Organocatalyzed Assembly of Chlorinated Quaternary Stereogenic Centers

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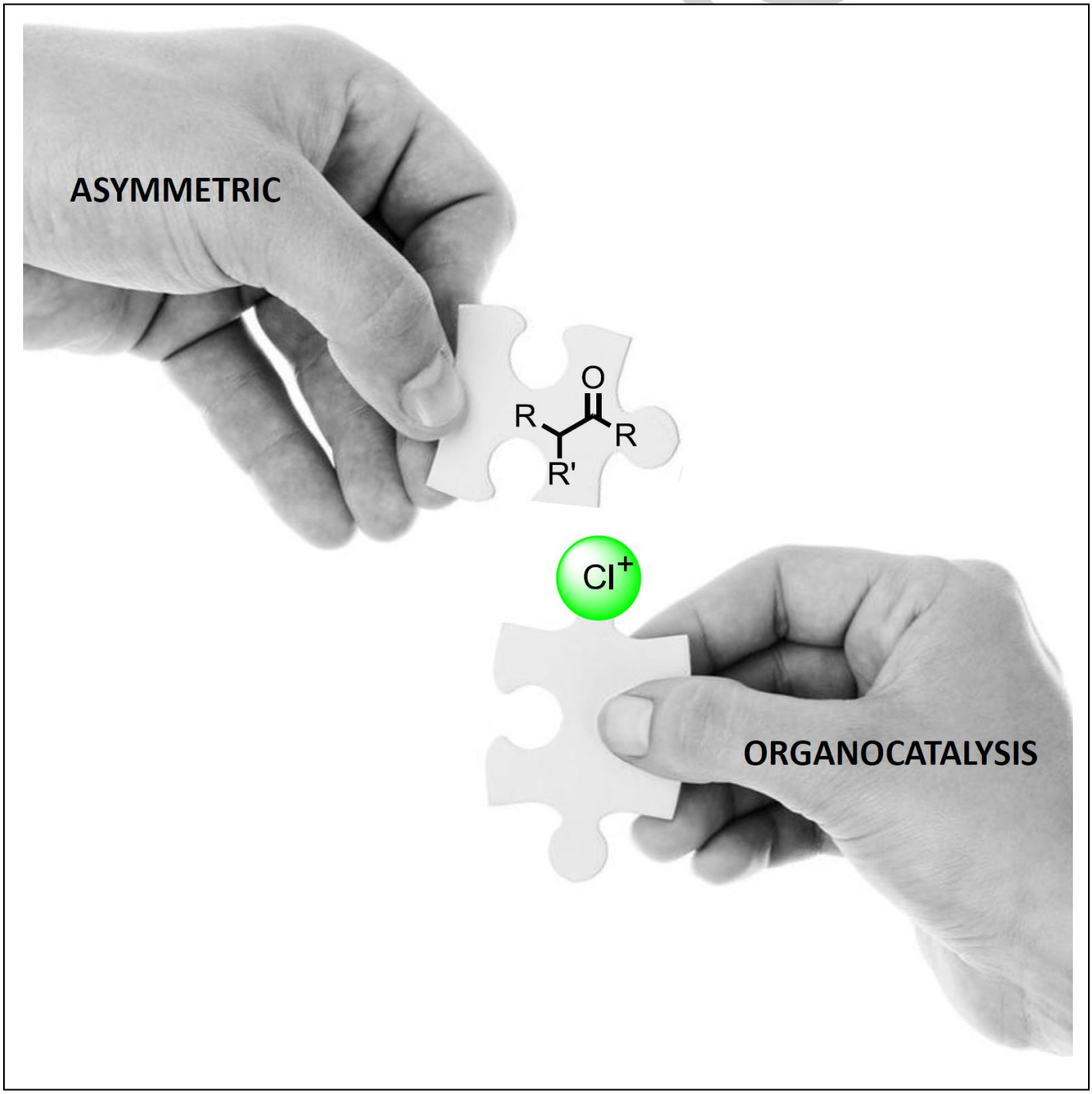

Abstract: The catalytic asymmetric construction of chiral quaternary stereocenters is always a continuous area of research in organic chemistry. In this sense, when a chlorine atom takes part in a quaternary stereocenter, the difficulty of its synthesis increases along with the significance of the resulting products. This is true, not only because of the intrinsic interest of such chlorinated molecules, but also because they are considered as highly valuable chiral building blocks in organic synthesis, as they can be converted to more complexes molecules by a simple S_N2 displacement. Among the different strategies followed to create chlorinated quaternary stereogenic centers, organocatalysis has played a pivotal role during the last decade. In this review, a comprehensive analysis of such organocatalyzed transformations, which are mainly focalized on the the α-chlorination of carbonyl compounds, is presented.

1. Introduction

Currently, about 85 percent of all pharmaceuticals (prescription and over-the-counter) contain or are manufactured using chlorine. Moreover, of the top-selling pharmaceutically active compounds contain chlorine, since chlorinated analogues of drugs have been often shown to provide metabolic stability compared with their parent compounds without loss in substrate binding affinity.[1]

Additionally, molecules possessing stereocenters containing a chlorine atom are considered highly versatile building blocks in organic synthesis, since they can be converted and further elaborated to other functionalities by simply S_N2 displacement. [2]

On the other hand, the installation of a chlorine atom in an enantioselective manner is not an easy task. The main difficulties are related to the high reactivity of the chlorinating agents which sometimes can promote themselves the chlorination of the prochiral centers in an uncatalyzed pathway.

Due to these reasons, it is not surprising that the catalytic asymmetric synthesis of such chlorinated molecules has attracted the curiosity of the organic chemistry community and has been intensively investigated in the past few years.

The first successful approximations to accomplish this purpose were develped on metal catalysis.[2],[3] However, the irruption of asymmetric organocatalysis during the last fifteen years has permitted to perform this task in the absence of metals.[4]

While construction of chlorinated tertiary stereocenters by means of organocatalytic methods has been widely explored in the last years using strategies such as enamine catalysis,[5] only a few successful catalysts have been shown to be highly selective in the enantioselective construction of chlorinated quaternary stereocenters.

Thus, the aim of this Focus Review is to highlight those organocatalytic enantioselective strategies focused on the challenging installation of chlorinated quaternary stereogenic centers, being the majority of those strategies based on the α-chlorination of carbonyl compounds. For the sake of clarity, the activation mode of the organocatalysts employed will be the criterion followed to classify the next sections and subsections. In each of them a comprehensive overview of the most recent literature in this topic will be presented.

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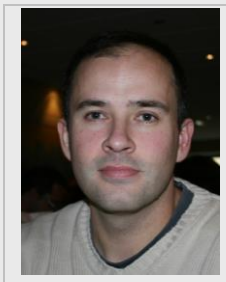


Isidro M. Pastor was born in Alicante (Spain) and studied chemistry at the University of Alicante, from which he obtained B.Sc. (1996) and M.Sc. (1997) degrees. He received his doctorate in 2000 from the University of Alicante. In 2000, he joined the research group of Prof. Hans Adolfsson at the Arrhenius Laboratory (Stockholm University, Sweden) as a postdoctoral fellow until the end of 2002. In 2003, he returned to the University of Alicante where he was appointed Teaching Assistant in 2003, Assistant Professor in 2004, Lecturer in 2007 and Associate Professor in 2010. His research interests are in the field of organometallic chemistry, heterocyclic chemistry, metal-organic frameworks and catalysis.

Gabriela Guillena was born in Alicante (Spain) in 1970 and received her B.Sc. degree (1993) from the University of Alicante. After spending one year as postgraduate student in the group of Prof. D. Seebach (ETH, Zürich), she returned to the University of Alicante and received her M.Sc. (1995) and Ph.D. (2000) degrees. After two years as a postdoctoral fellow in the research group of Prof. G. van Koten (University of Utrecht, Netherlands), she returned to the University of Alicante where she became Assistant Professor (2003) and Associate Professor (2007). In 2015 she obtained the habilitation to become Full Professor. Her current research interest is focused on new organic methodologies and asymmetric organocatalysis.

Alejandro Baeza was born in Alicante (Spain) in 1979. After studying chemistry at the University of Alicante, he received the M.Sc. (2003) and Ph.D. degrees (2006) from the same university. In 2007 he joined Prof. Pfaltz group in Basel University as postdoctoral researcher where he spent 3 years. In 2010 he moved back to Alicante working as Associate Researcher, being since 2015 Assistant Professor. His main research interests are focused in the development of new methodologies, especially in green chemistry and asymmetric catalysis area.

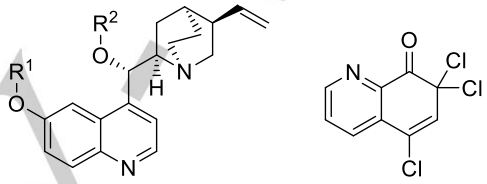
2. Non-covalent Interactions

2.1. Amine-based Organocatalysis

The use of chiral tertiary amines to catalyze the asymmetric chlorination was first reported by the group of Bartoli and Melchiorre, being the early example of an organocatalyzed process for such transformation.[6] Thus, cinchona alkaloid derivatives were evaluated as chiral base to promote the enolization of 1,3-dicarbonyl compounds which subsequently reacted with the halogen source. Benzoylquinidine **1a** (Figure 1), in 5 mol-%, allowed the chlorination of different cyclic and acyclic *β*-keto esters, producing the corresponding chlorinated derivatives in fairly good yields and with excellent optical purity (Figure 2).[6] The chlorination of cyclic diketones proceeded smoothly to give the expected products with moderate enantioselectivity. The authors pointed out the importance of the chlorine source in order to maximize the asymmetric catalyzed halogenation versus the uncatalyzed formation of the enol, with trichloroquinolinone **2** (Figure 1) being the best agent. The mechanism probably occurs via the formation of a tight ionic intermediate **3** with the protonated chiral amine, and the presence of an inorganic base helping the proton transfer (Scheme 1).

Meng and co-workers have tested other diterpenoid alkaloids bearing secondary and tertiary amines, such as vincamine, vinpocetine, cytisine, galantamine, sinomenine and six lappaconitine derivatives, as organocatalysts in the enantioselective chlorination of β-keto esters using *N*-chlorophthalimide as chlorine source.[7] Nevertheless, only moderate selectivities were achieved (up to 68% ee) employing 10 mol% of the catalyst.

A variety of amino diol derivatives, which have been obtained easily by transformation of protected D-glyceraldehyde, have been also tested as organocatalysts in the enantioselective chlorination of cyclic β-keto esters.[8] Among them, organocatalyst **4** (Figure 3) proved to be the most efficient, producing comparable results to the obtained by employing cinchona derivatives. The reactions mediated by **4** were performed using *N*-chlorosuccinimide (NCS), as chlorine source, at room temperature or 0 ºC during 24 h, albeit double amount of catalyst **4** was needed (10 mol%) compared with **1a**.



1a [R^1 = Me, R^2 = Bz]
1b [R^1 = H, R^2 = Bn]

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Figure 1. Cinchona alkaloid derivatives **1** (organocatalysts) and trichloroquinolinone **2** (chlorine source).

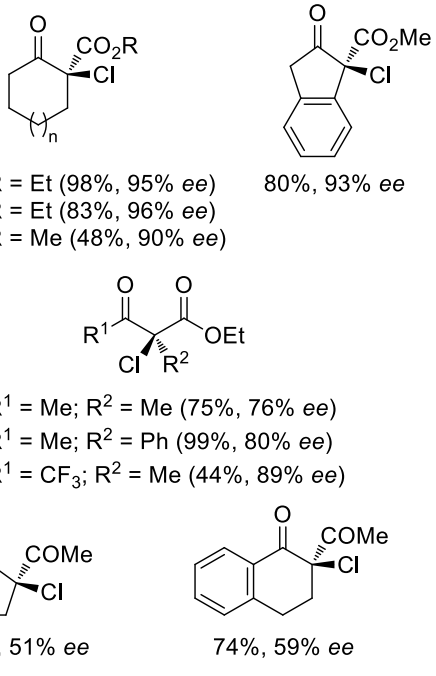
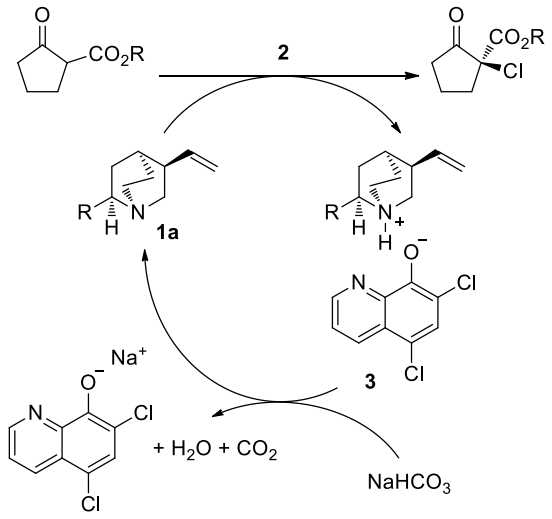


Figure 2. Asymmetric chlorination products obtained using benzoylquinidine (**1a**) as chiral organocatalyst .



Scheme 1. Proposed mechanism for chlorination of 1,3-dicarbonyl compounds catalysed by cinchona derivatives.[6]

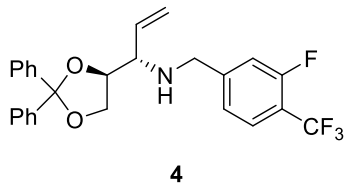


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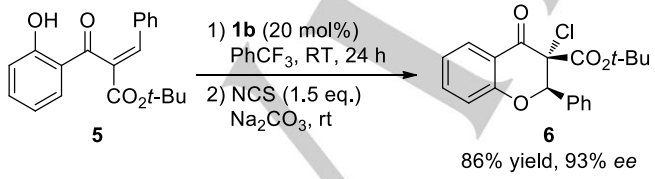
Figure 3. Amino diol derivative **4** employed as organocatalyst.

Cinchona alkaloid derivatives, have been described as organocatalyst in the synthesis of flavonones via oxa-Michael addition followed by a decarboxylation reaction when performing the reaction with alkylidene β-keto esters, such as **5** (Scheme 2). Interestingly, the enolate intermediate produced after the oxa-Michael addition can be transformed into the chlorinated product **6** mediated by the same organocatalyst **1b** through electrophilic chlorination with NCS (Figure 1) with excellent enantioselectivity (Scheme 2).[9] Thus, the organocatalyst plays a dual role in this transformation.

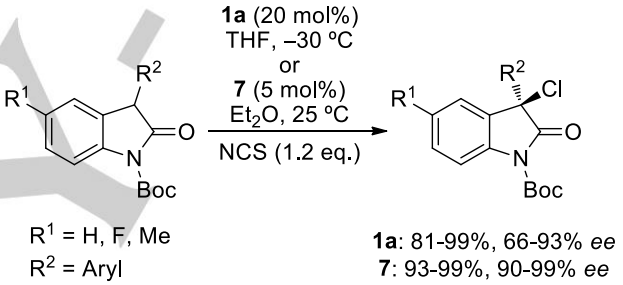


5 **6**

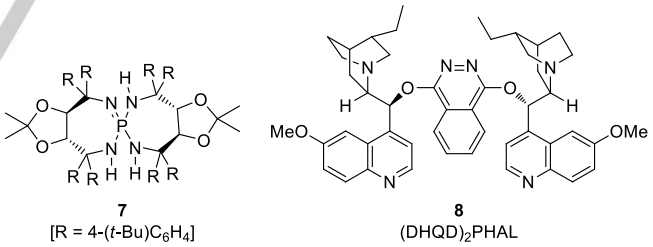
86% yield, 93% *ee*

Scheme 2. Organocatalytic intramolecular oxa-Michael addition/chlorination tandem reaction.

The enantioselective chlorination of 3-aryloxindoles has been achieved using *N*-chlorosuccinimide (NCS) as chlorine source. The first report employed cinchona alkaloid derivatives as organocatalyst, performing the reaction under mild conditions. Among the organocatalyst tested, *O*-benzoylquinidine (**1a**) gave the best results in terms of enantioselectivity. Solvent, temperature and protecting group in the oxindole nitrogen proved to have influence in the outcome of the reaction, being the effect higher on the selectivity than on the activity of the quinidine derivative. Thus, different chlorinated oxindoles were obtained by reaction in tetrahydrofuran (THF) at –30 ºC using 20 mol% of catalyst (Scheme 3).[10] More recently, chiral iminophosphoranes prepared from tartaric acid have been reported as efficient organocatalyst in the chlorination of 3-aryloxindoles. This type of organocatalyst proved to be better than cinchona alkaloids. Indeed, iminophosphorane **7** (5 mol%) catalyzed efficiently the chlorination reaction in diethyl ether at room temperature, providing the corresponding products with good to excellent yields and enantioselectivities (Scheme 3).[11] Moreover, organocatalyst **7** was also active in the chlorination of 3-benzyl and 3-methyloxindole with good enantioselectivities (90% *ee*).



Scheme 3. Enantioselective chlorination of oxindoles mediated by **1a** and **7**.

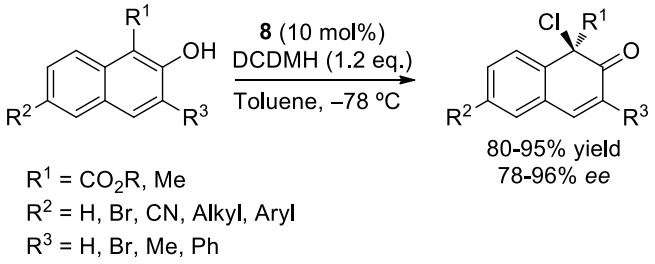


7 [R = 4-(*t*-Bu)C_6H_4] **8** $(DHQD)_2PHAL$

Figure 4. Organocatalysts: iminophosphorane **7** and cinchonine derivative **8** [$(DHQD)_2PHAL$].

The enantioselective chlorinative dearomatization of naphthols has been achieved employing a cinchonine derivative, such as the commercially available $(DHQD)_2PHAL$ **8** (Figure 4).[12] The protocol allowed the preparation of enantioenriched naphthalenones with a chlorine atom in a quaternary center. The reaction proceeded smoothly at low temperature (–78 ºC) using 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) as chlorinating agent. Several 2-naphthols were transformed by means of this methodology (Scheme 4).[12] The chlorination was successful with 1-hydroxy-2-naphthoate, although a different solvent (1/1 mixture $CHCl_3/CCl_4$) was needed. The authors clearly

demonstrated the synthetic utility of these products by performing different transformations onto them, rendering the corresponding highly functionalized tetralones.



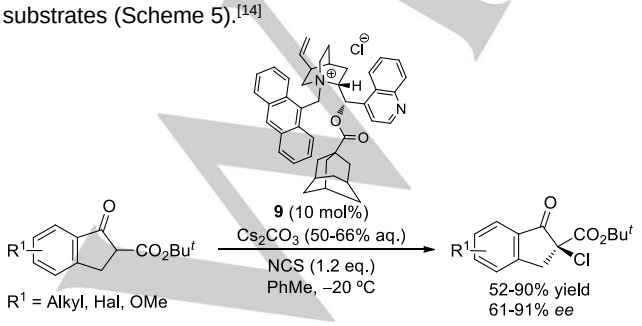
Scheme 4. Enantioselective chlorinative dearomatization of 2-naphthols.

2.2. Phase Transfer Catalysis

Asymmetric phase-transfer catalysis (PTC) is a remarkable method to synthesize enantioenriched compounds using different chiral quaternary salts which have been developed in the past decades.[13] This useful approach involves normally mild reaction conditions while using inexpensive and environmentally benign reagents and solvents. For this reason it is not surprising that PTC has been extensively used to create, among others, new C-C, C-N and C-O bonds in an enantioselective manner. For example, alkylation, aldol, Darzens, Mannich, hydroxylation, cyanation or cyclization reactions, and many more, have been carried out using such catalysts, being the most employed ones bifunctional chiral ammonium salts coming from natural and non natural sources such as cinchona or binaphtyl derivatives.

However, despite the extensive work already done in the PTC field, there are only a few examples in which the generation of a quaternary stereocenter bearing a chlorine atom is accomplished, being exclusively restricted to the asymmetric *α*-chlorination reaction of dicarbonyl compounds.

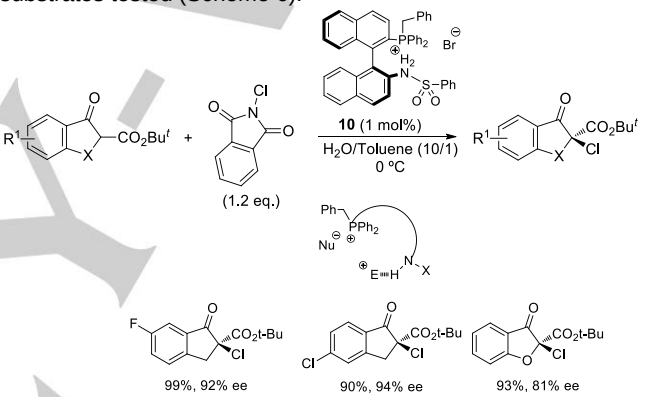
The synthesis of chlorinated quaternary centers using a common phase-transfer catalysis, an ammonium salt derived from cinchonine, was not publish until 2013. Thus, Lu and co-workers carried out the enantioselective *α*-chlorination of *β*-ketoesters using 10 mol% of catalyst **9**, cesium carbonate as a base and NCS (1.2 eq.) as chlorine source in toluene at −20 °C. Normally, good isolated yields and moderate to high enantioselectivities were obtained for the benzocondensed substrates (Scheme 5).[14]



Scheme 5. Cinchona alkaloid-based PTC chlorination of *β*-keto esters

Although, there is no a clear trend about how the nature of the substituents in the aryl ring affects the selectivity of the process, apparently the presence of electron donating groups, such as a methoxy group at the 5-position of the aromatic ring, seems to have a positive effect on the enantioselectivity. In this same article, the asymmetric fluorination reaction was also evaluated obtaining good results

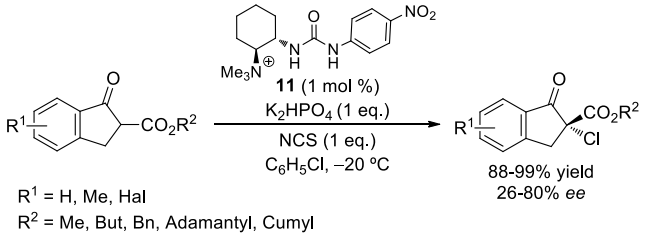
Nearly simultaneously, Maruoka *et al.* employed a quaternary phosphonium bromide bearing also a sulfonamide moiety as bifunctional chiral phase-transfer catalyst for the enantioselective chlorination of *β*-ketoesters. The reaction was performed employing as low as 1 mol% of **10**, *N*-chlorophtalimide (1.2 eq.) as chlorine source, water/toluene (10/1) as solvent at 0 °C. Under these reaction conditions, high yields and enantioselectivities were obtained with the three substrates tested (Scheme 6).[15]



Scheme 6. Amino-phosphonium salt **10** catalyzed chlorination of *β*-keto esters.

According to the authors, the catalyst has a bifunctional role, being the phosphonium group the responsible of nucleophile activation whereas the sulfonamide group coordinates the electrophile via hydrogen bond, approaching both substrates (Scheme 6). The same procedure was also applied in the sulfenylation reaction of 1.3-dicarbonyl compounds with excellent results.[15]

Finally, very recently, it has been published by Waser the asymmetric α-chlorination of β-ketoesters catalyzed by a bifunctional urea containing a quaternary ammonium salt. The optimized reaction conditions were 1 mol% of **11**, NCS as chlorine source (1.2 eq.), K_2HPO_4 (1 eq) as a base in chlorobenzene as solvent at −20 °C. The corresponding chlorinated products were isolated in good to excellent yields and moderate to good enantioselectivities (Scheme 7).[16]



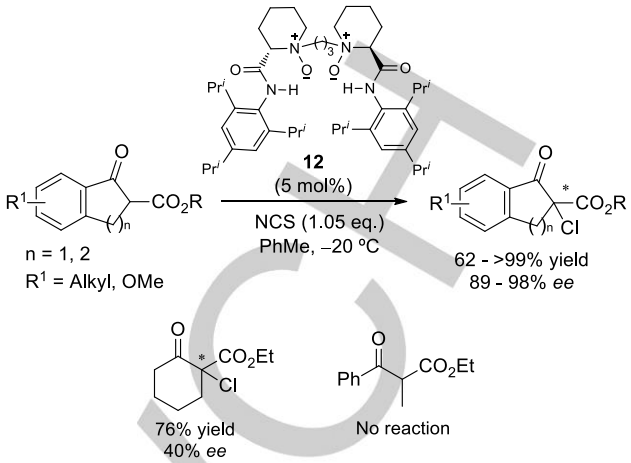
Scheme 7. Ammonium-urea derived catalyst **11** for chlorination of β-keto esters.

It is important to note that the selectivity of the process does not depend significantly on the nature of the aryl substituent but seems to be highly dependent on the ester functionalization. Thus, bulkier ester groups, such as adamantyl or cumyl, gave rise to the best enantiomeric ratios. The same activation mode as previously proposed by Maruoka´s group was assumed by the authors.

2.3. Hydrogen-Bond Catalysis

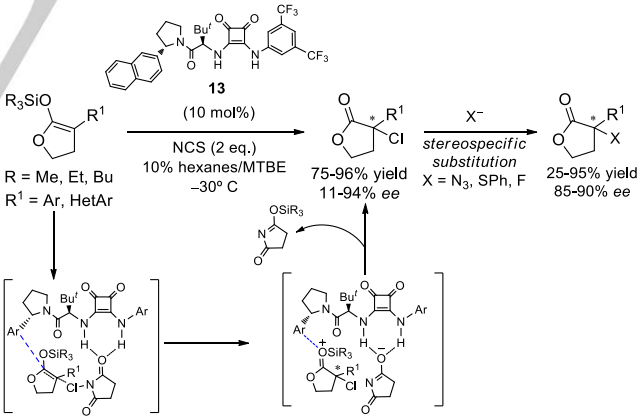
Despite the enormous growth that asymmetric hydrogen-bonding organocatalysis has experimented during the last years, the use of such type of catalysts for the construction of chlorinated quaternary stereocenters remains scarce and only a few examples can be found in literature. Within the processes that employs this kind of hydrogen-bond activation, it is necessary to distinguish between those consisting in the chlorination of prochiral compounds, and those in which the chirality is established by the action of the aforementioned organocatalysts onto a tertiary carbon already possessing a chlorine atom. When considering the first case, which can be conceived as a more challenging, but at the same time, as a more synthetically attractive strategy, the number of publications can be reduced, as far as we know, to three.

In this sense, the first example was reported by Feng and co-workers in 2010, where the *N,N'*-dioxide derivative **12** was employed as organocatalyst for the chlorination of different β-ketoesters with NCS (1.05 eq.) as chlorine source. Excellent results were obtained concerning both yields and enantioselectivities when benzocondensed derivatives were chosen as substrates. The use of other keto esters such as non-benzocondensed or acyclic ones, gave rise to a considerable drop in the enantioselectivity or to a failure in the reaction, respectively (Scheme 8). Although the mechanism of the reaction is not discussed, the *N*-oxide moiety on the catalyst seems to play a crucial role and the authors pointed out a possible hydrogen-bond activation.[17]



Scheme 8. Asymmetric chlorination of β-keto esters catalyzed by *N*-oxide **12**.

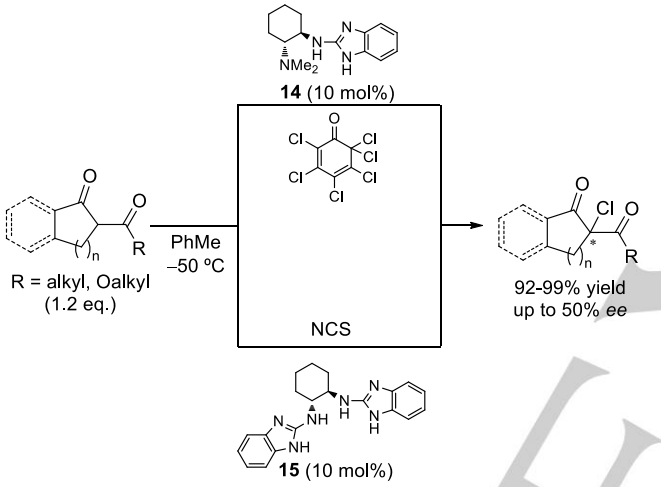
In 2015, the Jacobsen group reported the successful use of a chiral squaramide as a bifunctional catalyst capable to promote the asymmetric electrophilic chlorination of cyclic silyl ketene acetal through hydrogen-bond interactions as reflected in Scheme 9. According to the authors, the dual catalyst role comes from the somehow expected hydrogen bond activation of the electrophile and the no so evident aryl-transitien cation (π-cation) interaction. Under the optimized conditions, high yields and enantioselectivities were obtained in the majority of the cases regardless the silyl group and aromatic moiety employed. The utility of these new generated compounds possessing a chlorinated quaternary stereocenter was clearly demonstrated by S_N2 displacement with several nucleophiles.[18]



Scheme 9. Asymmetric chlorination of silyl ketene acetals catalyzed by squaramide **13** and synthetic applications.

More recently, our research group has reported the use of benzimidazoles **14** and **15** as hydrogen-bond organocatalysts for the α-chlorination of different cyclic 1,3-dicarbonyl compounds.[19] It was found that the use of different chlorinating agents were necessary for each catalyst in order to reach the optimal results. In both cases, high yields and moderate *ee*'s

were obtained, being the enantioinduction slightly superior when catalyst **14** was employed (Scheme 10). Based on previous works from the group concerning the use of such catalysts for the enantioselective α-functionalization of 1,3-dicarbonyl compounds, the bifunctional role of the catalysts was assumed, where the tertiary amino group in **14** or a benzimidazole moiety in **15** acted as base able to deprotonate the α-acidic proton of the nucleophile. The corresponding enolate would be coordinated through hydrogen bond with the benzimidazole and the protonated nitrogen could be an extra anchorage point for the chlorinating agent through an hydrogen-bond interaction with its carbonyl group (acting as Brønsted acid) (Figure 5). It is worth to note that despite both catalysts have the same configuration, opposite enantiomers were obtained in the chlorination product. Further studies revealed that the configuration of the final product depends on the chlorinating agent employed.[19]



Scheme 10. Asymmetric chlorination of 1,3-dicarbonyl compounds catalyzed by benzimidazole derivatives **14** and **15**.

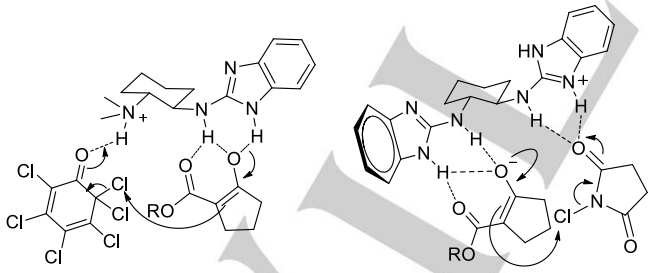
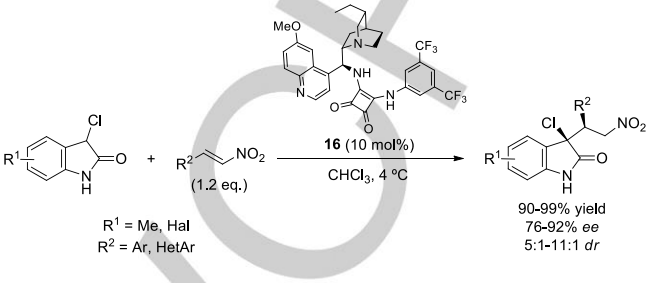


Figure 5. Proposed activation modes of organocatalysts **14** and **15**.

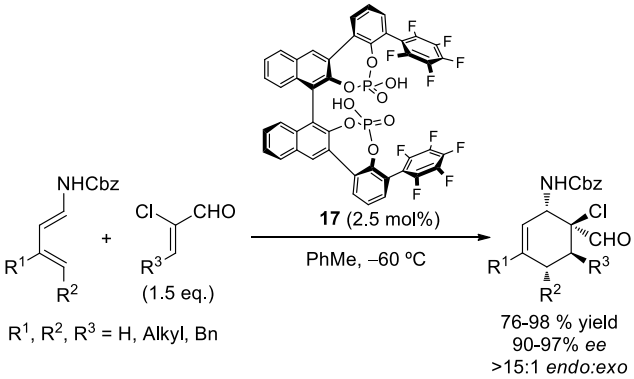
As previously mentioned, chiral quaternary chlorinated stereocenters have also been generated through hydrogen-bond organocatalysis using compounds bearing a chlorine atom on a tertiary prochiral carbon. Thus, cinchona-squaramide derivative **16** has been used by Kanger *et al.* for the Michael addition of 3-chlorooxindoles onto nitroolefins,[20] giving rise to the formation of two consecutive quaternary-tertiary stereocenters. The products were normally obtained with high yields and good to high enantio- and diastereoselectivities (Scheme 11). Once again, a dual role of the catalyst is proposed, being the tertiary amine and the squaramide moieties the responsible of deprotonation-activation of the chlorooxindole and the nitroalkene, respectively.[21]



Scheme 11. Asymmetric Michael addition of 3-chlorooxoindole catalyzed by squaramide **16**.

Shortly after, the group of Lu reported the very same reaction using also a similar amino-cinchona derivative although bearing a *O*-TBDPS-L-threonine-thiourea moiety instead of an squaramide. With this new catalyst the diastereoselectivities were further increased up to >25:1 in all the cases tested and the enantioselectivities achieved ranged 86-97% *ee*.[22] In addition, the corresponding enantioenriched 3-spirocyclopropyl-2-oxindoles were prepared in one pot by addition of an external base without erosion of the *ee*'s from the Michael products.

Another important class of catalysts able to activate substrates through hydrogen bond formation are chiral phosphoric acid derivatives. Despite their use being widespread in a myriad of organic transformations, there is only one recent example where a quaternary chlorinated stereocenter is formed involving the use of such catalysts. Specifically, this transformation consists in a Diels-Alder reaction between α-haloacroleins with substituted amidodienes, obtaining the corresponding cyclohexenes in high yields, excellent enantioselectivities and *endo:exo* ratios. The presence of two phosphoric acid derivatives allows the activation of both diene and acrolein (Scheme 12).[23,24]



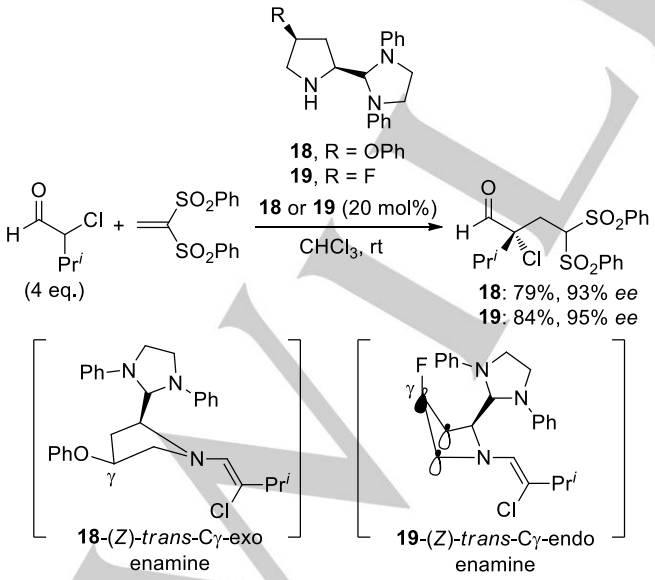
Scheme 12. Asymmetric Diels-Alder reaction catalyzed by **17**

3. Covalent Interactions

3.1. Iminium/Enamine-based Organocatalysis

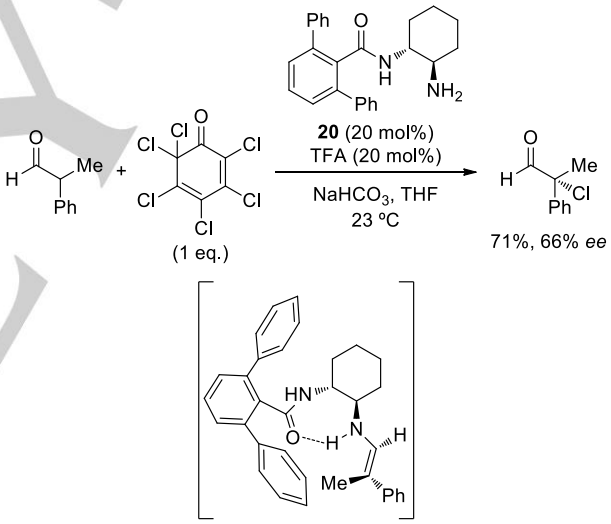
Organocatalysts activating the substrate of a given reaction through covalent interactions have been widely used and studied. Among them, chiral amines (aminocatalysis) are usually employed as catalysts activating the substrates by the reversible formation of a chiral intermediate, such as enamines, iminium ions, and iminium radical cations.[25] With respect to the organocatalyzed formation of chlorinated chiral quaternary stereocenters, both enamine and iminium activation modes have been employed. In this sense, in 2010, Alexakis *et al*. reported the use of chiral conformationally stabilized aminal-pyrrolidines as efficient organocatalysts for the conjugate addition of α-chloro-disubstituted aldehydes to vinyl sulfones.[26,27] As depicted in Scheme 13 for a representative example, both catalysts **18** and **19** afforded the corresponding Michael adduct with good isolated yields and excellent enantioselectivities. The obtained highly functionalized adducts are of high synthetic interest since can readily be converted in few steps to useful synthons via Diversity Oriented Synthesis.

Chiral pyrrolidines **18** and **19** are considered conformationally stabilized catalysts. As depicted in Scheme 13, both of them form the most stable *Z-anti* enamine with the chlorinated aldehyde, being only the *si* face available to attack the highly activated electrophile. However, in the case of catalyst **18**, a C_γ-*exo* conformer stabilization takes place due to the steric repulsion between the phenoxy group and the aminal, fixing the latter in the appropriate position above the enamine. On the contrary, fluorine insertion in the 4 position of catalyst **19** stabilizes the C_γ-*endo* conformer due to hyperconjugation effects over the adjacent σ C-H orbitals aligned with the σ* of the C-F bond. Interestingly, a kinetic resolution pathway was proposed for the conjugate addition with only one enatiomer of the starting chlorinated aldehyde being able to react with the electrophile.



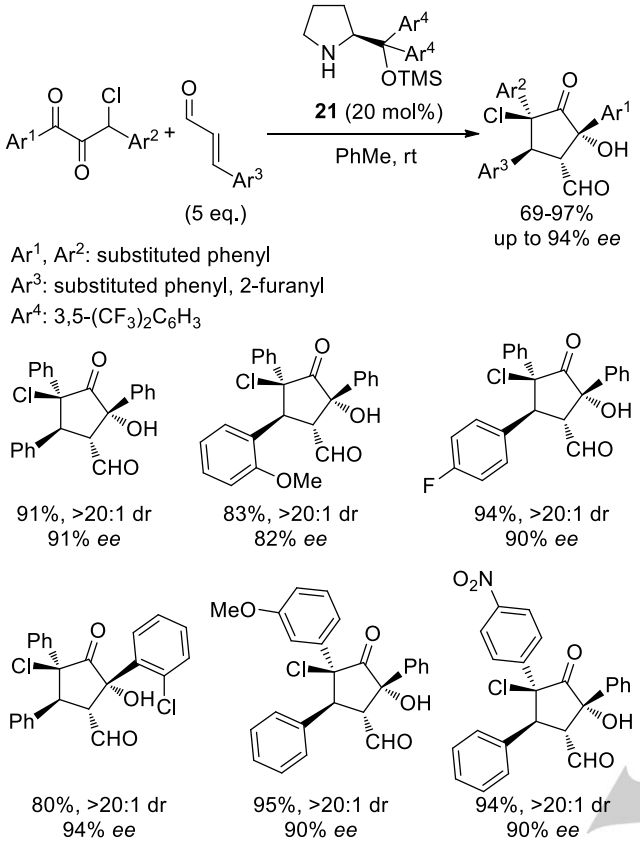
Scheme 13. Asymmetric conjugate addition of chlorinated aldehydes to vinyl sulfones.

A direct asymmetric organocatalyzed α-chlorination of α-substituted aldehydes, has been recently reported by Jacobsen *et al*.[28] In this case, chiral bifunctional primary amine **20**, derived from (1*R*,2*R*)-cyclohexane-1,2-diamine, has provided good results not only for the preparation of chiral chlorinated quaternary stereocenters, but also their hydroxylated and fluorinated counterparts. As shown in Scheme 14, the **20**-catalyzed chlorination of 2-phenylpropionaldehyde with 2,3,4,5,6,6-hexachlorocyclohexa-2,4-dien-1-one in THF at rt, led to the corresponding functionalized aldehyde in a moderate 66% *ee*. The formation of an (*E*)-*trans*-enamine, where an extra intramolecular H-bond between the benzamide carbonyl and the enamine NH rigidifies the catalyst backbone, perfectly explains the stereochemistry observed in the chlorination reaction. Also, one of the aryl rings of the terphenyl moiety is projected directly behind one face of the enamine, blocking the access to the incoming electrophile.



Scheme 14. Asymmetric chlorination of α-substituted aldehydes.

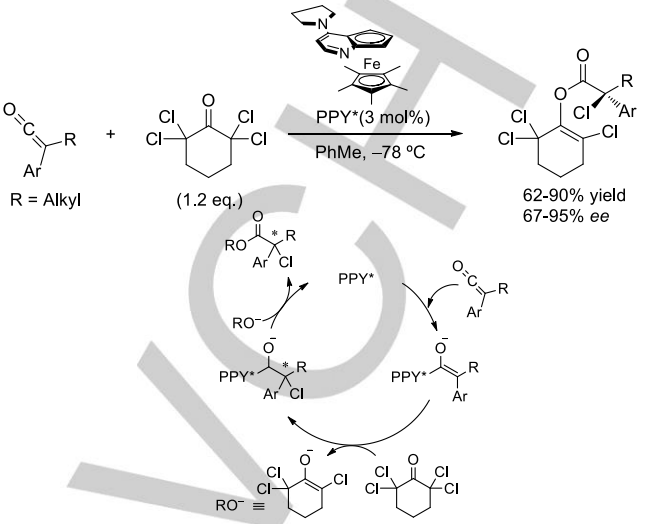
An organocatalytic domino Michael/Aldol reaction of acyclic 3-chloro-1,2-diones to aromatic α,β-unsaturated aldehydes has been successfully used to synthesize chlorinated cyclopentanone derivatives with four contiguous stereogenic centers in good yields, excellent diastereoselectivities (>20:1 dr) and enantioselectivities (up to 94% *ee*).[29] This transformation, which starts with the formation of a reactive chiral imminium intermediate between the Jørgensen-Hayashi catalyst and the corresponding α,β-unsaturated aldehyde, tolerates a large variety of electronically different substituents on both reactive partners (Scheme 15).



Scheme 15. Asymmetric organocatalytic domino Michael/Aldol reaction.

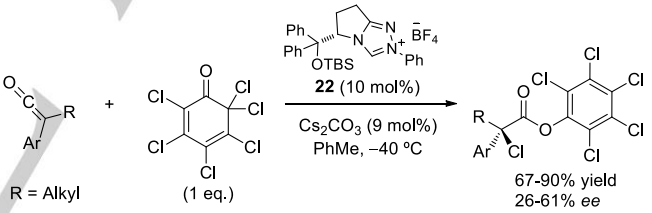
3.2. Other Covalent Organocatalysts

Apart of the most common enamine/iminium activation, other covalent interactions have been employed in order to install a chorine atom on a tertiary center in a enantioselective fashion. Inspired on the work developed by Letcka group for the asymmetric synthesis of secondary α-chloroesters from ketenes,[30] Fu and co-workers employed a planar-chiral derivative of 4-(pyrrolidino)pyridine (PPY*) as a nucleophilic catalyst able to generate chiral tertiary chlorides from ketenes. Thus, several aryl ketenes were evaluated using 2,2,6,6-tetrachlorocyclohexanone as a chlorinating reagent, giving rise to the corresponding products in good to high yields and enantioselectivites (Scheme 16). The authors proposed at least two possible mechanistic scenarios leading to the final products in which the catalyst shows its nucleophilic behavior. The one depicted in the Scheme 16 have been previously proposed for the authors in related works involving ketenes and, in addition, resembles Letcka's proposal for asymmetric synthesis of secondary α-chloroesters from ketenes. In this model, a chiral enolate is generated by nucleophilic attack of the catalyst onto the ketene moiety. This chiral enolate can react in an enantioselective fashion with the chlorine source. However, a possible pathway consisting in the formation of a chiral chlorinating agent from the reaction of the catalyst with chlorine source and subsequent reaction with an achiral enolate could not be ruled out.[31]



Scheme 16. Fu's asymmetric chlorination of ketenes.

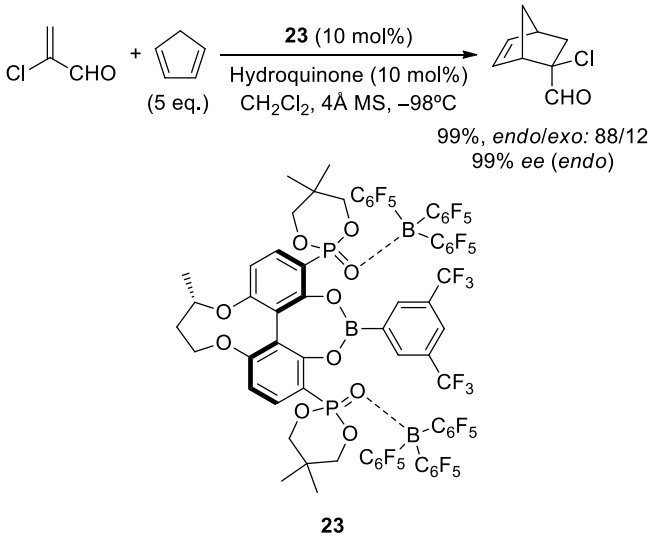
Finally, a similar strategy was followed by Smith and co-workers using, in this case, as nucleophilic catalyst the chiral NHC **22**. Under the optimized conditions high yields but moderate enantioselectivities for the chlorination of alkyl aryl ketenes were obtained (Scheme 17).[32]



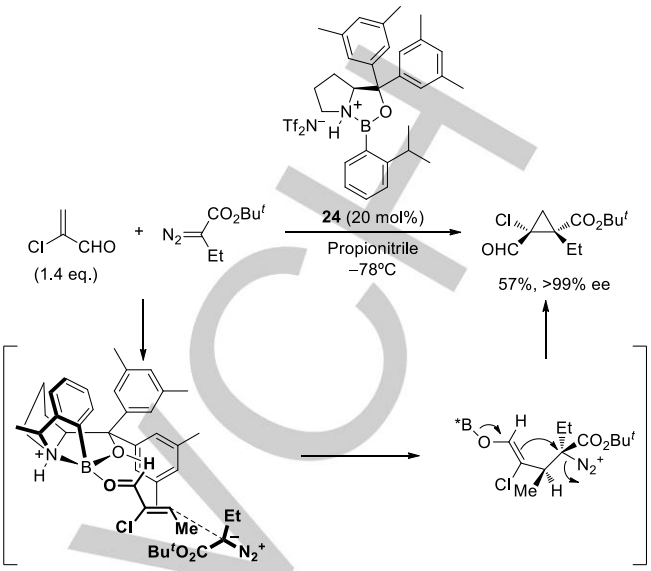
Scheme 17. NHC catalyzed asymmetric chlorination of ketenes.

3.3. Other metal-free activation modes

Taking advantage of the Lewis acid assisted chiral Lewis acid (LLA) catalysis,[33] an interesting catalytic enantioselective *endo*-selective Diels–Alder reaction between cyclopentadiene and α-chloroacrolein has been reported by Ishihara and co-workers[34] using the chiral conformationally flexible supramolecular catalyst **23** (Scheme 18). This remarkable enantioselective transformation, which requires hydroquinone as polymerization inhibitor, is the first *endo*-selective Diels-Alder reaction involving α-substituted acroleines, dienophiles which usually afford quaternary *exo*-adducts as major products.



Scheme 18. Enantioselective Diels-Alder reaction.



Scheme 19. Enantioselective cyclopropanation.

Regarding the structure and activation mode of **23**, the intermolecular acid–base coordinate bonds in the two P=O···B(C_6F_5)$_3$ moieties are critical for the flexibility of **23**, while the tris(pentafluorophenyl)borane moiety acts as a bulky functional group to form a chiral cavity around the Lewis acidic boron center increasing, at the same time, its Lewis acidity. Also, the electron donating ability of the chiral 1,5-dioxonane back-bond in **23** improves the P=O···B(C_6F_5)$_3$ coordination through a resonance effect avoiding a plausible B(C_6F_5)$_3$-catalyzed achiral reaction.

On the other hand, very recently a Lewis acid-catalyzed Michael-initiated ring-closure (MIRC) reaction between α-alkyl-α-diazoesters and electron deficient olefins has been described for the synthesis of chiral functionalized cyclopropanes containing chlorinated quaternary stereogenic centers.[35] Using the chiral oxazaborolidinium ion **24** as catalyst, Hwang, Ruy, and co-workers have developed a methodology that, although it has been mainly used for the preparation of brominated derivatives, it can be also employed for the diastereoselective (*trans*/*cis* > 20/1) synthesis of optically pure chlorinated cyclopropanes, as depicted in Scheme 5 for the reaction between α-chloroacrolein and α−ethyl-α-diazo-*tert*-butylester.

The observed stereochemistry of the **24**-catalyzed asymmetric cyclopropanation has been explained according to the pre-transition-state assembly shown in Scheme 19. As shown, the double bond of the 2-chloroacrolein is situated above the 3,5-dimethylphenyl group shields the *re* face (back) of the acrolein from attack by the diazoacetate. Also, due to the the dipole-dipole interaction between the two carbonyl groups, the *tert*-butyl ester group is situated away from the aldehyde when the diazoacetate approaches the β-carbon of acrolein for the 1,4-addition, which takes place over the *si* face (front) of the acrolein. Then, the corresponding intermediate cyclizes with loss of nitrogen to form the chiral cyclopropane.

4. Conclusions and Outlook

The main conclusion that becomes clear from this Focus Review is that the direct organocatalyzed construction of chlorinated quaternary stereogenic centers is still a major challenge. This arises from the fact that despite the outstanding growth that the organocatalysis field has experienced in the last decades, the organocatalysts able to perform this transformation in high levels of enantioselection are still scarce. In addition, the majority of the successful processes have a limited applicability, being basically restricted to the asymmetric chlorination of cyclic compounds. For this reason, further studies need to be conducted in order to find catalytic entities that could overcome these limitations, broadening the scope towards the use of lineal substrates.

In this sense, for a better design of such catalysts to have a better understanding of the whole process by means of mechanism elucidation it would be highly desirable.

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Keywords: Organocatalysis • Quaternary Stereocenters • Chlorination• Carbonyl Compounds • Asymmetric Catalysis

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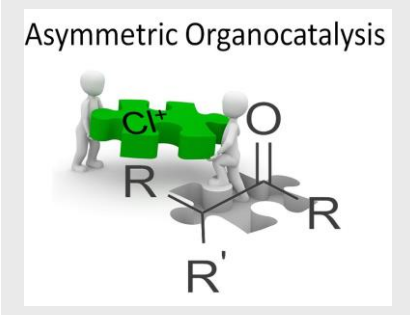
Layout 1:

REVIEW

The construction of quaternary chlorinated stereocenters is a particularly challenging and attractive topic for the organic chemistry community. The organocatalysis blossom in the last decades has prompted organic chemists to explore such strategy for this purpose. This review aim to gather the state of the art of the topic, presenting those successful examples and the limitations that must be overcome.



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Organocatalyzed Assembly of Chlorinated Quaternary Stereogenic Centers