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Enantioselective α-heterofunctionalisation of carbonyl compounds: organocatalysis is the simplest approach

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Dedicated to Professors C. Nájera and M. Yus

Abstract—Enantioselective organocatalytic processes have reached maturity in recent years with an impressive number of applications now available. The application of these advantageous methodologies to the construction of chiral α-hetereofunctionalised carbonyl compounds allows us to obtain important chiral building blocks, such as α-amino acids, α-amino alcohols, aziridines, epoxides, 1,2-diols and α-sulfenylated, selenenylated and halogenated carbonyl derivatives. Proline, imidazolidinone derivatives, cinchona alkaloids and their ammonium salts, as well as Brønsted acid derivatives, have been used as chiral catalysts for these purposes. A survey of contributions in this field will be discussed throughout this review.

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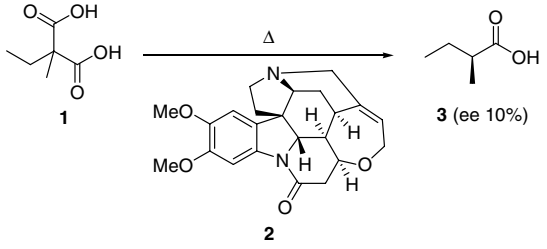
1. Introduction

Inspired by nature, where enantioselective reactions[1] are efficiently performed by enzymes,[2] synthetic chemists have developed new strategies to enantioselectively synthesise chiral compounds. While the end of the last century has been dominated by the use of transition metal catalysts to achieve this goal,[3] the use of organocatalysts is reaching its *golden age*[4] in this 21st century.

Organocatalysis, which can be defined as the 'acceleration of chemical reactions with an ideal substoichiometric amount of organic compounds, which do not contain any metal atom'[4e] has been known since Marckwald in 1904 carried out the decarboxylation of malonic acid **1** in the presence of brucine **2** to give valeric acid **3** with 10% enantiomeric excess (Scheme 1): this reaction being the first example of an enantioselective transformation.[5]



Scheme 1.

Despite this fact, it has only been over the last decade that the use of organic molecules as catalysts has emerged as an important area of research. This type of catalysis has several advantages when compared to biocatalysis or to the use of transition metal complexes as catalysts. The catalysts are usually more stable, less expensive, readily available and can be applied in less demanding reaction conditions. This type of catalyst can be easily incorporated onto a support facilitating their recovery and recycling. Moreover, the absence of using a transition metal makes this type of reaction an attractive tool for the synthesis of agrochemical and pharmaceutical compounds, in which the presence of hazardous metallic traces are inadmissible in the final product. In this strategy, these factors contribute to a superior atom efficiency,[6] avoiding the protection of the substrate and deprotection of the products, and allowing the direct synthesis of structurally complex molecules, even through asymmetric multicomponent reactions[7] as well as domino,[8] tandem[9] or cascade transformations.[10] Therefore, this synthetic strategy for chiral compounds could be important in the industry due to its versatility and its favourable environmental impact.

The aim of this report is to review all the achievements in the enantioselective α-heterofunctionalisation of carbonyl compounds using an organocatalyst strategy, presented by types of reaction, in which a new carbon-heteroatom bond is formed, excluding the reactions, which involve modification of the hybridisation of a previously functionalised carbonyl compound. The employment of this methodology leads to a wider range of important chiral building blocks, including α-amino acids, α-amino alcohols, epoxides, 1,2-diols, α-sulfenylated, α-selenenylated and α-halogenated carbonyl derivatives, many of which are very difficult to obtain by other strategies, with organocatalysis representing a very simple, easy and straightforward method for their synthesis.

2. Enantioselective α-amination of carbonyl compounds

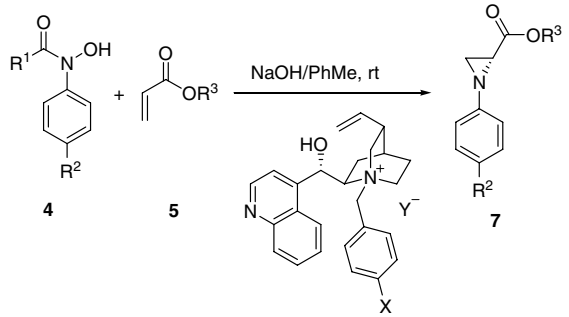
A large variety of natural products and drugs are nitrogen-containing molecules. Thus, the asymmetric introduction of a nitrogen atom at the α-position of a carbonyl compound via either electrophilic amination[11] or aziridination of α,β-unsaturated carbonyl compounds and further ring opening of the former chiral aziridine[12] provides a valuable route for the synthesis of chiral α-amino acids, esters, ketones and alcohols.

2.1. Aziridination of α,β-unsaturated carbonyl compounds

Chiral aziridines are widespread in asymmetric synthesis owing to their regio- and stereoselective ring opening.[13] There are numerous efficient methods for their asymmetric synthesis, using usually transition metals,[14] with the pure organocatalytic methods still being in their infancy.

The first reported aziridination reaction was performed using cinchona salt derivatives[15] under phase transfer catalysis conditions.[16] The reaction of different hydroxamic acids **4** as a nitrogen source with acrylate derivatives **5** in the presence of cinchoninium salts **6** gave the expected aziridines **7** (Table 1).[17] The ideal biphasic mixture was obtained after different trials, finding that solvents more polar than toluene gave worse results due to the possible disruption of the Coulombic interaction between ammo-

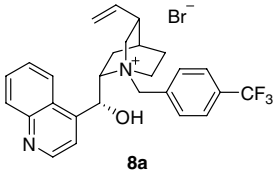
Table 1. Enantioselective aziridination of acrylic esters



Entry	R^1	R^2	R^3	Cat.	Yield (%)	ee (%)
1	Bu^t	H	Bu^t	**6b**	79	49
2	Bu^t	H	Me	**6b**	11	62
3	Bu^t	Br	Bu^t	**6b**	50	36
4	Ph	H	Bu^t	**6b**	23	53
5	Bu^t	H	Bu^t	**6a**	43	17
6	Bu^t	H	Bu^t	**6c**	18	18

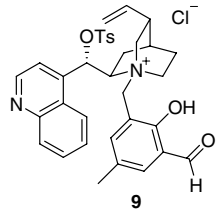
nium cation and enolate. Other bases gave either lower chemical yield or enantioselectivity. Somewhat more interesting was the study of the influence of the structural modifications of reagents. The electrophilic partner of the reaction was chosen as the corresponding *tert*-butyl acrylate since, although the enantioselectivity was slightly lower, the chemical yield was higher than using the related methyl acrylate. The best results were obtained using pivaloyl derivative as the nucleophilic nitrogen source, since the use of the related benzoyl compound or the bromo substituted reagent dropped the enantioselectivity (Table 1, entries 1, 3 and 4). Among nine different cinchoninium quaternary salts tested, catalyst **6b** gave the best results. Catalysts with a less electron withdrawing group such as **6a** gave worse results. Even, the counterion atom has a large impact on the results, with bromide salts giving a better result than the related chlorides (Table 1, entries 1, 5 and 6).

Surprisingly, the use of the so called pseudoenantiomeric catalyst cinchonidinium salt **8a** did not change the absolute configuration of the final aziridine **7** (50% yield and 28% ee).



8a

Better enantioselectivities were obtained with the modified cinchoninium salt **9** and its pseudoenantiomer cinchonidinium salt **10**,[18] in which the hydroxy group is derivatised as a tosyl ester. In this case, both catalysts acted, as expected, leading to both different aziridine enantiomers with similar enantioselectivities (up to 95% ee), with the enantiomeric excess being highly influenced by the presence of substituents on the aromatic ring of the hydroxamic acid **4**.



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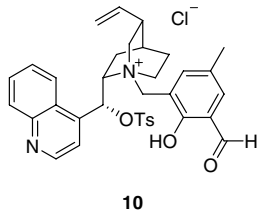
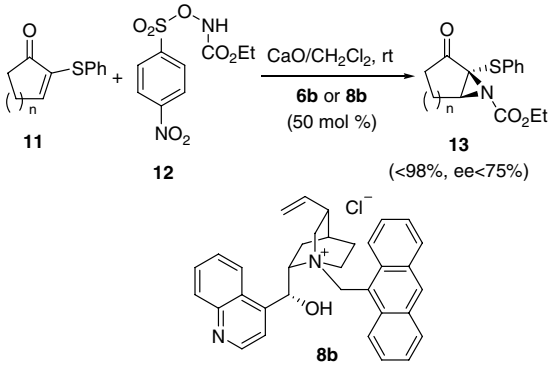


10

Recently, this methodology was extended to the aziridination of different cyclic α,β-unsaturated ketones **11** (Scheme 2), in which the phase transfer catalyst **6b** seemed superior to compound **8b**, with both pseudoenantiomeric catalysts giving the same final aziridine **13**, as in the first part of this section. It should be pointed out that the optimal conditions for this process were the biphasic solid/liquid phase and the source of nucleophilic nitrogen nosyloxycarbamate **12**.[19]

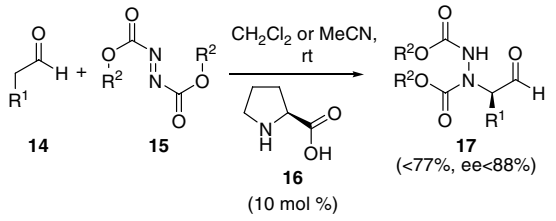


Scheme 2.

2.2. Direct α-amination of carbonyl derivatives

The enantioselective construction of molecules bearing a carbon–nitrogen bond via direct α-amination using readily available starting materials is one of many challenges for organic chemists, with it being one of the simplest and straightforward strategies to access important chiral molecules, such as α-amino acids, aldehydes and alcohols.[11b,20]

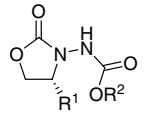
Almost simultaneously, Jørgensen et al. and List et al. reported for the first time the direct organocatalysed α-amination of aldehydes using L-proline **16** and different azodicarboxylate derivatives as the electrophilic nitrogen source (Scheme 3).



Scheme 3.

In the work of Jørgensen et al.,[21] the reaction was carried out in methylene chloride at room temperature using diethyl azodicarboxylate **15a** (DEAD, $R^2 = Et$) as electrophile, achieving 93% chemical yield and 95% ee. In this case, the product obtained was easily isolated just by the addition of water and simple extraction with diethyl ether. Furthermore, the yield and enantioselectivity did not change when performing the reaction on a gram scale. All these factors make this procedure very conveniently for an industrial large scale synthesis. Due to the relative high acidity of the hydrogen atom placed in the stereogenic centre of product **17** and to avoid its racemisation, an in situ reduction of aldehyde **17** can be carried out by using $NaBH_4$, with the final product after basic treatment being the corresponding oxazolidinones **18**. When the reaction was performed using the corresponding dibenzyl azodicarboxylate **15b** (DBAD, $R^2 = Bn$), the oxazolidinones **18** obtained could be transformed into the simple oxazolidinone by removing the protecting group and N–N bond cleavage. In a similar way, aldehydes **17** could be

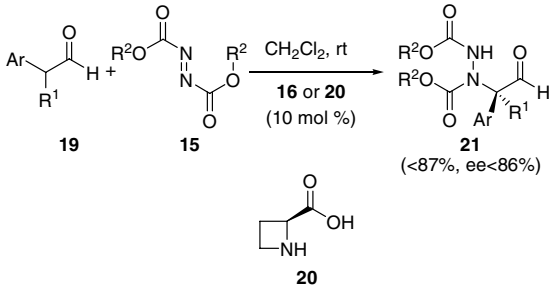
transformed into the corresponding chiral α-amino acids by a multiple step procedure involving the oxidation of the aldehyde and the final N–N bond cleavage using Raney nickel.



18
(<92%, ee<93%)

In List's report (Scheme 3),[22] the reaction was performed in acetonitrile as solvent at 0 °C and using dibenzyl and di-*tert*-butyl azodicarboxylate **15c** ($R^2 = Bu^t$) as electrophiles. Under these conditions, the endpoint of the reaction could be easily detected by the disappearance of the typical yellow color of azodicarboxylate and after in situ reduction, the corresponding amino alcohols could be isolated in practically quantitative yields and very high enantioselectivities (92–97% ee). Due to the crystalline character of these amino alcohols, their enantiomeric excesses could be further improved upon by simple recrystallisation.

The generation of molecules containing quaternary stereocentres is an even more difficult and challenging task in organic chemistry.[23] In this sense, some α,α-disubstituted amino acids, such as α-aryl α-methylglycines, possesses interesting biological activities. The enantioselective amination of α,α-disubstituted aldehydes is a useful indirect entry to the synthesis of this type of compounds.[24] Thus, the reaction of α-alkyl-α-aryl disubstituted aldehydes **19** with either DEAD **15a** ($R^2 = Et$) or DBAD **15b** ($R^2 = Bn$) catalysed by either proline **16** or L-azetidine carboxylic acid **20** yielded the expected aldehydes **21** with good enantioselectivity and yield in the case of using catalyst **16** and moderated for catalyst **20** (Scheme 4). The same reaction but using α,α-dialkyl aldehydes, gave, moderate enantioselectivities (up to 28% ee). As in the aforementioned cases, aldehydes could be easily reduced to the corresponding alcohols, cyclised to render the related oxazolidinones, as well as oxidised and deprotected to give the expected α,α-disubstituted amino acids.



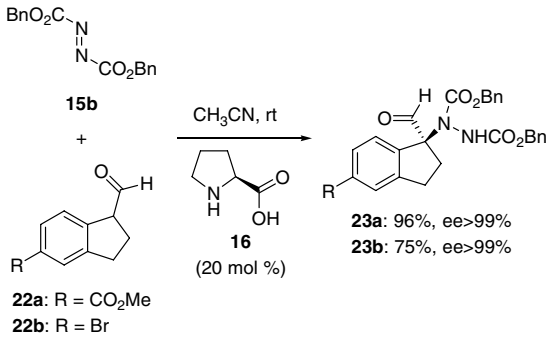
19 **15** **21** (<87%, ee<86%)

16 or **20** (10 mol %)

20

Scheme 4.

This strategy has been successfully applied to the synthesis of important medicinal amino acids, such as (*S*)-AIDA and (*S*)-APICA, which are metabotropic glutamate receptor ligands, which are used in the treatment of several neurodegeneratives diseases.[25] For this purpose, indanone carbaldehyde derivatives **22** were submitted to direct α-amination using DBAD **15b** and L-proline,[26] to give the expected products **23** as a single enantiomer and excellent chemical yields (Scheme 5).



15b

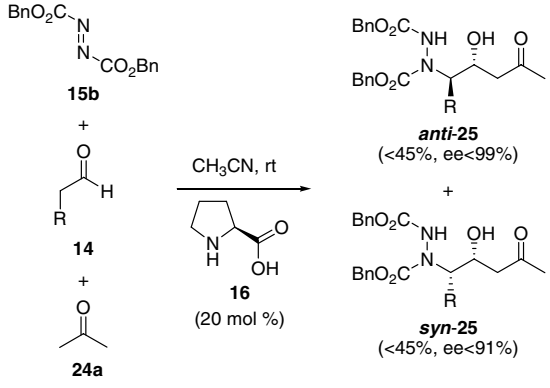
22a: R = CO_2Me
22b: R = Br

16 (20 mol %)

23a: 96%, ee>99%
23b: 75%, ee>99%

Scheme 5.

This type of synthesis has been shown to be compatible with a multicomponent reaction process,[7] especially with Mannich type reactions.[27] Thus, enzyme-like direct assembly of aldehydes **14**, diazocarboxylic ester **15b** and acetone **24a** provided a new route for the synthesis of optically active γ-amino ketones (Scheme 6). The success of this multicomponent reaction was due to the higher reactivity (100-fold) of the aldehyde over the acetone in the proline catalysed α-amination reaction. The further aldol reaction with the intermediate of type **17** yielded compounds **25** with good to excellent enantioselectivities. Study of this process showed that the razemisation of chiral intermediate **17** occurred previously to the aldol reaction, with the diastereoselectivity being close to zero.[28]



15b

14

24a

16 (20 mol %)

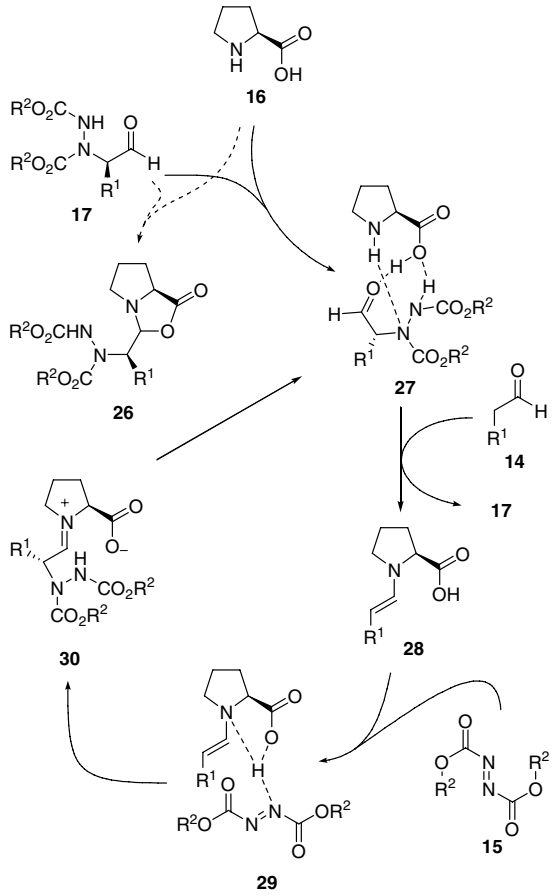
***anti*-25** (<45%, ee<99%)

***syn*-25** (<45%, ee<91%)

Scheme 6.

The possible mechanism of the direct amination of aldehydes was studied by means of kinetic measurements.[29] These investigations revealed that the reaction exhibited an autoinductive effect, that is the reaction product interacts with the original catalyst to form a more active and efficient catalyst. Thus, when an amino aldehyde of type **17** was mixed with L-proline **16** in a 1:1 molar ratio before the introduction of reactants, the reaction was notably faster than with the original protocol (only when using cata-

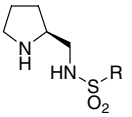
lyst **16**). Surprisingly, this rate enhancement was independent of the absolute configuration of the amino alcohol, either **17** or *ent*-**17**, with the outcome of the reaction only being determined by proline. Initially, oxazolidinone **26** was suggested as being responsible for this autoinductive effect, by improving the solubility of catalyst **16** (Scheme 7). However, this explanation was further rejected on the basis of the achieved data for the reaction rate versus product concentration, which was proportional. DFT calculations suggested an initial energy minimum adduct **27**, which involved three-point hydrogen bonding between catalyst **16** and the final product of the reaction, **17**. These hydrogen bonds positioned the nitrogen of the proline in such a way that its electron lone pair was accessible for the rapid attack on the incoming carbonyl group of the aldehyde substrate, rendering the expected enamine **28**. The approximation of diazocarboxylic ester **15** governed by the formation of a new hydrogen bond gave the transition state of type **29** responsible for the outcome of the reaction. The reaction between the enamine and diazocompound gave iminium **30**, which finally provided adduct **27**. The observed nonlinear effect is consistent with a kinetic resolution of proline in this autoinductive process.



Scheme 7.

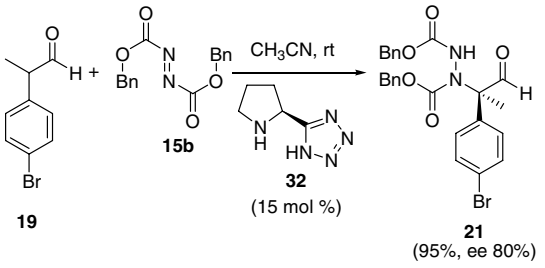
Not only proline but other catalysts have been used in the direct α-amination of aldehydes, many of which being designed with the aim of increasing the solubility and, therefore, the turnover number of the catalyst.

2-(Arylsulfonylaminomethyl)pyrrolidines **31** fulfil all the requirements to act as organocatalysts, since they possess a secondary amine, which allows the formation of an enamine by reaction with the corresponding aldehyde, while the presence of a sulfonyl group increases the acidity of hydrogen of the amide, facilitating the hypothetically required hydrogen bonding between enamine and diazocarboxylate derivative in the transition state. Independently of the aryl substituent, all catalysts of type **31** gave similar results (enantiomeric excess never higher than 87%). These enantioselectivities were clearly inferior to those obtained using proline.[30]



31: R = Ar

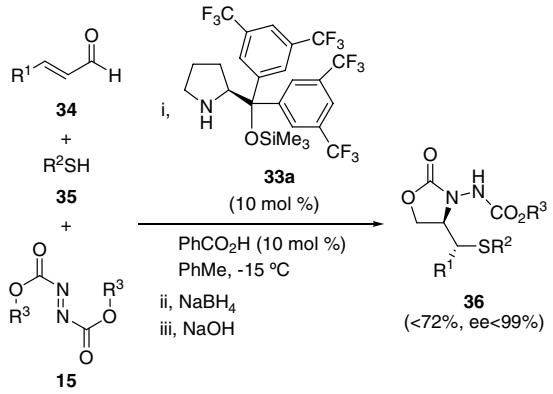
Tetrazole proline derivative **32** has been shown to be superior to proline **16** as catalyst in the reaction of substituted aldehyde **19** with DBAD **15b** to yield the expected α-amino aldehyde **21** with good enantioselectivity (Scheme 8). In the case of using L-proline, the enantioselectivity was only 44% and the time increased from 3 h to 5 days. The higher reactivity and selectivity of catalyst **32**, compared to proline, was attributed to the lower pK_a (8 in DMSO, 12 for proline) and its higher steric hindrance.[31] Aldehyde **21** has been used as an intermediate in the total synthesis of cell inhibitor BIRT-377.



Scheme 8.

Catalyst **33** was introduced to improve the poor enantioselectivity obtained in reactions between aldehydes and electrophiles with low hydrogen-bond acceptor character. This catalyst would provide high enantioselectivity by controlling the enamine geometry and through a very efficient face biassing. When catalyst **33** was used in the α-amination of aldehydes **14** with dialkyl azodicarboxylates **15**, oxazolidinones *ent*-**18**, obtained after a reduction step, showed a very high enantiomeric excess (90–97% ee). This catalyst was more efficient and its reaction faster than those using proline.[32] Remarkably, the absolute configuration of final products **18** was the opposite to that obtained when using L-proline **16**.

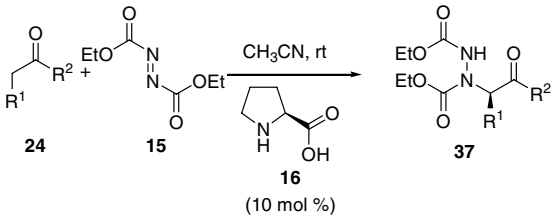
Catalyst **33a** allowed the synthesis of highly functionalised molecules **36** through a multicomponent reaction, followed by reduction and basic treatment (Scheme 9). The mechanism pathway seems to go through the formation of the corresponding chiral α,β-unsaturated iminium intermediate, which reacts with the soft nucleophilic thiol **35** in a Michael type process, to form the corresponding enamine, which in turn reacts with the diazo compound **15**. Further reduction under standard conditions and basic treatment gave oxazolidinones **36** with a high enantioselectivity (only one enantiomer in many cases) and high diastereoselectivities (around 80% de).[33]



Scheme 9.

Jørgensen et al. also pioneered in extending this reaction to ketones (Table 2).[34] The best results were obtained using DEAD **15** as the electrophilic source of nitrogen and, although for some ketones the enantioselectivity was higher in solvents other then acetonitrile, it should be pointed out that, in general, this solvent was the best choice. All reactions were regioselective, the major isomer in the amination occurring on the most substituted α-carbon atom to the carbonyl of ketone, with the larger substituent giving the higher enantioselectivity.

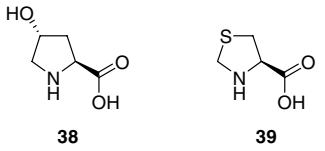
Table 2. Enantioselective direct α-amination of ketones



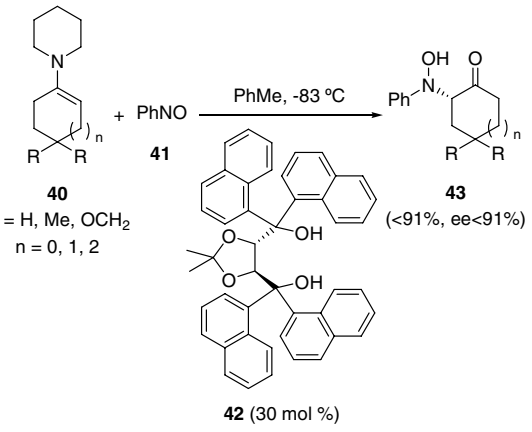
Entry	R^1	R^2	Yield (%)	ee (%)
1	Me	Me	80	95
2	Et	Me	77	98
3	Bn	Me	92	98
4	Pr^i	Me	69	99
5	Me	Et	79	94
6	–$(CH_2)_4$–		67	84

L-Azetidine carboxylic acid **20** has also been used for this reaction.[35] However, the enantioselectivity found was in general somewhat lower than using proline **16** and, contrary to the previous case, the increase of the length of substituents had a detrimental effect, not only in the enantioselectivity but also in the reaction rate.

Although L-proline **16** is an inexpensive catalyst, the use of modified proline derivatives for this and other related transformations makes their recovery a factor to be considered. The enantioselective direct α-amination of aldehydes and ketones has been carried out in ionic liquids as reaction media, in which the reuse of the catalyst can be performed.[36] The best ionic liquid was [bmim]BF_4 but the enantioselectivities found were significantly lower than for conventional media. Other catalysts tested, such as acids **38** and **39** had a lower turnover rate. Finally, it should be pointed out that the reaction using ketones gave an inseparable mixture of the mono **37** and diaminated products. This inconvenience could minimised by the use of an large excess of ketone.



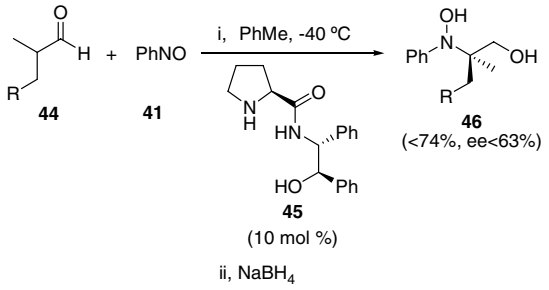
The α-amination of carbonyl compounds has also been accomplished by using a Brønsted acid catalyst, such as TADDOL derivative **42** (Scheme 10). The reaction of different enamines **40** with nitrosobenzene **41** in toluene at a low temperature exclusively gave the *N*-regioisomer **43**, with in general good results.[37]



Scheme 10.

The aforementioned amination can be performed without the preformed enamine just by using the prolinamide **45** (Scheme 11). The use of L-proline **16** as catalysts in the α-aminoxylation reaction with **41** contributed to the forma-

tion of the *O*-regioisomer, as will be introduced in the further Section 3.1.3. All these facts make these results more interesting, although they are modest.[38] The reason for this unusual behaviour can be attributed to the low acidity of the proton of prolinamide, which is unable to protonate the nitrogen atom but can protonate the oxygen atom of the nitroso derivative **41**, therefore making the nitrogen atom more electrophilic.



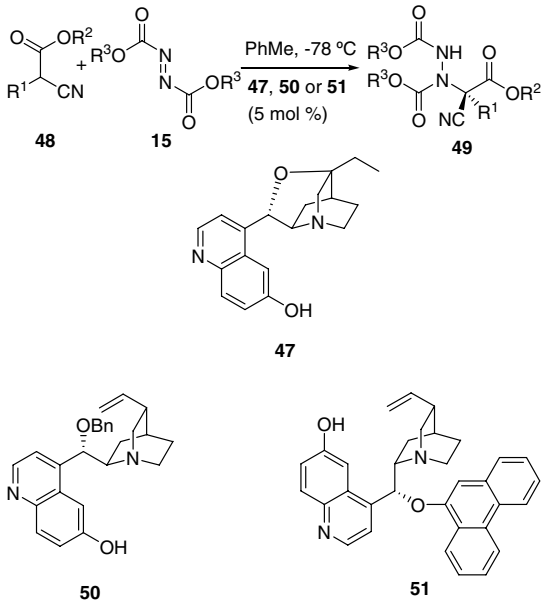
Scheme 11.

Jørgensen et al. recently introduced a new entry to the enantioselective direct α-amination of carbonyl compounds, which involves the use of chiral tertiary amine **47** (Table 3). The reaction was tested initially only with aryl cyanoacetates **48** (R^1 = aryl and heteroaryl) and the enantioselectivity of the reaction seems to be dependent on the bulkiness of the diazo compound used, the more bulky compound **15** the higher enantioselectivity. This was also true for the ester moiety. The presence of the substituents on the aryl group at either the *meta*- or *ortho*-position did not have any accountable influence on the results. Only a slight decrease in the enantioselectivity was accomplished with substrates bearing electron withdrawing or donating groups at *para*-position. The cleavage of the N–N bond of the final products **49** was easily performed using trifluoroacetic acid and SmI_2, an indirect entry to the synthesis of α-amino acids bearing quaternary stereocentres.[39]

Catalysts **50** and **51** have been introduced as alternative organocatalysts for the aforementioned amination (Table 3), achieving similar results.[40] These catalysts also showed a broad substrate scope, being successfully applied to *para*-, *meta*- and *ortho*-substituted aromatic α-cyanoacetate derivatives **48**. However, all attempts to extend the reaction to alkyl α-cyanoacetate (**48**, R^1 = alkyl) failed, giving very low enantioselectivities.

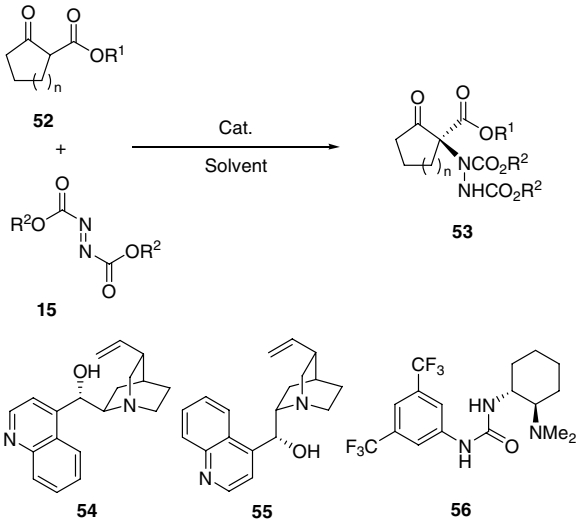
The substrate scope of catalyst **47** has also been tested with different β-ketoesters (Table 4, entries 1 and 2), obtaining good enantioselectivities not only for cyclic compounds such as **52**, but also for the related acyclic ones.[39] Cinchonine **54** and cinchonidine **55** have also been used for the same reaction (Table 4, entries 3–6) rendering the expected functionalised compounds **53** with somewhat lower enantioselectivities, but using a higher catalyst loading and temperature. The behaviour of these two catalysts is similar to pseudoenantiomers, since the absolute configuration of the final product in one, is the opposite of the other. It should be pointed out that the enantioselectivity dropped

Table 3. Enantioselective direct α-amination of cyanoacetates



Entry	R^1	R^2	R^3	Cat.	Yield (%)	ee (%)
1	Ph	Et	Et	**47**	>95	84
2	Ph	Et	Bu^t	**47**	>95	94
3	Ph	Bu^t	Bu^t	**47**	>95	>98
4	Ph	Et	Bu^t	**50**	92	97
5	Ph	Et	Bu^t	**51**	92	95

Table 4. Enantioselective direct α-amination of β-keto esters



Entry	Cat.	R^1	n	R^2	Yield (%)	ee (%)
1	**49**	Bu^t	1	Bu^t	99	89
2	**49**	Et	1	Bu^t	86	83
3	**54**	Et	1	Bn	95	88
4	**55**	Et	1	Bn	95	87
5	**54**	Et	2	Bn	92	84
6	**55**	Et	2	Bn	81	77
7	**56**	Me	1	Bu^t	90	60

considerably when acylic substrates were submitted to the amination process.[41] Also, the urea derivative of type **56** has been used, being clearly less efficient than previous catalyst.[42]

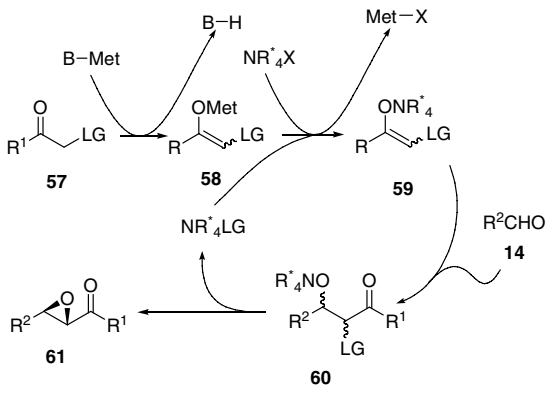
The direct amination process catalysed by cinchonine alkaloid derivative **47** has been expanded to substituted cyanoacetate derivatives, the amination reaction taking part at the allylic position with excellent enantioselectivities.[43]

3. Enantioselective α-chalcogenation of carbonyl compounds

3.1. C–O bond formation

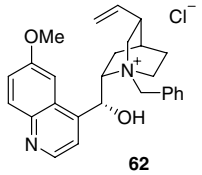
α-Oxycarbonyl moieties are present not only in many natural products but also in many highly versatile intermediates, since this moiety can be easily and selectively transformed into other functionalities, such as diols, halo and amino carbonyl compounds and epoxides. Indeed, chiral α-hydroxy carbonyl compounds have been successfully used in the preparation of biologically important compounds, such as carbohydrates, alkaloids and terpenes. A general strategy for the synthesis of these compounds involves the oxidation of preexisting C–H bonds using, in general, very toxic transition metals.[44] Organocatalysed procedures for this purpose are highly desirable and in recent years, following the early works of Wynberg, Juliá and Colonna, several different oxidation methods, as well as improvements of the known processes, have been successfully developed.

3.1.1. Darzens reaction. The Darzens condensation is one of the most useful methodologies for the construction of α,β-epoxy carbonyl compounds **61** with control of the two formed stereogenic centres. This reaction involves an aldol reaction (C–C bond formation), which normally requires stoichiometric amounts of base to achieve good yields. Only phase transfer catalysts (PTC), usually chiral ammonium halides (NR_4^*X) have been shown to be efficient in performing this transformation in a catalytic and enantioselective form (Scheme 12). After the formation of enolate **58**, the ammonium moiety of the catalyst exchanges with the metal to form a chiral enolate **59**, which reacts with the aldehyde to first give aldol product **60** and them after a cyclisation process, gave the final product **61**, and release the chiral ammonium derivative.



Scheme 12.

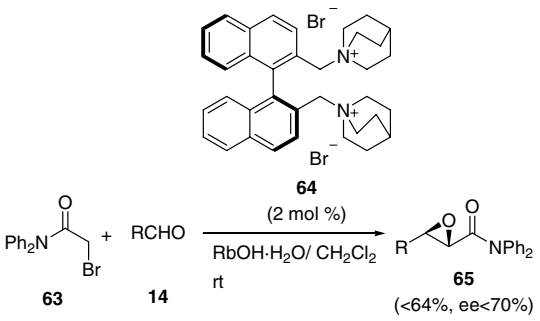
In this way, cinchona ammonium salts have been used as efficient catalysts for the enantioselective Darzens condensation. While, the first reported catalytic example using salt **62** and NaOH as base gave poor enantioselectivity (lower than 8% ee),[45] the use of cinchoninium quaternary salt **6b** improved the enantioselection up to 79% ee, when sterically demanding aldehydes were used in combination with 2-chloroacetone (**57a**: $R^1 = Ph$, $LG = Cl$).[46] However, when the reaction was performed using either a less congested or aromatic aldehyde, the reaction proceeded with moderate enantioselectivity. The modification on the benzyl moiety of ammonium salt did not produce an improvement in the results, with the protection of the hydroxy group as in ether giving very low enantiomeric excess. Catalyst **6b** promoted the enantioselective Darzens condensation of α-chloro ketones derived from α-tetralone under similar reaction conditions, to yield the corresponding spiro epoxides with enantiomeric excesses up to 86% and as a sole diastereomer.



62

A mechanistic study was performed in order to establish if the observed stereoselectivity was controlled by the aldol condensation between chiral enolate **59** and the aldehyde.[46b] However, from the results obtained, it can be concluded that the stereoselection was determined by a further kinetic resolution of intermediate **60**. The four possible stereoisomers, related to intermediate **60**, were prepared and treated with catalyst **6b** to prove this hypothesis. The *syn*-**60** isomers underwent a retroaldol reaction to give the starting aldehyde and carbonyl compound **57**, whereas the *anti*-**60** isomers, which can easily adopt the antiperiplanar conformation required to give the S_N2 type reaction, reacted to form the final compound **61**, with the reaction rate of both enantiomeric *anti*-**60** being quite different, and the remaining enantiomer suffering a retroaldol process.

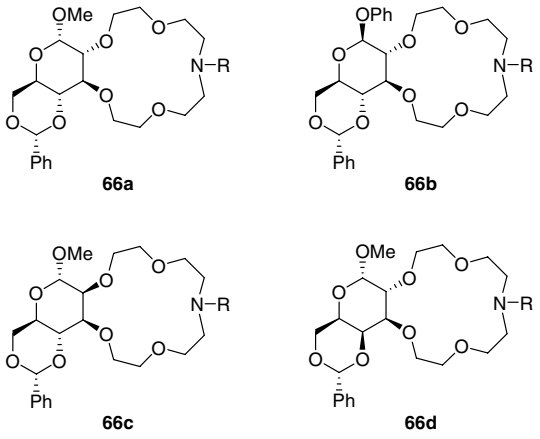
Phenylacetamide **63** can be also used as a starting material for the aforementioned reaction (Scheme 13). However, the results were slightly lower compared to the use of 2-chloroacetone, with the diastereoselectivity being lower than 80%. In this case, the chiral ammonium catalyst used was binaphthyl derivative **64** while the best result was obtained with RbOH as base, giving homogeneous enantioselectivities for compounds **65** when substituted benzaldehydes were used as the electrophilic partner of the reaction.[47]



Scheme 13.

The above quaternary ammonium salts have also been applied to the reaction using α-chloromethyl arylsulfones and chloroacetonitrile as starting materials,[48] with moderated results being achieved.

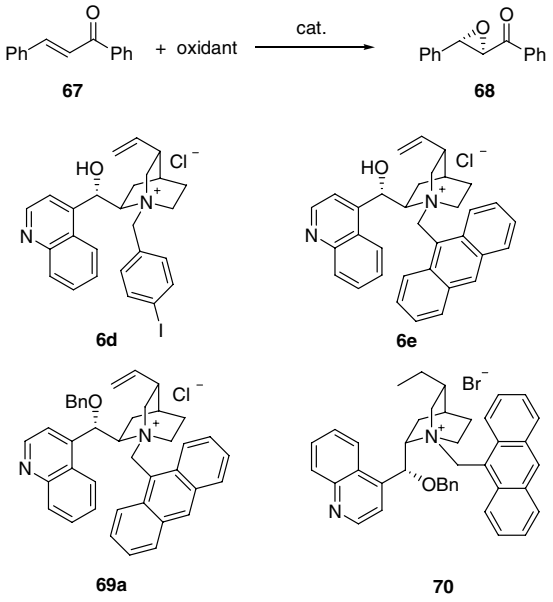
Besides the use of chiral ammonium salts as phase transfer catalysts, different azacrown ethers **66** derived from different sugars has been proposed as an alternative.[49] For all systems, the influence of the length of the R chain on nitrogen atom has been evaluated, finding that for compounds **66a**,**b** (glucose derivatives), the best results were obtained when R was 2-hydroxyethyl, whereas for compounds **66c**,**d**, the best results were obtained for the corresponding 3-hydroxypropyl derivative. In neither case was the enantiomeric excess higher than 74%.



3.1.2. Epoxidation of α,β-unsaturated carbonyl compounds. The asymmetric epoxidation[12b,50] is an extremely useful methodology to generate chiral compounds. Although methods for the enantioselective epoxidation of alkenes have been admirably performed over the last 30 years, achievements in the epoxidation of electron poor alkenes, such as enones, with high results have been less developed. In this case, a nucleophilic oxygen donor molecule is necessary for carrying out this transformation. Recently, a number of useful combinations of different types of organocatalysts and oxidative reagents have been elaborated.

Since the pioneering work of Wynberg et al.[51] for the epoxidation of chalcone derivative **67** using *N*-benzylquinine derivative **62** as the phase transfer catalyst, a 30% aqueous solution of H_2O_2 as oxidant and NaOH as base in toluene at room temperature (Table 5, entry 1), chiral phase transfer agents occupy a unique place. An inverse relationship between the dielectric constant of the solvent and the enantioselectivity was detected in these early works, with this correlation being attributed to the formation of a chiral ionic pair.

Table 5. Enantioselective epoxidation of chalcone



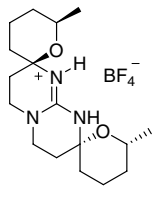
Entry	Cat. (%)	Oxidant	Product	Yield (%)	ee (%)
1	**62** (2)	H_2O_2	**68**	92	34
2	**6d** (5)	H_2O_2	*ent*-**68**	97	84
3	**6e** (10)	H_2O_2	*ent*-**68**	75	11
4	**69a** (10)	H_2O_2	**68**	<10	2
5	**6e** (10)	NaClO	**68**	71	23
6	**69a** (10)	NaClO	**68**	60	66
7	**70** (10)	KClO	*ent*-**68**	96	93
8	**70** (10)	TCCA	*ent*-**68**	90	89

Under similar conditions but using LiOH as base and the catalyst **6d**, results were highly improved (Table 5, entry 2). Enantioselectivities for other enones showed to be strongly dependent on the substituents, giving the best results for 1,3-diarylpropenone derivatives.[52] The reaction using the more crowded anthracenyl derivative **6e** and its related benzyl ether **69a** gave poor results, using an aqueous solution of H_2O_2. However, the change of the oxidant to NaClO highly improved the enantiomeric excess of the product (Table 5, entries 3–6).[53] Intriguingly, the outcome of the reaction changed, depending on the nature of the oxidant for ligand **6e**. Both facts could be explained due to a possible negative interaction of either H_2O_2 or substrate with the hydroxy group of catalyst, as well as H_2O_2 and the related ether group, by hydrogen bonding, which is not possible in the ether derivative **69a** when using NaClO. A wide range of different *E*-enones were

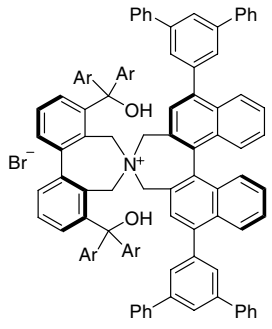
epoxidised with good enantioselectivities, the results of which were highly homogenous for different 1,3-diarylpropenone derivatives as well as for the related 1-arylpropenone derivatives. However, the results were much lower for 1-alkyl-3-arylpropenone derivatives. A study of the different factors affecting the reaction rate and selectivities was performed for the catalyst **69a**.[54] The rate of the reaction in toluene and using NaClO depended on the efficiency of the agitation and the concentration of both the oxidant and catalyst, being first order for NaClO and more complex for the catalyst. The reaction system appears to be saturated for a concentration of catalyst higher than 8×10^{-3} M; this factor can be attributed to a solubility effect. As the enantio- selectivity is concerned, it was dependent on the dielectric constant of the medium. Thus different mixtures of toluene and ethyl acetate showed an inverse relationship between enantiomeric excess of product **68** and the amount of ethyl acetate. This is in agreement with the previous observation that polar solvents or substrates decreased the enantioselectivity. The ion-exchange seems to be the rate limiting step.

High enantiomeric excesses were achieved using dihydrocinchonidinium salt **70** as catalyst and KClO as oxidant at −40 °C (Table 5, entry 7). Excellent results were obtained for a wide range of substituted 1-arylprop-2-en-1-one derivatives.[55] However, the change of oxidant agent to trichloroisocyanuric acid (TCCA) lessened the enantioselectivity (Table 5, entry 8), as well as the homogeneity of results.[56]

Other catalysts successfully used in the enantioselective epoxidation of (*E*)-enones are guanidine **71a** and binaphthylammonium salt **71b**. In both cases, the oxidant used was NaClO. Thus, when the catalyst **71a** was used in the standard epoxidation of enone **67** in toluene at 0 °C, the compound **68** was obtained with an excellent enantioselectivity (91%).[57] More effective seems to be the binaphthyl derivative **71b**, which was able to catalyse the epoxidation rendering the compound *ent*-**68** with a 96% ee.[58] The high enantioselectivity found for the last case was rationalised on the basis of the X-ray of catalyst, by the hypothetical formation of a chiral reaction cavity around the nitrogen atom, due to the geometrical disposition of the aryl groups.

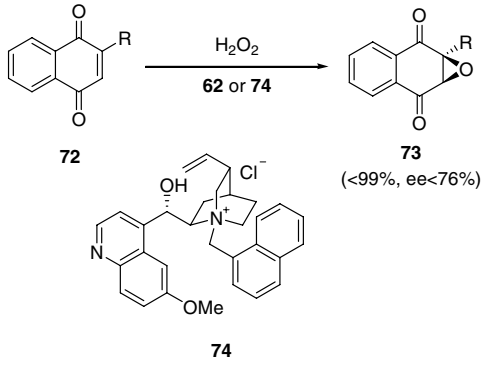


71a



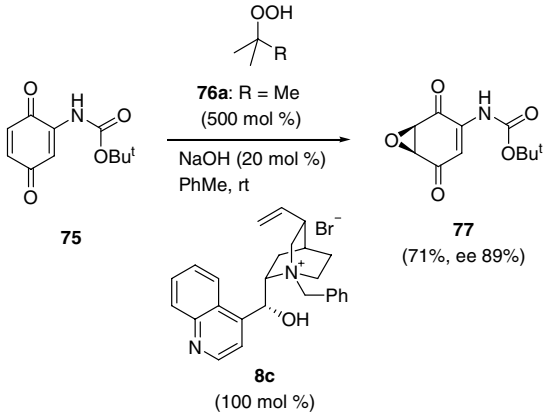
71b: Ar = 3,5-$Ph_2C_6H_3$

The enantioselective epoxidation of (*Z*)-enones is clearly more challenging using this methodology. In this field, of special interest are the quinone epoxide derivatives owing to their activity in metabolic processes, such as antimicrobial and antitumour activities. Although, initial attempts to oxidise quinone derivatives **72** using catalyst **62**, NaOH as base and aqueous solutions of H_2O_2 in toluene gave modest results (up to 45% ee),[59] the use of other catalysts or conditions could further improve these results (Scheme 14). Thus, the change of catalyst to ammonium salt **74**, as well as base, solvent and temperature (LiOH, $CHCl_3$, −10 °C) increased the enantioselectivity up to 76%.[52b,60]



Scheme 14.

Although, previous results in the enantioselective epoxidation of *Z*-enones using *tert*-butylhydroperoxide as oxidant,[61] catalyst **62** and NaOH as base proved modest and disappointing results (enantiomeric excess never higher than 20%), changing the catalyst to **8c** permitted the use of this methodology in the synthesis of manumycin A and related compounds.[62] Thus, the reaction of enone **75** with *tert*-butylperoxide **76a** (R = Me) using stoichiometric amount of catalyst **8c** gave epoxide **77** in good enantiomeric excess (Scheme 15). Two subsequent recrystallisations gave the pure enantiomer, which is the key asymmetric step in the synthesis of this natural product family. Surprisingly, the use of the so called 'pseudoenantiomer' of type **6** did not produce the opposite epoxide



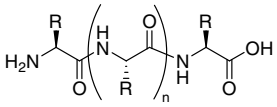
Scheme 15.

ent-**77**, but in fact compound **77** with very modest enantioselectivity.

Catalyst **8c** has also been used in the enantioselective epoxidation of different monoprotected naphthalene 1,4-diones with excellent enantioselectivities (up to 95% ee), in substoichiometric amounts (10 mol %).[63] The epoxides obtained in the above reactions are the key step in the synthesis of palmarumycin and preussomerin G, which are natural products isolated from various fungal cultures.

Other tertiary hydroperoxides have been also tested as oxidants for the epoxidation of different enones,[64] finding that cumyl hydroperoxide (**76b**, R = Ph) gave excellent results for rigid (*E*)-enones, as well as for (*Z*)-enones such as flavones.

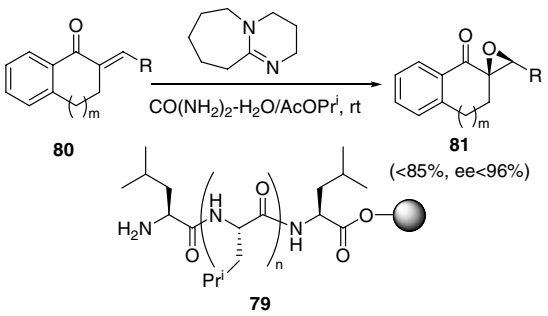
Acyclic chalcones can be epoxidised with a high degree of enantioselectivity by using polyamino acids **78**. We consider these compounds as truly organocatalysts, although owing to their molecular weight they should be excluded from this review. Synthetic polymers derived from alanine and leucine have been extensively used as catalysts in the so called Juliá–Colonna epoxidation,[65] and there are some excellent reviews dealing with their use.[66] Therefore, only works published very recently will be included.



78a: R = Me
78b: R = Pr^iCH_2

Commonly, the Juliá–Colonna epoxidation was carried out in a triphase medium: an aqueous phase, which contains the oxidant (H_2O_2) and the strong base, an organic phase, which contains the substrate and the final product, and the insoluble polyamino acid as the third phase, achieving under these conditions up to 98% ee for epoxide **68**. These conditions have several advantages such as the need for large quantities of catalyst, long reaction times and difficulties in the work-up process, which makes it an environmentally harmful process. Some modifications of the standard conditions have permitted the enantioselective epoxidation of less reactive enones. Thus, a non-aqueous biphasic reaction protocol, using polyleucine immobilised on polystyrene **79**, urea–H_2O_2 adduct and DBU, has been applied in the epoxidation of conformationally-restricted tetralones **80** to give the expected chiral epoxides **81** with enantioselectivities ranging 59–96% (Scheme 16). The R substituent in the starting enone **80** had little impact on the enantio selectivity. However, the size of the annulated ring (*m*) had a great importance; a small ring (*m* = 0 or 1) gave good results, while substrates with larger rings (*m* = 2) gave the worst enantioselectivities.[67]

The use of strongly basic conditions could lead to the slow degradation of the catalyst and the impossibility of the use of substrates with base sensitive functionalities. One of the possible solutions is the introduction of milder bases, such

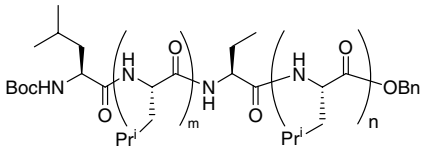


Scheme 16.

as bicarbonate salts, which are at the same time able to activate H_2O_2, and are inexpensive and safe.[68] Specifically, NH_4HCO_3 seems to be superior to $NaHCO_3$ in dimethoxyethane (DME) as solvent for the epoxidation of chalcone **67** with polyleucine **78b** to give the expected epoxide *ent*-**68** with high yield and 94% ee. The recovery and the catalyst could be reused 8 times without a reduction in either the chemical yield, or enantioselectivity.

Another improvement was introduced when the reaction was performed in the presence of phase transfer catalysts, which accelerated the reaction. For example, the addition of tetrabutylammonium bromide as co-catalyst increased the available concentration of the peroxide in the organic phase and, therefore, the reaction was faster. As a consequence, the amount of oxidant and base could be reduced from 30 equiv of H_2O_2 and 4 equiv of NaOH to 1.3 equiv of each, without any detrimental results.[69] The amount of polymeric catalyst can also be reduced. Under these new reaction conditions, a positive influence on the enantioselectivity was observed when pre-activation of catalyst **78b** by treatment with the basic media was performed. This pretreatment meant that polyleucine polymer **78b** sequestered the peroxide oxidant from the aqueous phase forming a new polyamido-peroxide gel, which was able to epoxide enones with good to excellent enantiomeric excess,[70] with this methodology being expanded to include aryl vinyl sulfones.

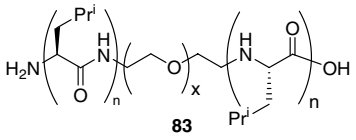
Not only the reaction conditions, but also the structure of polyamino acid catalyst, were changed in order to improve the initial results. Thus, several soluble polyleucine derivatives **82** containing α-aminobutyric acid residues have been synthesised and applied as catalysts in this epoxidation.[71] The introduction of a butyric residue in the mid section of amino acid oligomer promoted the α-helix formation and improved the solubility of catalysts in organic solvents. Different catalysts of type **82** were tested in the epoxidation of chalcone **67**, finding that the longer oligomer the better enantioselectivity (a maximum at *m* = *n* = 6 in **82**, 94% ee for product *ent*-**68**). The role of the amino acid in the N-terminus of catalyst was also studied. From previous work, it was deduced that the stereochemistry of this amino acid residue, as well as its protecting group, determined the enantioselectivity of the epoxidised product. However, the influence of different protecting groups apart from *tert*-butoxy carbonyl (Boc) in the case of using related catalysts **82** was minimal.



82

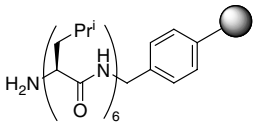
The above observation was further confirmed when different oligomers with 20 residues of leucine were prepared and tested in the same reaction; the protecting group on the N-terminus having a minimal effect on the enantioselectivity of the reaction. More surprising was the result obtained when the reaction was performed with an oligomer having five residues of (*R*)-leucine starting from the N-terminus, followed by 15 residues of natural (*S*)-leucine. In this case instead of obtaining epoxide *ent*-**68**, enantiomer **68** was achieved with 85% yield and 45% ee.[72] Therefore, only 25% of the residues of the catalyst dictated the stereochemical outcome of the reaction. The change of the (*R*)-residues along the oligomer showed that the penultimate and one before penultimate residues played a crucial role in the outcome of the reaction. Thus, when these positions were occupied by achiral glycine residues, the enantioselectivity dropped down drastically.

Another way to solubilise polyamino acid residues is their incorporation to a soluble polymer. Following this criteria, polyleucine residues were bonded to a polyethylene glycol derivative (PEG) rendering a new co-polymer **83**, which was soluble in organic solvents such as THF.[73] The epoxidation of chalcone **67** gave the expected epoxide *ent*-**68** in 80% yield and 98% ee. The catalytic activity of these co-polymers (**83**, *x* average 71) increased as the amino acid chain was reduced from *n* average 12.2 to 3.9, while maintaining the enantioselectivity. The FT-IR spectra of these catalysts showed the presence of an α-helix in all cases.



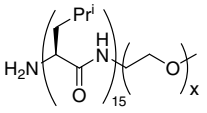
83

The activity of this polymer could be increased by enlarging the PEG chain. So, when polymer **83**, with *x* and *n* values about 453 and 8, respectively, was used as catalyst for the epoxidation of chalcone **67** using NaOH as base, and urea–hydrogen peroxide as oxidant, the expected epoxide *ent*-**68** was obtained in quantitative chemical yield and 94% ee after only 15 min.[74] Another soluble polymer **84** was obtained by polymerisation of aminomethylstyrene and attached to the corresponding leucine oligomer. This polymer was soluble in THF and methylene chloride. The epoxidation of chalcone **67** under the above conditions yielded the expected product *ent*-**68** in 92% yield and 97% ee after 1 h reaction time.[74] These catalysts were used in a continuous membrane reactor, with catalysts being retained by means of a nanofiltration membrane,[75] maintaining the same activity after 28 residence times.



84

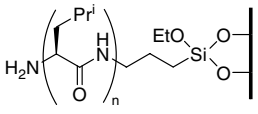
Some polymers derived from monoamino monomethyl polyethylene glycol (molecular weight ca. 5000) and natural leucine **85** have been tested as organocatalysts for the aforementioned epoxidation of chalcone **67**, rendering the expected epoxide *ent*-**68** in a quantitative yield and 96% ee, by using DBU as base and urea–hydrogen peroxide as oxidant.[76] Circular dichroism provided a useful technique to determine the helicity of this type of catalysts, finding that the level of α-helix correlated with the activity of catalysts.



85

A more extensive study on this correlation was carried out by anchoring a series of natural leucine (1–20 monomers) carrying N-terminal glycine residues (1–5 monomers) on TentaGel S NH_2.[77] It was concluded that only one helical turn (four amino acid residues are enough to form a α-helix) was the minimum structural requirement for obtaining efficient catalysts. The catalytic active zone was assumed to be formed by the N-terminal triad of the final α-helix segment, with only four leucine residues being necessary to obtain excellent enantioselectivities.

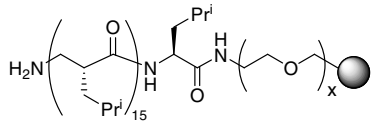
To circumvent the problem of handling the gel catalyst, the leucine residues were grafted to silica gel. Thus, the standard epoxidation reaction gave very high enantioselectivities (up to 93% ee) using the catalyst **86**, comparable to the homogeneous version.[78] The enantioselectivity depended on the number of amino acid residues, reaching the maximum for $n = 45$. Attempts to recycle the catalyst were made but, surprisingly, the weight of the recovered catalyst increased, thus decreasing the enantiomeric excess of epoxide product with each cycle, probably due to the adsorption of urea. This fact could be minimised by washing the catalyst with methanol after each cycle. In this way, the catalyst could be reused 10 times while retaining its activity and selectivity.



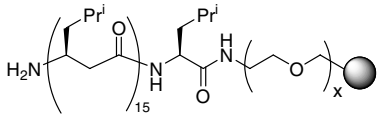
86

β-Amino acids form stable helices more readily than the related α-amino acids. However, the orientation of the

NH bonds in the β-helix is opposite to those of the α-helix. The peptide derivatives **87** were synthesised in order to test the influence of this new orientation on the enantioselectivity of the Juliá–Colonna epoxidation of (*E*)-enones.[79] Both catalysts were very ineffective for the reaction, and only after activation of catalyst **87a**, by basic treatment, could the enantioselectivity be improved up to a moderate 70%.



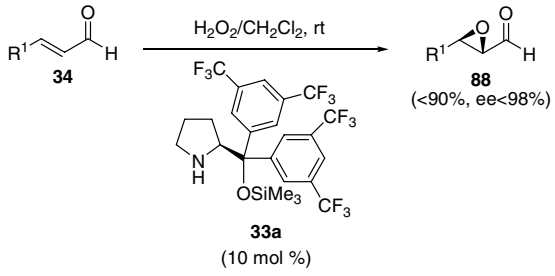
87a



87b

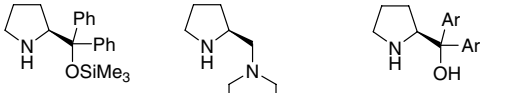
Kinetic studies of the Juliá–Colonna epoxidation using polyleucine **78b** indicated that the reaction proceed via a fast reversible addition of hydrogen peroxide anion to form a racemic enolate, followed by a slow intramolecular stereoselective nucleophilic displacement of hydroxide to form the final chiral non-racemic epoxide. The role of the catalysts is, on one hand, the stabilisation of the initially formed enolate through the oxy-anion hole formed by the amidic groups located near to the N-terminus of peptide. On the other hand, this stabilisation is higher for one of the two enantiomeric enolate intermediates, favouring kinetic resolution of the racemic mixture.[80]

Besides the success obtained in the epoxidation of enones by either phase transfer catalysts or polyamino acid derivatives, there is no example of the related reaction with aldehydes. Jørgensen et al. introduced very recently the use of chiral amine **33a** as a soluble catalyst for the enantioselective epoxidation of α,β-aldehydes **34** to give the expected epoxide **88**, in general, in excellent enantioselectivities (Scheme 17). As far as the oxidants are concerned, similar results could be obtained not only with H_2O_2 but also urea–hydrogen peroxide and even organic peroxides. As far as solvents are concerned, it should be pointed out that the reaction could be performed in solvents other than CH_2Cl_2 with only a slight decrease of the enantioselectivity, even in the case of using the environmentally safe mixture of water–ethanol. The proposed mechanism consists of the formation of the corresponding iminium ion by condensation of amine **33a** with aldehyde **34**, which suffers the nucleophilic attack of peroxide derivative at the β-position, leading to an enamine. The intramolecular nucleophilic attack of this enamine to the peroxide moiety gave the corresponding iminium epoxide, which after hydrolysis liberates the final epoxide **88** and the starting amine **33a**.[81]



Scheme 17.

The use of other organocatalyst, such as **33b**, **89** and **90**, under similar conditions, did not improve the aforementioned results.[82] However, the change of the oxidant to either solid sodium percarbonate or *tert*-butyl hydroperoxide **76a** as well as the solvent to $CHCl_3$ allowed the enantioselectivity to reach higher than 95%.

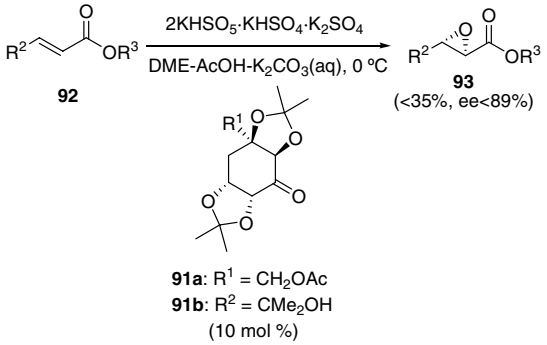


33b **89** **90a**: Ar = Ph **90b**: Ar = 3,5-$Me_2C_6H_3$

Organocatalysts **90a**,**b** have been also applied in the enantioselective epoxidation of different chalcones using *tert*-butyl hydroperoxide **76a** as oxidant and nonpolar solvents such as hexane, to afford the expected chiral epoxides with good results (80% chemical yield and 91% ee for epoxide **68**).[83] Under these conditions, the conformationally fixed tetralone **80** seemed to be unreactive, while the *s-trans* vitamin K_3 (R = Me in **72**) was epoxidased but with very low ee. A linear effect was observed for the epoxidation of chalcone **67**, suggesting only a single chiral molecule was involved in the mechanism.

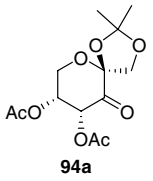
Not only oxidants with nucleophilic character but also intermediates of electrophilic nature can be used in the enantioselective epoxidation of α,β-unsaturated carbonyl compounds. Among the possible candidates, dioxirane reagents have been successfully used for this purpose. Contrary to the usual nucleophilic oxidants, dioxiranes add to double bonds in a concerted manner. These dioxiranes could be easily in situ prepared by reaction of Oxone® ($2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$) with chiral ketones.[84] Chiral ketones derived from quinic acid, such as compounds **91**,[85] which have been successfully used in the enantioselective epoxidation of electron rich olefins, have also been applied to the epoxidation of electron poor olefins such as chalcone **67** or α,β-unsaturated esters **92** (Scheme 18) to give the corresponding epoxides with good enantioselectivity, albeit with modest chemical yields.

Owing to the low reactivity of the in situ formed dioxiranes, they suffer decomposition processes to give the corresponding Bayer–Villiger oxidation products. Therefore, new ketones with enhanced stability have been introduced to perform the aforementioned epoxidation. One of these ketones was the fructose derivative **94a**, which efficiently

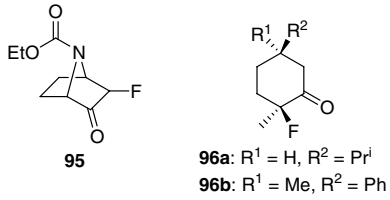


Scheme 18.

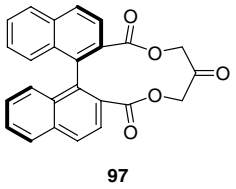
catalysed the oxidation of different cinnamate esters with higher yields (40–96%) and improved enantioselectivities (up to 97% ee).[86] Surprisingly, the epoxidation of the related ethyl (*Z*)-cinnamate gave a lower result (84%, 44% ee).



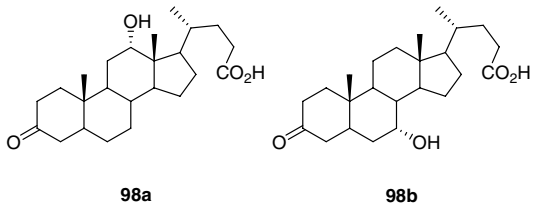
The use of α-fluoroketone derivatives as catalysts for the aforementioned epoxidation have been less effective. The epoxidation of methyl cinnamate using the tropinone derivative **95** gave the expected epoxide with modest results (33%, 64% ee).[87] The use of organocatalysts **96** did not improve the enantioselectivity but did improve the chemical yield (up to 97%).[88]



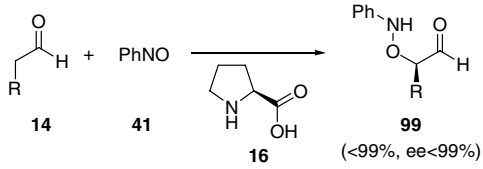
Chiral ketone **97** showed a very high reactivity, and therefore the loading amount could be reduced from the typical 10–0.3 mol %, with the enantioselectivity being up to 95%.[89] Whereas the stereoselectivity was explained as a consequence of a π–π interaction between the aromatic rings of ligand **97** and of substrate **92**, the high chemical yield was attributed to the higher stability of the chiral ketone, owing to the presence of two electron withdrawing ester moieties. The study of the substrate scope showed that the bulkiness of ester moiety (R^3 in **92**) did not play an important role with regards to the enantiomeric excess of product **93**. However, the steric hindrance of the substituent of double bond (R^2 in **92**), as well as the geometry of the double bond, had a great impact on the enantioselectivity, with the best results being obtained for *E*-olefins with aryl phenyl substituents. The protocol was also successfully applied to primary cinnamides.



Different ketones **98** derived from bile acids have been used in stoichiometric amounts as catalysts for the epoxidation of cinnamate derivatives **92**. Moderate to good enantioselectivities were obtained with ketone **98a**. The enantiomeric excess obtained for substituted cinnamate esters depended on the substitution, so electron-donating groups at the *para*-position of the phenyl ring gave the best results, while electron-withdrawing groups at the *ortho*-position led to moderate ee.[90] The outcome of the reaction was governed by the hydroxy moiety, with catalyst **98b** giving the opposite enantiomeric product compared to **98a**.



3.1.3. Aminoxylation of aldehydes and ketones. Among the already existing methods for the asymmetric synthesis of chiral α-hydroxy carbonyl compounds, the direct enantioselective α-aminoxylation of carbonyl compounds is one of the most important strategies for achieving this purpose.[20b,91] Nitroso compounds,[92] in particular nitrosobenzene, are useful electrophiles for performing this type of reaction, although its nitrogen versus oxygen reactivity should be carefully controlled through the election of appropriate catalysts and reaction conditions (compare Schemes 11 and 19).

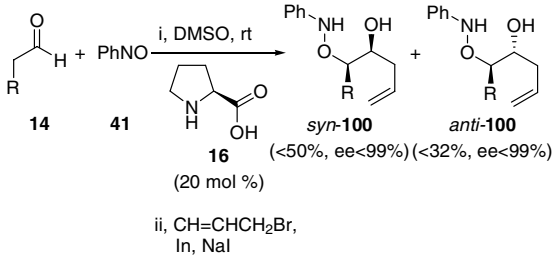


Scheme 19.

Almost simultaneously and independently, Zhong,[93] McMillan et al.[94] and Hayashi et al.[95] reported in this order the first direct α-oxidation of aldehydes **14** using natural proline **16** and nitrosobenzene **41** with high yields and excellent enantiomeric excess (Scheme 19), differing only in the reaction conditions. Whereas Zhong performed the reaction in DMSO as solvent and at room temperature using 20 mol % of organocatalyst, McMillan et al. and Hayashi et al. carried out the same reaction at lower temperatures (4 and −20 °C, respectively) in order to minimise the possible homo aldol reaction, and used less polar sol-

vents such as $CHCl_3$ and CH_3CN. The optimum catalyst loading was 5 mol % for the last two protocols. However, this amount could be reduced to 0.5 mol %, while maintaining the high enantioselectivity but increasing the reaction time. The substrate scope was very broad, with it being applied to alkyl and aryl substituted aldehydes. In order to facilitate the isolation of products **99**, they were reduced to the corresponding primary alcohols by a one-pot addition of $NaBH_4$. Related chiral diols could be obtained by further hydrogenation on palladium–charcoal or by treatment with substoichiometric amounts of copper sulfate.

The end of the reaction could be easily seen by the color changing from green to orange and allowed the in situ transformation of aldehydes **99** by a second reaction process. Hence, after the α-aminoxylation reaction process, the in situ formed aldehyde **99** was submitted to an allylation process promoted by indium, giving the expected diols **100** as mixture of ca. 4:1 diastereomeric ratio, and enantiomeric excess up to 99% for both diastereoisomers (Scheme 20).[96] The nitrogen–oxygen bond could be cleaved by treatment with ethanol in the presence of 30 mol % of copper(II) acetate. This reduction did not affect the sensitive carbon-carbon double bond present in diols **100**.

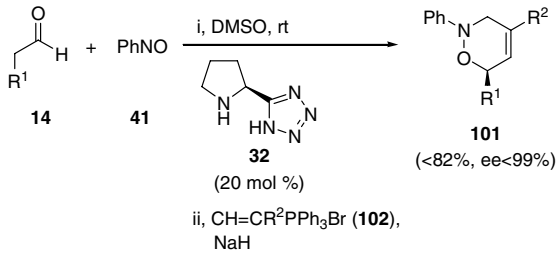


Scheme 20.

Aldehydes **99** could be also trapped by a Wadsworth–Emmons–Horner reaction with diethyl (2-oxopropyl)phosphonate under basic conditions (LiOH) to give the corresponding γ-hydroxy-α,β-unsaturated ketone. It is noteworthy that the possible racemisation did not take place under the basic conditions of the last reaction, since the final hydroxy ketone derivative could be isolated with enantiomeric excesses of up to 99%.[97]

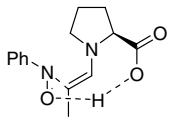
Different chiral dihydro-1,2-oxazine derivatives **101** were obtained when the enantioselective α-aminoxylation reaction was catalysed by a tetrazole proline derivative **32**, in which the in situ formed aldehyde reacted subsequently with vinylphosphonium salt derivatives **102** (Scheme 21). The possible mechanism pathway involves the Michael type addition of a nitrogen atom of aldehyde intermediate **99** on the phosphonium salt to form the corresponding ylide derivative, which in turn reacts with the carbonyl moiety to form the corresponding cyclic derivative.[98]

A quantum mechanical computational study was carried out in order to establish the origin of the regioselectivity displayed by nitrosobenzene and the stereoselectivity of



Scheme 21.

the obtained aldehydes **99**.[99] From the different proposed pseudosix-membered transition state structures, the most stable seemed to be *O-anti*-**102**. This transition state involves the attack of (*E*)-*anti* enamine to the oxygen of nitrosobenzene **41**, adopting its phenyl group in a pseudo-axial position and *anti* with respect to the carbonyl group of proline. These calculations predicted a 99% ee for the products, which are in agreement with the obtained experimental value (97% ee). The heteroatom selectivity could be explained by the higher basicity of the nitrogen atom versus the oxygen one, which led to its preferential protonation, with the oxygen atom becoming more electrophilic. Therefore, the energies of the transition state for the nitrogen attack are generally higher than those for the oxygen one.

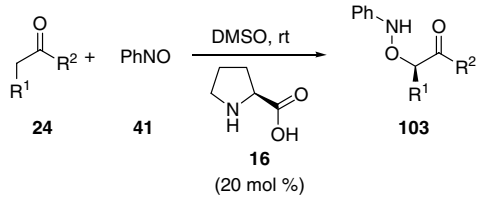


O-anti-**102**

Kinetic studies of the aforementioned transformation (Scheme 19) showed a high auto acceleration in the reaction rate,[100] suggesting an improvement of the catalyst over time. Once the substrate inhibition was discarded, a proline-product adduct (enamine-like intermediate) was suggested as the improved catalyst. This new catalyst reacts with the initial aldehyde to form an intermediate bearing two enamine moieties, one of which was formed by the proline and the final hydroxy aldehyde **99** while the second one was formed by the previous aminohydroxy derivative and the initial aldehyde **14**. Presumably, the reaction of nitrosobenzene **41** takes place on this double enamine intermediate.

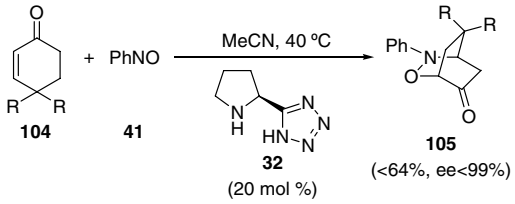
The scope of this protocol was further extended to ketones (Table 6), obtaining the expected hydroxy ketones **103** with excellent enantioselectivities, even in the presence of small amounts of water (<25%).[101] In order to improve the chemical yield and to prevent the formation of the related dihydroxy ketone derivative, the addition of nitrosobenzene should be performed very slowly. In the case of using acyclic ketones, a small amount of racemic α-amino ketone derivative was always obtained. Remarkably, when the reaction was performed using methyl ketones, the reaction took place exclusively at the methylene moiety. The use of other proline derivatives such as compound **38**, did not

Table 6. Enantioselective direct α-aminoxylation of ketones



Entry	R^1	R^2	Yield (%)	ee (%)
1	Me	Me	75	>99
2	Me	Et	65	99
3	CH_2=$CHCH_2$	Me	68	>99
4	Pr^i	Me	58	>99
5	–$(CH_2)_4$–		70	>99
6	$CH_2C(OCH_2CH_2O)(CH_2)_2$		94	>99

produce any appreciable improvement. Hydroxy ketones **103** could be easily transformed into the corresponding diols by diastereoselective reduction of the carbonyl group (diastereoselectivy around 40%) and hydrogenolysis using PtO_2 as catalyst. The absence of a nonlinear effect was attributed to the presence of only one chiral proline in the mechanism pathway of the reaction. Moreover, DFT calculations for the cyclohexanone case showed that the most probable transition state was similar to the one calculated for aldehydes (*O-anti*-**102**).



Scheme 22.

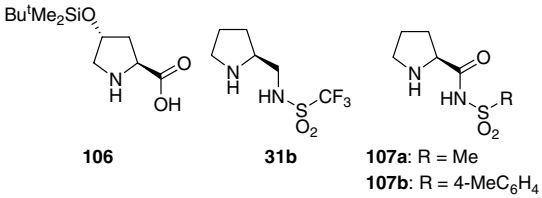
Extension of the above work to the α-aminoxylation of ketones quickly followed.[102] In this new protocol, the solvent used was DMF at 0 °C decreasing the loading of proline to 10 mol %. As for the previous case, the slow addition of nitrobenzene was crucial in order to obtain good chemical yields. The regioselectivity was almost complete for the cyclic ketones while for acyclic ketones a mixture ca. 1:1 of α-hydroxy and α-amino ketones was obtained. This methodology was also successfully applied to the enantioselective desymmetrisation[103] of 4-monosubstituted and 3,5-disubstituted cyclohexanones, with ee up to 99%.

This methodology has recently been used as the key step in the total synthesis of fumagillol, RK-805, FR658145-demethylovalicin and ovalicin.[104] The common compound in these syntheses was prepared by the reaction of 1,4-cyclohexanedione monoethylene ketal with nitrosobenzene in DMF at 0 °C to give the expected ketone (Table 6, entry 6) with 93% chemical yield and as only one enantiomer.

Proline-based tetrazole catalyst **32** was also applied to the α-aminoxylation of ketones,[105] with results being similar to those obtained using proline **16**. This catalyst was applied successfully in a tandem *O*-nitroso oxidation/Michael-type reaction process (Scheme 22).[106]

Another sequential reaction was also applied in the enantioselective desymmetrisation of polysubstituted cyclohexanones, using proline **16** as well as its tetrazol derivative **32** as catalysts. In this case, an excess of nitrosobenzene was used, since it is not only the electrophilic partner of the reaction, but also the reducing agent for the in situ cleavage of the N–O bond in the final phenylaminohydroxy ketone derivative **103**, directly yield the related hydroxy ketone.[107]

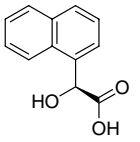
Another organocatalyst proposed as an alternative to the proline was the hydroxy proline derivative **106**, which was able to catalyse the enantioselective α-aminoxylation of ketones very efficiently, yielding the final products **103** after only 1 min and with good chemical yields and excellent enantioselectivities.[108] Remarkably in this case, neither α-amino ketones nor dihydroxy ketone derivatives could be detected in the crude reaction mixture. Moreover, this catalyst could perform the reaction with substrates, which failed with proline, such as cycloheptanone (50%, >99% ee). The versatility of this chiral compound was also illustrated by catalysis of the sequential *O*-nitroso oxidation/Michael-type reaction process depictured in (Scheme 22), giving the final product **105** as only one enantiomer.



Triflamide **31b** has been used as an organocatalyst in the reaction of ketones, as well as aldehydes, with nitrosobenzene to give the expected hydroxylated carbonyl compounds with high levels of enantioselectivity.[109]

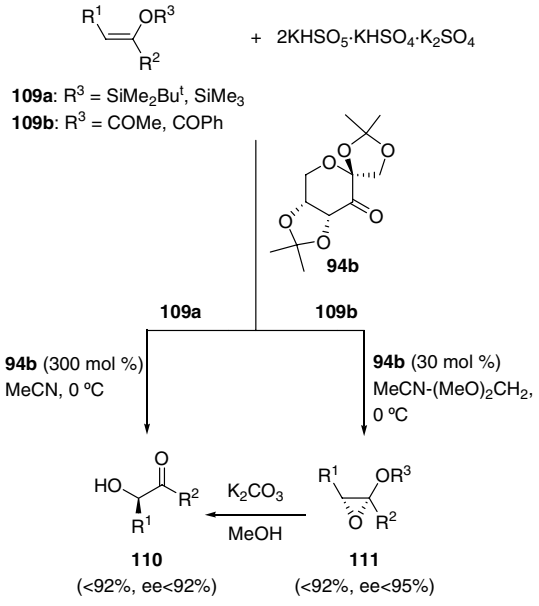
The acidic sulfonylimide derivatives **107** have also been used in the aforementioned α-aminoxylation of ketones.[110] However, the yield when using these catalysts proved a problem, owing to the high amount of dihydroxy ketone by-product obtained (around 25%). A similar problem occurred in the sequential *O*-nitroso oxidation/Michael-type reaction process, in which the chemical yield was rather modest (never higher than 25%), although the enantioselectivities were excellent.

Not only are derivatives from proline able to catalyse this transformation derivatives from proline, but also hydroxy acids such as 1-naphthyl glycolic acid **108** can be used as organocatalyst in the reaction of nitrosobenzene **41** with, in this case, enamines **40** to yield, after work up, the corresponding hydroxy ketone **103** with good chemical yields and enantiomeric excess ranging from 70% to 92%.[37]



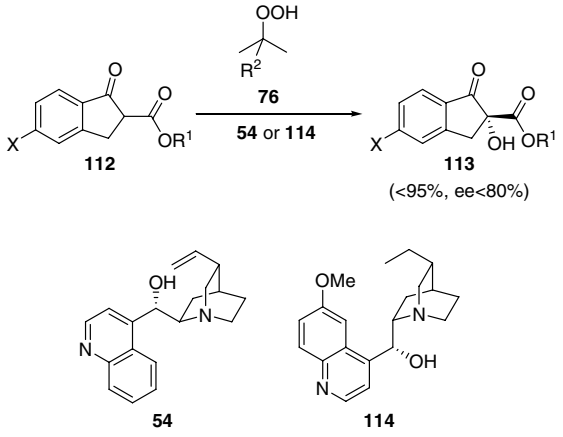
108

3.1.4. Miscellaneous oxidation processes. The direct asymmetric synthesis of α-hydroxy carbonyl derivatives is possible by the use of other methodologies.[111] For instance, the oxidation via silyl enol ethers **109a** with Oxone® ($2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$) in the presence of excess of fructose derivative **94b** lead directly to chiral α-hydroxy ketones **110** with good enantioselectivities (Scheme 23).[112] The amount of ketone catalysts **94b** could be reduced to 0.3 equiv in the case of using tetralone enol ethers, obtaining the enantiomeric excesses up to 83%. This protocol has been extended to the corresponding enol ethers **109b**, with the corresponding epoxide **111** being isolated with excellent results (Scheme 23). The treatment of chiral epoxides **111** with K_2CO_3 in methanol afforded the corresponding α-hydroxy ketone **110**. Meanwhile, a thermal rearrangement of former epoxide **111** directly gave the corresponding α-alkanoyloxy ketone, which after typical hydrolysis, gave the expected α-hydroxy ketone *ent*-**110** with an opposite absolute configuration. This methodology is a illustrative example of the asymmetric synthesis of both enantiomers using the same chiral promoter.[113]



Scheme 23.

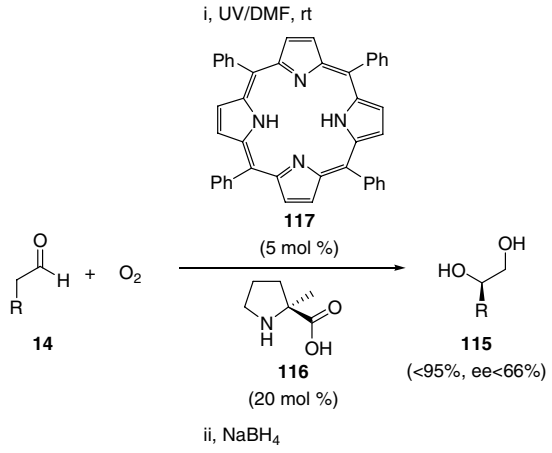
Not only oxone but also other oxidants can be used in the preparation of hydroxy carbonyl derivatives. *tert*-Butyl hydroperoxide (**76a**: $R^2 = Me$) has been used in the enantioselective oxidation of 2-alkoxycarbonyl indanone derivatives **112** ($X = Cl$, $R^1 = Me$) catalysed by amine **54** to give the expected compound *ent*-**113** in moderate enantiomeric excess (50%), with this chiral compound being the starting material for the synthesis of pyrazoline-type insecticide indoxacarb.[114] The use of chiral dihydroquinine **114** in combination with cumyl hydroperoxide **76b** ($R = Ph$) at room temperature seems to be a more promising protocol (Scheme 24), since the expected hydroxy carbonyl compounds **113** could be obtained with excellent chemical yields and good enantiomeric excess.[115]



Scheme 24.

The use of molecular oxygen as an oxidant on these reactions would permit the development of more sustainable processes.[116] This challenge was firstly overcome by the oxidation of 2-alkyl indanone derivatives to give the corresponding chiral 2-alkyl-2-hydroxy indanones with enantiomeric excess up to 79%.[117] The reaction was accomplished by using a aqueous-toluene biphasic medium and in the presence of substoichiometric amounts of phase transfer ammonium salt **8a**, the reaction was further extended to the related 2-alkyl tetralone derivatives with similar results.

Aldehydes can be also hydroxylated with molecular oxygen in the presence of α-methyl proline **116** to give, after final reduction, diols **115** with moderate enantioselectivities (Scheme 25). The excitation of molecular oxygen by ultraviolet light (UV) in the presence of tetraphenylporphine



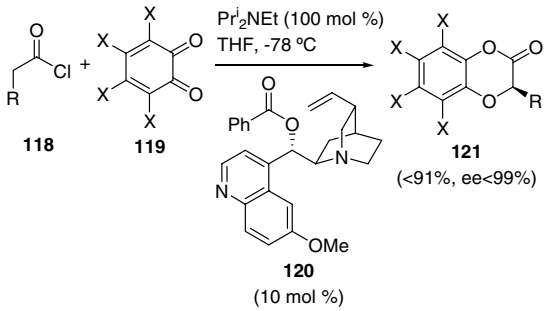
Scheme 25.

(**117**) permitted the generation of singlet molecular oxygen in appreciable amounts, which is the real reactive agent. This intermediate reacts with the highly nucleophilic enamine formed from the aldehyde **14** and amino acid **116** to give the corresponding α-hydroperoxide intermediate, with its presence excluding the possible 1,2-cycloaddition forming a dioxetane intermediate as the alternative pathway.[118]

This methodology has been further extended to cyclic ketones with similar results.[119] In this case, the reaction was carried out in DMSO as solvent and with the natural amino acid L-alanine to give the best enantioselectivities. These results have had an important impact on our knowledge of possible prebiotic chemistry, since it seems to indicate that terrestrial amino acids could catalyse the asymmetric introduction of molecular oxygen in organic compounds, serving as a plausible first step in the homochirality transfer to other bioorganic molecules.

The hydroxylation of ketones has also been performed using other oxidants, such as iodosobenzene and *trans*-2-(*p*-methylphenylsulfonyl)-3-phenyloxaziridine, and L-proline **16** and proline amine **89** as catalyst, giving similar results to those obtained using molecular oxygen (enantiomeric excess never higher than 77% for compounds of type **110**).[120]

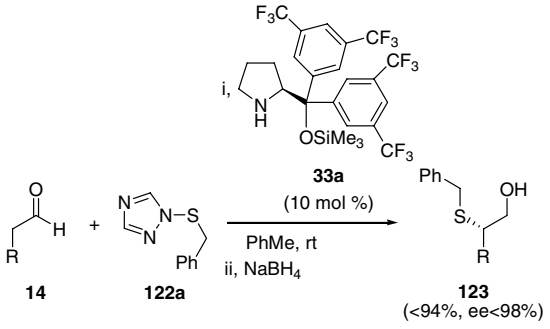
Very recently, the incorporation of an oxygen atom at the α-position of a carbonyl compound has been accomplished by means of a [4+2]-cycloaddition process (Scheme 26). The reaction of acyl chloride **118** with different *o*-quinones **119** in the presence benzoylquinidine **120** gave lactone **121** with excellent enantioselectivities.[121] The plausible mechanism pathway involves the formation of the corresponding ketene by reaction of an acyl chloride with the Hünig's base, followed by the addition of the chiral amine to render the corresponding chiral ketene enolate zwitterion intermediate, which undergoes cycloaddition and, after liberation of chiral amine, gives the final lactone. Compounds **121** could be easily transformed into the corresponding chiral methyl α-hydroxy esters without racemisation by a standard methanolysis followed by an oxidation of a phenoxy ether with cerium ammonium nitrate (CAN).



Scheme 26.

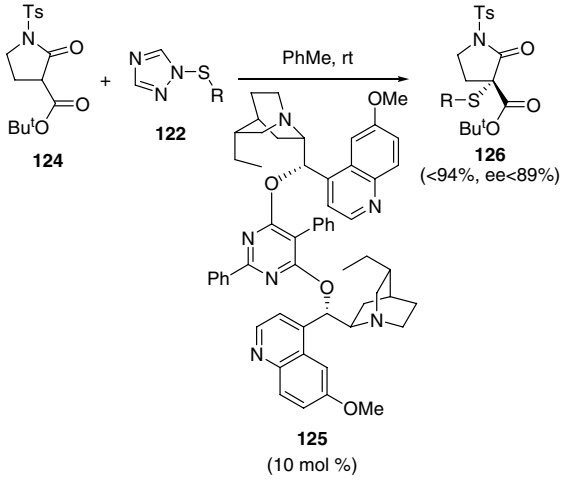
3.2. Sulfenylation reactions

Despite the synthetic potential of α-sulfenylated carbonyl compounds, their asymmetric synthesis generally involved the use of chiral auxiliaries. Therefore, the development of enantioselective protocols avoiding the use of poisonous transition metals is still highly desirable. Jørgensen et al. have achieved this goal (Scheme 27). The reaction of aldehyde **14** with electrophilic sulfur source triazole **122a** in the presence of substoichiometric amounts of catalyst **33a**, gave after final reduction and hydrolysis, chiral 2-benzylsulfanyl alcohols **123** with excellent results.[32,122] Upon prolonged reaction times, the aldehyde obtained racemises and/or led to the α,α-disulfenylation products, therefore, the reaction time was a parameter to be strictly controlled. This protocol has been also expanded to the synthesis of alcohols bearing quaternary stereocentres,[23] just by using the corresponding dialkyl substituted aldehyde, with the enantioselectivity dropping to 61%.



Scheme 27.

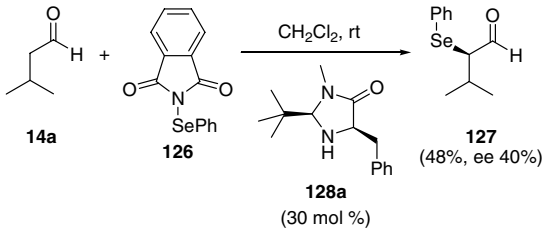
The sulfenylation of 1,3-dicarbonyl compounds, such as cyclic β-keto esters **52**, indanone derivatives **112** and pyrrolidone **124**, could be carried out by using substoichiometric amounts of dihydroquinidine **125** and different triazole derivatives **122**, to afford the expected chiral products with moderate to high enantioselectivities (Scheme 28). It should be pointed out that the nature of the R substituent on the reagent **122** did not have any important effect on the enantioselectivity of the reaction. However, the bulkiness of the ester moiety of the 1,3-dicarbonyl compound had an accountable effect; the more crowded the ester moiety the higher enantioselectivity. Other alkaloids tested as catalysts gave lower results.[123]



Scheme 28.

3.3. Selenenylation reaction

Contrary to the oxidation methods, or even to sulfenylation, which presents at least two protocols, the α-selenenylation of carbonyl compounds is in its preliminary stage. In fact, there is only one example,[124] in which isovaleraldehyde **14a** reacted with *N*-(phenylseleno)phthalimide **126** to yield the expected α-functionalised aldehyde **127** in the presence of imidazolidinone **128a**, with moderate results (Scheme 29). This result could be slightly improved upon by the use of 2-(tosyaminomethyl)pyrrolidine **31a** (Ar = 4-MeC$_6$H$_4$) up to 60% ee. However, the use of the related catalyst **31b** reduced the enantiomeric excess to 30%. A similar reaction using cyclohexanone and catalyst **31b** gave the expected α-seleno cyclohexanone with good chemical yield but very low enantioselectivity (88%, 18% ee). Despite these modest results, it should be pointed out that this work opens up the field and other organocatalyst will improve upon these results soon.



Scheme 29.

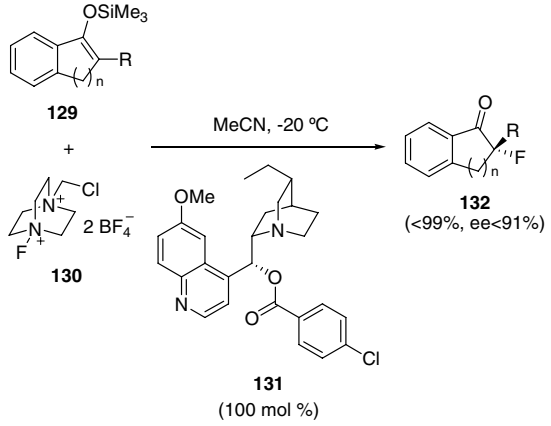
4. Enantioselective α-halogenation of aldehydes and ketones

Halogenated compounds are useful intermediates in organic synthesis due to the fact that this functionality serves as a linchpin for further transformations.[125] Therefore, the enantioselective formation of these compounds is a deserved objective in asymmetric synthesis, with organocatalysis having shown its potential in this type of transformation. Diatomic dihalides, commonly used as halogenating reagents, are far too reactive for asymmetric synthesis. Therefore the recent development of milder sources of electrophilic halogen has been crucial for achieving this purpose.

4.1. Fluorination reactions

Fluorine is the most electronegative element in the periodic table and its incorporation in organic compounds alters, sterically and electronically, the properties of molecules, affecting their pK_a, dipole moment and hydrogen bonding capacity. Furthermore, the carbon-fluorine bond is strong, conferring a special stability and reactivity to fluorinated compounds. All these facts, together with their high metabolic stability, made these compounds ideal candidates for applications in medical chemistry.[126] Therefore, the enantioselective synthesis of fluorinated products represents an interesting synthetic challenge.

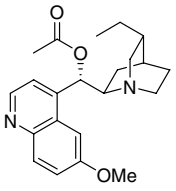
The aforementioned problem was first addressed with an organocatalytic approach.[127] Thus, the reaction of silyl enol ether **129**, derived from substituted either indanones or tetralones, with selectfluor **130** as an initial source of electrophilic fluorine atom catalysed by stoichiometric amounts of dihydroquinine ester **131** gave the expected fluorinated cyclic ketones **132** with moderate to good enantioselectivities (Scheme 30). Better results were found for indanone derivatives **132** ($n = 1$) compared to their related tetralones **132** ($n = 2$). The substitution also had an important effect on the enantioselectivity, with compounds bearing benzyl substituents giving the highest enantiomeric excess.



Scheme 30.

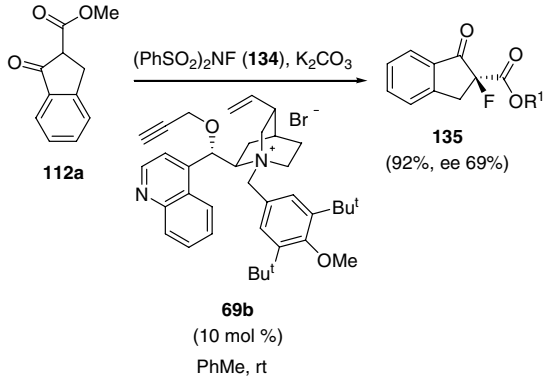
The enantiomeric excesses obtained were surprisingly higher when the so called pseudoenantiomer **133** was used as catalyst. This permitted the extension of the above methodology to other ketones, such as the cyclic β-keto ester of type **52** and their benzocondensated compounds of type **112**, as well as to aryl cyanoacetates **48**, achieving the α-fluorinated derivatives with enantioselectivities up to 87%.[127] As far as the mechanism is concerned, it seems that the cinchona alkaloid reacted at first with selectfluor **130** to generate the corresponding *N*-fluoro alkaloid derivative, which is the real electrophilic fluorinating agent. ^{19}F NMR experiments of the mixture of both reagents and

crystallographic studies support the existence of this intermediate. Other *N*-fluoro cinchona alkaloid derivatives have been proposed as alternatives.[128] However, the enantioselectivity found was noticeably lower.[129]



133

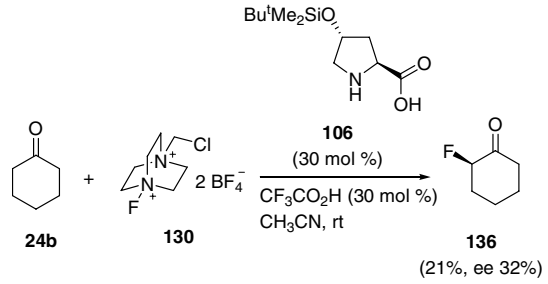
The first real breakthrough in organocatalytic enantioselective fluorination was published in 2002,[130] when the fluorination of benzocondensated β-keto ester **112a** was accomplished via the use of *N*-fluorobenzenesulfonimide **134** and substoichiometric amounts of quaternary ammonium salt **69b**, which act as a phase transfer catalyst (Scheme 31). Although the enantiomeric excess of the final product **135** was modest, this work showed the possibilities of the substoichiometric version.



Scheme 31.

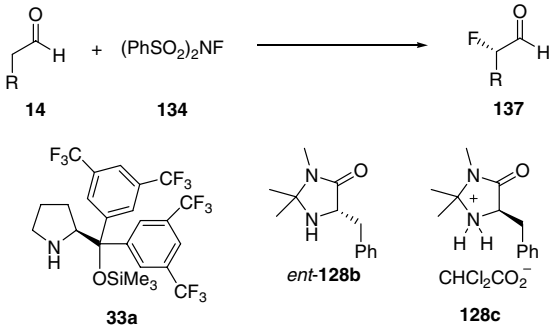
Not only phase transfer catalysts, but also proline derivatives can be used as organocatalyst for the fluorination of carbonyl compounds. Thus the reaction of cyclohexanone **24b** with selectfluor **130** in the presence of substoichiometric amounts of trifluoroacetic acid and catalyst **106** gave the expected ketone derivative **136** with a rather low enantioselectivity (Scheme 32). This result could not be improved by the use of other systems such as L-proline **16**, its hydroxy derivative **38** or prolinol **90a**.[131]

The fluorination of aldehydes has been, however, more successful (Table 7). This goal was achieved almost simultaneously by Jørgensen et al., Barbas et al. and MacMillan et al. with a difference of only days in the submission date. In all cases the selected fluorinating agent was *N*-fluorobenzenesulfonimide **134**. Thus, when catalyst **33a** was used, the expected products **137** were achieved with moderate to good chemical yields and excellent enantioselectivities



Scheme 32.

Table 7. Enantioselective direct α-fluorination of aldehydes



Entry	Catalyst (%)	R	Yield (%)	ee (%)
1	**33a** (1)	C_6H_{13}	55	96
2	**33a** (1)	Bn	74	93
3	*ent*-**128b** (30)	C_6H_{13}	94	86
4	*ent*-**128b** (30)	Bn	97	88
5	**128c** (20)	Bn	71	96

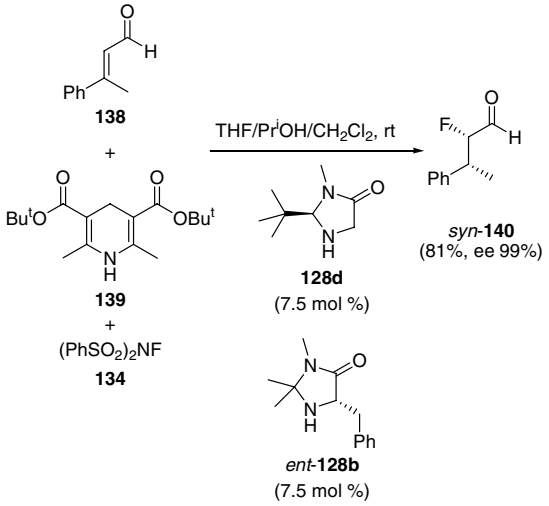
(Table 7, entries 1 and 2). It should be noted that the fluorinating agent **134** reacted with catalyst **33a** to give the corresponding prolinol of type **90** in typical solvents, such as methylene chloride or acetonitrile. This prolinol derivative was inactive for the reaction and therefore products **137** were obtained in low yields. This side reaction did not take place in methyl *tert*-butyl ether at room temperature, allowing the diminution of the amount of catalyst to 1 mol %.[132] The use of another fluorinating agent, such as selectfluor **130** gave worse results since the desilylation reaction could not be avoided. In order to avoid the possible racemisation of aldehydes **137** upon isolation by silica gel, they were reduced in situ with $NaBH_4$ to the corresponding alcohols. The whole process gave excellent enantioselectivities independent of the nature of the aldehyde. Initial mechanistic studies showed the presence of a small nonlinear effect.[32]

Imidazolidinone *ent*-**128b** in dimethyl formamide at 4 °C has shown to also be efficient for this type of transformation.[133] In this case, the amount of catalyst had to be increased up to 30 mol %, but the chemical yield was excellent (Table 7, entries 3 and 4).

Imidazolidinone derivative **128c** was also used, with the reaction medium being mixtures of THF and isopropanol

at −10 °C, achieving good chemical yields and excellent enantioselectivities for the corresponding aldehydes *ent*-**137** (Table 7, entry 5).[134] Although the standard catalyst loading used in this study was 20 mol %, this amount could be reduced to only 2.5 mol % without a decrease in the enantioselectivity but with a detrimental effect on the reaction time. The protocol permitted the fluorination of different aldehydes with a broad range of functionalities maintaining the very high enantioselectivity.

The combination of two discrete catalysts **128d** and *ent*-**128b** permitted the synthesis of α-fluorinated aldehydes **140** with excellent results (Scheme 33). The mechanism pathway could be defined as a tandem process: the first is a hydride transfer from the Hantzsch ester **139** to the iminum intermediate, previously formed by the reaction of α,β-unsaturated aldehyde **138** and chiral amine **128d**, followed by hydrolysis to render an aliphatic aldehyde intermediate. The second one is the fluorination, which takes place by reaction of *N*-fluorobenzenesulfonimide **134** with the enamine formed by previous reaction of the aliphatic aldehyde intermediate and the chiral amine *ent*-**128b**. The final hydrolysis gave aldehyde *syn*-**140** with a diastereomeric excess higher than 95%.[135] The related aldehyde *anti*-**140** could be obtained by combination of chiral amines **128d** and **128b**, with practically the same results (62%, de 90%, ee 99%). This example illustrates that the diastereoselective and enantioselective outcome of this asymmetric multicomponent reaction[7b] can be modulated by the judicious selection of simple chiral catalysts.



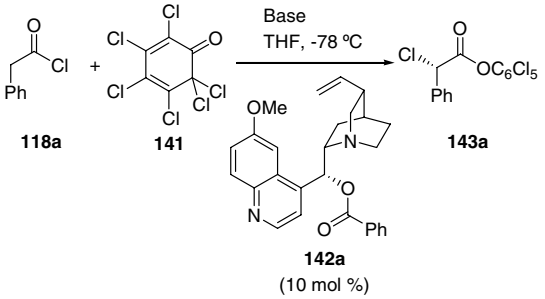
Scheme 33.

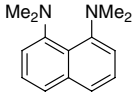
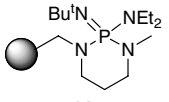
4.2. Chlorination reactions

Chiral α-chloro carbonyl compounds are especially versatile organic compounds due to their potential for further synthetic transformations. For instance, chiral α-chloro aldehydes are good substrates for the synthesis of optically active amino acid derivatives, epoxides and amino alcohols by simple and conventional organic transformations without racemisation.

The first chlorination of carbonyl compounds was accomplished by Lectka et al. through a double process of enantioselective chlorination and esterification.[136] The ketene generated by deprotonation of acyl chloride **118** with a strong base, reacts with chiral tertiary amine **142a** to give a chiral zwitterionic enolate, which reacts with the electrophilic chlorine source **141** to render a chlorinate acyl ammonium salt. This intermediate undergoes, in turn, a transacetylation with the in situ formed perchlorophenol to give the final product of type **143**, regenerating the starting chiral amine **142a**. Results are relatively sensitive to the stoichiometric base used (Table 8). Thus, when the proton sponge **144** was used, only a moderate amount (40%) of final halogenated ester **143a** was obtained, albeit with high enantiomeric excess. This low yield was partially due to the easy ring-chloration of base **144** and the consequent liberation of pentachlorophenol, which competes with the base for the starting acyl chloride **118a**. As an alternative, the ketene was quantitatively generated when a THF solution of acyl chloride **118a** was passed through a funnel at −78 °C containing the basic BEMP-type resin **145**. This ketene solution was added to a solution containing all reagents, affording the expected product **143a** with a good result (Table 8, entry 2). Under these conditions, the expected opposite enantiomeric product *ent*-**118a** was obtained with similar results, when the pseudoenantiomer **120** was used.

Table 8. Enantioselective direct α-chlorination of acid derivatives



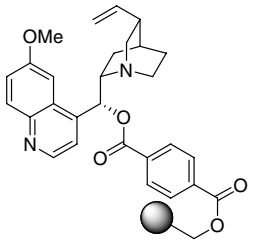
Entry	Base	Yield (%)	ee (%)
1	 **144**	40	95
2	 **145**	80	99
3	NaH/15-crown-5	63	95
4	$NaHCO_3$/15-crown-5	68	90

Other bases tested, such as NaH and $NaHCO_3$, gave similar results; although the latter reduces the economical reaction cost and facilitates the purification. It should be pointed out that the deprotonation of the starting acyl chloride did not take place when $NaHCO_3$ was alone, which implies that this base only intervenes as a final scavenger of hydrogen chloride, with the chiral

amine being the initial base. The reaction rates of both the NaH and $NaHCO_3$ protocols are proportional to the concentration of chlorinating reagent **141**. These results were explained on the basis of a reversible enolate formation, which did not vary its concentration over the time.

This protocol could be expanded to other aryl and alkyl substituted acyl chloride derivatives, even to acyl bromide derivatives, obtaining in all cases, similar results. However, the reaction with the related acyl fluorides gave the expected products **143** with very low yields and low enantioselectivities. In all cases, the presence of water should be avoided since it reacts with the chlorinating agent to render hypochlorite and the perchlorinated phenol, which competes for the starting reagent.

Quinine has been anchored to a Wang resin to give the catalyst **142b**, which could be used as a stoichiometric base in the aforementioned chlorination process in a column-based flush and flow system with similar results to the previously mentioned.[137] The alkaloid-derived beads can be easily regenerated just by flushing Hünig's base through the column. This methodology has been applied to the synthesis of a precursor of the metalloproteinase inhibitor BMS-275291, which is in stage III clinical trials as a treatment for cancer.

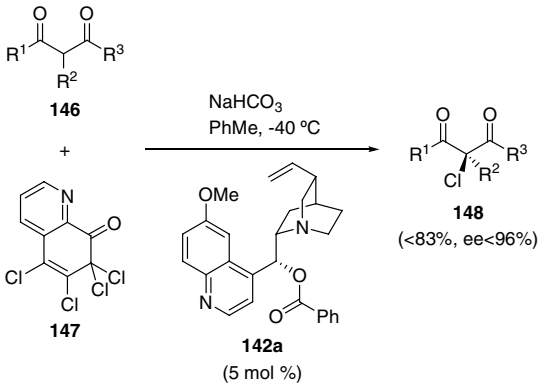


142b

Benzoyl quinine **142a**, as well as its pseudoenantiomer **120**, has been used as a catalyst in the direct α-chlorination of 2-substituted 1,3-dicarbonyl compounds **146** (Scheme 34). Among the chlorinated reagents tested, quinolinone derivative **147** gave the best results. With regards to carbonyl compounds, it should be pointed out that the enantioselectivities for 1,3-diketones were lower than for β-keto esters, with the best results being obtained for cyclic esters of type **52** and the related benzocondensated compounds **112**.[138]

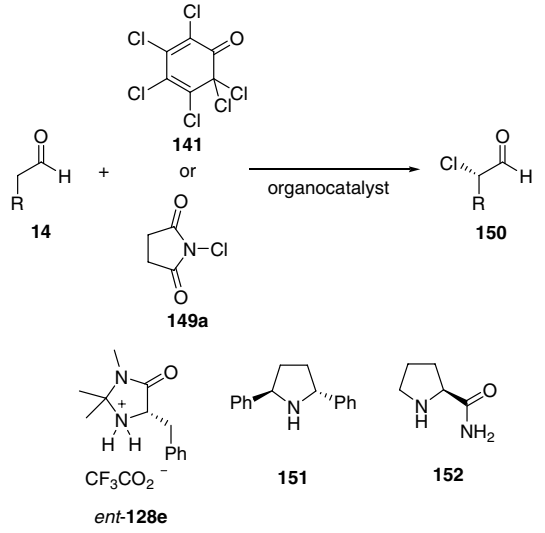
Aldehydes **14** can also serve as substrates for the α-chlorination process (Table 9). Thus, compound *ent*-**128e** (5 mol %) is able to catalyse the chlorination of aldehydes using reagent **141** in acetone at −30 °C, to afford the corresponding products **150** with high yields and enantioselectivities, independent of the bulkiness of the aldehyde substitution (entries 1 and 2).[139] The mild conditions permitted the presence of acid sensitive functionalities.

The aforementioned transformation can also be carried out with simple and inexpensive *N*-chloro succinimide **149a**.[140]



Scheme 34.

Table 9. Enantioselective direct α-chlorination of acid aldehydes

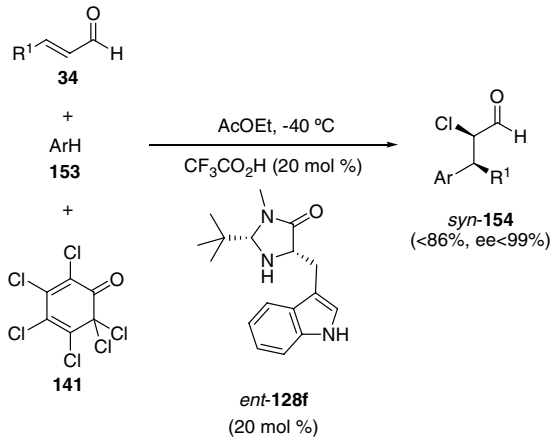


Entry	Catalyst	Chlorinating reagent	R	Yield (%)	ee (%)
1	*ent*-**128e**	**141**	*c*-C_6H_{11}	87	94
2	*ent*-**128e**	**141**	$PhCH_2$	92	80
3	**151**	**149a**	$PhCH_2$	99	78
4	**152**	**149a**	$PhCH_2$	82	95

In this case either C_2-symmetric pyrrolidine **151** or prolinamide **152** in 10 mol % could be successfully used (Table 8, entries 3 and 4), with the reaction conditions being milder than in the previous case (methylene chloride at room temperature). The obtained chiral α-chloro aldehydes **150** are configurationally stable to neutral pH silica purification, although they can be easily transformed into a wide variety of different compounds, such as epoxides after reduction with $NaBH_4$ and KOH treatment, and acids after oxidation with $KMnO_4$. All these transformations took place without decreasing the initial enantiomeric excess, showing the versatility of these compounds.

DFT calculations of the possible mechanism of the chlorination of aldehydes using catalyst **151** did not show any face biasing on the classical enanime intermediate.[140b] The HOMO *N*- and C_α-orbital coefficients were calculated

to be 0.312 and 0.253, respectively, indicating that the nitrogen in the enamine had the highest electron density and might be expected to be the most nucleophilic centre towards the chlorine electrophile. On the basis of these calculations, the reaction pathway was expected to proceed through a kinetically controlled N–Cl bond formation, rather than a direct addition of the chlorine atom to the enamine carbon atom. This *N*-chloro enamine ammonium intermediate underwent a rapidly 1,3-sigmatropic rearrangement to give the thermodynamically favoured α-chloro iminium derivative. The absolute configuration of the final product was due to a favourable rotation in the *N*-chloro enamine ammonium intermediate to maximise the orbital overlap, according to the computational studies. The absence of a nonlinear effect in the reaction indicates strongly that only one chiral molecule **151** was involved in the reaction pathway, indirectly confirming the above calculation results. Moreover, due to the fact that the chlorine source was not directly involved in the formation of the final sterocentre, the use of other chlorinating reagents would provide the same results. This hypothesis was confirmed by the use of reagent **141**, which rendered the same results as using **149a** with regards to the enantioselectivity.



Scheme 35.

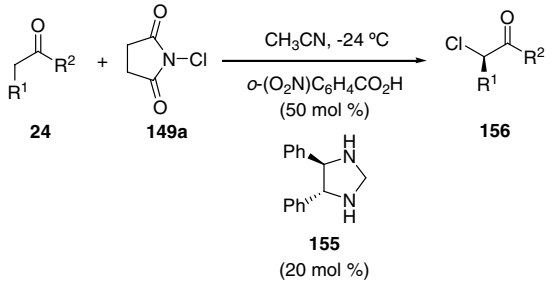
Finally, kinetic studies showed that the rate determining step was the hydrolysis of aforementioned α-chloro iminium derivative. Since water and acids facilitate iminium hydrolysis, their influence on the reaction rate was studied. The addition of 10 mol % of butyric acid (the same amount as the catalyst **151**) and 2 equiv of water to the reaction media doubled the reaction rate with respect to the reaction without additives, with the reaction rate being constant throughout the reaction time and independent of the concentration of additives.

Different α,β-unsaturated aldehydes **34** have been also used as starting materials in a Michael-chlorination cascade process (Scheme 35). The reaction of different electron rich heteroarenes **153**, such as furans, thiophenes and indoles, with Michael acceptors **34** and chlorinated reagent **141** in the presence of substoichiometric amounts of chiral catalyst *ent*-**128f** gave compounds *syn*-**154** with excellent diastereomeric excess (always higher than 90%) and enantioselectivities. Meanwhile the chemical yields were moderate to good, with the results being almost independent of the structure of the aldehyde used.[135]

Less reactive starting carbonyl compounds such as ketones **24** have been successfully chlorinated with inexpensive reagent **149a** by using imidazolidine **155** (Table 10).

The initial trials gave moderate chemical yields due to polychlorination of the starting ketone, as well as the organocatalyst. However, these processes could be suppressed by the use of acetonitrile as solvent. The addition of different carboxylic acids had a beneficial effect not only on the reaction rate, as in the above example, but also on the enantioselectivities and chemical yields, with *ortho*-nitrobenzoic acid to give the best results. Under these conditions, different ketones were monochlorinated with moderate to good chemical yields and excellent enantioselectivities, the latter

Table 10. Enantioselective direct α-chlorination of ketones

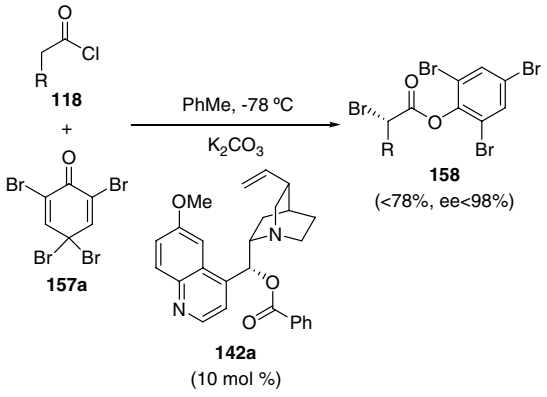


Entry	R^1	R^2	Yield (%)	ee (%)
1	Et	Et	62	86
2	Pr^n	Pr^n	40	89
3	$-(CH_2)_5-$		82	97
4	$-(CH_2)_2O(CH_2)_2-$		72	98
5	$-(CH_2)_2NBoc(CH_2)_2-$		76	93

being practically independent of the ketone as well as the presence of functional groups.[141]

4.3. Bromination reactions

The enantioselective construction of chiral α-bromo carbonyl compounds has been achieved by using two main processes. The first one involves a double α-bromination esterification process of acyl chlorides **118** catalysed by chiral alkaloid **142a**, using quinone **157a** as the brominating agent to yield esters **158** with excellent enantioselectivities (Scheme 36).[142]



Scheme 36.

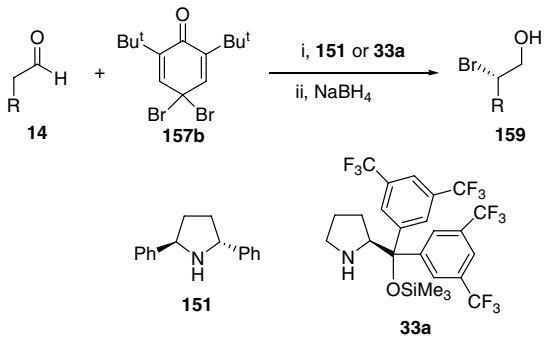
Higher yields and enantioselectivities were obtained by using catalyst **151** for the α-bromination of aldehydes.[143] In this case, quinone **157b** was used as the best brominating agent, since the cheaper agent *N*-bromo succinimide **149b** led to worse yields and enantiomeric excesses. The obtained results seemed to be strongly dependent upon the chosen solvent, with a 1:1 mixture of methylene chloride and pentane giving optimal results. As in previous cases, the addition of benzoic acid and water was necessary in order to accelerate the reaction, permitting the lowering of the temperature, which prevented undesirable reactions, such as polybromination processes and bromination of the catalyst. Under these conditions, not only linear but also branched and cyclic aldehydes were brominated with good enantioselectivities (Table 11, entries 1 and 2). The application of catalyst **33a** to the same transformation gave similar results (Table 11, entries 3 and 4),[32] but had the advantage of using only methylene chloride as solvent, with the presence of additives being avoided.

Surprisingly, only catalyst **155** has been applied for the α-bromination of ketones.[143] The best brominating agent was again compound **157b**, with the presence of benzoic acid in the reaction mixture being compulsory. The brominated ketones were isolated with up to 91% ee, after reduction to the corresponding alcohols.

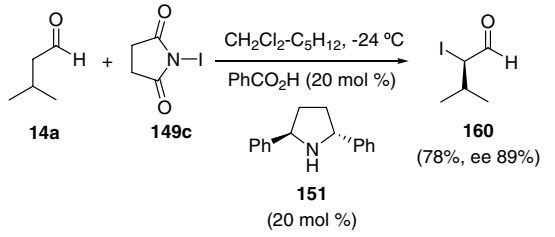
4.4. Iodination reaction

There is only one example where iodide was incorporated at the α-position of a carbonyl moiety using an organocatalyst strategy (Scheme 37), with the protocol being a simple extension of the previous bromination work.[143]

Table 11. Enantioselective direct α-bromination of aldehydes



Entry	Catalyst (%)	R	Yield (%)	ee (%)
1	**151** (20)	Pr^i	87	96
2	**151** (20)	Bu^t	94	89
3	**33a** (20)	Pr^i	74	94
4	**33a** (20)	Bu^t	71	95



Scheme 37.

5. Conclusions and perspectives

This report has shown the impressive amount of enantioselective synthetic uses that organocatalysts have obtained from the simple enantioselective preparation of epoxides to the more challenging construction of carbonyl compounds bearing α-halogenated stereocentres.

The application of organocatalysts for these transformations permitted the preparation of very valuable chiral compounds with exclusion of any trace of hazardous transition metals and with several advantages from an economical and environmental point of view. Among these advantages, superior atom efficiency, simple procedures and manipulation make these protocols very attractive for industry.

Despite the large number of contributions and results obtained in a relatively short period of time, many challenges remain. Generally a high catalyst loading should be used for these transformations. Thus, fine tuning the properties of these organocatalysts by structural modifications would allow a decrease in the amount of catalyst, favouring their incorporation by industry. The recoverability of catalysts

should also be taken in account. All these factors are necessary for a better understanding of the mechanism involved in these transformations.

Finally, one can reasonably expect that in the near future more efficient catalytic systems with a wider scope of reaction and other applications will appear.

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