Asymmetric Reactions Enabled by Cooperative Enantioselective Amino- and Lewis Acid Catalysis

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Asymmetric reactions enabled by cooperative enantioselective amino- and Lewis Acid catalysis.

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Abstract

Organocatalysis, the branch of catalysis that uses small organic molecule as the catalyst, has rapidly enhanced its importance in the field of Asymmetric Catalysis in the last decade, so much that is now comparable to metal catalysis and biocatalysis. Organocatalysis is rationalized and classified by a number of so-called activation modes, on the basis of the formation of a covalent or not-covalent intermediate between the organocatalyst and the organic substrate. Among all the organocatalytic activation modes, enamine catalysis and iminium catalysis are widely used for the practical preparation of valuable products and intermediates, both in academy and industry. In both cases chiral amines are employed as catalysts. Enamine activation mode is generally employed in the reaction with electrophiles, while nucleophiles are engaged in iminium activation mode. Normally, in both modes the reaction occurs through well-organized transitions states. A large variety of partners can react with enamines and iminium ions, due to their sufficient nucleophilicity and electrophilicity, respectively. However, despite the success, organocatalysis still suffer from narrow scopes and applications. Multicatalysis is a possible solution for these drawbacks, because the two different catalysts can synergistically activatethe substrates, with a simultaneous activation of the two different reaction partners. In particular, in this review we will summarize the reported processes featuring Lewis acid catalysis and organocatalytic activation modes synergically acting and not interfering with each other. We will focus our attention to the description of processes in which good results cannot be achieved by organocatalysis or Lewis acid catalysis independently used. In these examples of cooperative dual catalysis, a number of new organic transformations have been developed. The review will focus on the possible strategies, the choice of the Lewis acid and the catalytic cycles involved in the effective reported combination. Some important key points about the rationale for the

effective combinations will be also included. π-Activation of organic substrates by Lewis acids, *via* formation of electrophilic intermediates, and their reaction with enamines will be also discussed in this review.

Keywords: enamine, Lewis acid, catalysis, activation, concerted reactions, synergistic catalysis.

1. Introduction: the activation modes in organocatalysis

Organocatalysis has reached nowadays an outstanding level of development and sophistication.[1] The key publications were reported by MacMillan,[2] Barbas and List [3] in the 1990s, and other important papers considerably expanded the field soon after. The *activation mode* involved in the organocatalytic reactions is considered as the best rationalization of the many reported examples (Figure 1).[4] This rationale has been a crucial step to classify, understand and develop organocatalytic reactions.[5] The formation of electrophilic (iminium) or nucleophilic (enamine) key intermediates is recognized as a crucial event for further development of organocatalytic reactions.[2,3] In these activation modes the organocatalyst is covalently involved in the formation of a stable species acting as a nucleophile (in enamine catalysis) or an electrophile (in iminium catalysis) (Scheme 1). Nucleophilicity and electrophilicity of these relatively stable intermediates have been studied and characterized by Mayr.[6] According to the scale developed by Mayr himself, it is possible to classify the transient enamines or iminium ions and compare them to other well-known and established nucleophiles and electrophiles.[7] Mayr's equation, i.e. Log k = S_N(E + N), relates the rate of a bimolecular reaction, where an electrophile and a nucleophiles are involved, with their electrophilicity (E parameter, for the electrophile) and nucleophilicity (N parameter, for the nucleophiles). Based on such equation, a quite simple "rule of thumb" can be inferred: it is possible to observe a reaction between an electrophile and a nucleophile within 16 hours if E + N > –5.[7] This powerful and simple rule is still effective also when dealing with organocatalytic processes.[8] The transient enamine intermediates, formed in the enamine activation mode, feature nucleophilicity parameters ranging between 12–16 on the Mayr scale (a silyl enol ether is placed at 4–7 of the same scale, for sake of comparison).[9] On the other hand, the electrophilicity of iminium ions is 5–7 orders of magnitude higher than common Michael's acceptors, such as unsaturated esters.[10] Therefore, it is not surprising that many reactions were developed with these activation modes.[11] The nucleophilicity parameter (N) of the enamines derived from Hayashi-Jørgensen catalyst and MacMillan (for the depiction displaying Hayashi-Jørgensen catalyst and MacMillan catalyst see Figure 3) has been evaluated [12] as well as electrophilicity parameters (E) for different reactions partners. Since a reaction between an enamine and an electrophile will take place if E + N > –5, according to the Mayr equation,[7] it is possible to predict a variety of suited electrophiles able to react with enamines.[13] However, although enamines are potent nucleophiles (N = 12–14), electrophiles with E < –18 are out of the possibility to be employed. Moreover, side reactions, such as self-aldolization and formation of unsaturated products, occur during the organocatalytic process. Also in the case of iminium activation, the electrophilicity of chiral iminium intermediates with Hayashi-Jørgensen and MacMillan catalysts has been reported, and on the basis of the Mayr equation, suitable nucleophiles capable of

observable reaction can be predicted. However, the possibilities to employ enamine or iminium catalysis can be enhanced by the utilization of Lewis acids in synergistic catalysis.

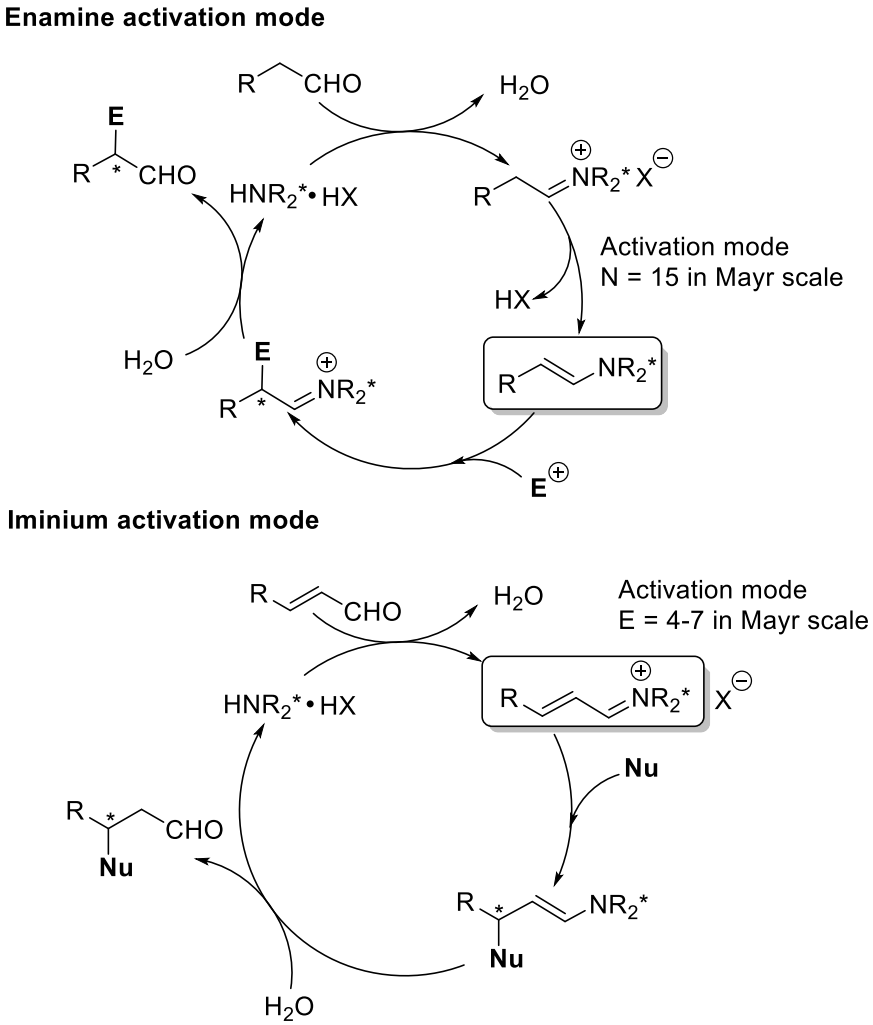


Figure 1. Enamine and iminium activation mode.

1.2. General activation of an organic substrate with a Lewis acid

According to IUPAC recommendation, Mayr clarified that, differently from Lewis acidity and basicity that are thermodynamic terms, electrophilicity (E) and nucleophilicity (N) refer to kinetics.[14] In terms of general activation of substrates, the Lewis acid activates a weak electrophile (for example a carbonyl) via coordination (Figure 2), enhancing its electrophilicity. This can be easly understood envisioning the different electrophilicity of benzaldehyde and benzaldehyde coordinated to boron halides in the Mayr scale.[15] There are more than 11 orders of magnitude between the

electrophilicity of the two species (benzaldehyde E = –12.90 in DMSO; benzaldehyde·BCl_3 E = +1.12), and this is the reason why Lewis acid compounds are used to activate carbonyls towards nucleophiles. Therefore, Lewis acids can be employed to form new electrophilic species, enhancing the scope of the reactions promoted by organocatalysis. On the other hand, Lewis acid can active electrophiles that have an insufficient electrophilicity to engage reactions with nucleophiles (enamines or others), speeding up the reaction, or in the case of prochiral substrates, enhancing the simple diastereoselectivity of the process. While aldol reaction was reported when organocatalysis was rediscovered,[3] the admission of Lewis acids capable of influencing the outcome of the reaction by coordinating carbonyls (**I**), were reported later. In addition, the construction of organocatalyst incorporating a Lewis acid moiety it was also reported (**II**). Then Lewis acid were found to be able to promote difficult reactions, by forming electrophilic carbenium ions for alkylation of enamines. In fact, the coordination of the Lewis acid to allylic or propargylic alcohols can induce the formation of stabilized carbenium ions (such as in **III** or **IV**).[16] Lewis acid have also the ability to form oxocarbenium **V,**[17] iminium **VI**,[18] and acyliminium **VII**[19] intermediates from suitable precursors.[20] Finally, Lewis acid can also activate triple bonds via π-type coordination such as in **VIII**.[21]

Lewis Acids induced formation of electrophiles by activation

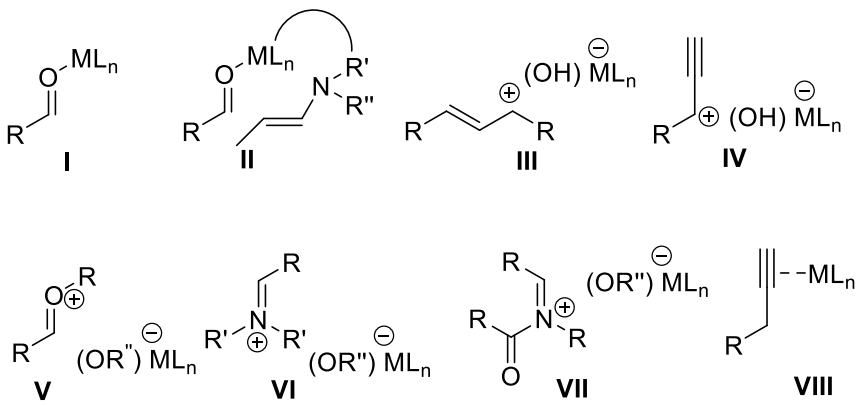


Figure 2. Lewis acids activation modes for enamine and iminium dual cooperative metal catalysis.

1.3. Important principles for enamine-Lewis acid synergistic catalysis

A certain type of reactions was developed through cooperative enamine-Lewis acid catalysis. Thanks to the use of organocatalysis, the low stereoselectivities/yields were further improved, as highlighted by the significant examples here reported. The major area of development through the combination of Lewis acids with enamines was related to α-alkylation of aldehydes and ketones. Due to the unsurmountable difficulties related to the deactivation of the organocatalyst employed for the reaction by the alkylating agent, the problem related to the α-alkylation of aldehydes and ketones

was commonly referred as the "Holy Grail of organocatalysis".[22] In fact, until now, only one effective organocatalyst for the direct alkylation of branched aldehydes with benzylic halides was described.[23] Therefore, the combination of Lewis acids with poor electrophilic alkylating agents was used to overcome the shortages in the alkylation of carbonyl derivatives (again, as a consequence of the Mayr equation: weak electrophiles are kinetically unable to react with enamines). In addition, another general and important drawback arises in the organocatalytic activation modes of enamine and iminium catalysis: the presence of water – as a coproduct of the enamine formation – which is also necessary for the recycling of the organocatalyst (see Figure 1).[24] In all the catalytic cycles reported in most articles, water is released during the formation of enamines, and is believed to react with an intermediate for the liberation of the observed organic product and for the recycling of the organocatalyst. The organocatalyst is used normally in 20 mol% and the presence of a co-catalyst – normally a Brønsted acid – is mandatory. The obtainment of a relevant concentration of chiral enamines is forced by the employment of acid co-catalysts and it is influenced by the aldehydes used in the organocatalytic reaction. The acidity of the Brønsted acid is relevant to the catalytic cycle and influences the rate determining step of the reaction. In addition, in some cases even the basicity of the Brønsted base associated with the acid can have an influence on the progress of reaction, especially when the C–C bond formation is not the rate determining step of the reaction.[25]. Since water is present in organocatalytic mediated processes, both in enamine and iminium activation modes, the compatibility of Lewis acids and electrophiles with water is a key point for the synergistic use of Lewis acids and organocatalysis. Many chiral Lewis acids that are not compatible with the presence of water were developed in the past years for asymmetric catalytic reactions.[26] Therefore, the first step towards the concerted use of a Lewis acid in an organocatalytic processes, is recognizing which Lewis acids are compatible with the presence of water. If the Lewis acid does not interact with the water present in the reaction media, the recycling of the organocatalyst becomes possible. On the other hand, if the Lewis acid reacts with water, the recycling of the organocatalyst becomes slow and difficult, since water is consumed as it hydrolyses the Lewis acid leading to inactive oxo-species. Furthermore, since amines are normally employed in the enamine and iminium activation modes, the Lewis acid used in the synergistic reaction needs to be able to selectively activate electrophiles in the presence of amines, or alternatively it needs free coordination sites, determining a reversible equilibrium in the presence of basic amine donors. Under these important standpoints, it is worth mentioning that Kobayashi tested the use of rare-Earth metal triflates[27] in the fundamental studies about Lewis acid catalysts in water or water-containing solvents.[28] The researches carried out by Kobayashi established empirical criteria to define a Lewis acid which is compatible with water.[29] Based on a test performed on a standard Lewis acid promoted reaction, Kobayashi screened many Lewis acids (Group 1–15 metal chlorides, perchlorates, and triflates) finding that Fe(II), Cu(II), Zn(II), Cd(II), and Pb(II) salts were able to perform Lewis acid activation of electrophiles in aqueous media. The catalytic activity of the metals was correlated both to their hydrolysis constants in water (K_h), and the exchange rate constants for coordination of water molecules in the inners ligand sphere of the Lewis acid (water exchange rate constants, i.e. WERC).[30] The active metals have pK_h values between 4.3 and 10.08. If the pK_h is less than 4, a rapid reaction of the Lewis acid with water occurs, with the release of protons that can cause the protonation of the amine organocatalyst. On the other hand, a strong Lewis can strongly interact with the amine (a Lewis base) or the nucleophile present in the reaction conditions. If the value of pK_h is too high, the Lewis acid is unable to activate the less Lewis

basic organic substrate. The ability of water to coordinate the Lewis acid and to saturate all the available coordination sites determines the rate of the reaction in the presence of water, or when water is used as reaction solvent. If a large (and fast) exchange rate of the coordinated water is possible, the Lewis acid can be an effective catalyst in water. A large WERC value, i.e. > of 10^6, allows the sufficiently rapid exchange between the coordinated water molecules and the Lewis acid. Metals with suitable values of pK_h and WERC, could be used for organocatalytic Lewis acid promoted reactions, but they are less efficient. Nevertheless, indium(III) salts, that have not optimal values for being an active Lewis acid in water, are quite suitable for organocatalytic reactions. Some metals like Mn(II), Ag (I) and In(III) feature parameters close to the limit values, nevertheless such "borderline metals" can still be considered compatible Lewis acids. It is difficult to establish a quantitative prediction for the Lewis acidity in aqueous media, but the two above-mentioned criteria can serve to arrange suitable combinations for organocatalysis in the presence of Lewis acids. Another aspect that requires further comments is the counter ion associated with the Lewis acid. Non-coordinating counter ions (triflate, PF_6^-, BF_4^-) need to be tested first. Among the results obtained by Kobayashi, it is important to mention the possibility to stabilize water hydrolysable Lewis acids like $Bi(OTf)_3$ with tailored ligands.[31] $Ga(OTf)_3$ is another metal salt that is known to rapidly decompose in the presence of water with the release of protons, but it was adapted to promote Lewis acid reactions with enolsilanes in the presence of adapted ligands inhibiting its hydrolysis.[32] Despite the difficulties to quantify the content of water in organocatalytic reactions, water is also capable of enhancing the Lewis acidity of compatible acids. Studies reported by Kobayashi clarified that the amount of water is crucial to form "naked" active Lewis acids.[33] The principles (fast rate exchange and high pK_h) established by Kobayashi can give an idea about the type of Lewis acids which should be chosen for the organocatalytic processes. The presence of secondary or primary amines, generally used in 20 mol% amount, also needs to be considered for the choice of the Lewis acid. Lewis acids that can coordinate amines in irreversible manners need to be avoided. Finally, organocatalytic amino processes are generally performed with a large amount of the aldehyde, in order to have a reasonable concentration of the enamine. A large excess of the aldehyde can compete with the activation of the electrophile for an effective synergic action. Despite the limitations and shortcomings, the use of Lewis acids in enamine catalysis has found applications in several interesting reactions here summarized.

1.4. Principal organocatalysts employed in synergistic catalysis in the presence of Lewis acids

The principal most-used organocatalysts like proline, proline derivatives, or other five-membered heterocycles, used in combination with Lewis acid are illustrated in Figure 3.

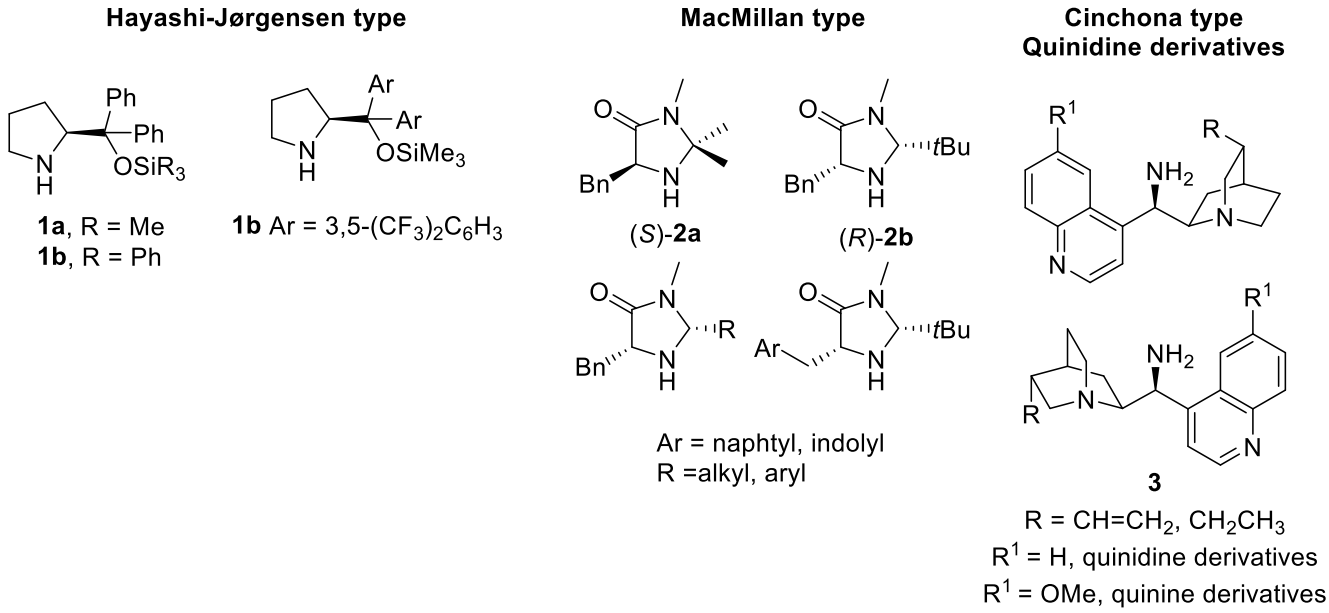


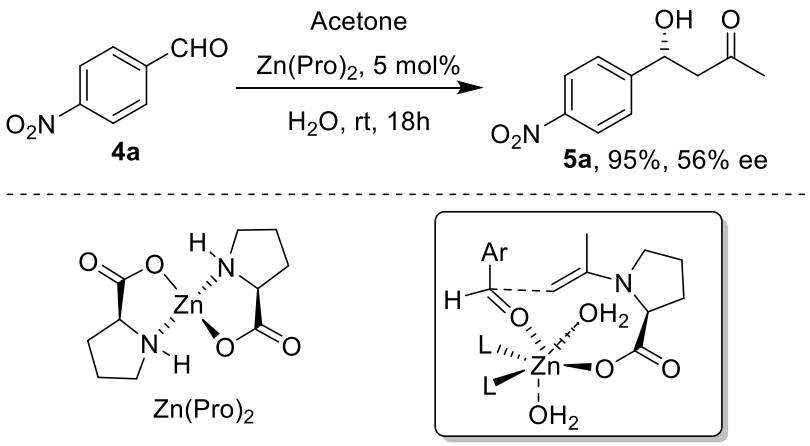
Figure 3. Working horses in organocatalysis: principal effective organocatalysts of enamine and iminium activation.

Diaryl-pyrrolidine derivatives, the Hayashi-Jørgensen organocatalysts (**1**), and the imidazolidinone MacMillan type catalysts (**2**) are often used in stereoselective catalysis via enamine or iminium ion. They are readily prepared from available starting materials. The Hayashi-Jørgensen organocatalysts are obtained using the inexpensive D or L proline as starting material, after simple protection, addition of aryl Grignard reagent, and final silylation step.[34] The MacMillan type catalysts are obtained from commercially available aminoacids, after formation of the corresponding methyl amide derivative. Then, a cyclization reaction with a ketone or an aldehyde takes place in the presence of Brønsted or Lewis acids. Historically, the MacMillan catalysts obtained by reaction with acetone were described first.[35] In subsequent generations of MacMillan catalysts, aldehydes were utilized in the cyclization step. In these cases, the separation of the two so-formed diastereoisomers (*cis*, *trans*) needs to be performed,[36] because the *cis* or *trans* imidazolidinone can have totally different behaviors and catalytic abilities in the reactions.[37] It is also important that the stereochemical integrity of the organocatalyst is maintained during the reactions. *Trans* to *cis* equilibration can occur, especially if the reaction is performed under irradiation (photoredox catalysis)[38] and this can cause deactivation of the catalytic system. Although hundreds of organocatalysts were prepared and tested,[39] and in some cases improved results were found concerning some aspect, "i.e. low catalytic loadings",[40] the commercially available catalysts are those depicted in Figure 3. One of the major issues for neophytes in the field is which catalyst is the most appropriate and which one to select. Normally, both types of catalysts are tested for a new reaction. However, a significant difference can be noted between the two type of catalysts considering the electrophilicity and nucleophilicity of the generated intermediates, iminium ions and enamines, that derived from Hayashi-Jørgensen and MacMillan type catalysts.[41] Generally, the Hayashi-Jørgensen type catalysts produce the most

nucleophilic enamines and they are employed in many α-alkylation of carbonyl compounds occurring via enamines,[42] while the MacMillan catalyst produces the most electrophilic iminium ions. The differences can be significant, and for example, the enamines derived from Hayashi-Jørgensen catalysts are 5 orders of magnitude more nucleophilic that enamines derived from MacMillan type catalysts. Electrophilicity and nucleophilicity parameters can be relevant to understand the experimental data. For example, the enamine derived form 2-phenylacetaldehyde and the Hayashi-Jørgensen catalyst has the following parameters: N = 10.56, S_N = 1.01 in MeCN; so, it is a nucleophile able to react with β-nitrostyrene (E = –13.9) at 0 °C with excellent control of the stereoselectivity. However, the same enamine gave just moderate results in terms of yields when the same Michael type of reaction is performed with the less electrophilic methyl vinyl ketone (E = –16.8). While in the first case the Mayr equation is verified in the second cases the reaction is predicted to be less efficient. In addition, the reaction with β-nitrostyrene requires just 5 mol% of catalytic loading, while, in presence of methyl vinyl ketone, a higher catalytic loading (30 mol%) is compulsory.[36] As we said, the position in the Mayr's scale of enamines derived from MacMillan catalysts is almost 3–5 orders of magnitude less nucleophilic than the corresponding enamines derived from the Hayashi-Jørgensen catalysts. Starting from this statement it is possible to understand that electrophilic fluorinating reagent such fluorobenzensulfonimide (NFSI)[43] and electrophilic chlorinating reagents such as 2,3,4,5,6,6-hexachlorocyclohexa-2,4-dien-1-one[44] are suitable reagents for imidazolidinone-catalyzed α-halogenations of aldehydes.

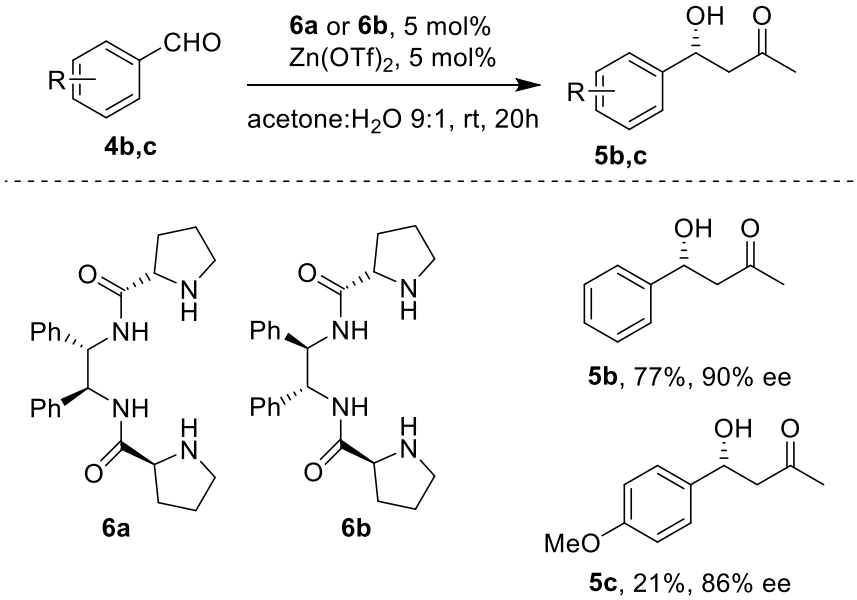
1. Enamines and Lewis acids for direct aldol reaction (activation mode I)

The rediscovery of organocatalysis started with the proline asymmetric direct aldol reaction, and as soon as the activation mode was clarified, asymmetric cross aldol reactions were studied.[45] In general, only a very limited combination of aldehydes was found to give good reactivity. Although MacMillan reported the capacity of proline to catalyze asymmetric cross-aldol reactions between nonequivalent aldehydes by slow addition of reagent using a syringe pump,[46] the addition times were optimized for each aldehyde-aldehyde combination. Thioacetal aldehydes were then selected because sterically and electronically deactivated towards enamine formation.[47] The proline is acting as bifunctional organocatalyst that serves to activate a "donor" aldehyde or ketone, via enamine formation with its amine functionality, for addition to a suitable acceptor, that is activated by the carboxylic acid. In order to improve yields, compatibility and the possibility to enhance the scope of cross aldol reactions, a new design of the organocatalysts was investigated. Many studies have been directed to mimic the mode of action of Aldolase(II), an enzyme which is able to catalyze aldol reactions through an active zinc center. Amino acids-Lewis acid salts (e.g., Zn, Rb, or Li prolinate salts) were used as catalysts for C−C bond-forming reactions.[48] Using a metal salt able to link directly the carboxylate group of the organocatalyst, it is possible to generate a Lewis acid moiety for enamine catalysis (Scheme 1). The authours proposed a mechanism involving a zinc-assisted enamine, where zinc complexation stabilizes the enamine intermediate in water, making the condensation with the aldehyde possible.



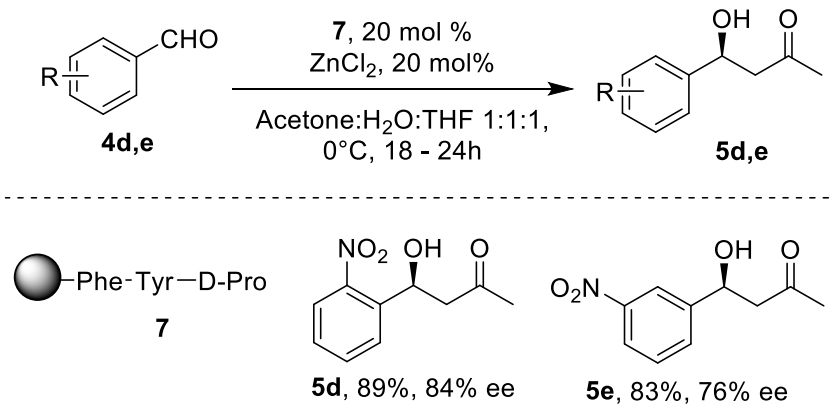
Scheme 1. Zn-proline catalyzed direct aldol reaction in aqueous media.

Chiral bis(prolin-amides) **6a** and **6b**, readily synthesized in two steps from protected proline and chiral diphenylethylenedi-amines were used in combination of zinc triflate for direct aldol reactions (Scheme 2).[49] The reaction gave high enatioselectivities (86–98% ee) and diastereoselectivities in favour of the *anti* product when unfunctionalized ketones were reacted with aldehydes using a low catalyst loading (5 mol%), in the presence of $Zn(OTf)_2$ as Lewis acid.



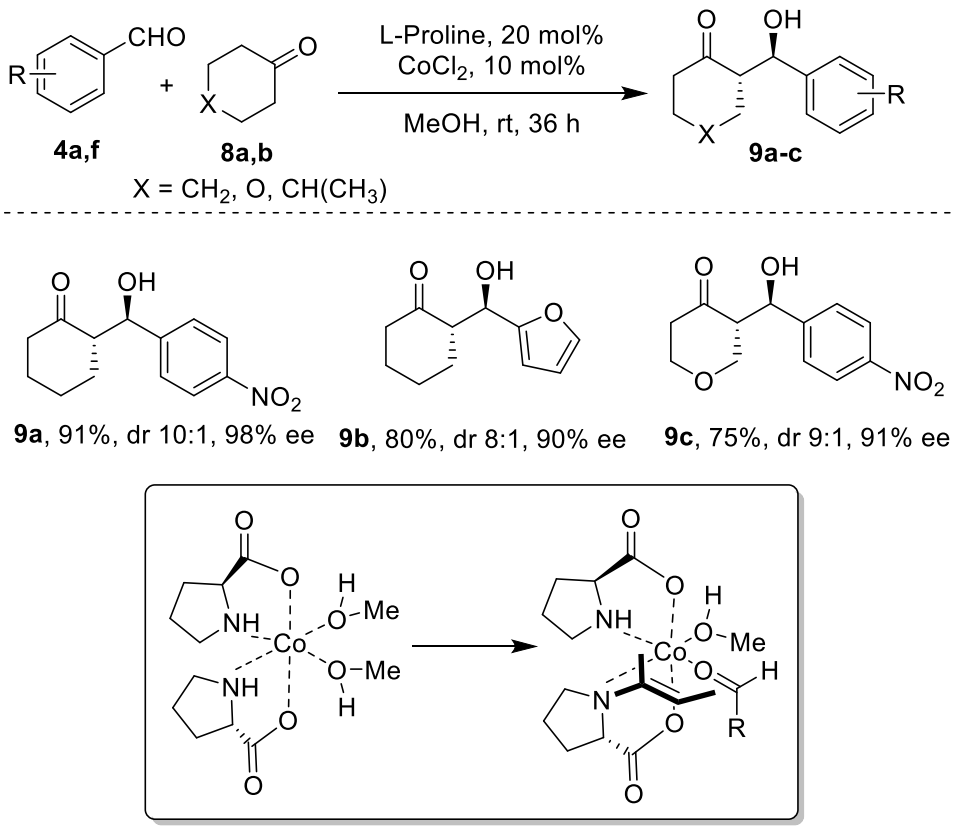
Scheme 2. Zn-prolineammide catalyzed direct aldol reaction in the presence of water

The combination (*S*)-proline with (*S,S*) diphenyl amine was more selective that the the catalyst formed between (*S*)-proline and (*R,R*)-diphenylamine. The new organocatalyst developed was able to coordinate zinc that can act as a Lewis acid in water. For proven that the reaction was promoted by a zinc complex the catalytic activity was tested by adding triflic acid to the organocatalyst. From the measured reaction rate the authors concluded that $Zn(OTf)_2$ was not hydrolyzed, although the structure of the complex, and the coordination mode was not suggested. Chiral C1-symmetric prolinamides based on *o*-phenylenediamine were also investigated in the presence of zinc triflate (5 mol%) as catalyst.[50] Good yields (up to 98%) and ees (up to 94% ee) were obtained for the addition of cyclohexanone to a variety of aromatic aldehdyes. Andreu and co-workers were able to clarify the coordination of zinc salts with prolinamide.[51] It is important to remark that the presence of water in these reactions is beneficial, as performing the reaction in absence of any solvent, with an excess of carbonyl compound (cyclohexanone) gave only traces of product. The enantiomeric excess is regulated by the quantity of water, and, when more water is added, the Lewis acid used for promoting the addition was $Yb(OTf)_3$. As follows by what we discussed in the introduction, application of an ytterbium complex seems here to give a much more water-tolerant catalyst. Zinc is also assisting the enamine formation, essential for the asymmetric aldol reaction. The authors assumed that zinc as an aqua complex is coordinated to amide and to carbonyl group of aldehyde in achiral surrounding, but the exact nature of the transition state was not reported. The use of Lewis acid compatible with water was studied in detail by Penhoat.[52] Water compatible Lewis acids ($ZnCl_2$, $FeCl_3$, $HgCl_2$, $CuCl_2$,$FeSO_4$, $InCl_3$, $Sc(OTf)_3$, $MgCl_2$, $YbCl_3$, $CdCl_2$, $PdCl_2$) were evaluated in the model reaction between cyclohexanone and *p*-nitrobenzaldehyde catalyzed by L-proline, using DMSO/water solvent mixture. Although different Lewis acid were able to improve both enantiomeric excess and diastereoselection compared to the use of proline alone, the reserchers selected the use of inexpensive and not toxic $ZnCl_2$ for the reaction scope. Replacement of chloride anions by another counter ion (i.e a triflate) was causing a lower stereoselectivity. Although the identity of the complex formed in the reaction conditions was not disclosed, the results obtained in terms of conversion and stereoselectivitiy were suggesting a formation of a complex 2:1 of the type $[(L\text{-}Pro)_2ZnCl_2]$12 complex. In similar solvent mixtures Lutz and Bakker were able to isolate and characterize by X-ray analysis such kind of complexes.[53] As in Nature, natural enzymatic processes are working by bifunctional catalysis[54], several example that tried to imitate it have been designed in asymmetric synthesis. Several examples of proline/pyrrolidine molecule with inserting a structure able to coordinate a Lewis acid to form the bi/multifunctional catalytic system were reported. Not only proline but dipeptides and tripeptides were studied as catalysts for aldol reaction in the presence of Lewis acid. A PEG-PS resin-supported tripeptide/zinc chloride catalytic system was developed for use in the direct asymmetric aldol reaction of acetone with aldehydes in aqueous media.[55] The advantage to use an organocatalyst bounded to a resin was the facile separation of the catalyst form the reaction mixture by filtration. The authors showed that the catalyst was reusable for five times without significant change in its activity and selectivity, that was however moderate (ee 71-84%). Wang reported a proline derivative incorporatating a hindered tridentate ligand with the aim to coordinate a Lewis acid in proximity, without suffering of inactivation of proline due to the coordination of the Lewis (Scheme 3).[56]



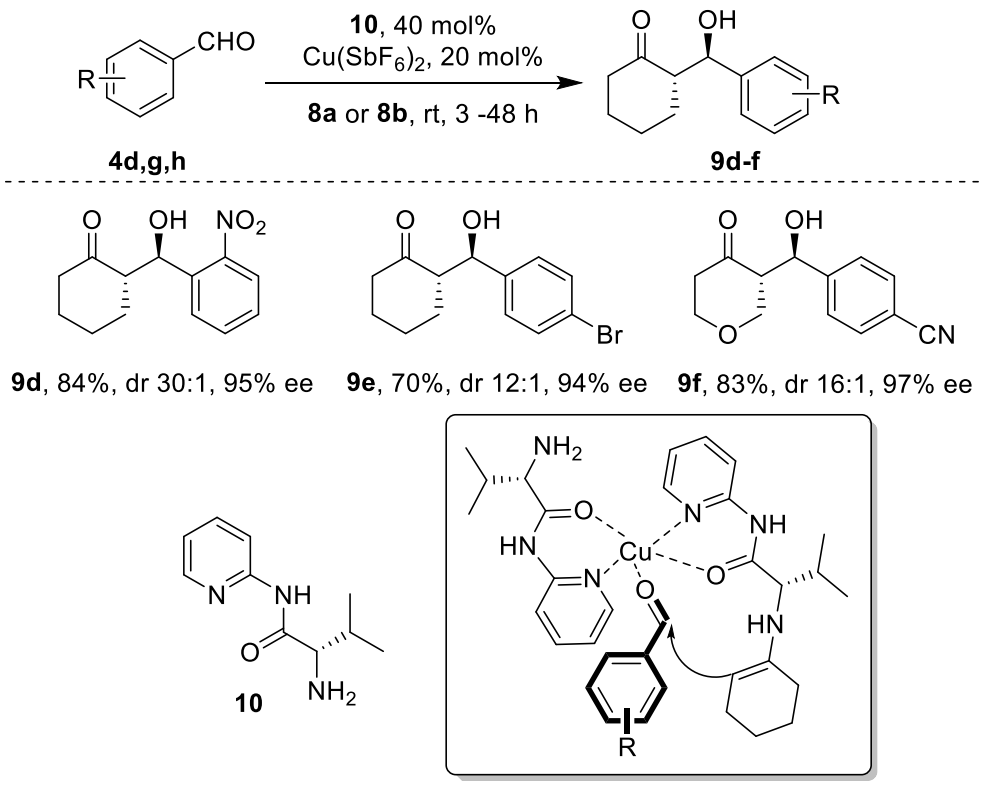
Scheme 3. Aldol reaction with a supported catalyst in the presence of $ZnCl_2$.

Different Lewis acid were tested and was discovered that Cu(II) Lewis acid bearing not coordinating anion gave good enantiomeric excesses. DFT calculations (B3LYP) in conjunction with the 6-31+G(d) basis set were carried out to verify that the optimal coordination geometry of the copper complex was avoiding interaction with the pyrrolidine. The reaction was investigated with an array of aldehdyes, gaving the aldol products in high yields (60–95%) and good enantioselectivity (85–91% ee) for electron-poor aldehydes, while electron rich aldehydes gave inferior results both in term of yields and stereoselectivities. Remarkably, whwen 2-butanone was employed, not only the enantiomeric excess was excellent, but the diastereoselectivity was also quite high (*anti*/*syn*, 30:1): unfortunately, also the linear product was generated in comparable yields. The authors have suggested a model for the obtainment of the R-configurated aldol products. Their rationale suggested that metal Cu(II) served as a Lewis acid activating the aldehyde, and the pyrrolidine ring forming the reactive enamine intermediate. Raiser in exploring another compatible Lewis acid described the catalytic system formed by the combination of $CoCl_2$ and L-proline (1:2).[57] The system was found to be an excellent catalyst for the aldol reactions of cyclic ketones and acetone with aldehydes in MeOH (Scheme 4). The results were excellent in terms of yields (up to 93%) and ees (99% ee). In addition, the system showed a remarkable diastereoselectivity (*anti*/*syn* up to 45:1) compareted to the use of proline as the sole catalyst. It is important to mention that it was possible to apply the catalyst system also with aliphatic aldehydes (isopropyl and cyclohexyl).



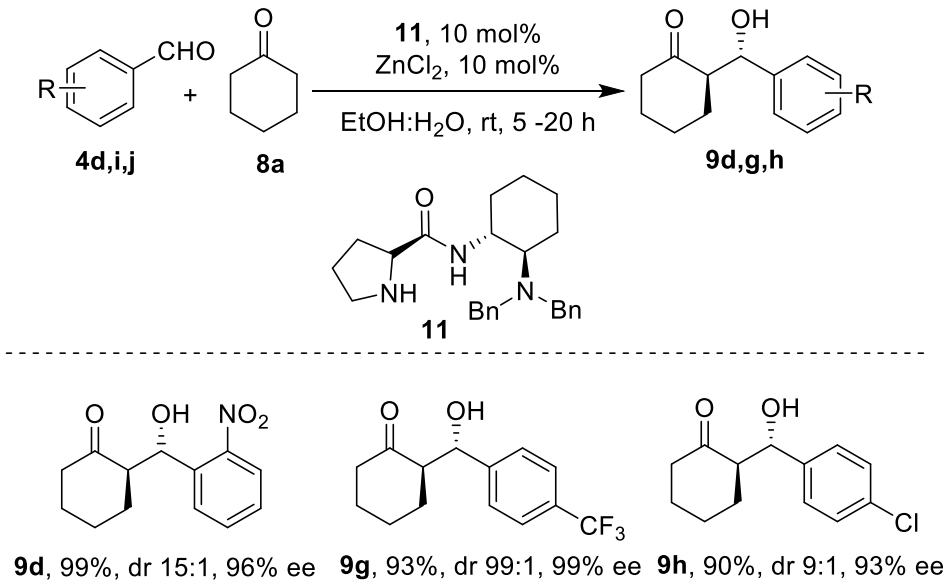
Scheme 4. Direct aldol reactions of cyclic ketones with aldehydes catalyzed by cobalt/proline in MeOH.

The authors have supposed the formation of an octahedral cobalt complex, that upon the liberation of HCl in solution, forms of the key enamine (Scheme 4). In all the discussed examples, the authors have taken advantage by proline in the design of the catalytic system. Wang introduced a class of primary amine-metal Lewis acid bifunctional catalysts based on a simple bidentate ligand (Scheme 5).[58]



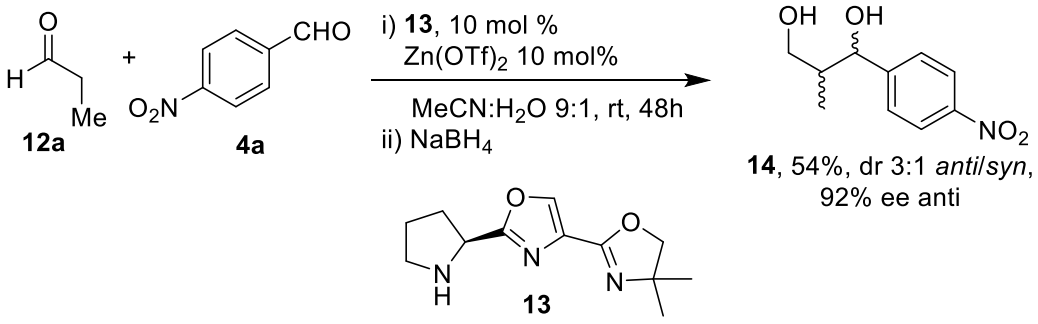
Scheme 5 Primary amine-metal Lewis acid bifunctional catalyst

The catalyst was simply prepared by the coupling reactions between *N*-Boc protected L-amino acids and 2-aminopyridine followed by deprotection. The pyridine moiety was introduced with the aim to coordinate a Lewis acid, and bring in proximity the metal center and the enamine formed with the primary amine. Guided by the precedent work, reported in this review, the authors have investigated $Cu(SbF_6)_2$ as lewis acid and they have established the optimal ligand to metal ratio (2:1). Other metal examined (Co, Zn, Yb) gave inferior results. The reaction was carried out with a variety of aldehydes in neat conditions, affording the desired aldol products in good yields and stereoselectivities. It is important to report that the organocatalyst alone was unable to promote the aldol reaction of the cyclohexanone with aldehydes, and the presence of Lewis acid was mandatory in order to observe the reaction. Chiral prolinamides based on cyclohexanediamine were investigated by Fu,[59] as catalysts able to obtain β-hydroxy ketones in good diastereoselectivities (dr up to 99:1) and high enantioselectivities (up to 99% ee) (Scheme 6). The reaction was carriet out in EtOH:H_2O as reaction solvent employing $ZnCl_2$ as Lewis acid catalyst (10 mol%). What is of interest about this work is the possibility to perform larger-scale asymmetric aldol reactions on 20 mmol of aromatic aldehydes, using a catalyst loading of 10 mol%, with quite good stereoselection.



Scheme 6. Asymmetric aldol reactions of cyclohexanone with various aryl aldehydes in the presence of water.

The incorporation of heterocyclic into chiral pyrrolidine for the organocatalysis in the presence of Lewis acid was reported.[60] The ability of bisoxazoline ligand to coordinate metals and to form stable and effective Lewis acid complexes[61] inspired the authors to incorporate bis-oxazoline ligand in the catalyst design (Scheme 7).

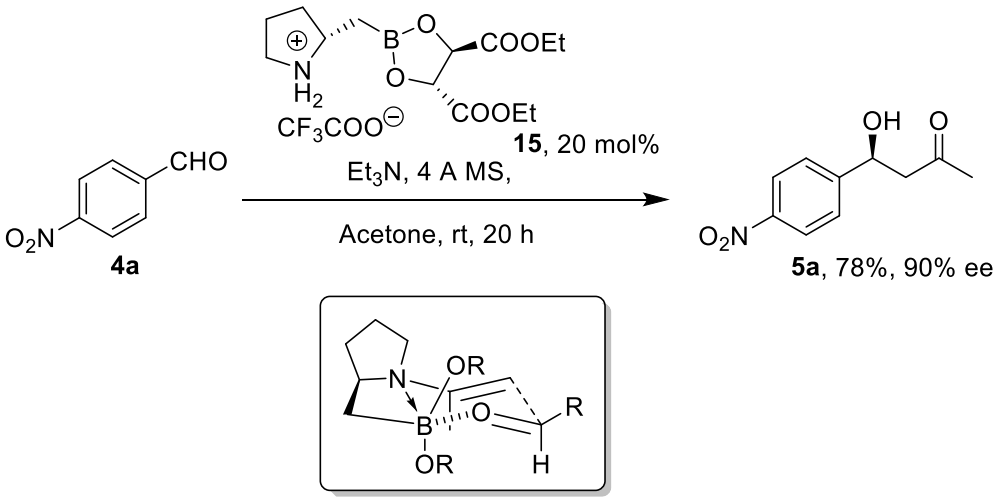


Scheme 7 Cross aldol reaction of nitrobenzaldehyde in the presence of the organocatalyst xx and $Zn(OTf)_2$.

The organocatalyst incorporating the oxazole was prepared in a multistep synthesis. The scope of the reaction was limited. NMR-spectroscopic studies, conducted in the presence of Lewis acid and catalyst **13**, showed that the zinc was able to coordinate the pyrrolidine moiety, in a dynamic binding process, descreaisng the performance of the catalyst.

2. Enamines and Lewis acids for direct aldol reaction (activation mode II)

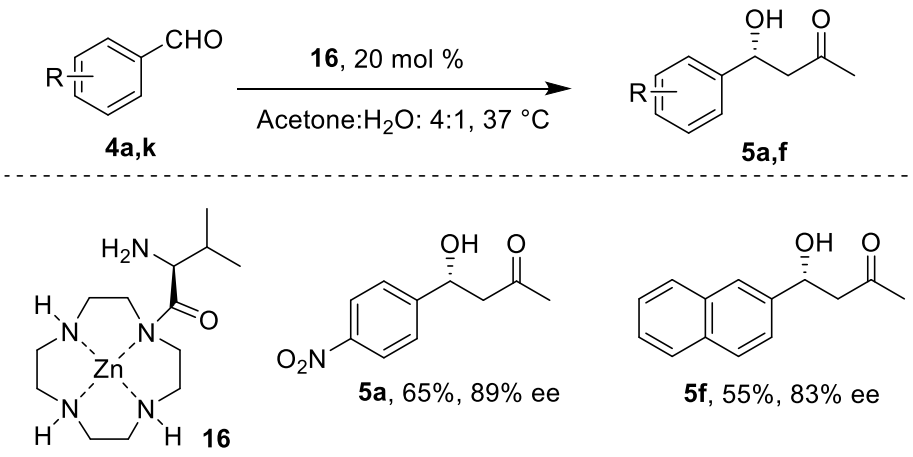
The Lewis acid organocatalysts combination described were obtained by mixing the Lewis acid with the designed organocatalyst ligand. Another strategy can consider the preparation of a synergic systems which have the distinct Lewis acid functionality and the organocatalyst within the same molecule. The design require the choice of a compatible Lewis acid, stable to be incorporated in the synthetic design. In this purpose, aminoboronic acids have suitable properties. In 2008 Whiting reported an example of a bifunctional enamine-Lewis acid catalysis.[62] The bifunctional amine-boronic acid catalyst was prepared through the insertion of a boronic acid or a boronic ester group on a chiral pyrrolidine fragment (Scheme 8). Such catalyst was able to catalyze the direct aldol reaction of 4-nitrobenzaldehyde with acetone.



Scheme 8. Enamine-Lewis acid cooperative bifunctional catalysis.

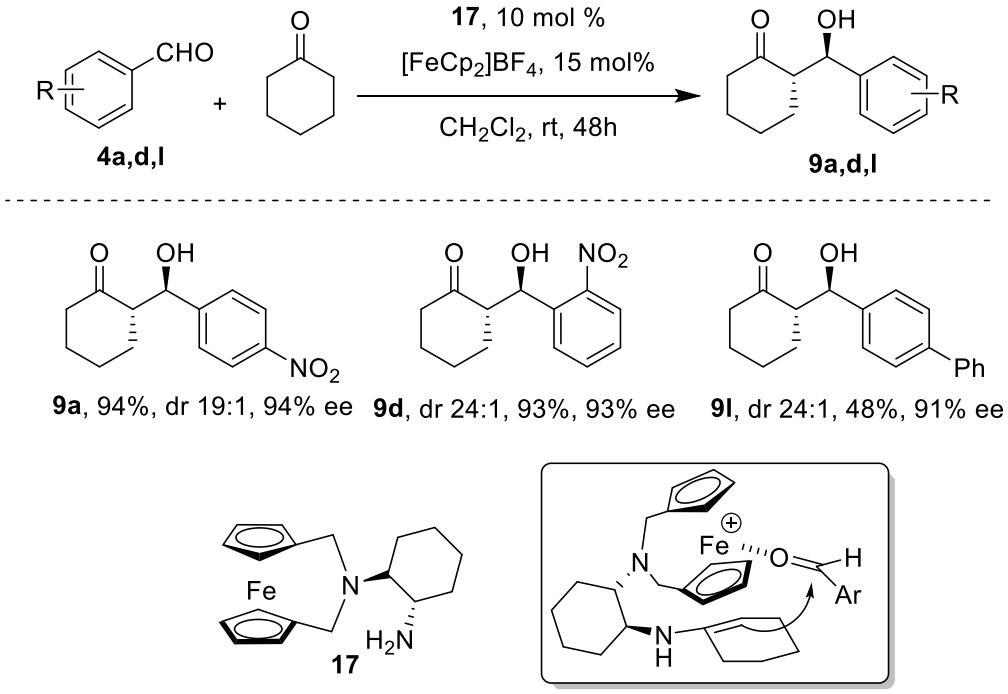
Other homologues of homoboroproline were prepared by asymmetric synthesis[63] and the performances in the aldol reaction were studied. The effect of the chain-length separation of the amino and boronate groups has on the intramolecular B–N coordination was crucial to determinate the catalytic properties. Many effective described systems were considered in organocatalysis with the presence of Zn(II) salts and an evolution of this idea is to link a stable zinc complexes to an organocatalyst. The Zn(II) complexes of proline derivatives have been demonstrated to have the ability to catalyze direct asymmetric aldol reactions in aqueous media, mimicking Aldolase enzime. On

the other hand, Zn(II) complex of cyclen (cyclen = 1,4,7,10-tetraazacyclododecane) is a good model for the naturally occurring Zn(II).[64] Therefore, Zn(II) cyclen derivatives may constitute an effective scaffold for preparing a hybrid Lewis acid organocatalysts. Following this line, different Zn(II) complexes of L-prolyl-pendant[12]aneN4, and L-valyl-pendant[12]aneN4 **16** (Scheme 9) were investigated as chiral catalyst for the enantioselective aldol reaction with different aldehydes, affording the desired aldol products in good chemical yields and high enantio-selectivities of up to 89% ee.[65] Remarkably, by the studies carried out the authors suggested that the amino acid components and the Zn^{2+} ions function generate the zinc enolate of acetone in a cooperative manner, thus permitting efficient enantioselective C-C bond formation. This work is an example that show how the incorporation of the Lewis acidic center in the catalyst design can alter the enamine mechanism.



Scheme 9 Asymmetric aldol reactions between acetone and various aldehydes in the presence of the catalyst **16**.

Cui, Luo, and Wu have described an aminocatalyst bearing a stereogenic ferrocenophane [66] capables, under redox control, of promoting an efficient asymmetric aldol reaction at room temperature with excellent yields and good stereoselectivities (Scheme 10).

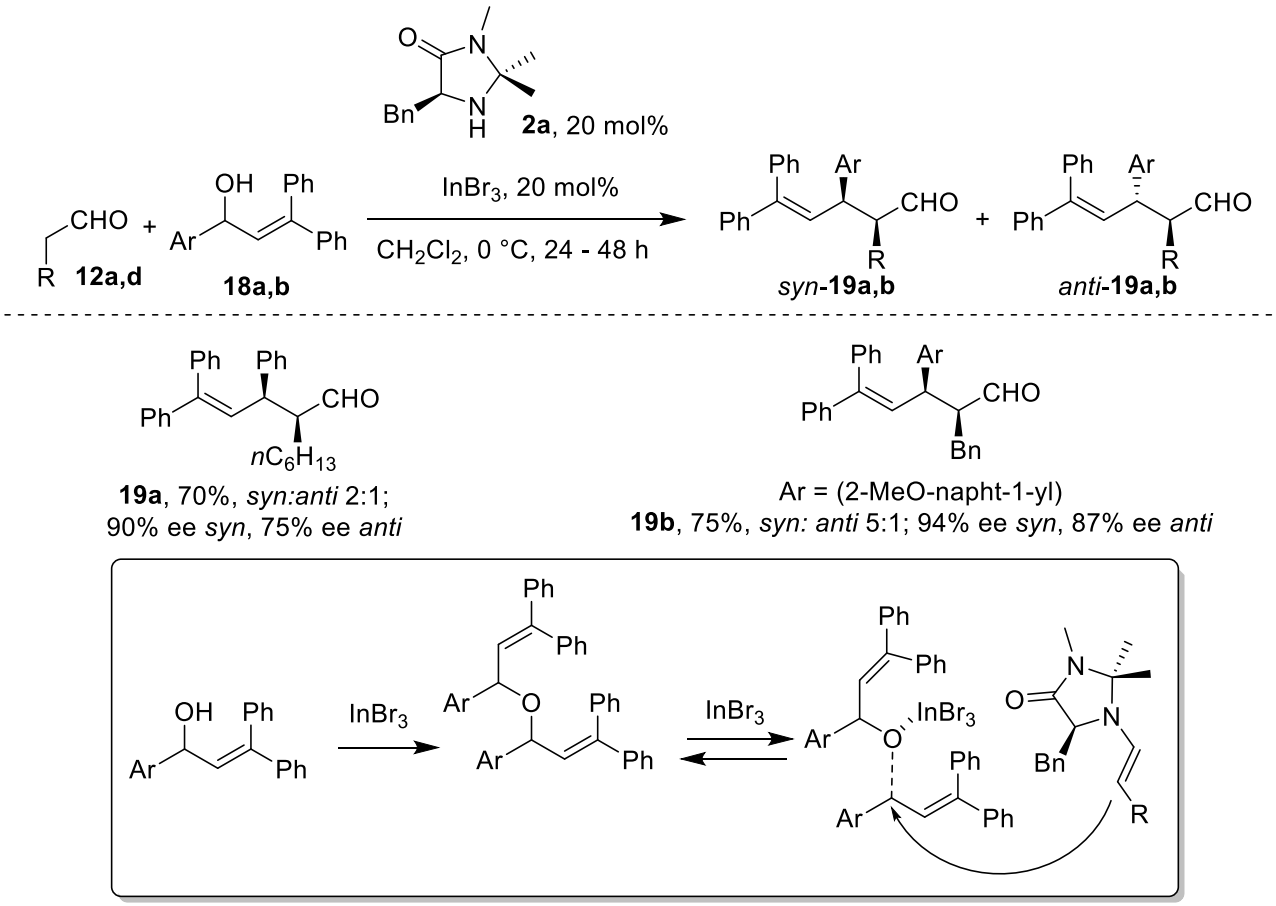


Scheme 10 Asymmetric reaction of cyclohexanone with aryl aldehdyes promoted by ferrocenium organocatalyst **17**.

The focus of the article was the design of a redox-active molecular catalyst that is possible to switch off and on by the use of redox chemistry. The introduction of the redox-active and stable ferrocene/ferrocenium moiety also served as phase-tag to allowing the catalyst recovery and reuse. The selective oxidation of ferrocene moiety was possible by employing ferrocenium tetrafluoroborate. What is peculiar with this catalyst is the control exercitated by the ferrocenium cation Lewis acidic center. In fact, when the authors have added to the ferrocene catalyst TFA or TfOH poor stereoselectivities were obtained. Protonated amine moiety is unable to direct the stereocontrolled aldol reactions. Instead ferrocenium moiety, obtained after oxidation of ferrocene, by coordination of carbonyl is able to direct the aldol reaction thorugh the suggested model depicted in scheme 10. Additionally, the system suffers of a strong matching/mismatching effect, as the use of (*S*,*S*)-N1,N1-dipropylcyclohexanediamine in the obtainement of the active catalyst gave only very low yield of product. What is interesting about the system is the possibility to switch ON/OFF the reaction, by the control exercitated with redox chemistry. The ferrocene catalyst is poorply performing system, and after 5 hours, only 5% of the desired aldol product was observed in the reaction of cyclohexanone with benzaldehyde. However, after oxidation with $[FeCp_2]BF_4$, the catalyst was more active affording the desired product in high yield with excellent diastereo- and enantioselectivity. The catalyst at this point can be switched OFF adding sodium hydrosulfite.

3. Enamine catalysis by S_N1-type reactions performed in the presence of Lewis acids: the formation of electrophilic carbon species (activation modes III and IV)

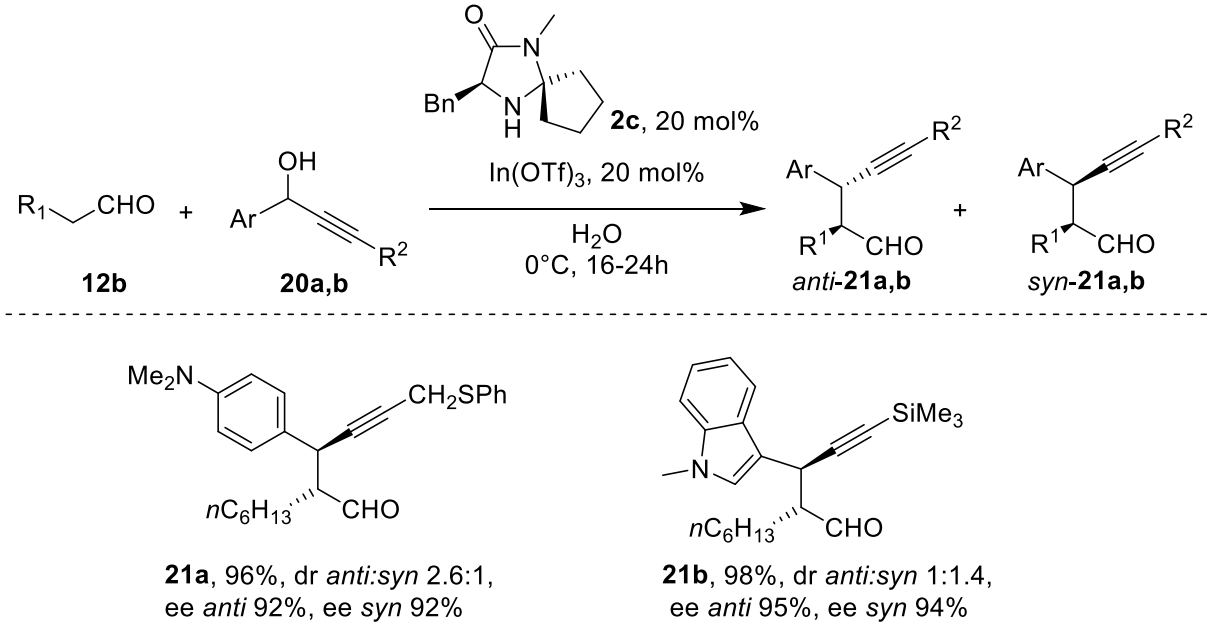
Formation of a carbenium ion from a suitable substrate by the addition of a Lewis acid can give quite interesting possibilities and enhance the repertoire of enamine catalysis. Organocatalytic S_N1-type reactions recently found a wide use in organocatalysis.[67] Reactions with stable carbenium ions and enamines were used by Mayr to establish the general nucleophilicity of enamines.[68] As previously discussed, the carbenium ions generated in the reaction conditions need to have the proper electrophilicity to react faster with the most nucleophilic species, i.e. the enamine, present in the reaction mixture. Looking at the Mayr scale, a limit of electrophilicity can be settled toward –1.5. Generally, electrophiles do not undergo the desired reactivity whenever their electrophilicity parameters are above the aforementioned limit. This is due to the lifetime of the carbenium ion, and its reversible reaction with water, that is present in the organocatalytic reaction environment. A typical example of this limitation is observed when allylic alcohols are used as reaction partners for organocatalytic alkylation. While other substituted alcohols, less electrophilic in terms of Mayr scale, can form a reactive carbenium ion as suitable partner for organocatalytic reactions,[69] phenyl substituted allylic alcohols form carbenium ions above the 0 of the Mayr scale, and no reaction is observed. However, the combination of a Lewis acid with the alcohol in organocatalytic reactions was found indispensable to generate these carbenium ions and to allow the reaction with enamine intermediates. In the presence of $InBr_3$ (20 mol%) it was possible to use allylic alcohols in organocatalytic stereoselective α-alkylation of aldehydes (Scheme 11).[70]



Scheme 11. Indium(III)-mediated stereoselective α-alkylation of aldehydes.

The reaction did not occur in the absence of indium(III) salt. As we have pointed out, indium is inserted in the short list of Lewis acids with the good features summarized by Kobayashi. To further discuss the peculiarity of the reaction, the use of the MacMillan catalyst **2a** was mandatory, as the Hayashi-Jørgensen catalysts were not active. Commonly, it is believed that the two type of catalyst, i.e. MacMillan and Hayashi-Jørgensen, are interchangeable in an organocatalytic process, but this is not always the case. First, as we have pointed out, the nucleophilicities of enamines derived from the two catalysts are different: the Hayashi-Jørgensen catalyst leads to a much more nucleophilic enamine, featuring a nucleophilic parameter almost 5 order of magnitude higher than the MacMillan-type one to the Mayr scale.[8a] In second instance, the Hayashi-Jørgensen catalyst is sensitive to desilylation processes, often leading to an inactive catalyst. It is important to stress that indium salt induces the formation of allylic ethers as a mixture of diastereoisomers, as depicted in the mechanistic picture. The allylic ethers are the resting state for the formation of the carbenium ion, that is reversibly generated by indium(III) from the allylic alcohols. In this concerted activation, the Lewis acid acts as a promoter for the formation of the electrophilic species, i.e. the carbenium ion. Although coordination of the Lewis acid to the MacMillan catalyst is possible, and in fact was observed by NMR, the study of

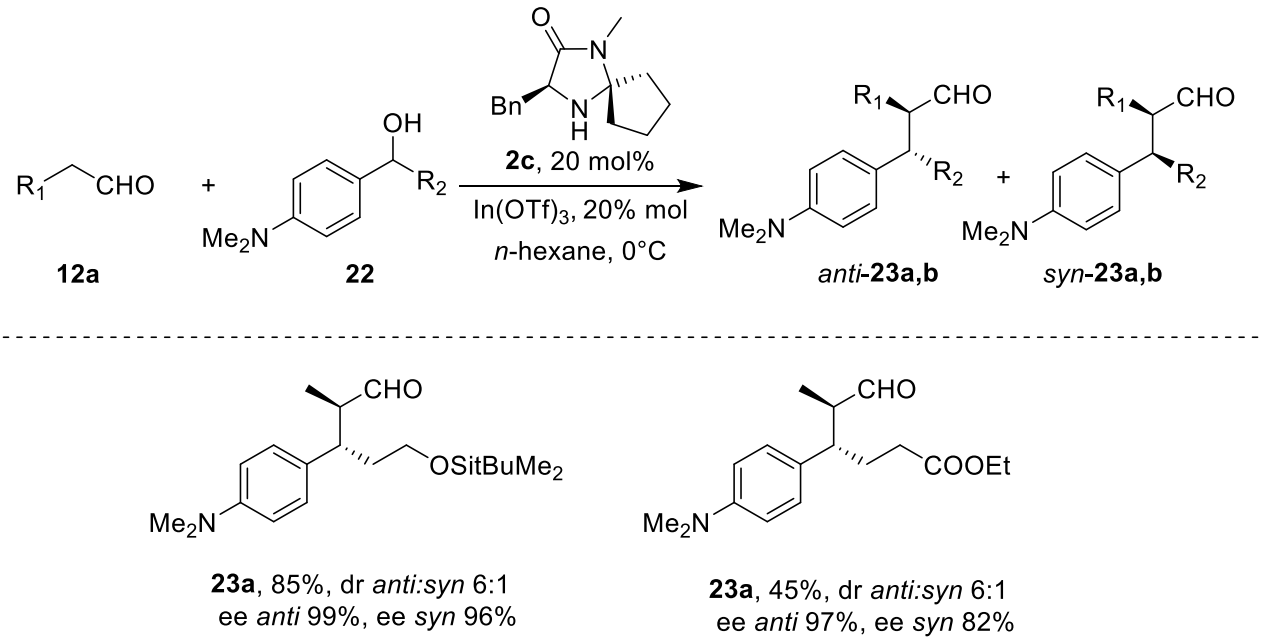
non-linear effect clearly showed that just a monomeric catalytic specie is responsible for the observed stereoselection. The chiral species transmitting the information is clearly the enamine, and the linear correlation between ee of the organocatalyst and ee of the isolated product indicates that the formation of multiple catalytic species during the enantio-determining step is not involveed. In other words, possible interactions with chiral indium complexes formed with the organocatalyst do not influence the enantio-determining step. Furthermore, it was mentioned in the introduction that indium is a borderline Lewis acid for its use in the presence of water, but it can be advantageously used in the presence of strong coordinating amines. By combining $In(OTf)_3$ with a MacMillan type of catalyst, it was possible to extend the S_N1-type reactions to the stereoselective addition of propargylic carbenium ions, generated from the corresponding alcohols (scheme 12).[71]



Scheme 12. Stereoselective propargylation with MacMillan catalyst in the presence of catalytic amount of $In(OTf)_3$.

Remarkably, the reaction occurs in water, and this underlines the powerful concepts related to the use of the Mayr table for setting up reactions. The most nucleophilic species, i.e. the enamine, reacts faster with the carbenium ion than water because there are more than 10 orders of magnitude between enamine and water nucleophilicities. Furthermore, the reaction allowed the use of propargylic alcohols carrying disubstituted triple bond that were not reactive in the allylidene electrophilic reaction mode. Nishibayashi reported a quite similar propargylation of aldehydes with a propargylic alcohol using slightly different conditions and reporting the use of $InBr_3$ or $FeCl_3$ to initiate the reaction.[72] In both the reports, only aryl propargylic alcohols are employed, and also in these cases, the use of strong electron-donating groups, such as dimethylamino and methoxy groups at the

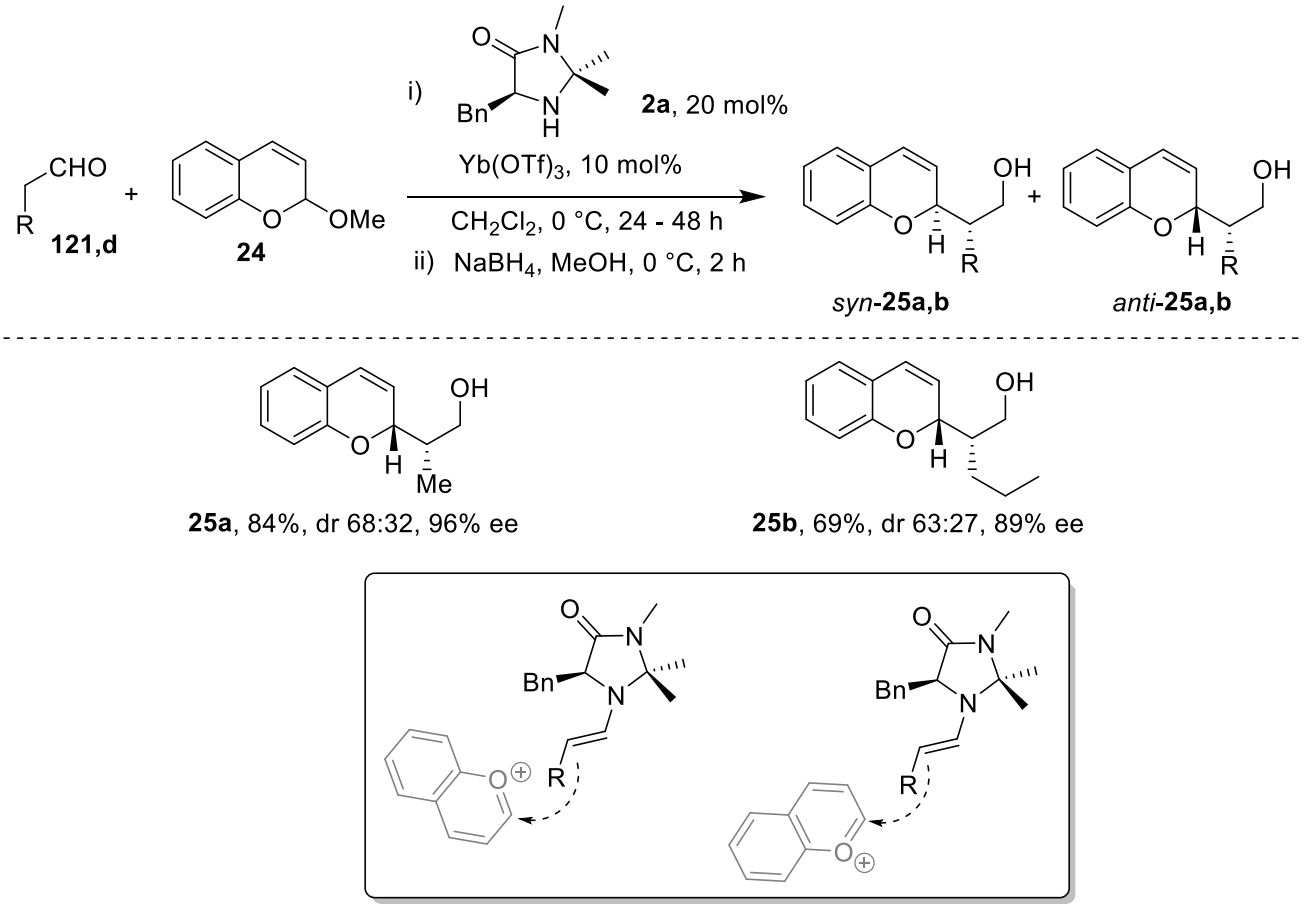
para- or ortho-position of the aryl substituent are mandatory for a good outcome of the reaction. This is due to the decrease of electrophilicity of the propargylic carbenium ion, that can be formed in the reaction conditions. Diaryl secondary alcohols are also suitable precursors for the generation of stabilized carbenium ions, if Lewis acids are employed in the presence of the organocatalyst **2c** (scheme 13).[73]



Scheme 13. Indium(III) promoted organocatalytic enantioselective α-alkylation of aldehydes.

The scope of organocatalytic S_N1-type reactions was enhanced to include benzylic and benzhydrylic carbenium ions performing the reaction in the presence of $In(OTf)_3$. High ee values and moderate drs were obtained using benzylic and benzhydrylic alcohols bearing strong donating aryl substituents. The presence of the para-dimethylamino aryl group was essential and we can take advantage of its presence in further chemical transformations. Not only indium can be employed in S_N1-type reactions, as a cooperative system, involving a diarylprolinol silyl ether with CuCl or $IrCl_3$ as active Lewis acids, has been found to be active in the highly enantioselective intermolecular α-alkylation of aldehydes with alcohols.[74] A wide variety of aldehydes and alcohols were used for the alkylation of functionalized aldehydes affording the desired products in high yields, excellent enantioselectivities, and good diastereoselectivities at room temperature. Regarding the activation mode depicted as **IV** Rueping has described[75] an asymmetric addition of aldehydes to prochiral oxocarbeniums to produce chiral 2H-chromene derivatives (Scheme 14). The system makes use of $Yb(OTf)_3$ (10 mol%) as

the achiral Lewis acid and a chiral imidazolidinone catalyst **2a** (Scheme 14) which simultaneously activates the electrophile and nucleophile. The products were obtained with moderate drs and this is due to the different possible approaches of the stabilized carbenium electrophile, as illustrated in Scheme 14. The products were further functionalized accessing different derivatives.

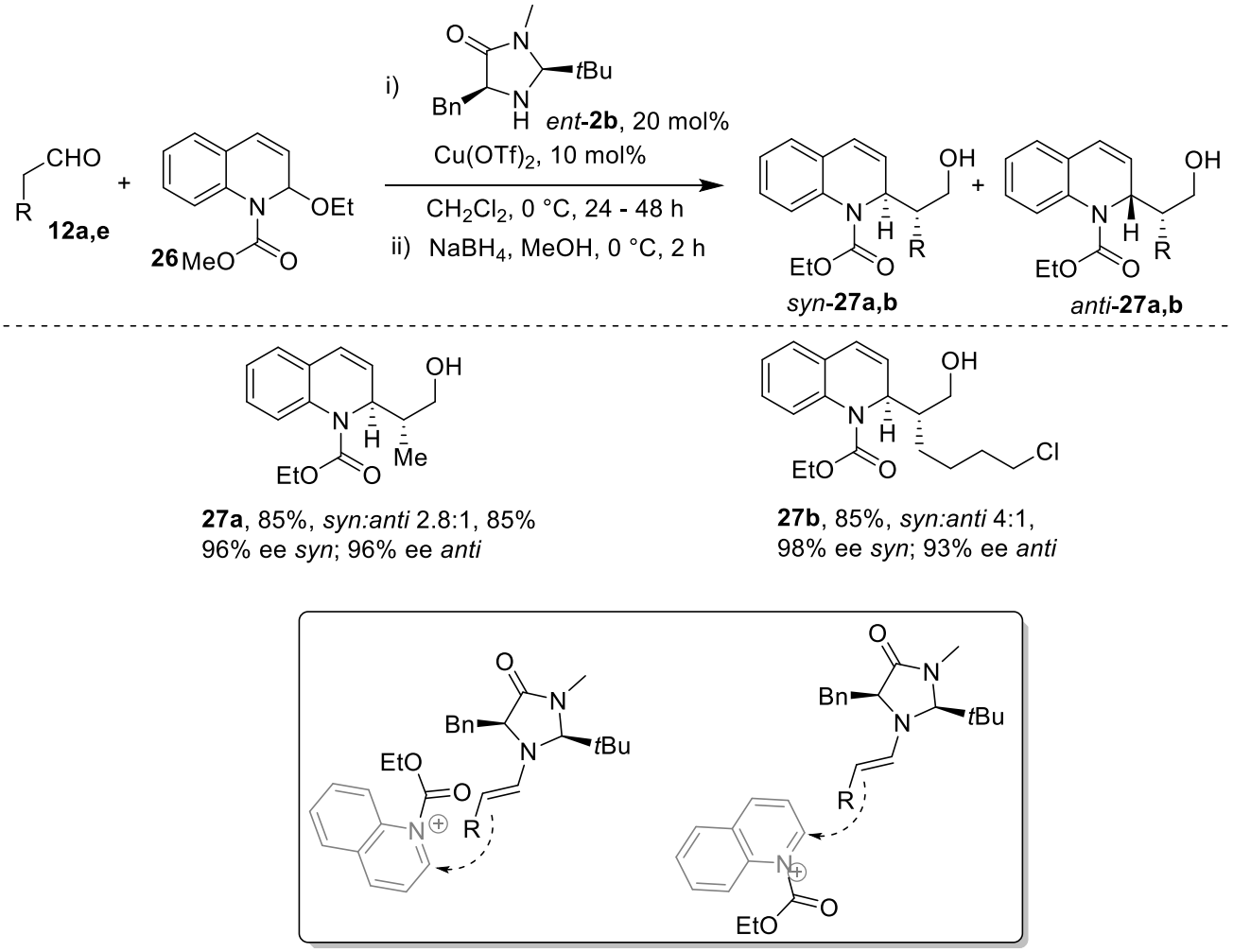


Scheme 14. Catalytic asymmetric addition of aldehydes to oxocarbenium ions by dual catalysis.

4. Acyliminium generated by Lewis acids in reaction with enamines

Synthetic methodologies for the formation of chiral isoquinoline and quinoline derivatives are important for accessing the corresponding alkaloids.[76] As acyliminum ions can be directly obtained by the addition of chloroformates or derivatives to isoquinoline and quinoline, the synthesis of chiral precursor by organocatalytic methodologies was investigated without the addition of Lewis Acids. However Jørgense reported that the addition of ehtylchloroformates to isoquinolines for activating them towards organocatalytic addition gave poor results[77] Instead, stable isoquinolinium salts, obtained by alkylation, were used in an intramolecular variant of the reaction.[77] Later Cozzi

reported the enantioselective addition of aldehydes to isoquinoliniums promoted by the Hayashi–Jørgensen catalyst;[78] moderate diastereoselectivity and excellent enantioselectivity were observed, and synthetic utility of the method was demonstrated by the total synthesis of a 13-alkyl-tetrahydroprotoberberine alkaloid. The generation of acylisoquinolinium ion by Lewis acids and their reaction with enamines, obtained *in situ* by condensation of an aldehyde with an organocatalyst, was described by Liu[79] and Pineschi[80]. Liu used of 2-ethoxy-1-methoxycarbonyl-1,2-dihydro-quinoline (EMDQ) **26** as precursor of acylquinolinium. Although $Yb(OTf)_3$ (10 mol%) was found to promote the reaction, an extensive screening revealed that $Cu(OTf)_2$ was the appropriate Lewis acid, in the presence of the MacMillan catalyst *ent*-**2b**. Although the simple diastereoselection was only moderate, the enantiomeric excesses obtained for both the diastereoisomers was excellent with a variety of aldehydes.



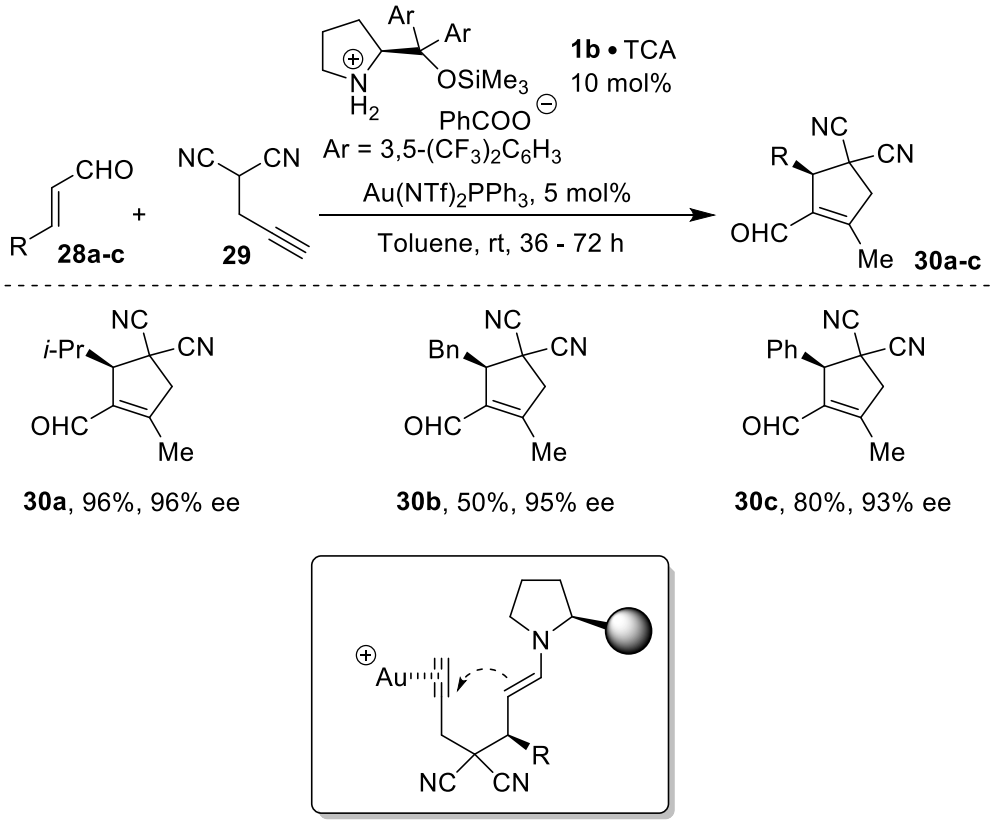
Scheme 15. Enantioselective alkylation of cyclic N-acyl hemiaminals with aldehydes

Pineschi reported the same type of reaction employing the Hayashi–Jørgensen secondary amine catalysts, in the presence of different indium salts. The best stereoselectivity was obtained in just one example using $In(OTf)_3$ (20 mol%) as Lewis acid catalyst, as the reaction was effectively catalized by employing Brønsted acids such as toluene sulfonic acid.

5. Enamine catalysis with π-Lewis

5.1. Use of gold salts and gold complexes in synergistic enamine catalysis

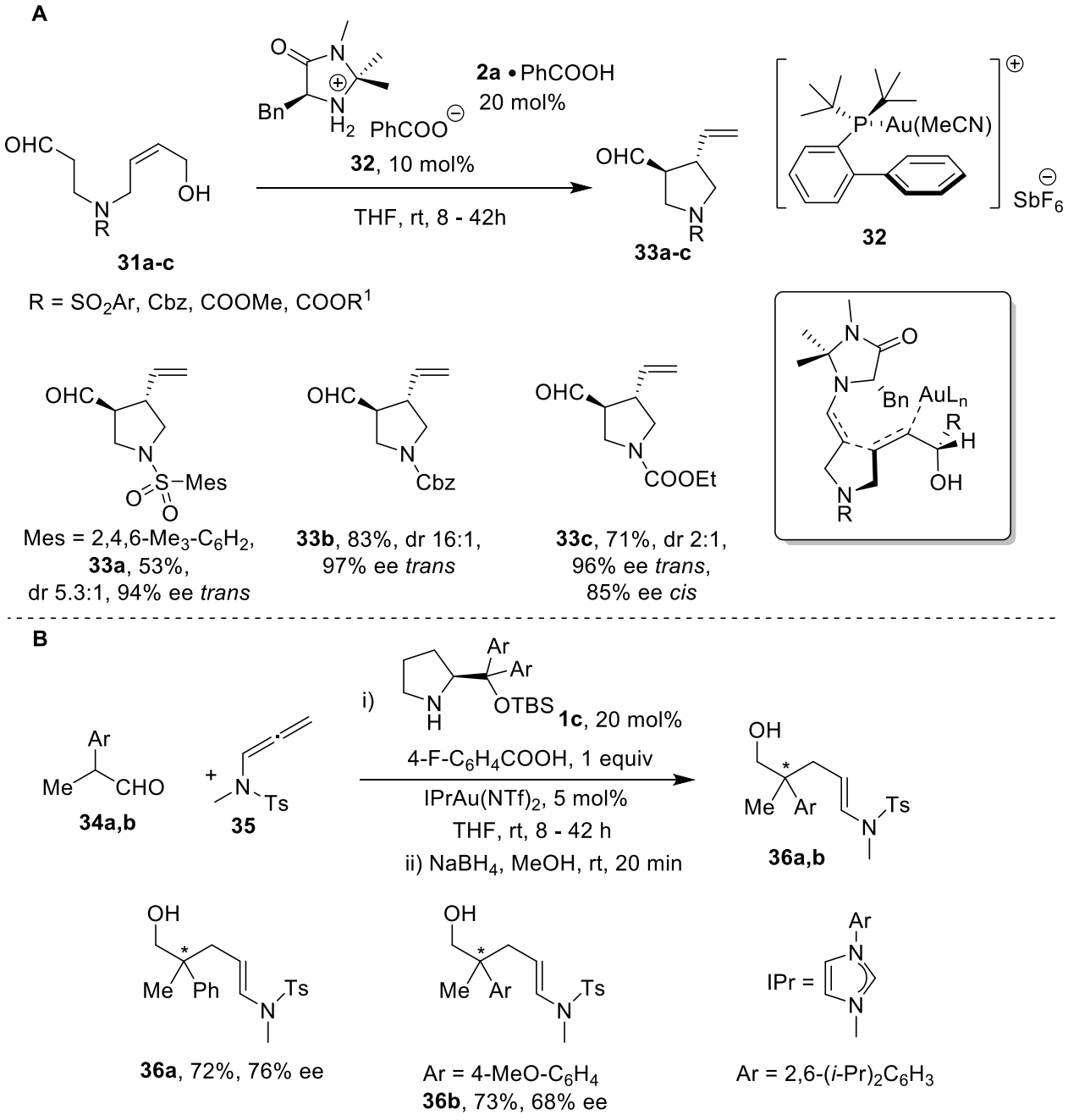
Gold catalysis[81] has recently grown with a flurry of research regarding gold(I) and gold(III) species applied to homogeneous and heterogeneous catalysis. The gold catalysis is essentially based on the ability of gold complexes to interact with alkene and alkynes and to behave as a carbophilic Lewis acid. The peculiar π-affinity, the tolerance for several functional groups and oxygen, the possibility to tailor achiral or chiral ligands for specific transformations, have contributed to the large number of published studies. In addition, ligands surrounding gold are able to differentiate the nature of gold carbenoid intermediates, and they can modify the reactivity, changing the character of the organogold intermediate from a gold-stabilized carbocation towards a gold carbene.The key character, that allows the marriage between gold catalysis and organocatalysis, is the general tolerance of the gold catalytic system towards moisture and air. In the activation performed by gold complexes, a stable organometallic gold species is formed after the addition of the nucleophile (enamine, in organocatalytic dual reactions). The successive protodeauration makes the gold complex available for further reactions. Taking advantage from the above-mentioned characters of gold catalysis, Kirsch[82] and Jørgensen[83] reported the formation of carbocyclic derivatives, through a mechanism in which a concomitant enamine formation, at the terminal aldehyde, and a gold π-acid activation at the triple bond terminus gave the observed product (Scheme 16).



Scheme 16. Carbocyclization of aldehydes with alkynes, promoted by a combination of gold catalysis with aminocatalysis.

This example it is also remarkable due to the fact that it represents an employment of iminium-enamine catalysis. The combination of thtwo activation modes have found plenty of applications in literature of organocatalysis,[84] expecially in multicomponent reactions.[85] The iminium activation of the unsaturated aldehydes undergoes with a Michael-type reaction with a suitable nucleophile, and the so-formed intermediate is an enamine. The in situ obtained chiral enamine is able to react with an electrophile present in the reaction medium. In the reported example, the intramolecular reactions led to a carbocyclic structure derived from the reaction between the enamine and the parallelly formed electrophilic gold triple bond complex. It is worth mentioning that normally, in these types of reaction, the Hayashi-Jørgensen type catalysts are preferred. This despite the fact that a Michael reaction requires the presence of a quite strong electrophile (represented by the iminium intermediate). The Hayashi-Jørgensen catalyst favors the entire process due to the fact that the second step of the reaction (the enamine attack) requires mandatorily an enhanced nucleophilic behavior. Despite the proof of concept, no enantiomeric excesses were observed for the reaction. An enantioselective variant of this carbocyclization reaction was later reported by Jørgensen.[83] Gold is not only able to activate π-electron density of triple bond of alkynes, but it is also able to activate other suitable substrates like allylic alcohols. In fact, allylic alcohols were activated by gold catalysis to

realize a catalytic enantioselective intramolecular α-allylic alkylation of aldehydes, through the combination of gold and aminocatalysis (Scheme 17, A).[86]

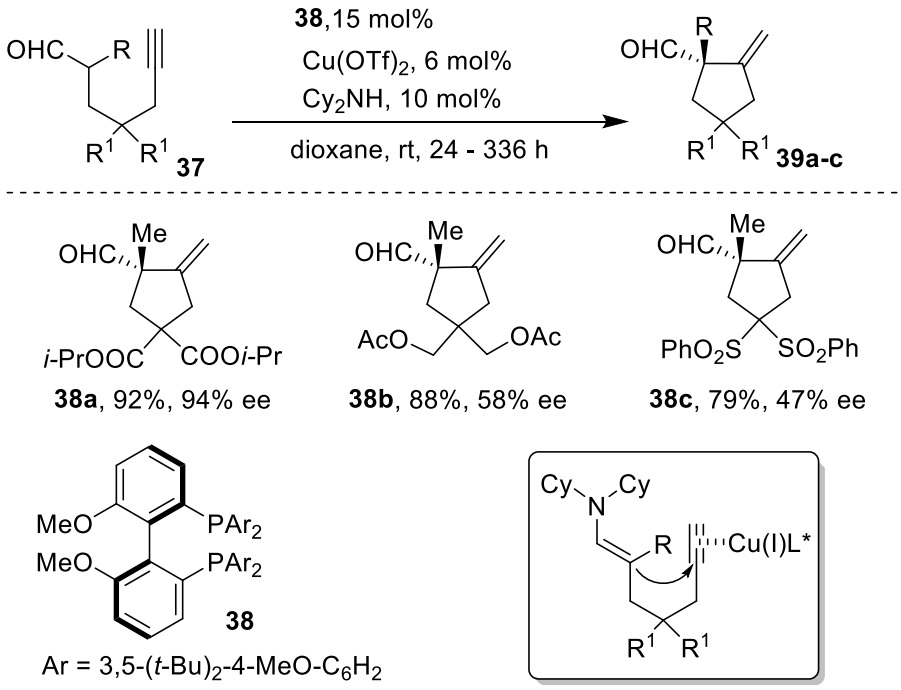


Scheme 17. Enantioselective α-allylic alkylation of aldehydes with alcohols with gold catalysis (A), and an intermolecular α-alkylation of aldehydes with allenamides (B).

A range of chiral secondary amines (Hayashi-Jørgensen catalyst, MacMillan I and II type of catalysts) and different binuclear chiral phosphine gold(I) complexes were tested in the model ring-closing reaction. Remarkably, decent levels of stereoselection was observed when the organocatalysts were merged with a cationic gold complex **32**, although the combined use of chiral gold complexes with achiral amino catalysts was proved largely unsuccessful. Apparently, the gold complex is able to activate the allylic alcohols through the formation of an electrophilic allylic cation. Furthermore, careful mechanistic evidences for an S_N2'-type mechanism were collected. In other words, although this activation is often described to occur through the formation of an allylic gold complex, the gold(I)-coordination with the olefin activates the alkene through the nucleophilic attack of the enamine. Deauration of the resulting organogold species, with concomitant elimination of water, leads to the formation of the observed double bond. Gonzales reported an intermolecular reaction of allenamides with aldehydes [87] using a diaryl prolinol silyl ether **1c** as the active catalyst in the presence of the ortho-fluorobenzoic acid as additive (Scheme 17, B). The same reaction was reported by Mascareñas and López.[88]

3.2. Use of copper salts as π-Lewis acids in synergistic enamine catalysis

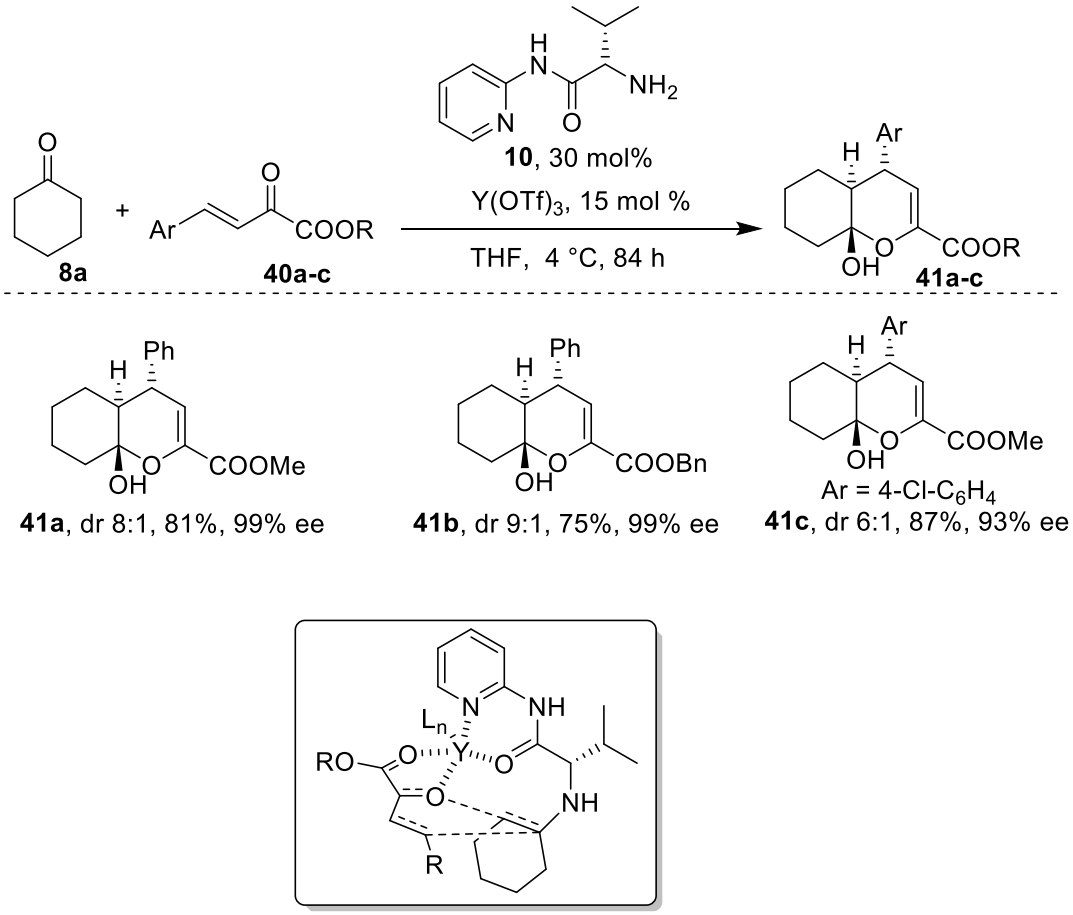
The ability of copper to form stable π-complexes with double or triple bonds is well-known in literature.[89] The Lewis acid organocatalyzed enantioselective preparation of different five-membered carbo- and heterocyclic structures through aminocatalysis and copper(I) activation of alkynyl α-disubstituted aldehydes was reported by Ratovelomanana-Vidal and Michelet (Scheme 18).[90] The authors found that the use of various Cu(I) salts, such as copper(I)-thiophene-2-carboxylate, tetrakis(acetonitrile) copper(I) tetrafluoroborate, the copper(I) triflate·benzene complex, and copper(I)chloride/silver triflate couple, gave lower enantiomeric excess. The active Cu(I) catalytic system was generated *in situ* through the reduction of copper(II) triflate with (*R*)-3,5-di-tert-butyl-4-methoxyphenyl-MeOBIPHEP (**38**) [MeOBIPHEP = (6,6'-dimethoxybiphenyl-2,2'-diyl)-bis(diphenylphosphine)] (the phosphine is oxidized to the corresponding phosphine oxide). The enamine intermediate was obtained by the use of a catalytic amount of cyclohexylamine, as the achiral organocatalyst. Other chiral amines, such as 1-(1-naphthyl)ethylamine, have also been tested by the authors, but no stereocontrol enhancement was observed. Dioxane was found to be the best solvent as long as the catalyst loading was properly adjusted, and various chiral cyclopentanes were obtained under the optimized conditions. Recently, the same research group expanded the obtained results making use of iron as a Lewis acid.[91]



Scheme 18. The enantioselective preparation of enantioselective of -methyl-substituted cyclopentanes mediated by organocatalysis and copper complexes.

4. Enamine catalysis in the presence of Lewis acids in multicomponent reactions: hetero-Diels-Alder and multicomponent reactions

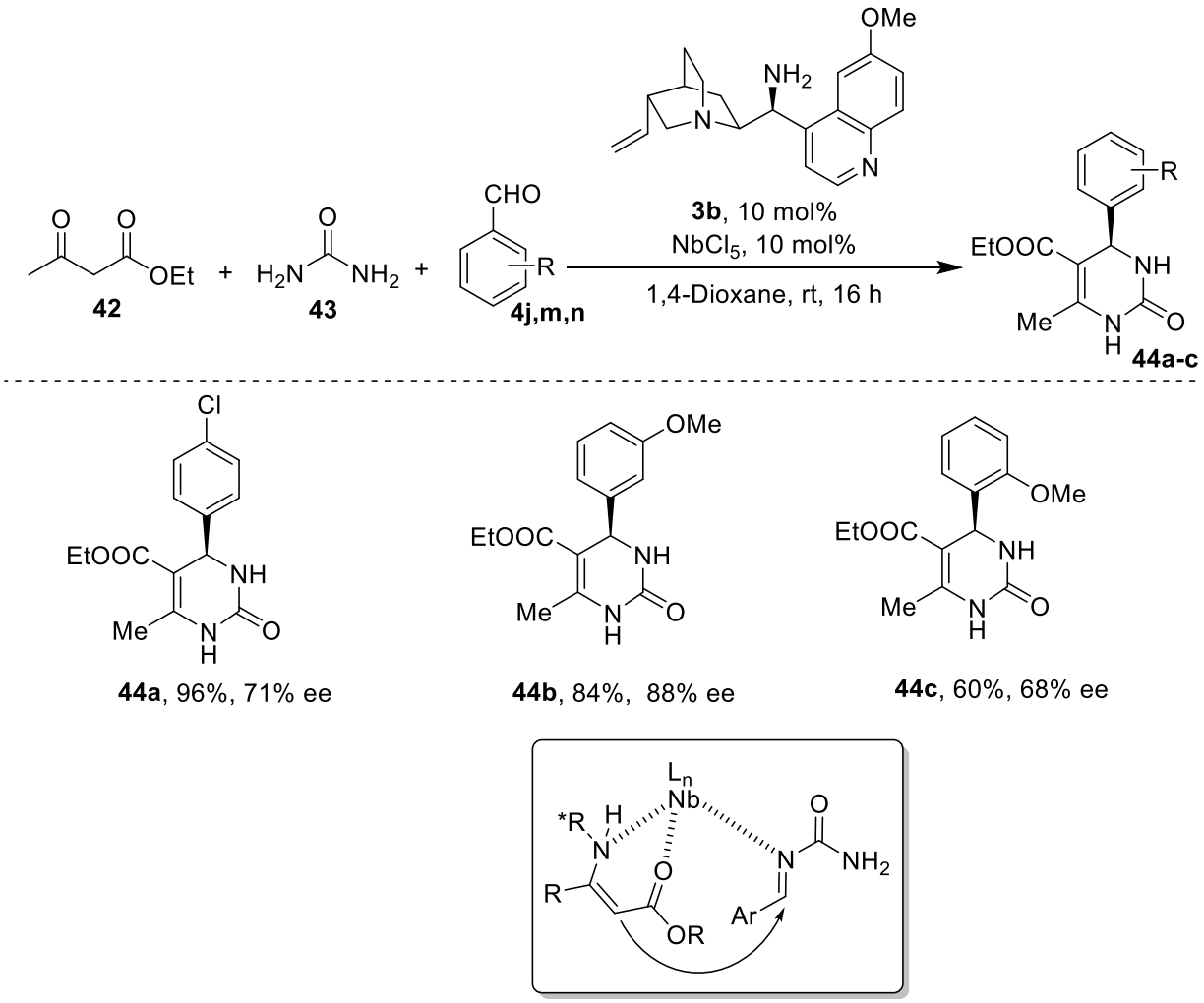
Multicomponent reactions (MCRs) has been one of the targets of organocatalysis for several reasons. The possibility to combine different activation modes, in particular iminium and enamine catalysis, can be advantageously used to drive consecutive reactions towards the obtainment of cyclic products. In addition, to diversity and complexity, the main advantage of multicomponent organocatalytic reactions relies in the possibility to control the formation of multiple stereocenters with high enantiomeric and diastereoisomeric excesses. To add interest to the multicomponent reactions, the organocatalytic simple reaction conditions with simple starting materials in a single reaction step have been applied to the synthesis of various enantiopure natural products and interesting intermediate for chiral drugs, dropping the number of required steps. Therefore, organocatalysis was employed to access optically pure compounds for pharmaceutical and agricultural applications. Organocatalysis was employed in asymmetric multicomponent reactions.[92] Although metal contamination can be a problem, particularly in drug synthesis, combination of Lewis acid catalysis with organocatalysis can unveil new possibilities. As an example of multicomponent reaction that takes advantage of both organocatalytic and Lewis acid activation modes, Wang described a direct enamine catalysis for the preparation of hetero Diels-Alder adducts (Scheme 19).[93]



Scheme 19. Asymmetric inverse-electron-demand hetero-Diels-Alder reaction.

Asymmetric inverse-electron-demand hetero-Diels-Alder (IED-HAD) reactions of electron-rich alkenes with electron-deficient enones can give a practical access to dihydro- and tetrahydropyran derivatives, common scaffolds present many natural products. The IED-HAD between cyclic ketones and β,γ-unsaturated-α-ketoesters was reported taking advantage of the enamine catalysis in the presence of Lewis acids. Bicyclic dihydropyrans were obtained in good yields and moderate diastereoselectivities by the use of a catalyst bearing a chelating group that was able to coordinate the Lewis acid and thus directing the reaction of the unsaturated carbonyl to the enamine. The Lewis acidity could be tuned depending on the metal could be tuned depending on the metal, and better results were obtained with by $La(OTf)_3$, $Yb(OTf)_3$ and $Y(OTf)_3$. On this regard, using the less basic aryl amine, suitable combinations with Lewis acids are much favorable.[94] Chiral primary amines were used in combination with Lewis acids to promote multicomponent reactions. Xu and Lai reported the 9-amino(9-deoxy)epiquinine **3b** (Scheme 20) and $NbCl_5$ co-catalyzed multicomponent reaction of β-ketoesters, urea, and aromatic aldehydes, allowing the easy preparation of enantioenriched 3,4-dihydropyrimidine-2(1H)-ones. The reaction is influenced by the presence of water and it needs to be carried out with compatible Lewis acids.[95] In the proposed reaction mechanism by the assistance of

Niobium, the chiral enamine intermediate (generated from β-ketoesters and chiral amine **3b**) reacts with N-acylimine (formed *in situ* from aldehyde and urea).

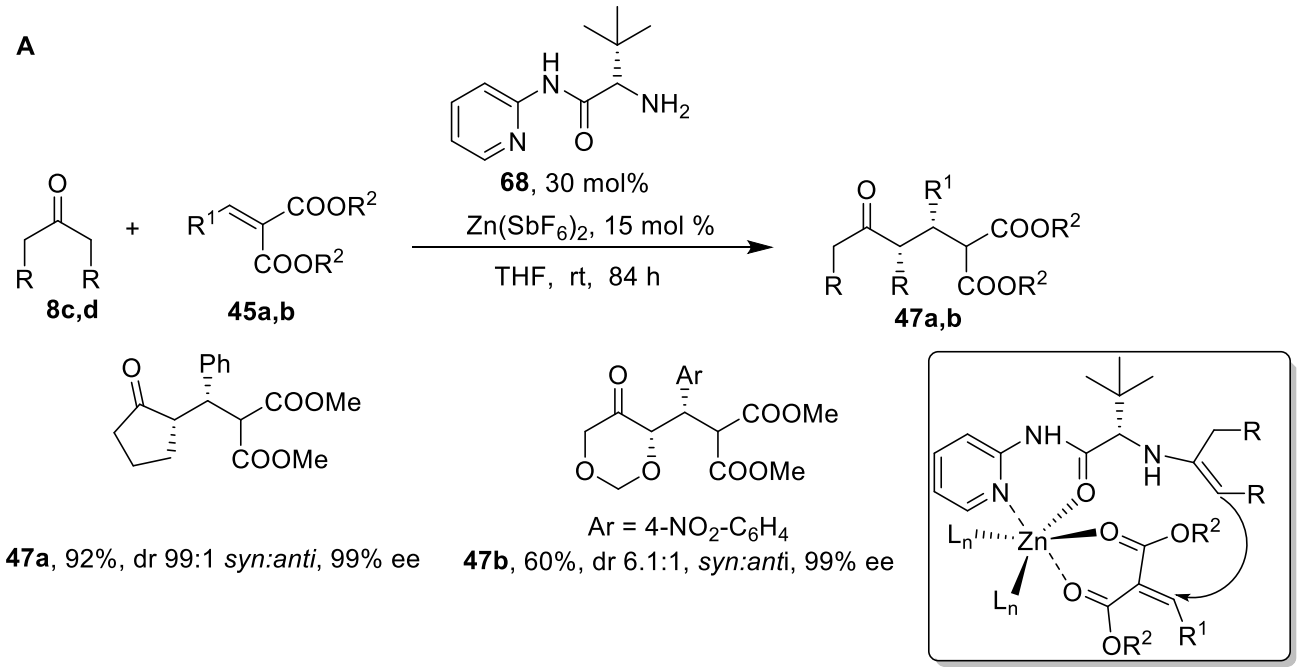


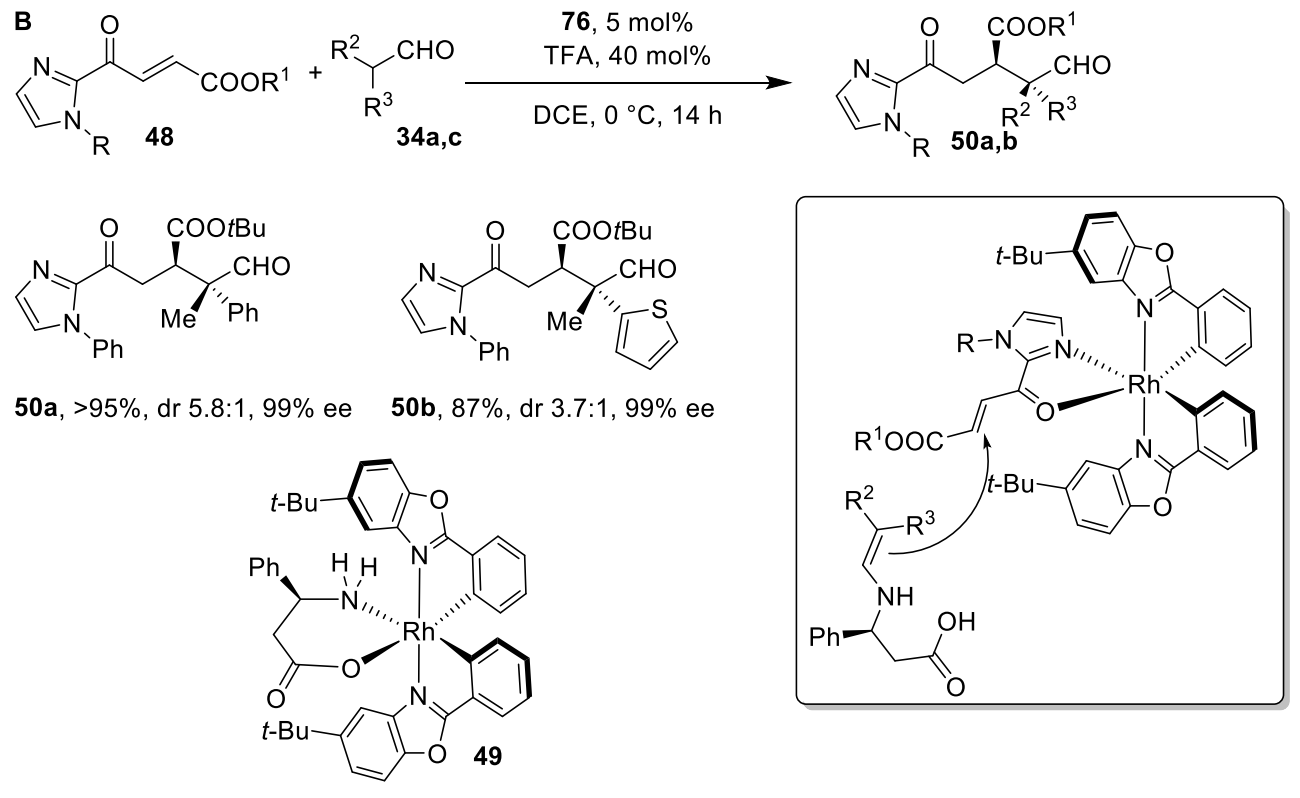
Scheme 20. $NbCl_5$/Primary amine catalyzed Biginelli reaction.

Another example of multicomponent reaction carried out by enamine catalysis merged with Lewis acids was the asymmetric aza-Diels-Alder reaction, a powerful methodology to obtain nitrogen-containing heterocycles. An example of a two-components organocatalytic asymmetric inverse electron-demand multicomponent reaction of aldehydes and *N*-sulfonyl-1-aza-1,3-butadienes was reported.[96] Spirocyclic oxindoles, especially those spiro-annulated with heterocyclic compounds, were recently subjected to intense studies, due to their interesting biological activities.[97] A methodology for the [4+2] cyclization reaction of but-3-en-2-ones and isatines affording spirooxindole tetrahydropyranones was also reported.[98]

5. Enamine catalysis in the presence of Lewis acids for Michael reactions

One of the most important C–C-bond-forming reactions in Organic Chemistry is the Michael-type addition.[99]. Although numerous theories were proposed to rationalize the behavior of different Michael acceptors, Mayr recently measured their kinetics with different nucleophiles in order to quantify their electrophilic character.[100] On the basis of the Mayr equation Log k = S_N(E + N), 15 new empirical electrophilicity parameters E for Michael acceptors were introduced in the Mayr scale. DFT calculations were performed to confirm the suggested reaction mechanisms and to explain the origin of the electrophilic reactivities. Iminium Michael acceptors are used in organocatalysis throught the iminium activation modes.[101] As we have briefly discussed in the introduction, electrophilicity of the chiral iminium derivatives were evaluated and the possibility to use different nucleophiles, under the general Mayr equation, was rationalized. However, to enhance the possibility offered by the activation mode, and to expand the possible nucleophiles, Lewis acids were employed also in the iminium activation mode. Wang, Xu and co-workers disclosed an example of reported Michael addition of ketones to alkylidene and allylidene malonates through the use of dual Lewis acid enamine catalysis (Scheme 21, A).[102]





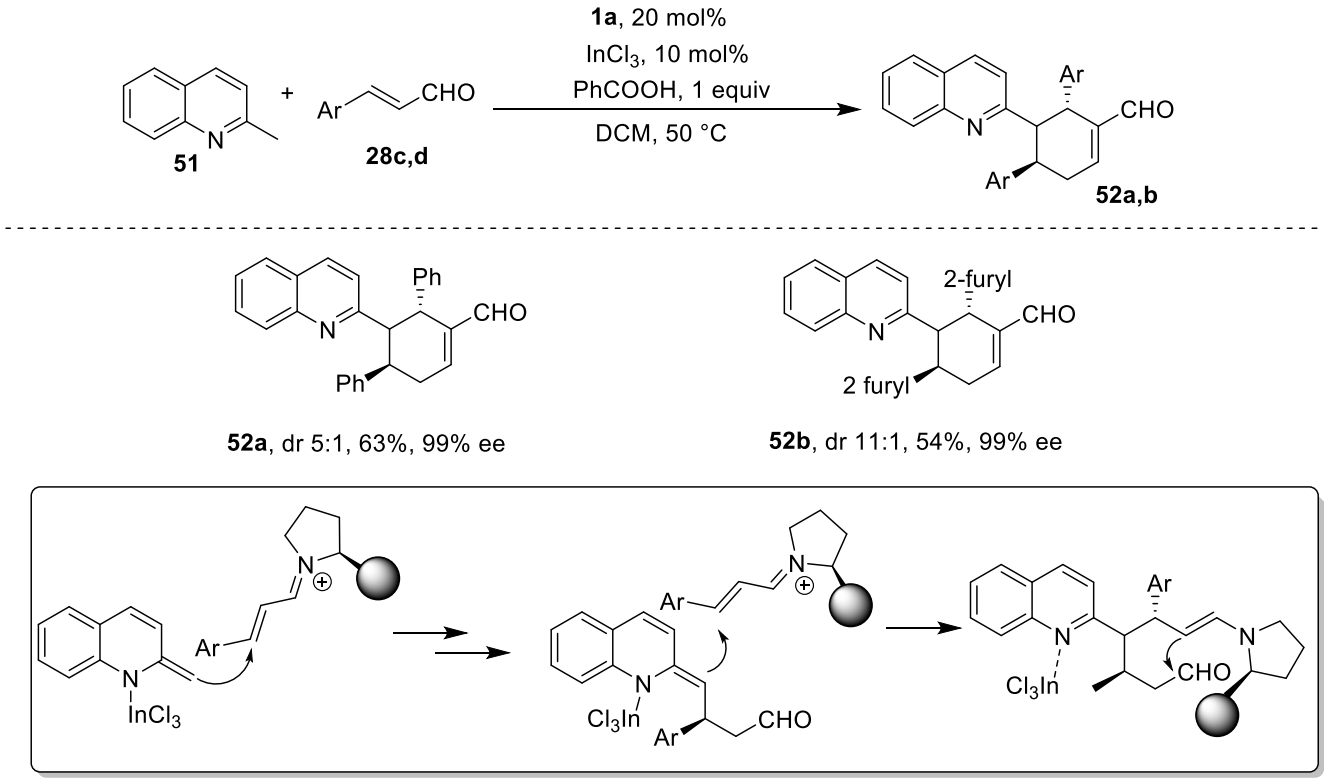
Scheme 21. Asymmetric Michael addition of ketones to alkylidene malonates (A), and a rhodium(III)/amine synergistically catalyzed enantioselective alkylation of aldehydes with α,β-unsaturated 2-acyl imidazoles (B).

Among all the Lewis acid screened, $Zn(SbF_6)_2$ was found the most effective catalyst, and THF was shown to be the best solvent for the optimized reaction conditions. Both five- and six-membered cyclic ketones, including ketones containing heteroatoms, were found reactive; alkylidene malonates and allylidene malonates bearing both electron-withdrawing and electron-donating groups were also suitable substrates. Meggers and Kang have simultaneously disclosed the 1,4-conjugate addition of branched aldehydes to α,β-unsaturated 2-acyl imidazoles in the presence of a chiral-at-metal rhodium complex catalyst (Scheme 21, B) with a (*S*)-3-amino-3-phenylpropanoic acid (L-β-phenylalanine) as a the organocatalyst. The proposed mechanism for the conjugate addition is shown in Scheme 21B. The chiral amine is coordinated to the rhodium complex and it is released upon protonation. Two coordination sites of the rhodium complex are available, after the release of the amine, for the activation of the 2-acyl imidazole substrate through a bidentate coordination. The primary amine liberated forms a chiral enamine reacting with the branched aldehyde, that reacts with the Michael acceptor in enantioselective manner. It is also important to mention, that the use of the other enantiomer of the amine leads to the same major stereoisomer, showing that the stereoselection of the reaction is principally controlled by the rhodium complex.[103]

6. Reactions developed through cooperative iminium-Lewis acid catalysis

In iminium activation mode, the organocatalyst generates an electrophilic intermediate, and the Lewis acid needs to be compatible with the presence of nucleophiles and it needs to participate in their activation. It is possible to make a distinction between the actions promoted by the Lewis acid. The Lewis acid, once again, can form an electrophilic organometallic species. On the other hand, fruitful combinations of Lewis acids and iminium catalysis were tested for sequential reactions. In the first step, the iminium activation, realized with the organocatalyst, can enhance the electrophilicity of unsaturated carbonyl compounds towards the nucleophilic addition. In the subsequent step, the Lewis acid induces other reactions, which are often cyclization reactions leading to cyclic products. Otherwise, it could activate the substrate towards the reaction with a nucleophile.

Jørgensen reported an interesting reaction using iminium activation mode, combining organocatalysis and Lewis acids.[104] In this work, he showed the possibility to functionalize inactivated alkyl quinolines with alkyl groups in the presence of $InCl_3$. Such metal salt used in catalytic amounts allowed the addition of alkyl quinolines to α,β-unsaturated aldehydes activated by an organocatalyst (Scheme 22). The reaction proceeds in a highly stereoselective manner through two cycles (Lewis acid and iminium ion catalyzed) and harsh conditions



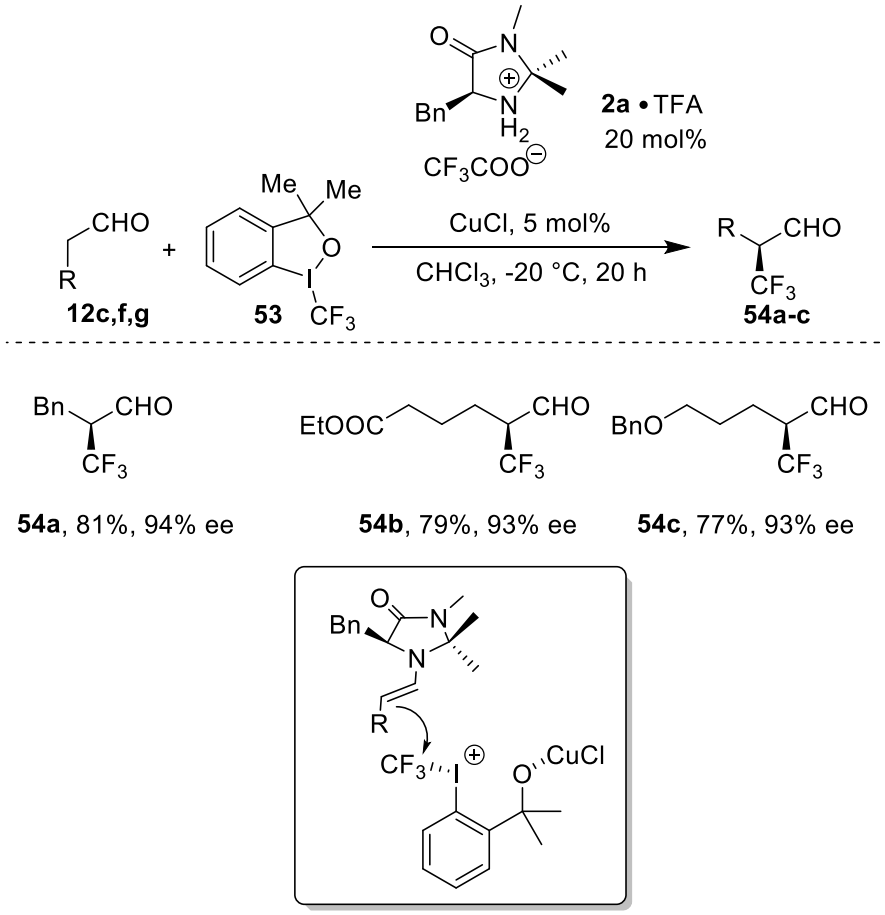
Scheme 22. Diastereo- and enantioselective functionalization of unactivated alkyl quinolines with α,β-unsaturated aldehydes.

Rios has reported the addition of benzoxazole to a Morita-Baylis-Hillman carbonate, to afford the alkyl-azaarene in a diastereoselective manner (up to 15:1 dr) and in good yields. The Morita-Baylis-Hillman carbonate is activated by DABCO in the presence of a Lewis acid (10 mol% AgOAc). An example of the enantioselective variant of the reaction was inserted in the paper, and a chiral *Cinchona* alkaloid was employed instead of a catalytic amount of DABCO. The enantioenriched product was obtained in 50% ee and with a dr of 15:1.[105] 1,3-Acetonedicarboxylic acid was used as pro-nucleophile in an iminium activation mode.[106] The keto-diacid was activated by copper Lewis acid catalysis, to give chiral cyclohexenones as final products in one single step in 94 to 99% ee.

7. Miscellaneous

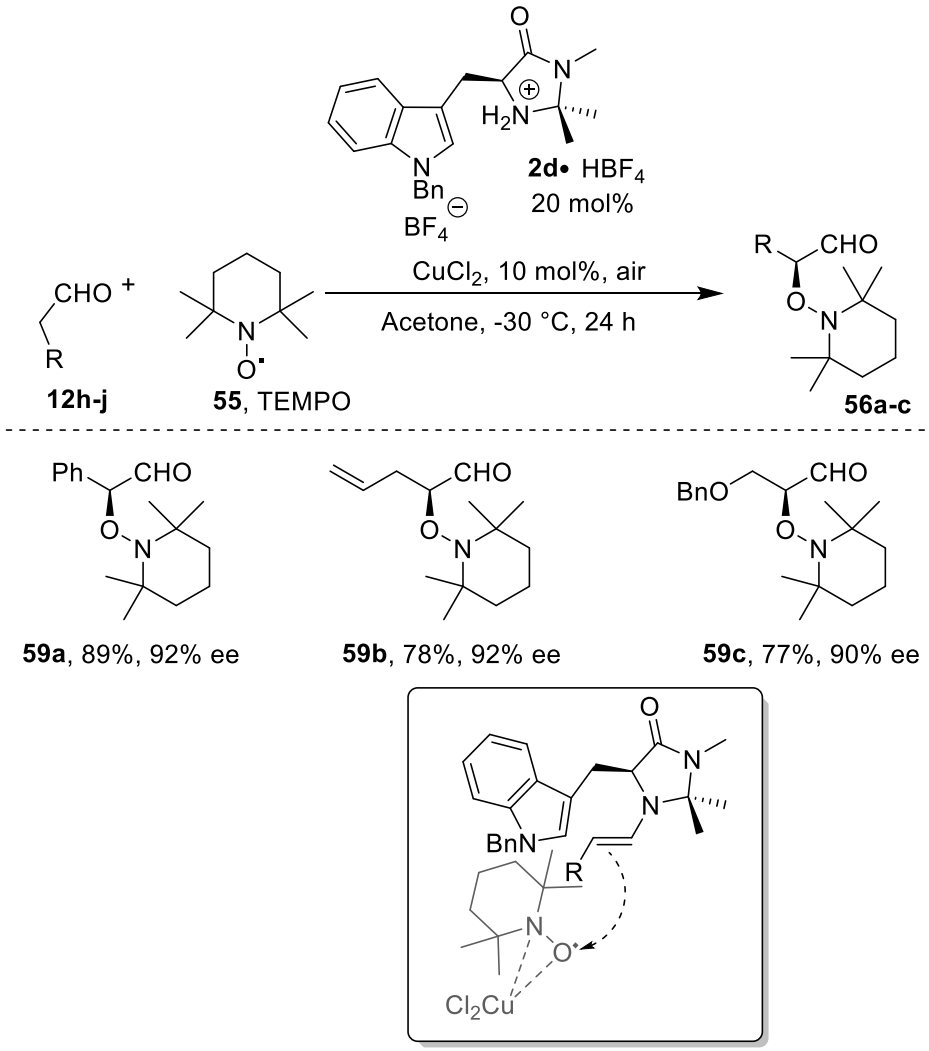
In the next examples, a Lewis acidic copper-mediated activation of substrates have been reported. Even if the use of copper catalyst is mandatory to observe the reaction, in these works the formation of new electrophilic copper species was not observed. Due to the importance of molecules incorporating a trifluoromethyl group (CF_3) in pharmaceutical, agrochemical, and materials science, the incorporation of such group in an efficient way has been the subject of many synthetic

efforts.[107] In 2010 MacMillan reported the use of 3,3-dimethyl-1-trifluoromethyl-1,2-benziodoxole **53** (Togni's reagent) in α-trifluoromethylation of aldehydes through enamine catalysis (Scheme 23).[108]



Scheme 24. The enantioselective α-trifluoromethylation of aldehydes with iodonium salt.

Although **53** is an electrophilic reagent, in absence of a Lewis acid, the yields obtained in the model reaction were quite low. After a survey of different Lewis acid – such as Fe(III), Sc(III), Cu(II) and Zn(II) – Cu(I)Cl was found to be the most suited ones. The Lewis acids are able to promote the I-O bond cleavage of the Togni's reagent to generate the highly electrophilic iodonium salt. A Cu(I)/Cu(III) catalytic cycle could not be proposed due to the fact that an enantiomeric excess was observed even employing Sc(III) (48% yields, 64% ee) and Zn(II) 52 % yields, 66% ee), and because the reaction was observable even employing $FeCl_2$. The use of stronger Lewis acids gave a lower enantiomeric excess. Lewis acidic copper catalysis was also employed in π-activation of multiple bonds. The enantioselective α-oxidation of aldehydes was reported using the Lewis acidic copper(II) in combination with TEMPO and the tryptophan derivative **2d** as organocatalyst (Scheme 24).[109]



Scheme 24. Enantioselective α-oxidation of aldehydes by synergistic catalysis.

From a precise mechanistic analysis of a precedent report,[110] MacMillan was able to demonstrate that the oxyamination reaction occurred via addition of the transient enamine to an electrophilic metal-TEMPO complex. Therefore, the interaction of specific Lewis acids with TEMPO was examined, and copper(II) was found to be a suitable Lewis acid able to coordinate TEMPO. In other words, the metal is not participating as an oxidant but the coordination of copper to the nitroxyl radical of TEMPO is occurring, generating η^2-type of complex with an electrophilic oxygen. The reaction showed a wide applicability and highly enantioselectivity, with a newly designed imidazolidinones.

10. Conclusions

The compatibility of Lewis acids with the various activation mode of organocatalysis have considerably enhanced the arsenal of the possible chemical reactions in the context of organocatalysis. Although the Lewis acids compatible with organocatalytic conditions seem quite limited, nevertheless many dual processes have been realized. Related to these synergistic or cooperative catalytic processes, many other possibilities can be explored, such as embedding Lewis acids in a MOF, or attaching the Lewis acids onto a solid support, thus modifying stability or inactivation pathways. In addition, flow chemistry and other advanced technological methodologies should be taken into account for further insights about these reactions, allowing not compatible combination between organocatalysts and Lewis acids. Not only the activation of carbonyls and imines by chiral Lewis acids can enhance the reactivity of the system, but all stereoisomers can be accessible now though matching/mismatching protocols. For sure, the combination between organocatalysts and chiral Lewis acids can be used to address stereochemical problems. The fine tuning of Lewis acid activity by ligands can enhance the compatibility and new interesting combinations could be possible. Organocatalysis will be combined with Lewis acids more and more in future, in order to address challenging problems and to find new reactivities. The future of these combinations is limited only by the creativity of researchers.

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