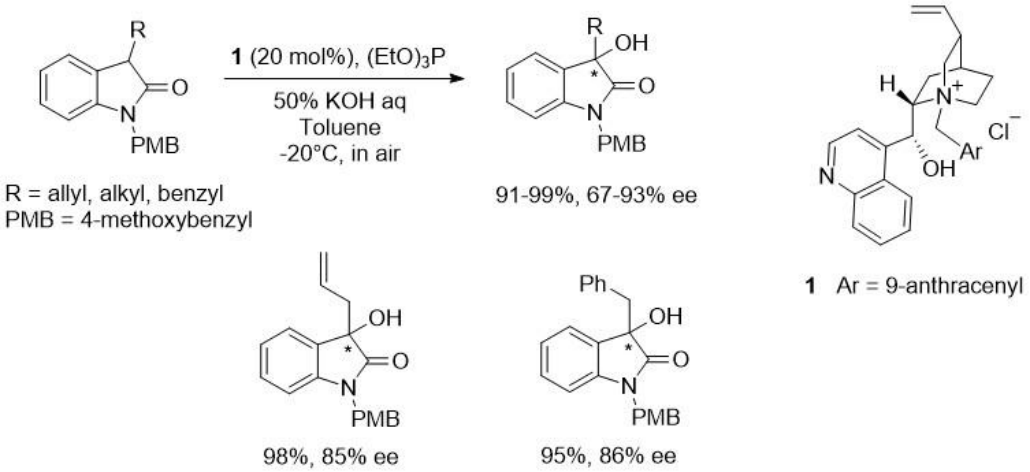

Figure 1: Catalytic asymmetric hydroxylation of oxindoles by using a phase-transfer catalyst.

More recently, the use of the cinchona alkaloid-derived dimeric phase-transfer catalyst **2** has been reported by Zhao and co-workers in the oxidation of acyclic as well as cyclic ketones [4], affording α-hydroxylated products in high yields and good stereoselectivities using molecular oxygen (Figure 2). Different solvents and P-based additives were screened and the best results were obtained by using 1,2-bis(diphenylphosphino)ethane (DPPE) as reductant.

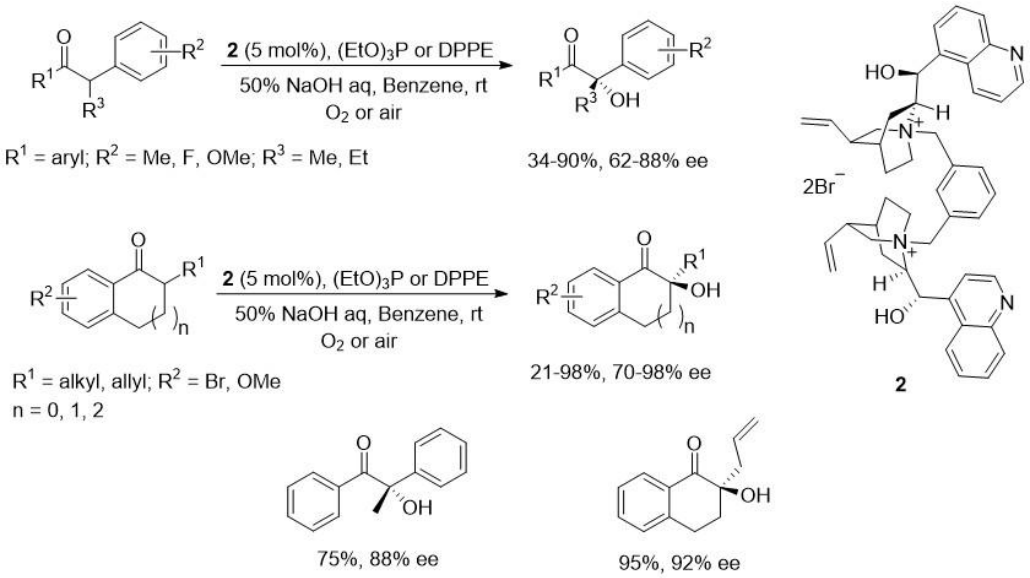

Figure 2: Asymmetric α-hydroxylation of acyclic and cyclic ketones by using a phase-transfer catalyst.

Molecular oxygen has also been used as an efficient oxidant in the enantioselective α-hydroxylation of 2-oxindoles catalyzed by pentanidiums as phase transfer catalysts. Contrary to all previous reports, in this methodology no reductant (triethyl phosphite or DPPE) was required (Figure 3) [5]. Several 3-hydroxyl-2-oxindoles were obtained with excellent enantioselectivities (86–98 % ee) and the authors proposed a two-step mechanism for the reaction: the enantioselective formation of hydroperoxide oxindole controlled by pentanidium, followed by its kinetic resolution, *via* reduction by the enolates of 3-substituted-2-oxindoles *in situ* generated under the basic reaction conditions. Under the same reaction conditions, the amount of hydroperoxide oxindoles obtained was related to the amount of molecular oxygen used in the reaction as well as to the addition of a strong inorganic base such as NaOH or KOH (Figure 3) [6].

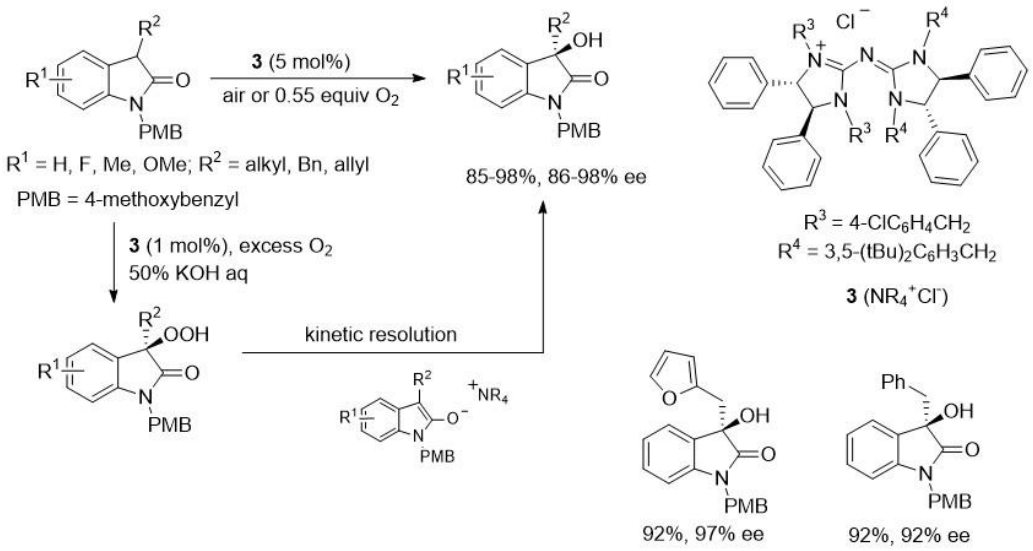

Figure 3: Pentanidium-catalyzed enantioselective α-hydroxylation of oxindoles with O_2.

As a further development of the strategy promoted by chiral phase-transfer catalysts using molecular oxygen as oxidant, Meng and co-workers explored the photo-oxygenation of β-keto esters under mild conditions [7]. The effect of different light sources was evaluated, as well as the influence of different sensitizers on the reaction process (Rose Bengal, methylene blue, tetraphenylporphyrin TPP). The optimized conditions depicted in Figure 4 were applied to a range of substrates and the products were isolated in high yields and moderate ees. Moreover, the free OH group at the C9 position of the organocatalyst proved to be fundamental for the enantiocontrol. The authors provided evidence of the involvement of $^1O_2$ in the hydroxylation process and proposed a plausible mechanism for the reaction (Figure 4). They also reported a different methodology for the α-hydroxylation of β-keto esters through catalysis by methylhydrazine and cinchona alkaloid, using O_2 as the oxygen source.

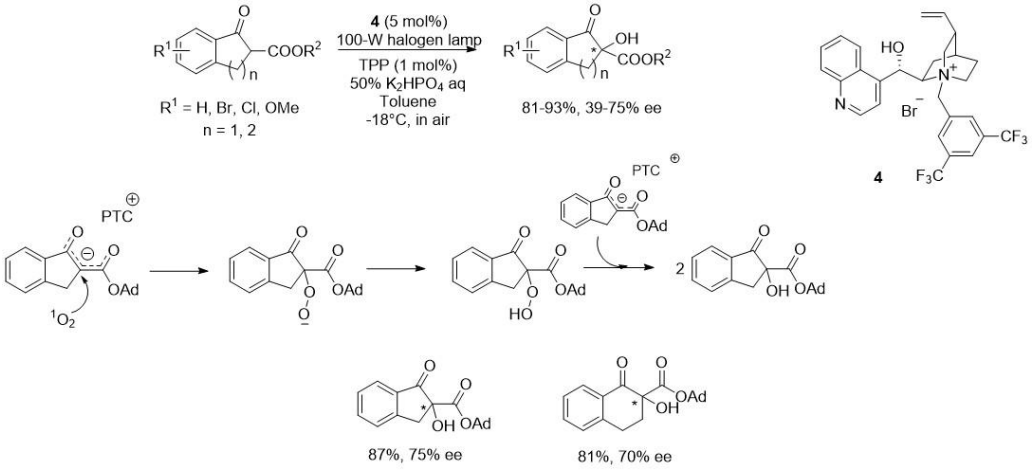

Figure 4: Asymmetric photo-oxygenation of β-keto esters and proposed mechanism for the reaction.

Enantioenriched α-hydroxy β-dicarbonyl compounds were obtained with excellent yields (up to 95 %) and interesting level of enantioselectivity (ee up to 85 %) [8].

Recently, a modification of the chiral phase-transfer catalyst to include a N-oxide moiety [9] (**5**, Figure 5) has been used in another photo-oxidative methodology with improved results compared to the modest enantioselectivity reported in Figure 4 for adamantyl α-hydroxy-β-keto esters

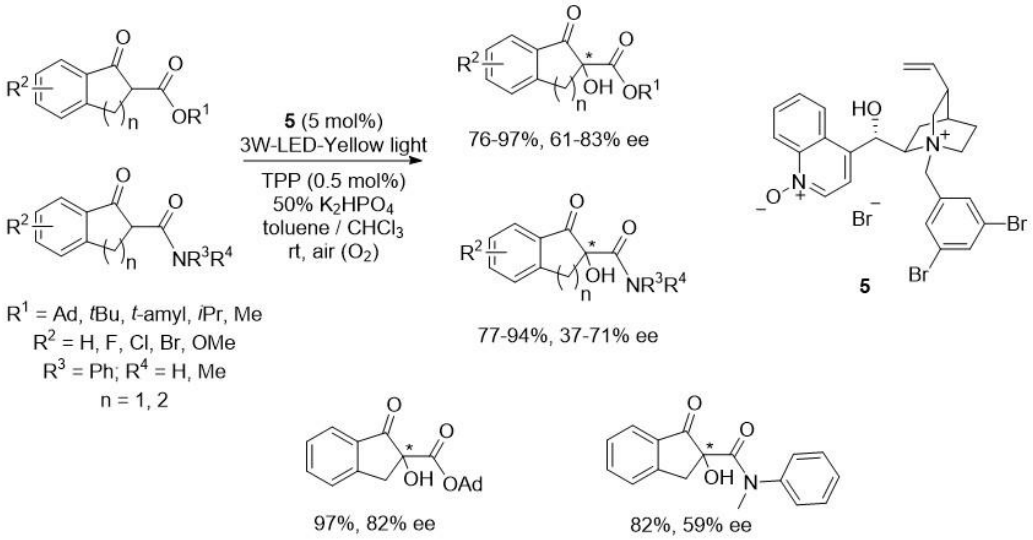

Figure 5: Enantioselective photo-oxygenation of β-dicarbonyl compounds catalyzed by **5**.

Furthermore, thanks to this cinchona-derived N-oxide asymmetric phase-transfer organocatalyst, the elaborated methodology could also be extended to other β-keto esters and β-keto amides (Figure 5), different from the adamantyl derivatives, with excellent yields and good enantioselectivities. Moreover, these catalysts could be easily recovered at the end of the reaction and reused without significant loss of reactivity or enantioselectivity.

The choice of the oxidant is fundamental for the sustainability of an oxidation reaction and undoubtedly molecular oxygen is the ideal choice but recently, hydrogen peroxide and organic hydroperoxides have emerged as useful alternatives for oxidations under metal-free conditions.

In 2017, Ooi and co-workers elaborated an efficient methodology for the asymmetric α-hydroxylation of oxindoles catalyzed by chiral 1,2,3-triazolium salts as phase-transfer catalysts (**6**), using hydrogen peroxide and trichloroacetonitrile under basic conditions (Figure 6) [10]. The authors suggested the *in situ* formation of peroxy trichloroacetimidic acid as the active oxygenating agent and in fact no oxidation products were detected in the absence of trichloroacetonitrile. The elaborated protocol tolerated the presence of both electron-donating and electron-withdrawing substituents on the oxindoles and the products were generally isolated in good yields and excellent enantioselectivities.

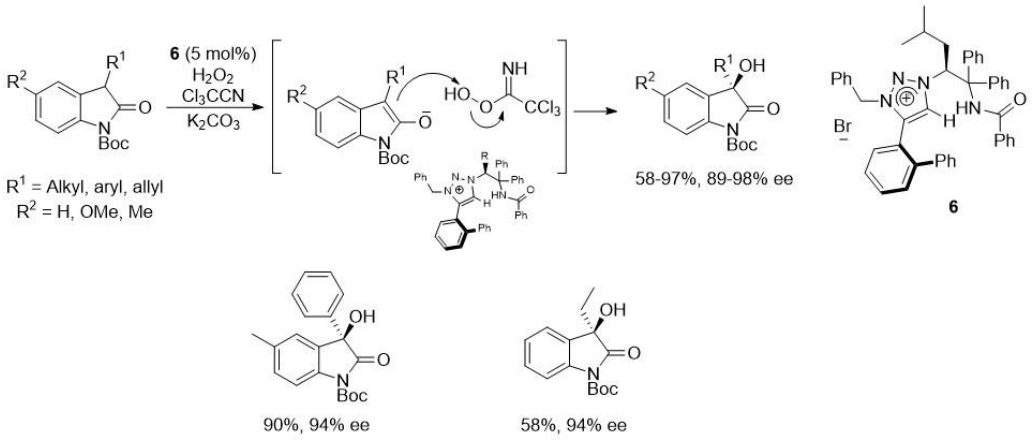

Figure 6: Asymmetric α-hydroxylation of 3-substituted oxindoles.

Cumene hydroperoxide (CHP) has been used as alternative oxygen-transfer reagent in stereoselective α-hydroxylations of carbonyl compounds. In 2012, Meng and co-workers reported the enantioselective phase-transfer catalyzed direct oxidation of 1-adamantyl β-oxo esters with CHP (Figure 7). The corresponding products were isolated with good yields and moderate to good ees [11]. Interestingly, the authors found that when modifying the hydroxyl and quaternary nitrogen groups of alkaloid catalysts **7** using bulky groups, the enantioselectivity reached 90 % but only for 1-indanone-derived β-keto esters (1-tetralone-derived β-oxo esters were also examined but they gave <35 % yields and moderate ees).

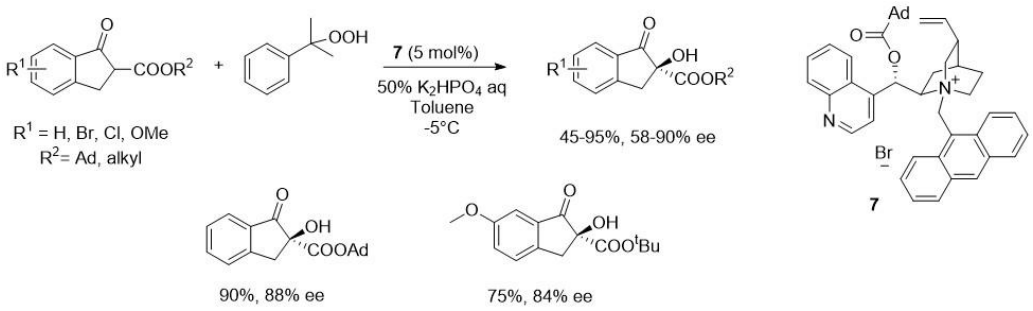

Figure 7: Asymmetric α-hydroxylation of β-oxo esters catalyzed by **7**.

Only one year later, Odagi and co-workers [12] achieved a highly enantioselective catalytic oxidation of 1-tetralone-derived β-keto-esters by using the guanidine-bisurea bifunctional organocatalyst **8** in the presence of CHP (Figure 8). The corresponding α-hydroxy-β-keto-esters were obtained in 82–99 % yields with high enantioselectivities (85–95 % ee). It was suggested that interactions between guanidine and β-keto ester and between the urea group and oxidant were important to achieve high enantioselectivity (Figure 8). Oxidants such as tBuOOH and oxaziridine were also tested, but the selectivity drastically decreased. The usefulness of this reaction was confirmed by applying it to the synthesis of a key-intermediate of *ent*-daunorubicin.

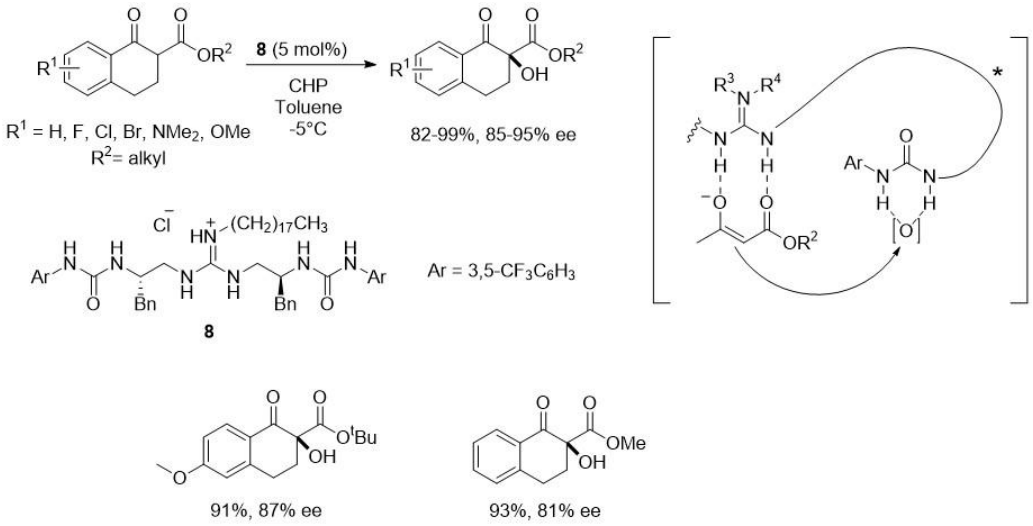

Figure 8: Catalytic asymmetric α-hydroxylation of β-keto esters by guanidine-bisurea **8** and proposed transition state model.

The origin of stereocontrol in guanidine-bisurea bifunctional organocatalyzed α-hydroxylation of tetralone-derived β-ketoesters in the presence of CHP was examined by DFT calculations [13]. The identified TS structure indicated that the β-keto ester group of tetralone interacts with guanidine and urea groups in the catalyst, and oxidant coordinates with the remainder of the urea group. Based on the insights provided by this TS model, the authors designed a new methodology for asymmetric synthesis of β- and γ-substituted tetralones by oxidative kinetic resolution reaction of tetralone-derived β-ketoesters, using guanidine-urea bifunctional organocatalyst and CHP. The kinetic resolution reaction of various tetralone derivatives proceeded with high selectivity. This methodology was successfully applied to the synthesis of (+)-linoxepin and rishirilide B [14].

In 2013, Lattanzi and co-workers [15] described the first enantioselective α-hydroxylation reaction of α-substituted β-keto amides by using the commercially available hydroquinine **9**/TBHP system (Figure 9). The products were obtained in good to high yields and up to 83 % ee, which could be improved by a single crystallization (up to 99 %).

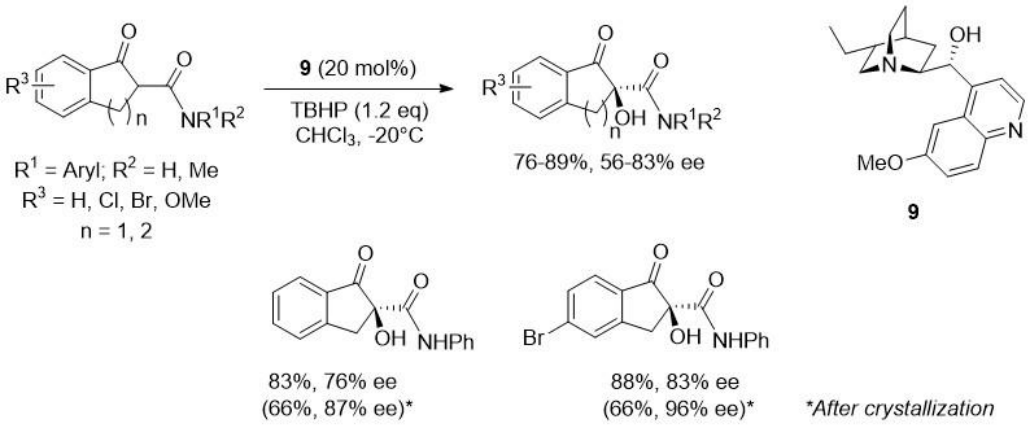

Figure 9: Asymmetric α-hydroxylation of β-keto amides.

CHP and H_2O_2, tested as alternative oxygen sources in the presence of hydroquinine **9** gave inferior results. Halogen atoms and electron-donating groups on the aromatic ring of the indane scaffold were well tolerated, whereas substrates with an aliphatic amido group reacted sluggishly at room temperature, affording the products in modest yields and ees. Interestingly, the authors investigated the nature of interactions between hydroquinine and β-ketoamide *via*[1] H-NMR, recording a number of spectra of **9** in $CDCl_3$ at room temperature, adding different amounts of substrate. The findings suggested that the catalyst OH group might be involved in hydrogen bonding interaction with the enolate of β-ketoamide.

Cinchona alkaloid derivatives have also been reported as efficient catalysts for the asymmetric α-hydroxylation of β-keto esters in the presence of CHP [16]. The reaction was successfully scaled up to a gram scale, without reduction in yield and ee. Then, this oxidative methodology was extended by Meng and co-workers [17] to different β-keto esters and β-keto amides using safe, commercially available peroxides (CHP, TBHP and H_2O_2) as the oxidant (Figure 10). Even in this case, compounds with aliphatic amido groups provided modest yields and ees. Moreover, under optimized conditions, non-cyclic β-keto esters did not react. Three possible transition states were proposed by the authors to elucidate the origin of the stereoselectivity of this reaction.

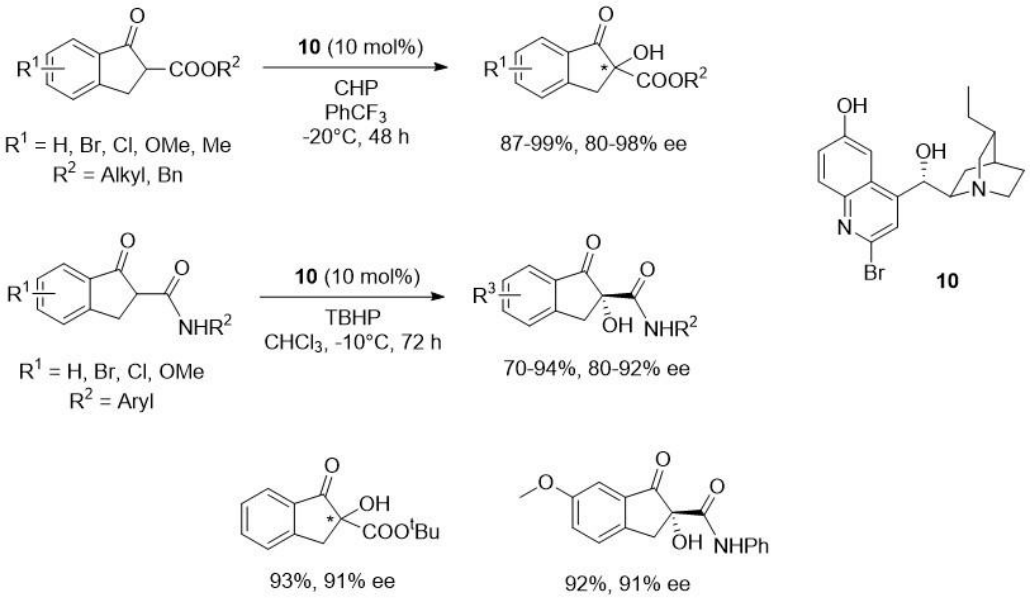

Figure 10: Asymmetric α-hydroxylation of β-indanone esters and amides.

Chiral bifunctional urea-containing ammonium salts were found to be very efficient catalysts for asymmetric α-hydroxylation reactions of β-keto esters, using racemic oxaziridines rac-**11** as oxygen-transfer reagents under base-free conditions, with enantiomeric ratios up to 99:1 [18]. This transformation was accompanied by a simultaneous kinetic resolution of the oxaziridine (Figure 11).

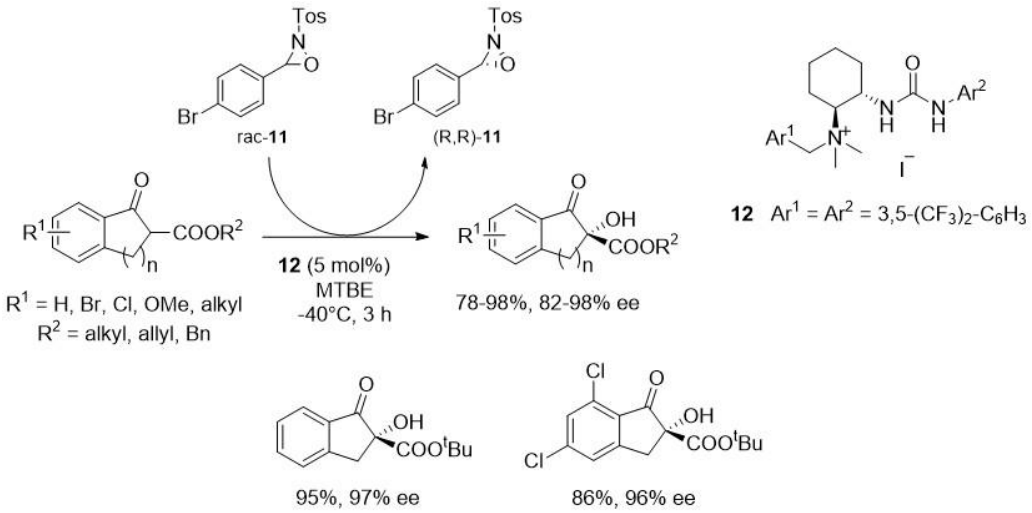

Figure 11: Asymmetric α-hydroxylation of β-keto esters by simultaneous kinetic resolution of rac-**11**.

Concurrently, Liu and co-workers developed a chiral bifunctional guanidine-catalyzed synchronous α-hydroxylation of β-keto esters and kinetic resolution of oxaziridines. The resolution could easily be performed on a gram-scale, without reduction in selectivity or yield [19]. In the presence of catalyst **14**, a variety of optically active oxaziridines and chiral α-hydroxy-β-keto esters were satisfactorily generated (Figure 12).

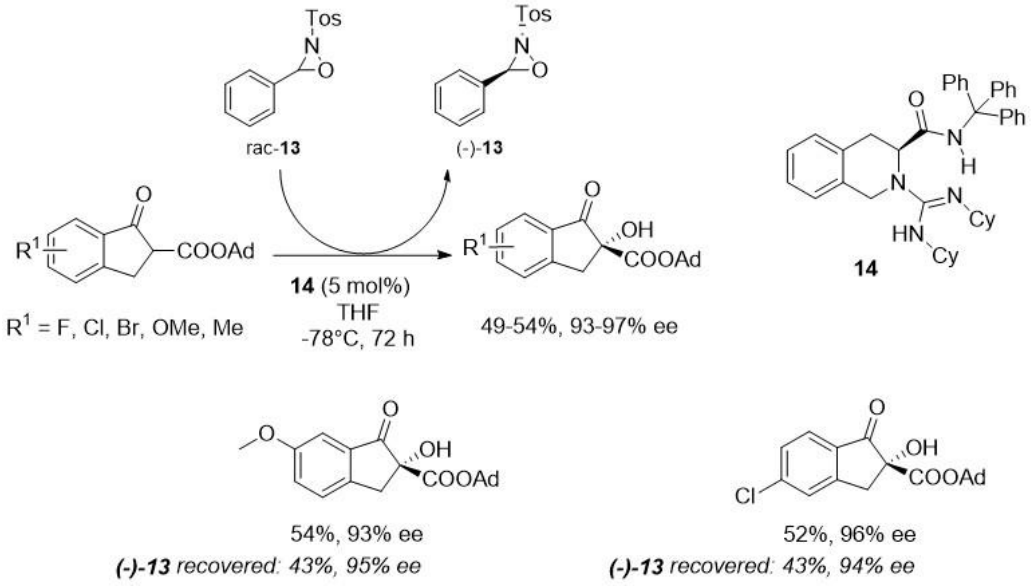

Figure 12: Asymmetric α-hydroxylation of β-keto esters by simultaneous kinetic resolution of **13**.

2.2 α-Benzoyloxylation

In 2012, Bencivenni and co-workers [20] explored the reactivity of cyclic ketones for the enantioselective synthesis of α-benzoyloxy derivatives using 9-amino(9-deoxy)epi-hydroquinidine **15** in combination with salicylic acid as cocatalyst, using dibenzoyl peroxide as the oxidant (Figure 13). Interestingly, salicylic acid was the best choice thanks to a fruitful hydrogen bond interaction between the hydroxyl group of the acid and the carbonyl groups of the benzoyl peroxide. This methodology was also effectively applied to the direct enantioselective synthesis of α-benzoyloxylated 1-indanone derivatives.

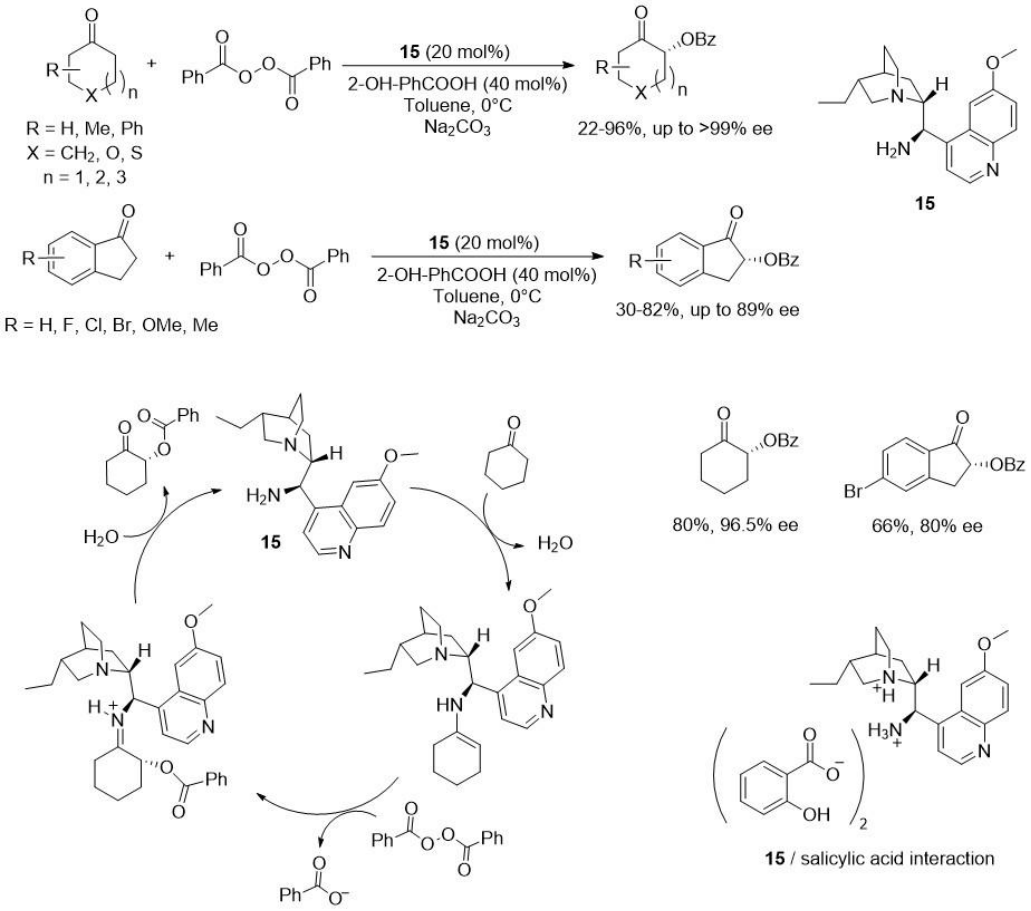

Figure 13: Asymmetric α-benzoyloxylation of ketones and proposed catalytic cycle for the reaction.

Recently, List and coauthors reported [21] the direct asymmetric α-benzoyloxylation of α-branched aldehydes and α-branched enals *via* enamine and dienamine catalysis, employing cinchona alkaloid-derived primary amine as the catalyst, benzoyl peroxide (BPO) as a readily available and inexpensive hydroxylation reagent and 10 mol % of the radical inhibitor 2,6-di-*tert*-butyl-4-methylphenol BHT (Figure 14). This methodology gave access to valuable aldehydes containing a quaternary stereocenter. The authors suggested that an external acid additive was unnecessary and that the Brønsted acid involved in the catalytic cycle could be the benzoic acid generated *in situ* after the first catalytic turnover, even though chiral acids **TRIP** (3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-bi-2-naphthol cyclic monophosphate) affected the enantioselectivity.

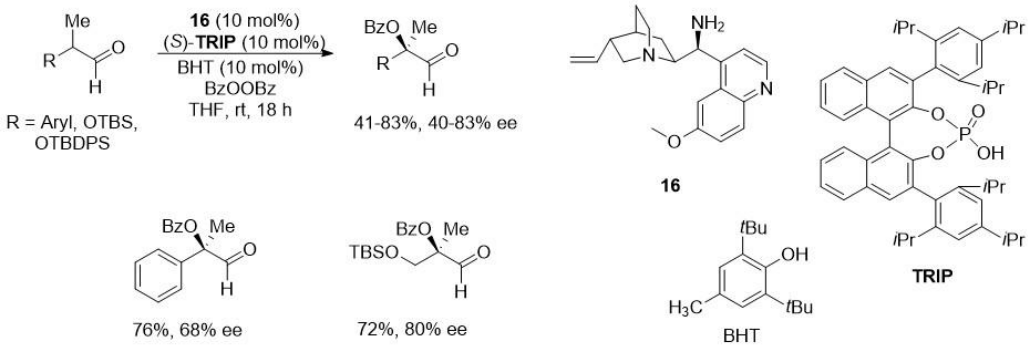

Figure 14: Enantioselective α-benzoyloxylation of α-branched aldehydes.

Their hypothesis on the role of benzoic acid was supported by the autocatalytic behavior of the reaction as confirmed by the sigmoidal curve observed plotting the results of the conversion of the aldehyde over time. The modest enantioselectivity observed in some examples was attributed to the formation of equilibrium mixtures of E- and Z-enamine intermediates, which are similar in energy but which furnish opposite enantiomers of the product.

In 2017, Maruoka and coauthors [22] reported an efficient synthesis of chiral tritylpyrrolidine derivatives as single stereoisomers (their precursors were mixtures of diastereoisomers which could be separated into single

stereoisomers by simple silica gel column chromatography). The potential of these molecules as novel chiral catalysts was evaluated in the asymmetric benzoyloxylation of 3-phenylpropanal with BPO, with results comparable in term of reactivity and selectivity to those reported by using other catalysts.

Luo and co-workers [23] developed an elegant direct asymmetric α-benzoyloxylation of β-ketocarbonyls catalyzed by primary amines. The reaction worked more cleanly under N_2, thus all the reactions were conducted under anaerobic atmosphere, in the presence of butylated hydroxytoluene (BHT) as a radical inhibitor and benzoyl peroxide as the hydroxylation reagent (Figure 15). Acyclic and cyclic ketoesters in the presence of benzoyl peroxide afforded the desired α-benzoyloxylation products in high yields and excellent enantioselectivities. A number of α-substituents on acetoacetates were well tolerated as well as various ester moieties, including those with sterically bulky groups. To further explore the versatility of the reaction, β-ketoamides were also examined, achieving good results. From a mechanistic point of view, the authors proposed three transition states: an H-bonding TS **I** to account for the R-selectivity, a N-oxide addition pathway **II** to give R-selectivity and an S-selective enamine N-oxide pathway **III**.

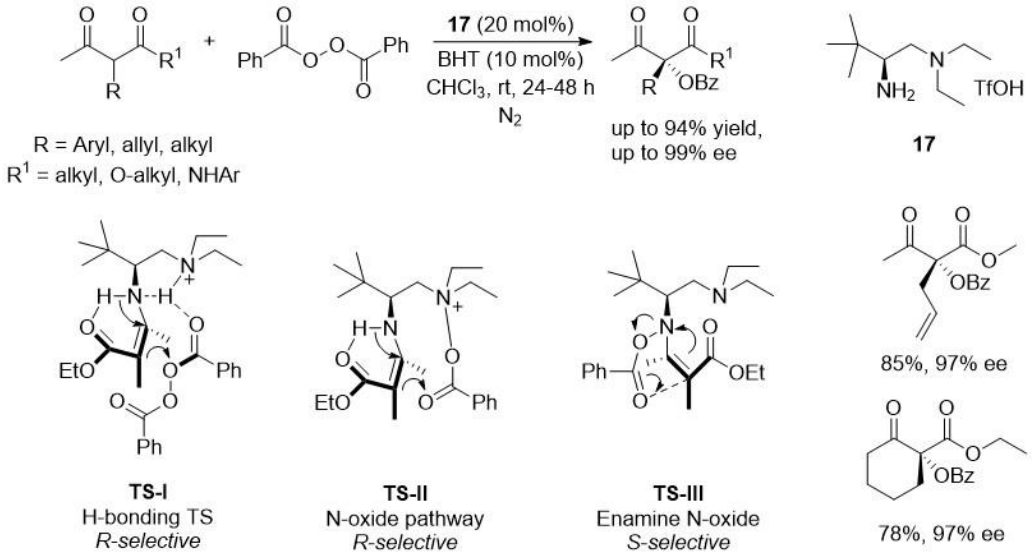

Figure 15: Asymmetric α-benzoyloxylation of β-ketocarbonyls and proposed transition states.

They suggested that the N-oxide pathways should be minor and disfavored and that the H-bonding directed addition would be the major productive pathway under the optimized experimental conditions (Figure 15).

One year later, Kanemitsu and Itoh published [24] the first enantioselective α-benzoyloxylation of α-monoalkylated malonic diesters promoted by a phase-transfer catalyst (Figure 16). Under the optimized conditions, the reaction was carried out in the presence of aqueous KOH and N-(9-anthracenylmethyl)cinchoninium chloride **18** by using BPO as the oxidant and afforded the corresponding products in excellent yields (up to 99 %) and high ees (up to 96 %). The utility of this methodology was demonstrated by its application in the synthesis of a mineralocorticoid receptor antagonist.

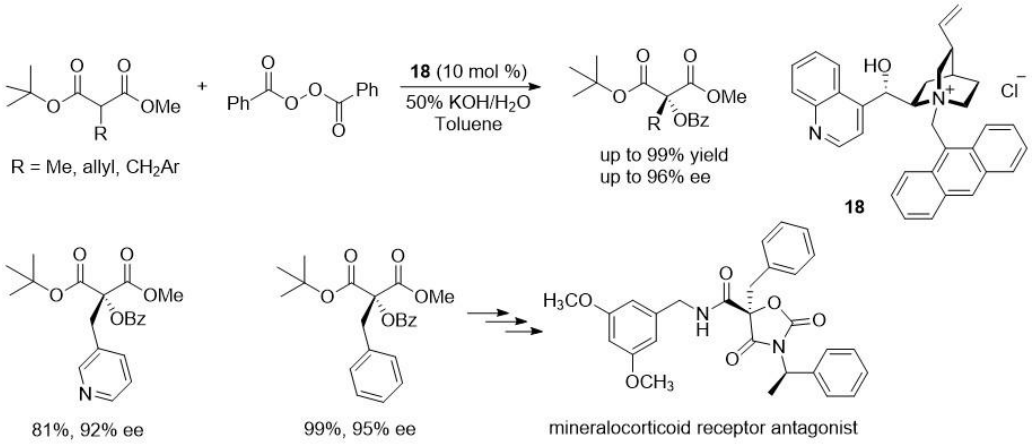

Figure 16: Enantioselective α-benzoyloxylation of malonic diesters and its application in the synthesis of a mineralocorticoid receptor.

Very recently, Meng and co-workers [25] have successfully applied a cinchona-derived N-oxide phase-transfer catalyst also in the α-benzoyloxylation of β-keto esters (Figure 17). In this way a range of substituted 1-indanone and 1-tetralone derivatives were synthesized with excellent yields and enantioselectivities under mild conditions. The methodology was also used at gram-scale, without reduction in efficiency and enantioselectivity and the catalyst can be easily separated at the end of the reaction and reused without loss of activity.

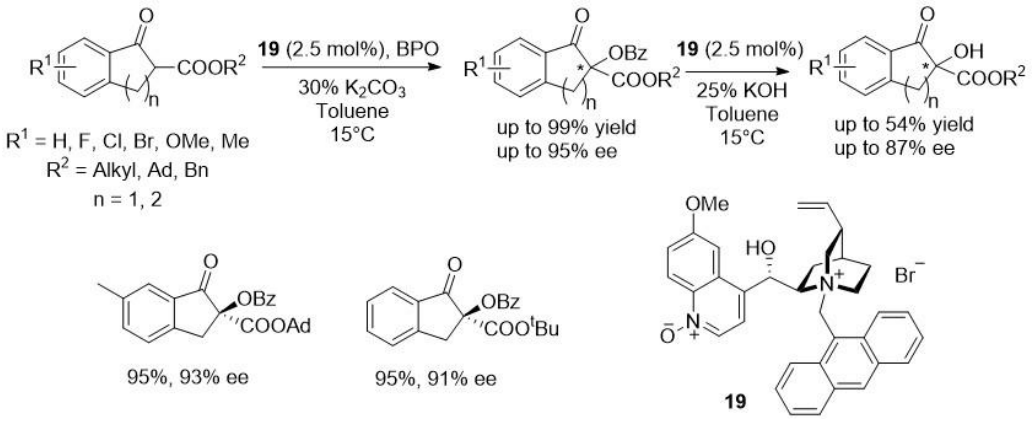

Figure 17: Enantioselective α-benzoyloxylation of β-keto esters.

From a mechanistic point of view, the authors proposed the deprotonation of the β-keto ester in the presence of a base followed by its reaction with the active BPO with formation of the α-benzoyloxylation product. In a possible transition state proposed by the authors, only the *Si*-face of the enolate was available for the reaction. Under the phase-transfer conditions, the α-benzoyloxylation product could be converted to the α-hydroxy derivative by kinetic resolution of the benzoates, for which only the *R* or *S* product was preferentially hydrolyzed.

2.3 α-Tosyloxylation

In 2012, Legault and co-workers [26] developed chiral iodoaryl oxazolines **20** as new catalysts for the α-tosyloxylation of propiophenone. In this case, *meta*-chloroperoxybenzoic acid (*m*-CPBA, slow addition) was used as the stoichiometric oxidant and *p*-toluenesulfonic acid (*p*-TsOH) as a source of tosylate nucleophile (Figure 18). The same authors reported [27] that the stereoinduction is exclusively controlled by the stereogenic center alpha to the oxazoline oxygen, as the epimer **20b** of catalyst **20a** led to an inversion of the sense of stereoinduction. Computational chemistry was used to rationalize the stereoinduction of the process, in particular, due to the excess of *p*-TsOH with respect to the catalyst, the oxazoline was driven to its protonated state. The protonation furnished the necessary activation to favor the formation of the reactive iodane intermediate (Figure 18), a much more electrophilic bis-cationic intermediate and in this structure the stereogenic center, near to the oxygen atom influenced the approach of the substrate. The introduction of an alkyl group *ortho* to the iodine center in the catalysts led to a drastic improvement in activity. Moreover, the best, although modest, selectivity was obtained after the introduction of a chlorine atom *para* to iodine (**20c**).

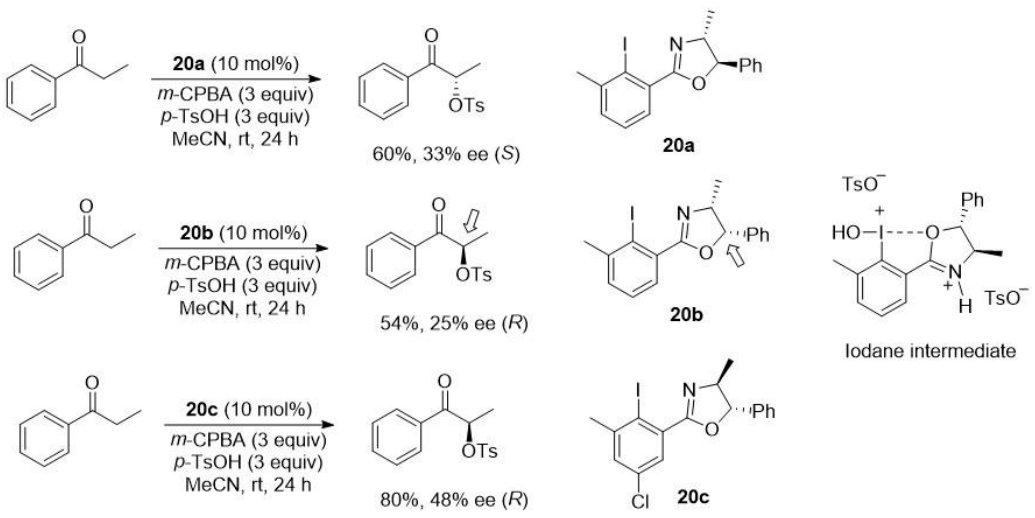

Figure 18: Enantioselective α-tosyloxylation of propiophenone.

Later, Berthiol et al. [28, 29] synthesized 3,3′-diiodo-BINOL-fused maleimides **21** as hypervalent iodine (III) organocatalysts, which were used in the α-tosyloxylation of ketones. With these catalysts, yields and ees were found to be comparable to the best results previously achieved using other organocatalysts (Figure 19).

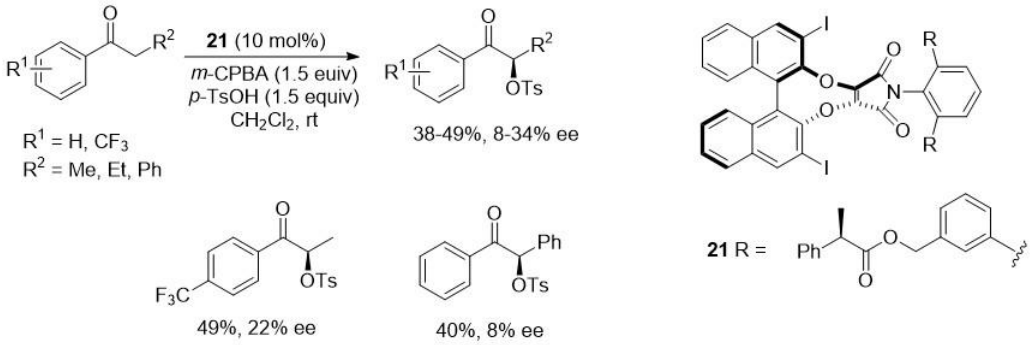

Figure 19: Asymmetric α-tosyloxylation of ketones.

The authors highlighted that the maleimide moiety was idoneous for obtaining moderate enantioselectivities, and the investigation of the reaction mechanism revealed that the steric crowding around the iodine center improved the enantioselectivity.

Recently, new chiral non-C_2-symmetric iodoarenes **22** have been found to be effective catalysts for the asymmetric α-tosyloxylation of ketones (Figure 20) [30]. In a plausible mechanism, proposed by Masson et al., the enol form of propiophenone reacted with the aryl-λ^3-iodane generated *in situ* from reaction of the chiral organocatalyst, *m*-CPBA and sulfonic acid (path B) to provide a C-bonded intermediate which was able to react with the oxygenated nucleophile in order to give the final product. However, an alternative mechanism involving an O-bonded iodane intermediate could be plausible [31] (path A) and the low stereocontrol in the reaction was attributed to the competition between these two different paths (Figure 20). AcOEt was found to be the best reaction medium and *m*-CPBA was the most efficient oxidant for the reaction. Furthermore, the same authors described an interesting strategy [32] in order to access highly atropoenriched 2-iodobiphenyls by means of Andersen's reagent under kinetic resolution conditions.

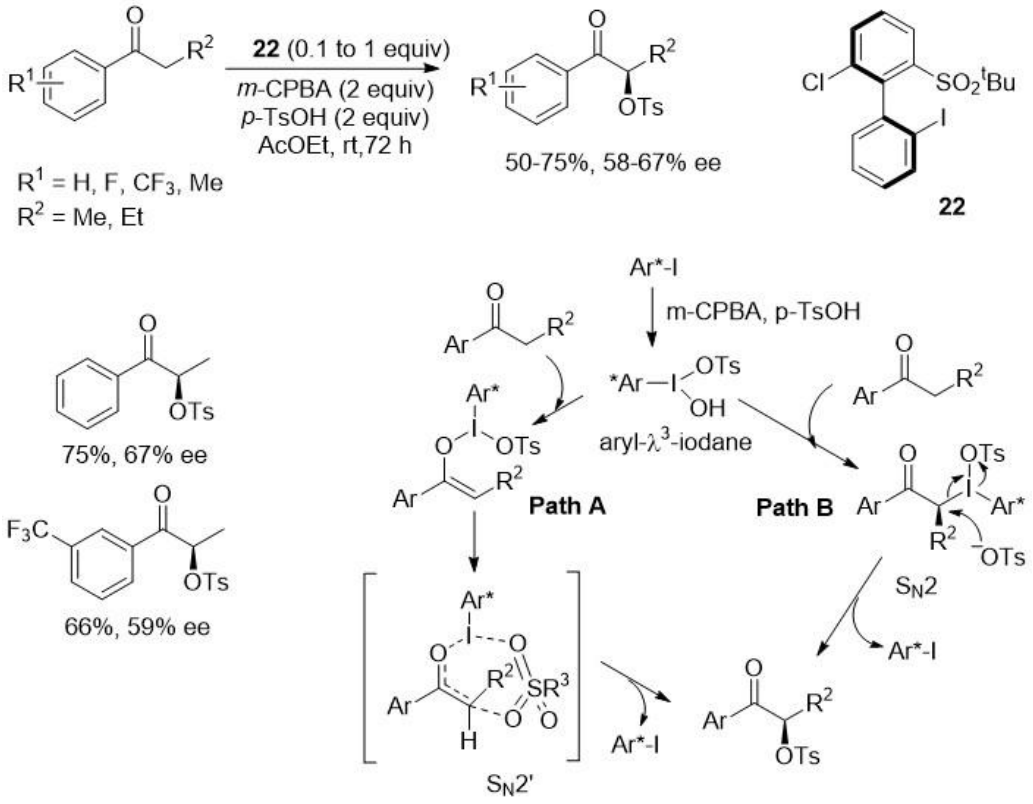

Figure 20: Enantioselective α-tosyloxylation of ketones and proposed mechanism for the reaction.

To avoid the low selective path A (O-bonded intermediate) and favor path B (C-bonded intermediate), Legault and Basdevant used enol esters and iodoarenes **23** as chiral iodine(III) reagents for the synthesis of α-tosyloxy ketones under stoichiometric and catalytic conditions [33] (Figure 21). The authors pointed out that while the reaction with ketones proceeded preferentially through a S_N2'-type mechanism (O-bonded intermediate), this pathway was inaccessible for enol derivatives (in this case the reaction proceeded through a C-bonded intermediate).

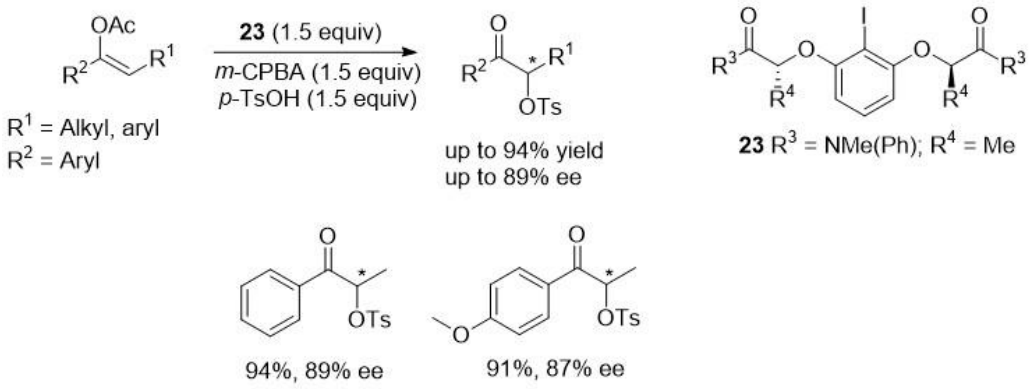

Figure 21: Enantioselective α-tosyloxylation of enol esters.

Iodoarenes **23** were also used by Coeffard and co-workers [34] in the asymmetric α-oxidation of α-substituted β-keto esters in the presence of *m*-CPBA as the oxidant (Figure 22). After a careful screening of experimental conditions, modest yields and satisfactory enantiomeric excesses were obtained for the synthesis of products with a quaternary stereogenic center.

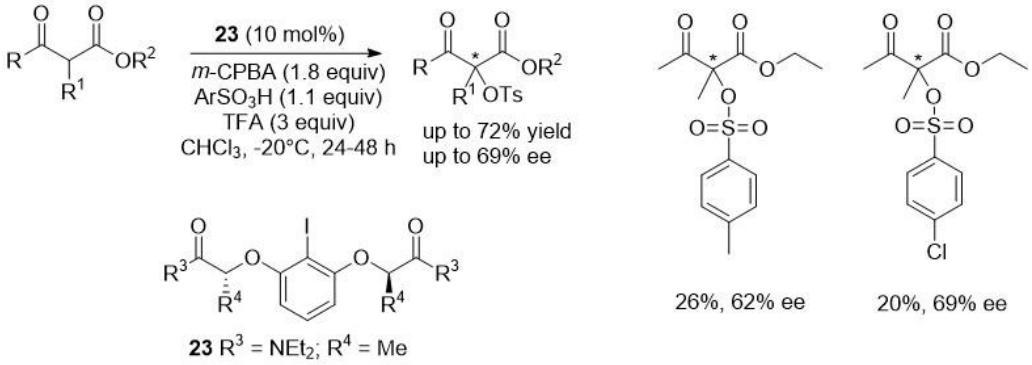

Figure 22: Enantioselective α-oxysulfonylation of α-substituted β-keto esters.

3 Dihydroxylation and dioxygenation of alkenes

One of the most useful and exploited oxyfuntionalization of the carbon-carbon double bond is the oxidation to 1,2-diols or their protected derivatives. This transformation is often reported as key-step in total synthesis of bioactive and natural compounds [35].

3.1 Dihydroxylation of alkenes

The stereoselective oxidation of alkenes enables the preparation of 1,2-diols, which are important derivatives for the synthesis of every-day life compounds such as sugars and a fundamental class of chiral ligands for metal-based catalysis. Among the metal-based systems, the Sharpless asymmetric dihydroxylation (SAD) provides a simple and readily available catalytic protocol for the preparation of *cis*-1,2-diols with high stereocontrol [36].

Chiral anion-controlled ion-pairing catalysis is an area of research showing brilliant examples of highly stereocontrolled transformations, exploiting noncovalent interactions provided prevalently by binaphthyl-derived chiral phosphate anion [37]. A complementary and still greatly underdeveloped approach foresees

the use of chiral cations for the control of metal anions. In this context, a pioneering example of dihydroxylation of alkenes has been reported by Brown in 2002, using stoichiometric amount of a cinchonidinium salt in the presence of MnO_4^- anions [38]. Although the enantioselectivity was low and the catalyst proved to be unstable under the oxidative conditions, this system attested the feasibility of ion-pairing to induce the stereoselective processes with metal containing anions.

In 2015, Wang, Tan and coauthors, disclosed stable dicationic bisguanidinium salts **24**, as catalysts for the enantioselective dihydroxylation and oxohydroxylation of α-aryl acrylates and α-aryl-β-alkyl acrylates, using $KMnO_4$ as the terminal oxidant (Figure 23) [39].

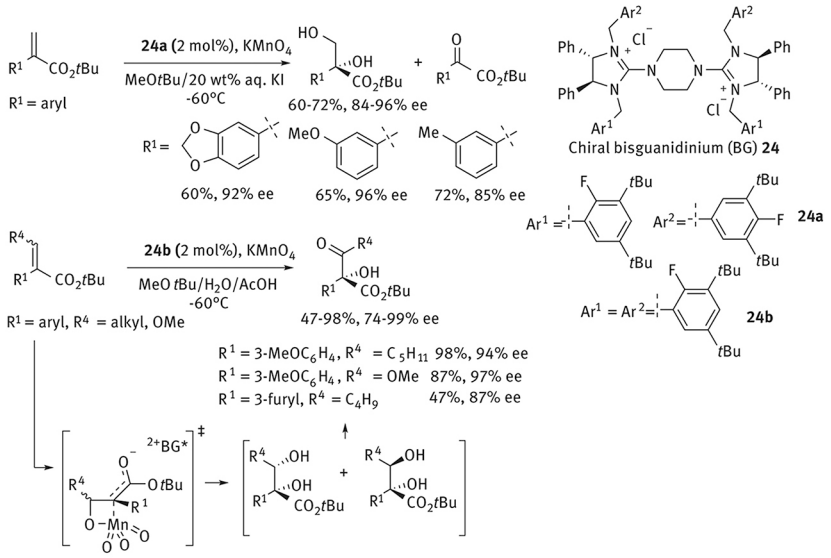

Figure 23: Enantioselective dihydroxylation and oxohydroxylation of acrylates.

When using catalysts **24**, readily accessed from a commercially available optically pure 1,2-diamine, the reactions proceeded at −60 °C in ethereal/water mixtures with only 2 mol % of the chiral salt to give diols, bearing electron-donating groups in the aromatic moiety, in moderate to satisfactory yield and higher ees. The presence of the α-ketoester as by-product was observed. α-Alkyl substituted acryates were transformed to diols with lower level of enantioselectivity. Interestingly, when employing mixtures of *Z*, *E*-trisubstituted enoates, the initially formed mixture of diastereoisomeric diols could be transformed under acidic conditions, into the oxohydroxy products with good to excellent ees. This outcome demonstrated that *Z*- and *E*-trisubstituted enoates afforded the same enantiomer of the product. The chiral catalyst **24**, being dicationic in character, should form stronger electrostatic interaction with the enolate anion derived from the attack of MnO_4^- toward the C-C double bond. At this stage, the chiral environment of the dication would dictate the stereoselectivity in the formation of the quaternary stereocenter of the cyclic mangate ester. The protocol can be considered a useful new tool which somewhat complements the SAD.

An interesting enantioselective diboration of alkenes has been reported by Morken and coauthors, using readily available carbohydrate-derived glycols [40]. The process is based on the knowledge that bis(neopentylglycolato)diboron reagent $B_2(neo)_2$ in the presence of Lewis basic alkoxides (YO^-) forms an ate-complex that would promote the reaction with unactivated alkenes. The relevant process for the stereocontrol relies on the reversible replacement of neopentyl glycol ligands with appropriate chiral alcohols to give optically pure ate complex. Specifically, the combination of catalytic loading of diol **25** or its pseudoenantiomer **26** and DBU as base in THF, after the one-pot oxidative treatment afforded the 1,2-diols in good yields and good to high enantioselectivity (Figure 24(a)).

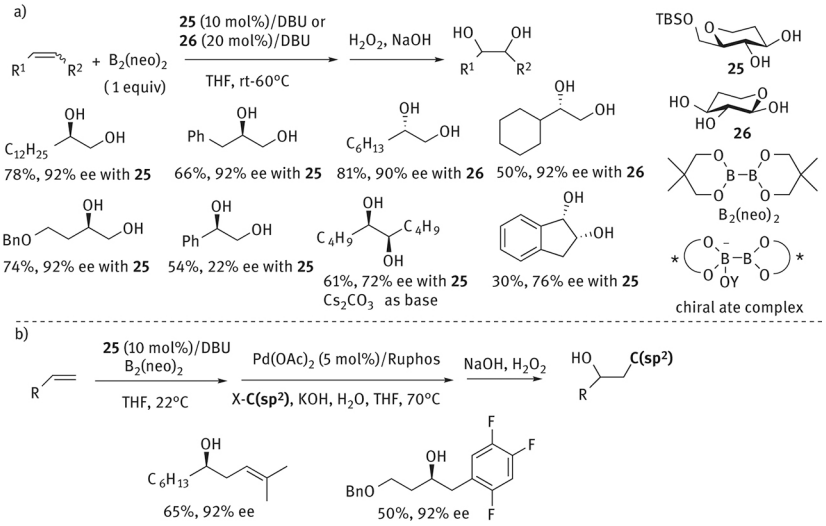

Figure 24: (a) Enantioselective diboration/oxidation of alkenes to 1,2-diols and (b) Cascade diboration/cross-coupling/oxidation sequence.

The transformation is of note as the chiral diols **25** and **26** derives from low cost D-glucal and L-rhamnal and both enantioenriched products are available by choosing the proper catalyst. Terminal alkenes, except styrenes, generally led to the final diols with high ees and the process could be scaled up to 10 g of starting alkene. More challenging internal alkenes, furnished the 1,2-diols in excellent diastereoselectivity and good enantiocontrol. The procedure could be coupled with Pd-catalyzed cross-coupling reactions in a cascade fashion, performing the subsequent step on the crude mixture of the previous step, useful to prepare secondary non racemic alcohols (Figure 24 (b)).

3.2 Dioxygenation of alkenes

An appealing approach for the asymmetric oxidative difunctionalization of carbon-carbon double bond relies on the employment of optically pure hypervalent iodine compounds [41]. These molecules have been increasingly used over the years as an environment-friendly alternative to toxic heavy metal oxidants. The dioxygenation of alkenes by this class of reagents was applied in intramolecular manner to construct heterocycles containing one or two contiguous stereocenters and more recently in the intermolecular version.

In 2012, Fujita illustrated a first catalytic dioxygenation of alkenes mediated by chiral hypervalent iodine precatalyst **27**, trifluoroacetic acid as an activator and *m*-CPBA as the terminal oxidant (Figure 25) [42]. Precatalyst **27** is oxidized by the terminal oxidant to give a chiral organoiodane(III) species able to attack the carbon–carbon double bond to form a iodonium intermediate. Intramolecular nucleophilic attacks of the OH and the carbomethoxy groups occur with inversion of configuration at the carbon atoms to give the dihydrofuran-fused isochromanones with complete diastereoselectivity in moderate yields and moderate to high enantioselectivity.

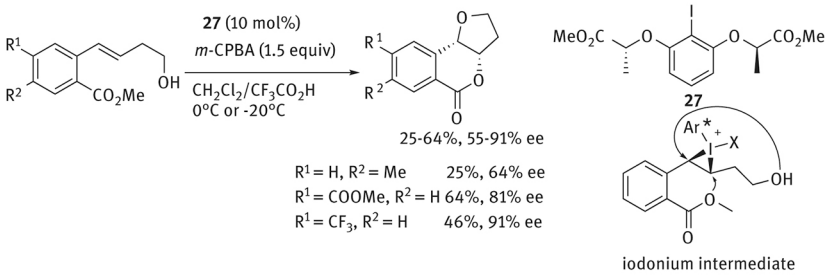

Figure 25: Asymmetric oxylactonization of alkenes with C_2-symmetric iodoarene.

The selectivity of the reaction is not complete due to the competitive epoxidation of the double bond by the terminal oxidant. The same group reported a trifluoroacetoxylactonization of *ortho*-alk-1-enylbenzoates to 3-alkyl-4-hydroxyisochroman-1-ones catalyzed by a set of chiral iodo-based precatalysts (Figure 26) [43]. This transformation is related to that one reported in Figure 25. In this case, trifluoroacetic acid represents the external nucleophile attacking the chiral iodonium intermediate to give the trifluoroacetoxylactone, easily hydrolyzed to products **29** and **30**. The process catalyzed by one of the most effective compounds **28**, provided

four lactones in a variable ratio, with the enantioenriched *cis*-isochromanone **29** as the most abundant with up to 98 % ee, regioselectively obtained via a 6-*endo* ring closure. A parallel detrimental racemic epoxidation, followed by ring-opening to *anti*-derivatives **31** and **32** occurred, thus suppressing the final yield of lactone **29**.

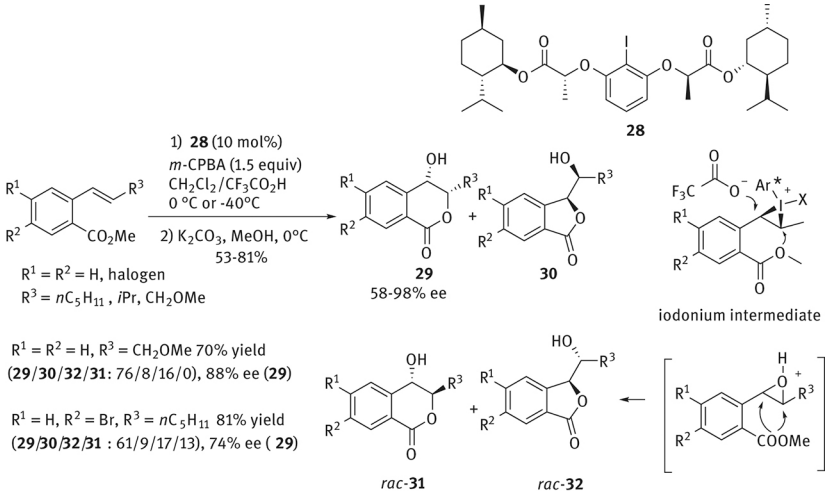

Figure 26: Stereoselective oxylactonization of *ortho*-alk-1-enylbenzoates.

In 2017, Masson and coauthors illustrated a tosyloxy- and phosphoryloxy-lactonization of 4-pentenoic acid derivatives mediated by precatalyst **33** under stoichiometric amount of *m*-CPBA and sulfonic or phosphoric acids at 0 °C (Figure 27) [44]. The γ-(hydroxymethyl)-γ-butyrolactones were isolated in acceptable yields and good ee values. Only one example of reactivity, leading toward the corresponding δ-butyrolactone, proceeded with lower conversion and enantiocontrol.

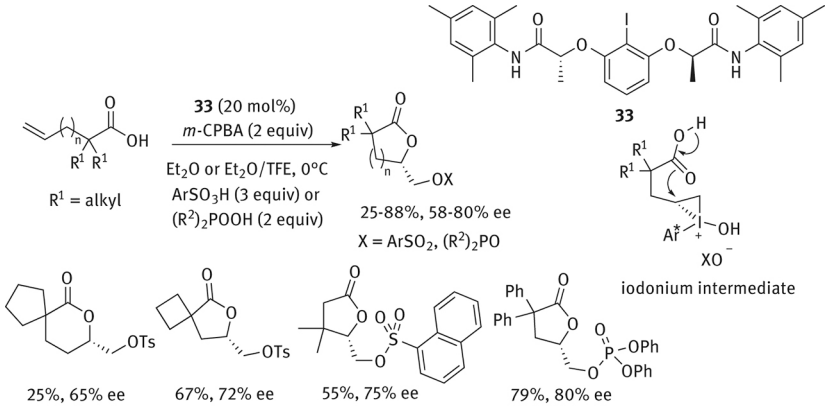

Figure 27: Enantioselective tosyloxy- and phosphoryloxy-lactonization of 4-pentenoic acid.

Optimized reaction conditions prevented the epoxidation of the terminal carbon–carbon double bond, leading to a more selective process. Mechanistically, the oxidation of precatalyst **33** by *m*-CPBA would form a chiral λ^3-aryliodane species, which would be attacked by the alkene moiety to give a chiral iodonium intermediate.

This in turn would undergo 5-*exo*-closure to a iodonium species, followed by sulfonyl or phosphoryl nucleophiles substitution. This approach represents a straightforward route to γ-(hydroxymethyl)-γ-butyrolactones, useful intermediates for the synthesis of natural products [45].

The chiral lactones were produced with low to moderate optical purities by alternative organocatalyzed BV reaction (30–42 % ee) [46]. The first intermolecular example of asymmetric dioxygenation of alkenes mediated by hypervalent iodine organocatalysts has been illustrated by Muñiz and coauthors in 2016 (Figure 28) [47].

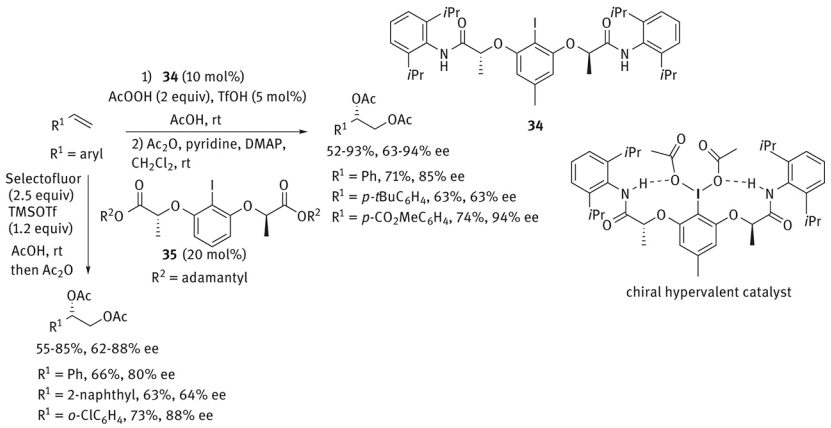

Figure 28: Enantioselective diacetoxylation of styrenes.

A variety of stryrenes was reacted using precatalyst **34** at 10 mol % loading, peracetic acid and catalytic loading of triflic acid in acetic acid as solvent, leading to the enantioselective formation at room temperature of two regioisomeric acetoxy alcohols.

The mixture was then treated with acetic anhydride to obtain the diacetoxylated products in good yields and up to 94 % ee. The protocol has the advantage to use a more convenient oxidant source, whose by-product is the reaction solvent. The X-ray structure of a few chiral active hypervalent catalysts was determined for the first time, showing a supramolecular chiral helical ensemble around the iodine atom. This feature has been ascribed to H-bonding interactions of the amide moieties with the oxygen atoms of the acetoxy ligands, which persisted also in solution. Hence, the helical chirality was suggested to play a role in the control of the asymmetric induction in carbon-carbon double bonds oxidation generally mediated by hypervalent catalysts having this structure. The same group shortly after showed that bislactate precatalyst **35** promoted the same process using Selectfluor as an alternative terminal oxidant, and trimethylsilyl triflate (TMSOTf) as the activator (Figure 28) [48]. Moreover, *trans*-cinnamyl alcohols were reported as suitable internal alkenes for the diacetoxylation to give, under the same conditions, the triacetoxylated products in good to high diastereo- and enantioselectivity (dr > 80/20 and ee from 78 % to 96 %).

4 BV oxidation and oxidative desymmetrization

The BV oxidation is one of the fundamental transformations in organic synthesis useful to directly transform ketones to the corresponding esters or lactones. The most traditional approach to carry out this transformation uses organic peracids as oxygen source [49]. However, over the last years, more attention has been paid to the development of new green chemistry methods that exploit atom-efficient and mild oxidants such as hydrogen peroxide or molecular oxygen [1b-c, 51]. Particular efforts have been directed toward the development of enantioselective processes and, among metal-free protocols, excellent enantioselectivity has been achieved by enzymatic systems, such as mono-oxygenases [50]. Despite the considerable efforts, the development of organocatalytic BV oxidation protocols using H_2O_2 is considered to be one of the most challenging issues in synthetic chemistry [1b-c, 53]. The main reason could be ascribed to its low activity and strong acids or metal promoters generally required [50e, 54].

Before 2012, few examples of organocatalytic asymmetric BV reactions have been reported essentially focused on prochiral cyclobutanones. The first organocatalyzed BV oxidation, reported by Murahashi [51], showed the use of planar-chiral C_2-symmetric bisflavinium perclorate catalyst **36** in the oxidation of 3-aryl-substituted cyclobutanones with hydrogen peroxide. The resulting chiral lactones were isolated in moderate yield and up to 74 % ee. (Figure 29). In 2008, Miller reported two preliminary examples of oxidative desymmetrization of cyclic ketones promoted by the oligopeptide catalyst **37**, using the combined action of carbodiimide and hydrogen peroxide to generate transient peracids upon exposure to carboxylic acid catalyst (Figure 29) [47].

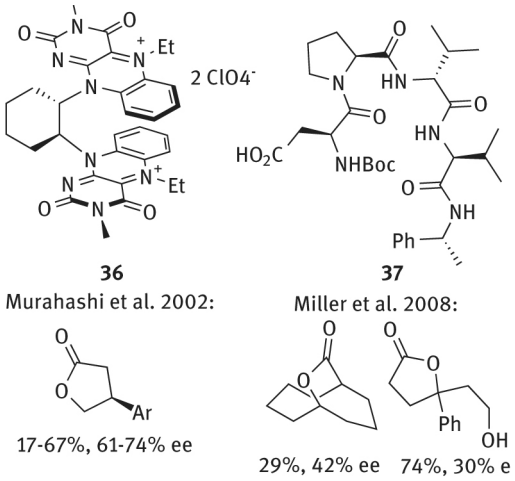

Figure 29: Organocatalysts used for enantioselective Baeyer–Villiger oxidations with H_2O_2 and relative chiral products reported before 2012.

The most remarkable results in the field of asymmetric organocatalyzed BV reactions were achieved by Ding and coauthors who, from 2008 to 2011, published their studies on enantioselective BV oxidations promoted by chiral BINOL- and H_8-BINOL-derived phosphoric acids of the type **38** of 3-substituted and 2,3,4-trisubstituted tricyclic cyclobutanones to γ-lactones using aqueous hydrogen peroxide as oxidant [52]. Exploiting chiral phosphoric acid/H_2O_2 systems, the γ-lactones were isolated in quantitative yield and good to high enantioselectivity (55–95 %) (Figure 30(a)). The reaction mechanism was studied based on experimental and theoretical findings and the authors proposed that the bifunctional activation of the reagents through hydrogen-bonding interactions is central to the catalysis. The catalyst simultaneously increases the electrophilicity of the carbonyl carbon, acting as a general acid, and the nucleophilicity of hydrogen peroxide in the addition step **39**. It promotes the dissociation of the hydroxyl group from the Criegee intermediate in the rearrangement step **40** (Figure 30(c)). The authors extended the use of H_8-BINOL-derived phosphoric acid **38**/H_2O_2 system also to a divergent kinetic resolution of racemic 2,3-disubstituted bicyclic cyclobutanones via asymmetric BV oxidation. Two chiral lactones were obtained in moderate regioisomeric ratio and generally low ees for the major regioisomer and much higher enantioselectivity for the minor one (74– > 99 % ee) (Figure 30(b)).

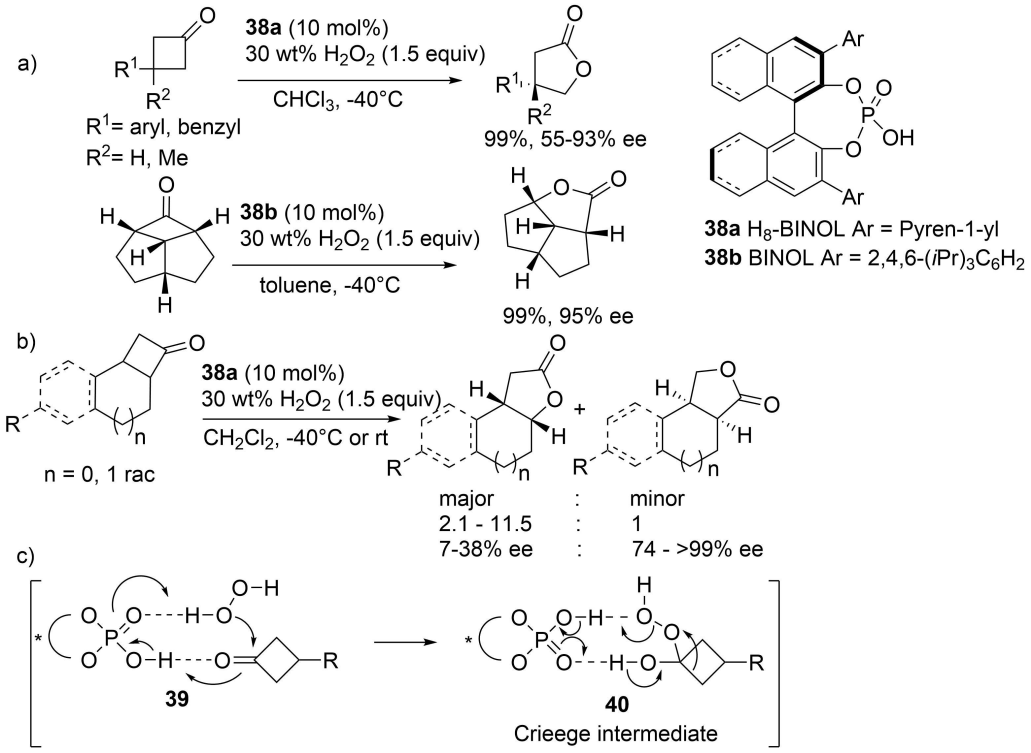

Figure 30: Chiral phosphoric acid catalyzed: (A) enantioselective BV reaction and (B) divergent kinetic resolution via BV oxidation. (C) Mechanism of the chiral phosphoric acid catalyzed asymmetric BV reaction of 3-substituted cyclobutanones.

In 2012, Kotsuki and coauthors reported a new environmentally friendly and mild method, organocatalyzed by thioureas, for the BV oxidation of cyclobutanones using H_2O_2 in Et_2O as the oxidant, working in toluene at room temperature (Figure 31) [53]. A variety of aryl and alkyl substituted cyclobutanones were oxidized to γ-lactones in high yields, observing the normal mode of migratory aptitude of the ketonic alkyl moiety. Unfortunately, other cyclic ketones such as cyclopentanones and cyclohexanones gave only the corresponding peroxide Criegee intermediates. By ^{13}C NMR experiments it was demonstrated that catalyst coordinates with cyclobutanone via hydrogen-bond interactions. The authors reported preliminary attempts to develop an asymmetric version of the methodology using chiral thioureas, without observing any asymmetric induction.

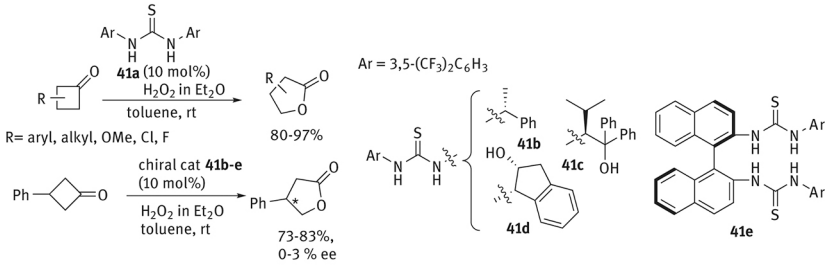

Figure 31: BV oxidation of cyclobutanones catalyzed by thioureas.

As cited before, in 2008 Miller and coauthors developed a peptide-catalyzed BV oxidation exploiting an acid/peracid catalytic cycle which had already proven particularly effective in the electrophilic epoxidation [52]. Even if in the BV oxidation the peracid has opposite functionality, acting as a nucleophile, this catalysis concept proved to be applicable in the oxidation of ketones. The catalytic acid/peracid cycle for the BV oxidation is depicted in Figure 32. The side-chain of a peptide-embedded aspartic acid **42** shuttles between the peracid oxidation state **44** and a carboxylic acid resting state **42**. In more detail, the carboxyl moiety of the catalyst is activated by diisopropyl carbodiimide (DIC) generating the intermediate **43**. Capture of intermediate **43** by H_2O_2 leads to the formation of peracid **44** which, via the classical BV reaction, leads to product esters, regenerating **42** for a new catalytic cycle. The nucleophilic cocatalyst 4-dimethylamino pyridine (DMAP) is necessary to guarantee catalyst turnover, since peracid **44** may react with excess DIC or O-acyl urea **43** to give inactive diacyl peroxide **45** [54]. DMAP enabled perhydrolysis of the diacyl peroxide **45** to regenerate the active peracid **44**.

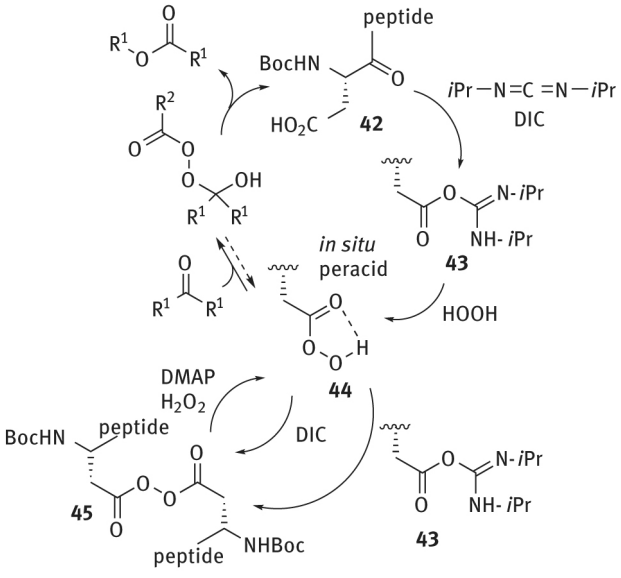

Figure 32: Acid/peracid catalytic cycle for the BV oxidation promoted by aspartate-containing peptide.

In 2014, the authors exploited a combinatorial approach in order to find the optimal peptide sequence able to catalyse the oxidization of relatively unstrained ketones, such as cyclohexanones and cyclopentanones, to afford products with both regio- and enantioselectivity [55]. An on-bead library of catalysts was synthesized and tested in a model kinetic resolution via BV reaction, identifying the most suited peptide motif sequence. Finally, the optimization and identification of mechanistic roles of the different regions of the catalyst led to the choice of the best catalyst **46** to promote the regio- and enantioselective BV oxidation of cyclic ketones bearing amide, urea or sulfonamide functional groups (Figure 33 and Figure 34). These catalysts, by means of directing

group interactions, showed the ability to overturn the regioselectivity exhibited by *m*-CPBA, that is, the intrinsic migratory aptitude of substrates, giving access to generally disfavored BV products (Figure 33).

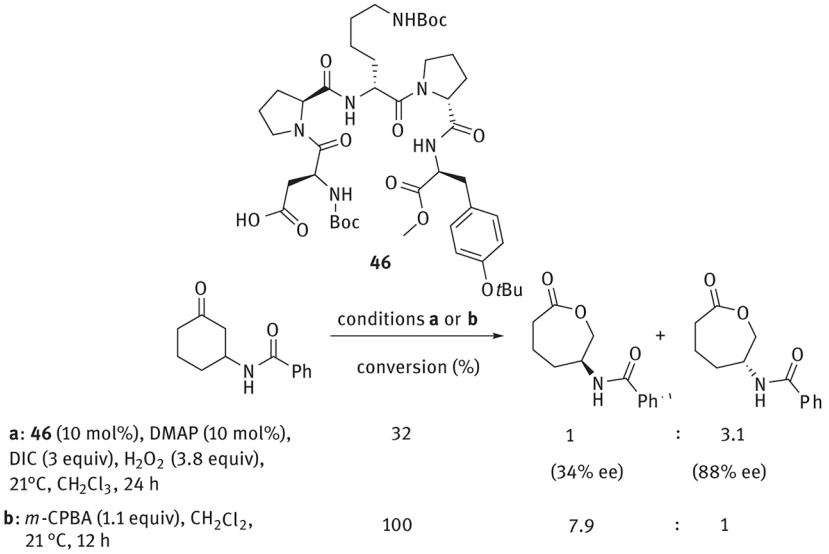

Figure 33: Effect of peptide catalyst **7a** on regioselectivity of BV oxidation.

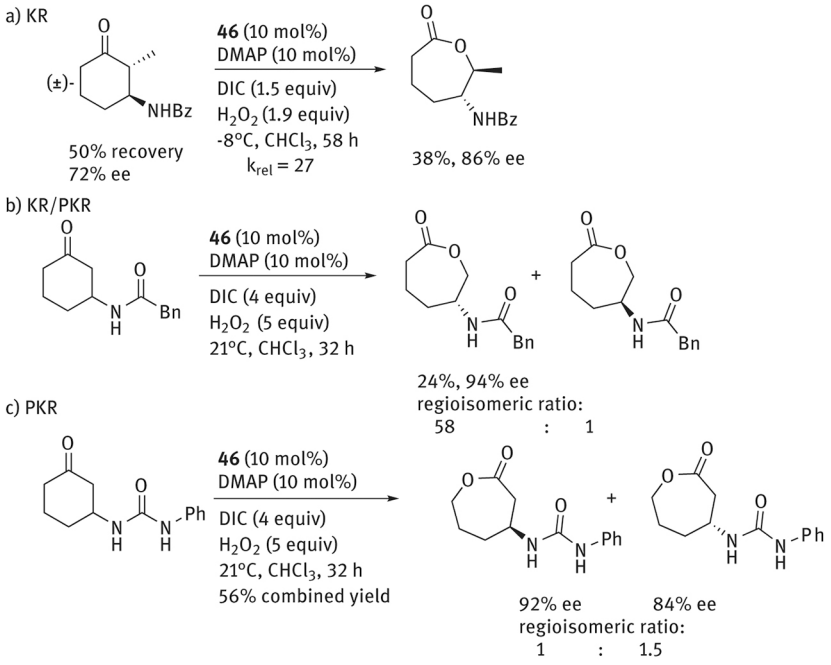

Figure 34: Selected substrates to show the distinct modes of reactivity promoted by catalyst **46.**

They suggested that both types of selectivity arise from the interactions between the peptide and H-bonding functionality of the substrate. Moreover, depending on the substrate, the catalyst is able to promote different reaction mechanisms, from classical kinetic resolution (KR) to parallel kinetic resolution (PKR) [56] (Figure 34).

The first example in Figure 34 (equation a) represents a classical kinetic resolution in which only the "*m*-CPBA-disfavored" lactone was isolated in 38 % yield and 86 % ee and the starting ketone was recovered in 50 % yield and 72 % ee (k_{rel} = 27). The second oxidation (Figure 34(b)) is a case in the middle between KR/PKR, since each substrate enantiomer affords a different regioisomer but at different rates, allowing the isolation of the "*m*-CPBA-disfavored" lactone in 24 % yield (regioisomeric ratio > 58:1) and 94 % ee. In the third example (Figure 34(c)), the cyclohexanone undergoes an oxidation with PKR behavior, in which the product "*m*-CPBA-disfavored" and the "normal" lactone, result of the intrinsic migratory aptitude, are formed in near equal quantities with similar ees.

Later, Miller and Anslyn reported a synergistic bioinformatics-inspired combinatorial and chiroptical study of peptide catalysts to set up the enantioselective BV oxidation of substrates lacking directing groups [57].

Investigation on protein loop sequences which have been observed to interact with tetrahedral anions, structurally similar to the Criegee intermediate, led to the identification of two families of peptide catalysts able to promote the enantioselective BV oxidation of a sterically challenging *cis*-2,6-diphenylcyclohexanone. This substrate is a minimum model of highly encumbered ketones found in terpene and polyketide natural products (Figure 35(a)).

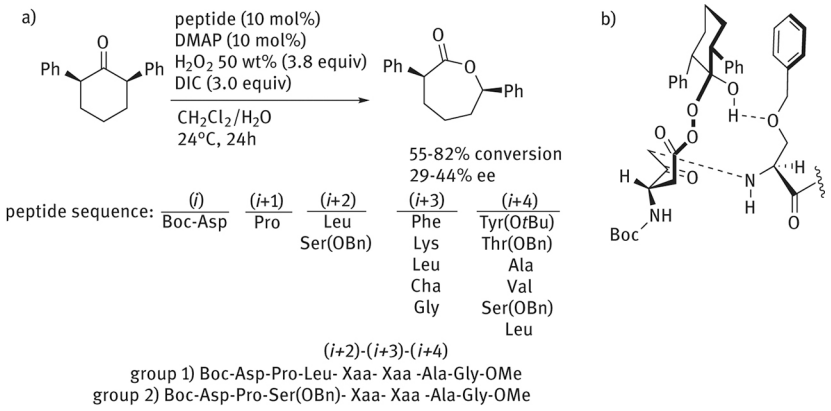

Figure 35: (A) Peptide catalysts for the BV oxidation of encumbered directing group-free ketone. (B) Hypotesized H-bonding interactions between Criegee intermediate and Ser(OBn) side-chain.

One family universally has an O-benzyl serine residue in the $(i + 2)$ position, while the second group has an $(i + 2)$ leucine residue, where (i) is the position of N-terminal residue N-(*t*-butoxycarbonyl)-L-aspartic acid followed by an L-proline residue at $(i + 1)$ position. The authors suggested a mode of asymmetric induction where the H-bond interactions between the $(i + 2)$ residue and the catalyst-bound Criegee intermediate are crucial for the asymmetric induction (Figure 35(b)).

In 2016, Yamamoto and coauthors, reported the first application in asymmetric BV reactions of a supramolecular assembly, an ion-pair catalyst derived by *in situ* assembly of a chiral flavinium and a cinchona alkaloid dimer [58]. The idea was the generation of a supramolecular catalyst by self-assembly via non-covalent interactions, of a chiral base, that induces the stereoselectivity, and a catalytically active molecule, an active flavinium specie. Flavin derivatives are known promoters of BV oxidation, using molecular oxygen or hydrogen peroxide. Nevertheless, they provided limited stereoselectivities, due to their conformational changes during the redox cycle. A variety of 3-substituted cyclobutanones were oxidized with good to excellent enantioselectivities, up to 96 % ee (Figure 36). The authors proposed a model of the transition state depicted in Figure 37. The chiral flavinium is linked with the matched chiral cinchona dimer by π–π and ionic interactions, setting a selective orientation in which there is no steric interference between the ethyl group of the DHQ and the phenyl group next to N^1. The hydrogen peroxide, deprotonated by the other basic site, attacks the iminium of the flavinium generating a hydroperoxy specie which reacts with the less-hindered face of the cyclobutanone. The latter likely being activated by H-bonding with ammonium of cinchona alkaloid, producing the Criegee intermediate that rearranges to produce the enantioenriched γ-lactone.

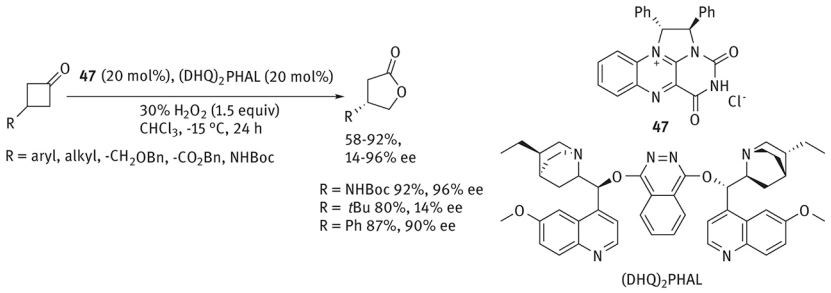

Figure 36: Self-assembled flavinium-cinchona alkaloid dimer organocatalyst for enantioselective BV oxidation.

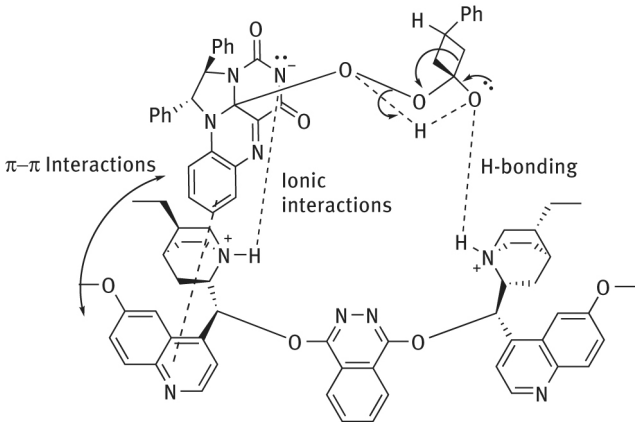

Figure 37: Hypothesized transition state of BV oxidation of 3-phenylcyclobutanone catalyzed by flavinium-cinchona alkaloid dimer.

Oxidative enantioselective desymmetrization of prochiral and *meso*-compounds has been also reported. Zhao and coauthors described the enantioselective oxidation of 1,2-diols using N-bromophthalimide (NBP), organocatalyzed by quinine derived urea **48** at room temperature, in a mixed solvent system ($CHCl_3$/PhCl 10:1) (Figure 38(a)) [59]. The method gave access to the corresponding α-hydroxy ketones in good yields (65–94 %) and good to excellent enantioselectivity (66–95 % ee) starting from diaryl-substituted *meso*-1,2-diols. The catalytic process was selective toward diol mono-oxidation and the overoxidized dione was produced in traces. When starting from dialkyl-substitued diols, the resulting α-hydroxy ketone was isolated in lower yield and enantioselectivity (Figure 38(a)).

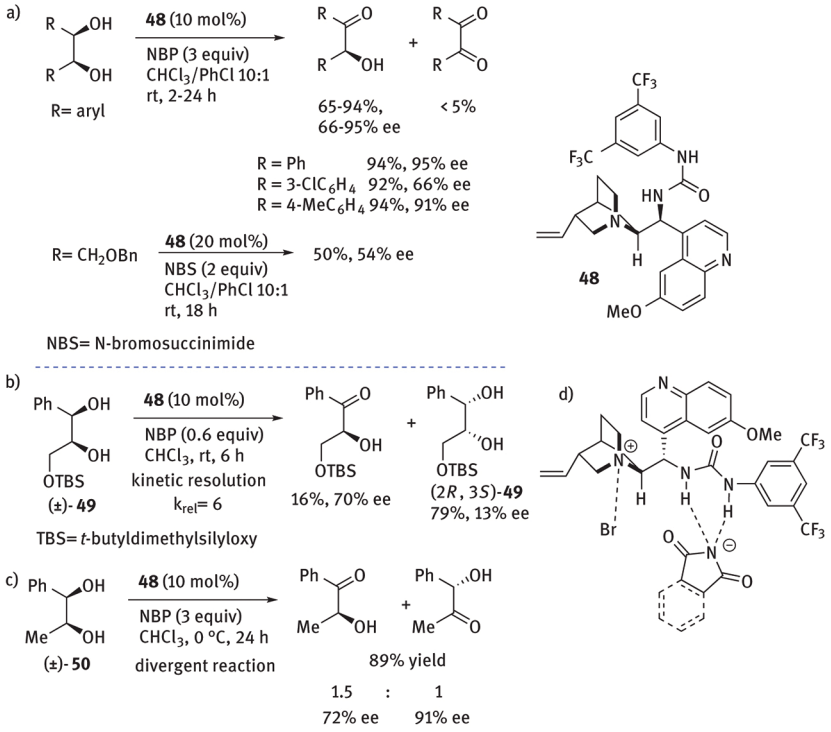

Figure 38: (A) Enantioselective oxidative desymmetrization of meso-diols organocatalyzed by quinine-derived thiourea. (B) Kinetic resolution and (C) divergent reaction on racemic diols. (D) Model of Lewis base and H-bond donor catalytic abilities of quinine-thiourea.

The less efficient oxidation of dialkyl-substituted diols was exploited in the resolution of racemic *syn*-diols via classical kinetic resolution or divergent reaction, depending on the substrate (Figure 38(b, c)).

The authors speculated that H-bonding interactions among the catalyst urea moiety, the phthalimide and diol are pivotal in the organization of a rigid transition state accounting for the high enantioselectivity. Moreover, the quinuclidine nitrogen of the catalyst is involved in complexation with NBP (Figure 38(d)).

An interesting strategy for the enantioselective organocatalyzed desymmetrization of 2-substituted and 2,2-disubstituted 1,3-diols was reported in 2014 by Houk and Zheng [60]. The desymmetrization of 2-substituted

1,3-diols represents a more challenging task given the pro-stereogenic center distance from hydroxyl group and primary alcohols are stronger nucleophiles. The 1,3-diols were protected with benzylidene acetals, able to undergo a selective oxidation by dimethyldioxirane (DMDO), forming an "ortho ester" intermediate **51** (Figure 39). Since a proton transfer process is involved to transform intermediate **51** into the final product, the authors envisioned that chiral phosphoric acids, could promote this step inducing enantioselectivity. A wide variety of 2-substituted and 2,2-disubstituted 1,3-diols were transformed into the corresponding products in high yields and enantioselectivity, using the chiral phosphoric acid **TRIP** (Figure 39).

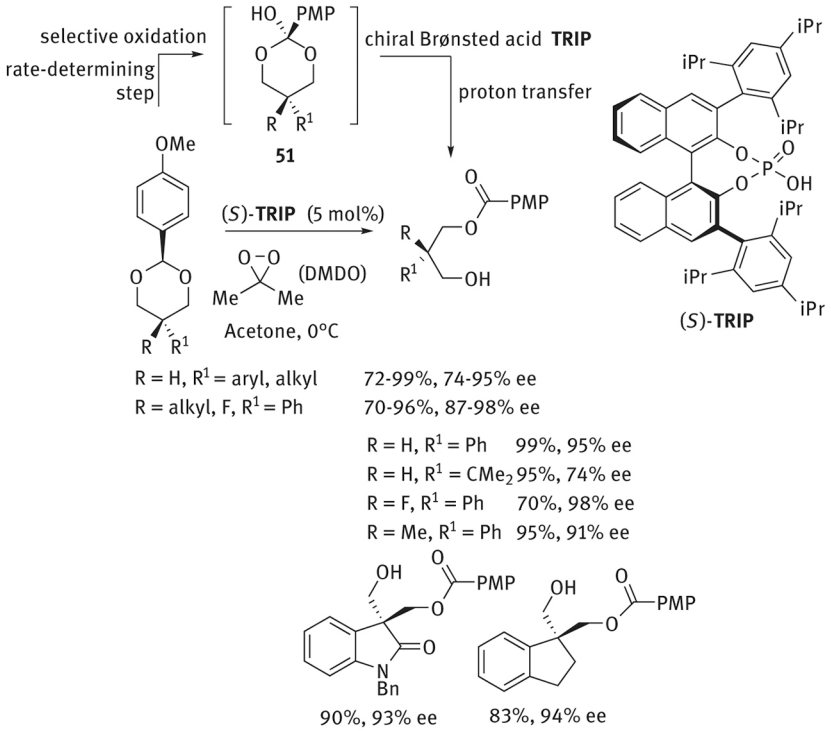

Figure 39: Chiral phosphoric acid catalyzed enantioselective desymmetrization of 2-substitued and 2,2-disubstituted 1,3-diols.

The DFT study of the mechanism showed that the oxidation of acetal by DMDO is the rate-determining step and the proton transfer is significantly accelerated by the phosphoric acid. Attractive aryl–aryl interactions between benzylidene moiety of the substrate and 2,4,6-triisopropylphenyl group of the catalyst were identified as crucial for the enantiocontrol.

In 2018, Zheng applied this approach to the enantioselective synthesis of acyclic α-tertiary amines via desymmetrization of 2-substituted 2-nitro-1,3-diols (Figure 40) [61].

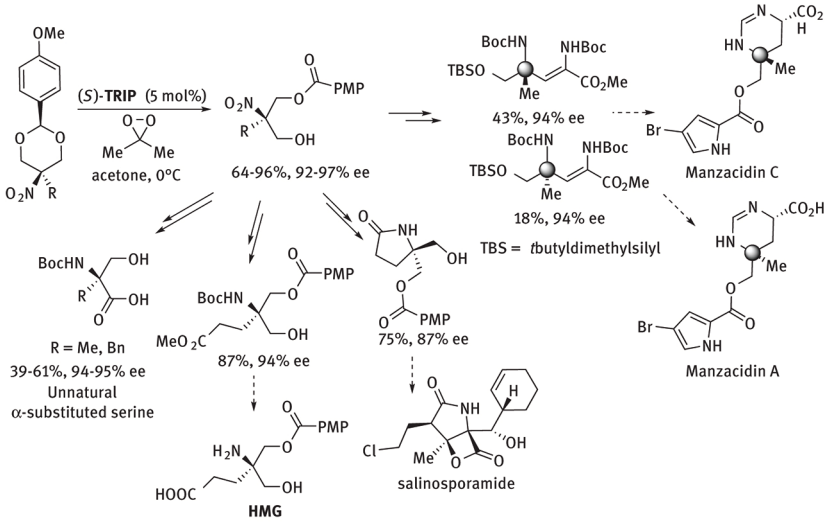

Figure 40: Chiral phosphoric acid catalyzed enantioselective desymmetrization of 2-substituted 2-nitro-1,3-diols for the synthesis of acyclic α-tertiary amines.

The protocol allowed to isolate a wide variety of chiral 2-nitro-1,3-diols in high yields and enantioselectivity, giving access to optically active valuable building blocks such as unnatural α-alkyl serines, precursors of hydroxymethyl glutamic acid (HMG) and natural product salinosporamide. Furthermore, the formal synthesis of chiral manzacidines, a family of bromopyrrole alkaloids isolated from sponges, was accomplished.

5 Miscellaneous

The development of sustainable methodologies which employ readily available molecular oxygen and visible light source received a lot of attention in the last years, becoming an important area of research in catalytic oxidation reactions [62]. The 2,2-disubstituted indolin-3-ones are molecular units found in pseudoindoxyl alkaloids and natural products. Therefore, simple and sustainable methods focused on their stereoselective approach are highly desirable. In this context, a first example on an enantioselective cascade aerobic oxidation and semipinacol rearrangement reaction of 2-aryl-3-alkylsubstituted indoles via photoredox and hydrogen-bonding catalysis was illustrated by Lu and coauthors in 2014 (Figure 41) [63].

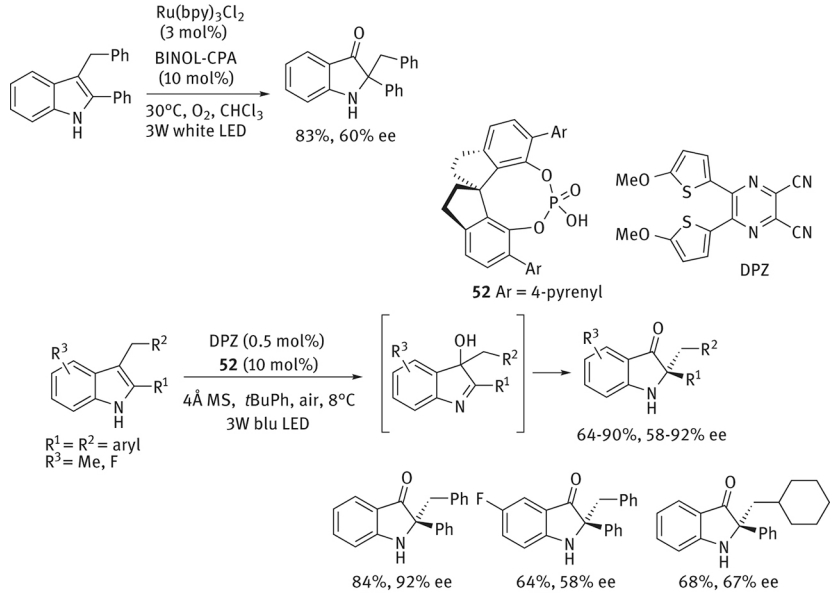

Figure 41: Enantioselective visible light-driven photo- and organocatalyzed access to 2,2-disubstituted indolin-3-ones under aerobic conditions.

Irradiation of the reaction mixture containing substituted indole, catalytic loadings of $Ru(byp)_3Cl_2$ as the photoredox catalyst and a BINOL-based phosphoric acid, afforded the 2,2-disubstituted indolin-3-one in 83 % yield and 60 % ee. This enantioselective cascade reaction was recently in-depth investigated by Jiang, Zhao et al. combining the dicyanopyrazine-derived chromophore (DPZ) as an organic photoredox catalyst and a SPINOL-based spirocyclic phosphoric acid **52** [64].

Under aerobic and slightly different reaction conditions, the 2-aryl-3-alkylsubstituted indoles, were converted into the 2,2-disubstituted indolin-3-ones, via the formation of intermediate 3-benzyl-2-phenyl-3H-indolin-3-ol, in good yields and good to high ee values (Figure 41). Single-electron transfer of DPZ as the photoredox catalyst to oxidize indole to a radical cation species, then captured by molecular oxygen, was demonstrated. Preliminary investigations on the stereoselective outcome of the cascade process showed the primary role of catalyst **52** to foster the conversion to the product. Moreover, catalyst **52** would be involved in the enantiocontrol of the first oxidation, whereas the intermediate 3-benzyl-2-phenyl-3H-indolin-3-ol would act as a chiral promoter for the semipinacol rearrangement.

6 Outlook and perspectives

In the last 6 years, new methodologies to stereoselectively oxidize readily available carbonyl compounds, alkenes and heterocycles have been developed by using a variety of organocatalysts such as bifunctional or

phase transfer catalysts derived from cinchona alkaloids, BINOL or SPINOL-based phosphoric acids, bisguanidinium salts, diols, peptides, hypervalent iodine-based compounds. These organocatalysts were employed in fundamental oxyfunctionalization reactions, thus becoming either alternative or complements to well-known metal-based catalyzed processes. Given the continuous request of a less-polluting and energetically convenient chemistry for the production of fine chemicals, it is likely to expect that future developments will focus on the synthesis and application of new organocatalysts suitable to work under greener oxidative and visible light conditions. Indeed, in this context, competitive stereoselective methodologies are truly awaited.

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