catalysts

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Review

Organocatalysis and Beyond: Activating Reactions with Two Catalytic Species

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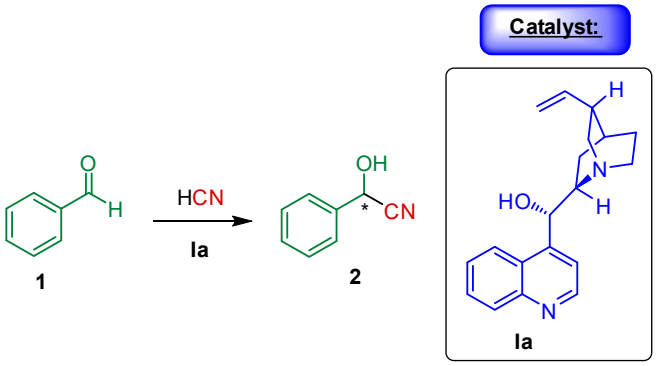
Abstract: Since the beginning of the millennium, organocatalysis has been gaining a predominant role in asymmetric synthesis and it is, nowadays, a foundation of catalysis. Synergistic catalysis, combining two or more different catalytic cycles acting in concert, exploits the vast knowledge acquired in organocatalysis and other fields to perform reactions that would be otherwise impossible. Merging organocatalysis with photo-, metallo- and organocatalysis itself, researchers have ingeniously devised a range of activations. This feature review, focusing on selected synergistic catalytic approaches, aims to provide a flavor of the creativity and innovation in the area, showing ground-breaking examples of organocatalysts, such as proline derivatives, hydrogen bond-mediated, *Cinchona* alkaloids or phosphoric acids catalysts, which work cooperatively with different catalytic partners.

Keywords: organocatalysis; metallocatalysis; photocatalysis; synergistic; cooperative; asymmetric; catalysis

1. Introduction

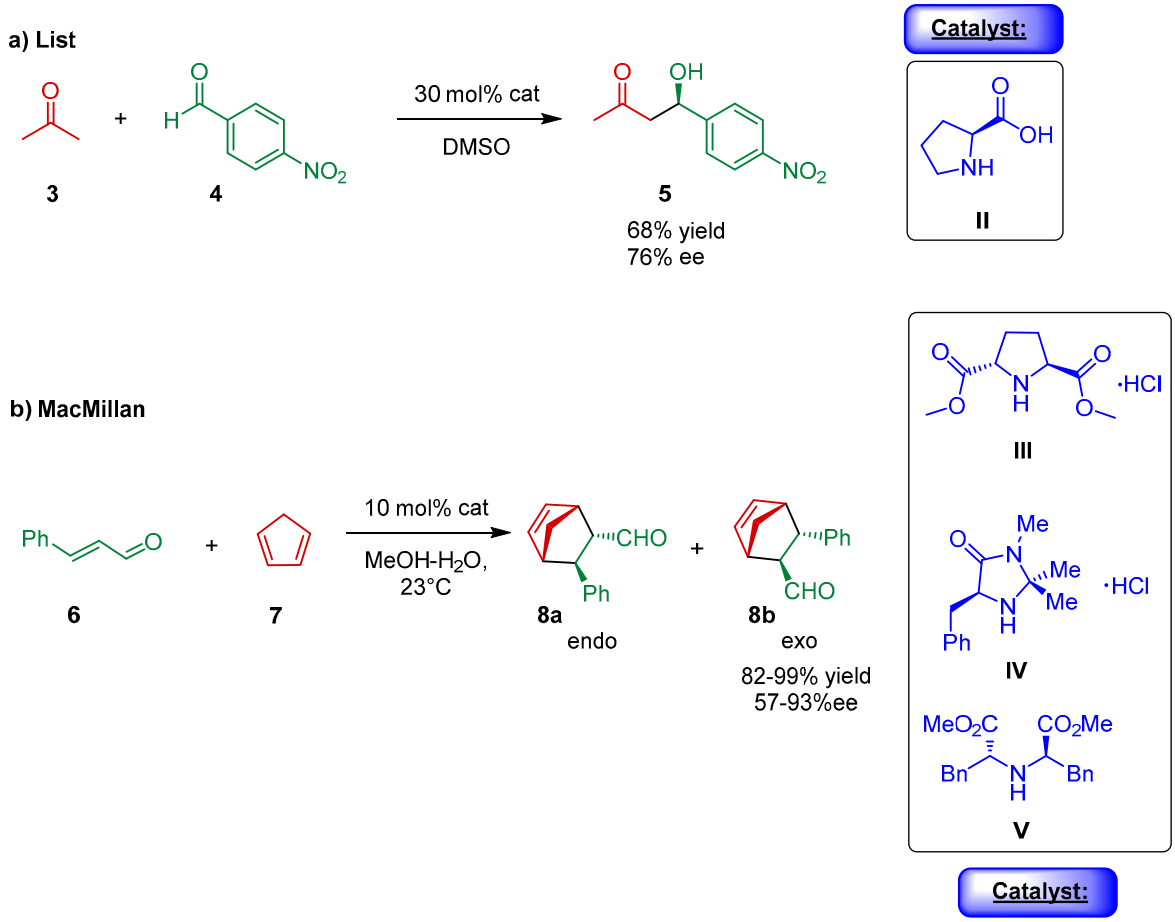
The origins of asymmetric organocatalysis date back to the intuitive experiment of two remarkable scientists, Bredig and Fiske, during the first decade of the 1900s. They reported the first enantioselective addition reaction of HCN to benzaldehyde **1** mediated by *Cinchona* alkaloids as organocatalyst [1] (Scheme 1).



Scheme 1. Addition of HCN to benzaldehyde **1,** performed by Bredig and Fiske.

In hindsight, the results obtained were a breakthrough as it was the first use of a small organic molecule as a catalyst. For several reasons, however, asymmetric organocatalysis was not born;

it was probably only at the beginning of the new millennium that the field was mature enough to bloom. This is testified by the fact that two ground breaking pioneers in the field of organic chemistry, Benjamin List [2] (Scheme 2a) and David MacMillan [3] (Scheme 2b), simultaneously reported two different, albeit complementary, activations with aminocatalysts, giving birth to a "Gold Rush" in organocatalysis [4]. In particular, their studies highlighted the possibility of carrying out asymmetric reactions with organocatalysts based on enamine or iminium ion or activation.



Scheme 2. (**a**) Ketone activation via aminocatalysis, performed by List; and (**b**) aldehyde activation via aminocatalysis, performed by MacMillan.

The main advantage of using organocatalysts derives from their user-friendliness: No anhydrous conditions are required; they are highly stable in a broad range of temperatures and in most common chromatographic and reaction conditions; and moreover, their waste disposal operation has a lower environmental impact respect to other catalysts.

Inspired by this new technology platform, several scientists discovered a large variety of catalysts, which directly came from the chiral pool or undergo synthetic modifications to generate analogous compounds positively impacting the economy of the entire process, thanks to the availability and affordability of the starting materials [5].

An incredible range of organocatalysts capable of promoting enantioselective reactions were found, enabling transformations thanks to different activations, via iminium ion or enamine activation [6], via protonation or deprotonation (chiral basic [1] or acidic catalysts [7]), coordination via hydrogen bond [8,9], and via steric hindrance [6,10,11] (Figure 1). The combination of the different activations in one catalyst to interact with different reaction partners is noteworthy; a bifunctional, or multifunctional, catalyst is a molecule which exhibits more than one functional group capable of interacting and orientating with two different substrates during a catalytic process [12].

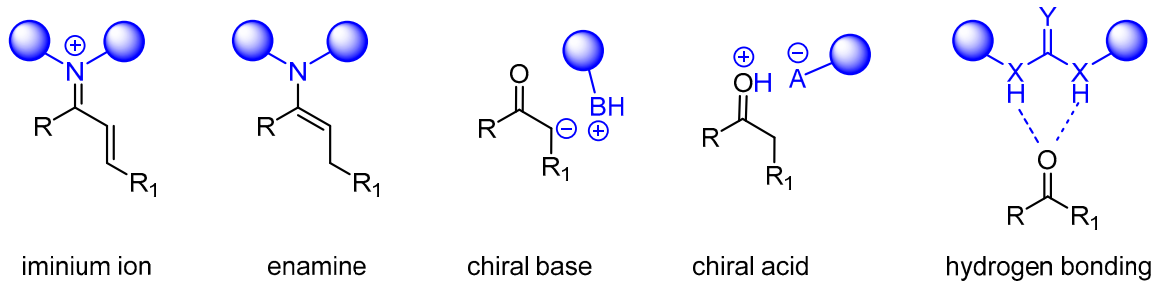


Figure 1. Different methods of substrate activation.

With the purpose of imitating the perfect performance of enzymes, chemists began to synthesize a few bifunctional catalysts able to bring together the different reaction partners.

These compounds have different multiple catalytic sites spaced out by a linker or spacer, which confer to its structure a proper dimension, rigidity and geometry in order to perform the reaction in a stereoselective way. The benefit of this modus operandi is directly linked to entropic energy: keeping the activated reacting partners in proximity and orientating them in a specific way to obtain the desired product with stereocontrol.

A remarkable deficiency of this process is correlated to the many synthetic steps needed to obtain these catalysts. As an alternative and complementary approach, some research groups focused on synergistic catalysis, a relatively new technology platform which allows the simultaneous activation of both reaction partners by two distinct catalytic cycles. The reduction of the ΔE(HOMO-LUMO) causes a substantial decrease in the activation energy of the desired reaction, which increases the constant rate driving the desired pathway compared to possible side reactions (Figure 2).

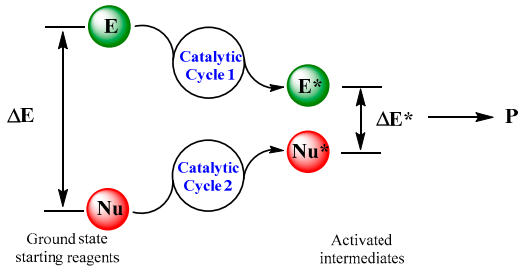


Figure 2. Synergistic catalysis.

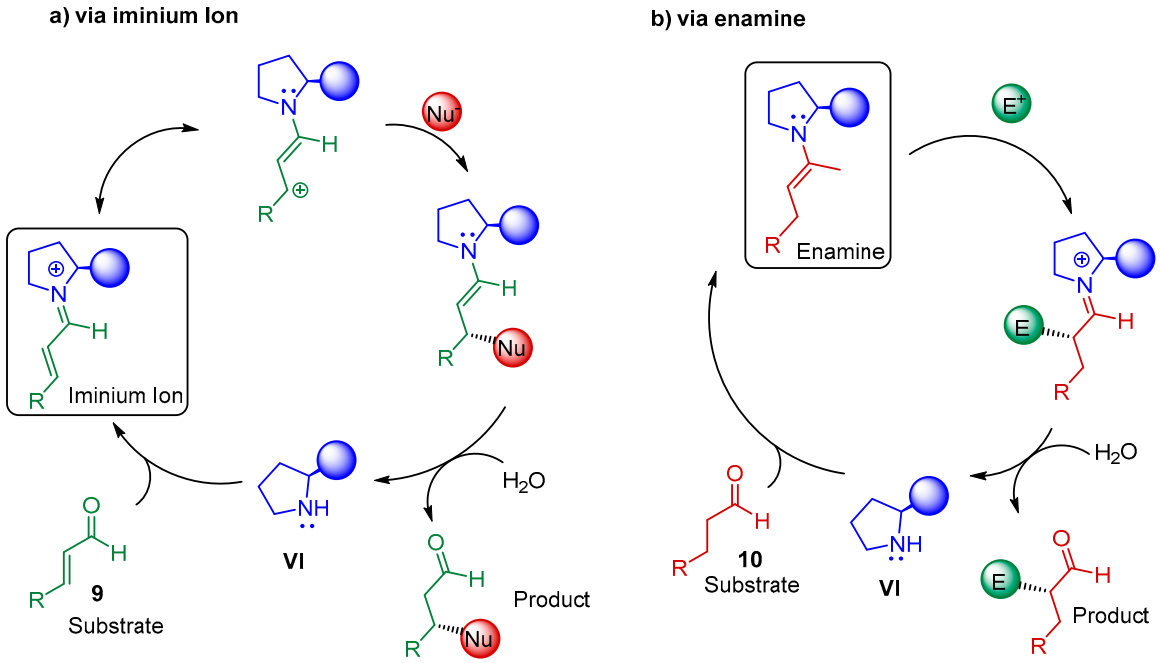
The activated species can rapidly react, making reactions possible that would otherwise be inefficient or even impossible with traditional mono-catalysis methods. The reaction between two intermediates present in low sub-stoichiometric concentrations should be, in principle, difficult; however, considering kinetic aspects, the reaction between two activated intermediates should be promising due to the narrowing of the HOMO-LUMO, which causes a large decrease in the activation energy and, as a consequence, increases the rate constant to drive the desired synthetic pathway.

While nature takes advantage from physical separation between catalytic moieties in the enzymes active sites, a synergistic catalytic system could undergo self-quenching, rendering both catalysts inactive. For this reason, research groups interested in catalysis involving two or more catalytic cycles which act in cooperation, need to select the catalysts combination judiciously. Synergistic catalysis opens the possibility to screen several combinations of a wide range of catalysts for a particular reaction. In this scenario, synergistic catalysis attracted increasing interest in the academic community.

In this review we will focus on selected strategies and reports that exploit synergistic catalysis with disrupting innovation; the cooperation of organocatalysts with other catalytic species of different nature, such as organo-, metal- or photo-catalysts, will be discussed.

2. Proline-Derivatives Catalysis

Proline is the only natural α-amin oacid with a secondary amine; its nitrogen, part of the pyrrolidine heterocycle, has an increased pK_a with respect to other amin oacids. Thanks to the carboxylic acid moiety, proline can also behave as a bifunctional catalyst: The nitrogen can act as a Lewis base while the carboxylate portion as a general Brønsted acid. Following condensation of the nitrogen with carbonyl compounds, proline activates reagents via the corresponding enamine or iminium ion [2]. Proline can be used to functionalise α,β-unsaturated aldehyde **9** with nucleophiles, via iminium ion, or saturated aldehydes **10** with electrophiles via enamine (Scheme 3). When proline itself is used as a catalyst, the carboxylic moiety will aid in imparting stereoselectivity by orienting the approaching reaction partner via an intermolecular hydrogen bond.



Scheme 3. Proline activation modes: (**a**) via iminium ion, (**b**) via enamine.

To improve enantioselectivity and to expand the applicability of proline beyond H-bond acceptors, proline derivatives bearing steric hindered groups, or longer alkyl chains were prepared [6,9]. Catalytic equivalents of proline, such as imidazolidinone-based MacMillan catalysts or prolinamides derivatives, also proved extremely successful [3,4].

Proline and its derivatives effectively catalyze a multitude of reactions; an interesting example is the asymmetric intramolecular aldol reaction, a breakthrough report by Hajos-Parrish-Eder-Sauer-Wiechert [13,14]. This reaction was used by two distinct industrial research groups who discovered a synthetic strategy to obtain a very versatile intermediate in organic synthesis, the Wieland–Miescher ketone [15].

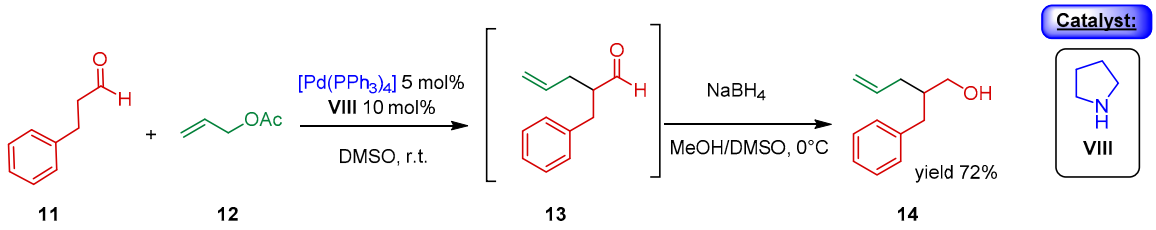
Proline was also used in asymmetric synthesis to obtain compounds of natural or pharmacological interest, such as steroids [16], or eritromicine antibiotics [17]. It was also exploited in different and more versatile reaction pathways, such as the cyclisation of racemic diketones [18], or to effect Knoevenagel condensation [19,20], Mannich reactions, and many more [21].

2.1. Synergistic Catalysis with Proline-Based Catalysts

2.1.1. Combination with Transition Metal-Based Catalysts

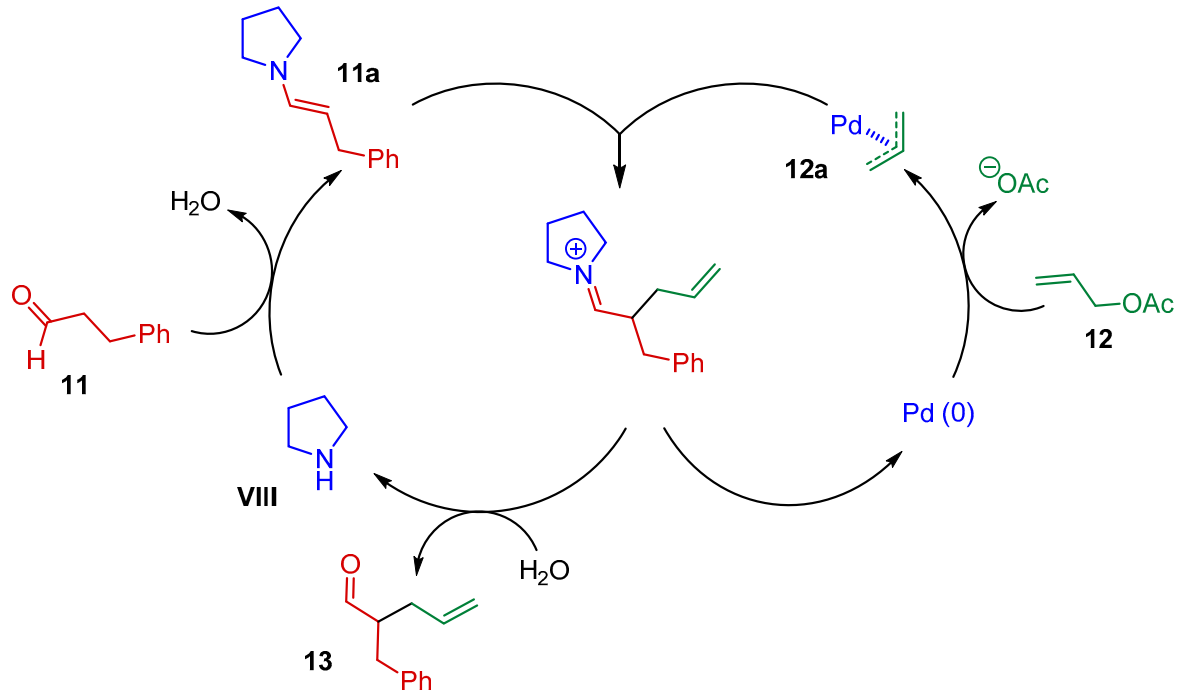
The combination of transition metal catalysis and organocatalysis gained increasing recognition, improving several reactions [22]. One of the first groundbreaking examples of metal- and organo-catalysis working in concert was reported by the Cordova research group in 2006 [23].

They proposed a direct catalytic allylic alkylation of aldehydes and cyclic ketones. The intermolecular α-allylic alkylation reaction, which has the advantage of being highly chemo- and regio-selective, was performed through an unprecedented combination of palladium and enamine mediated catalysis. They described the reaction of 3-phenylpropionaldehyde (**11**, 3 equiv.) with allyl acetate (**12**, 1 equiv.) in the presence of a catalytic amount of palladium catalyst [$Pd(PPh_3)_4$] (5 mol%) and pyrrolidine **VIII** (10 mol%) in dimethyl sulfoxide at room temperature. The corresponding α-benzylic alcohol **14** was isolated in 72% yield after 16 h by reduction with $NaBH_4$ of the α-allylic alkylated aldehyde **13** (Scheme 4).



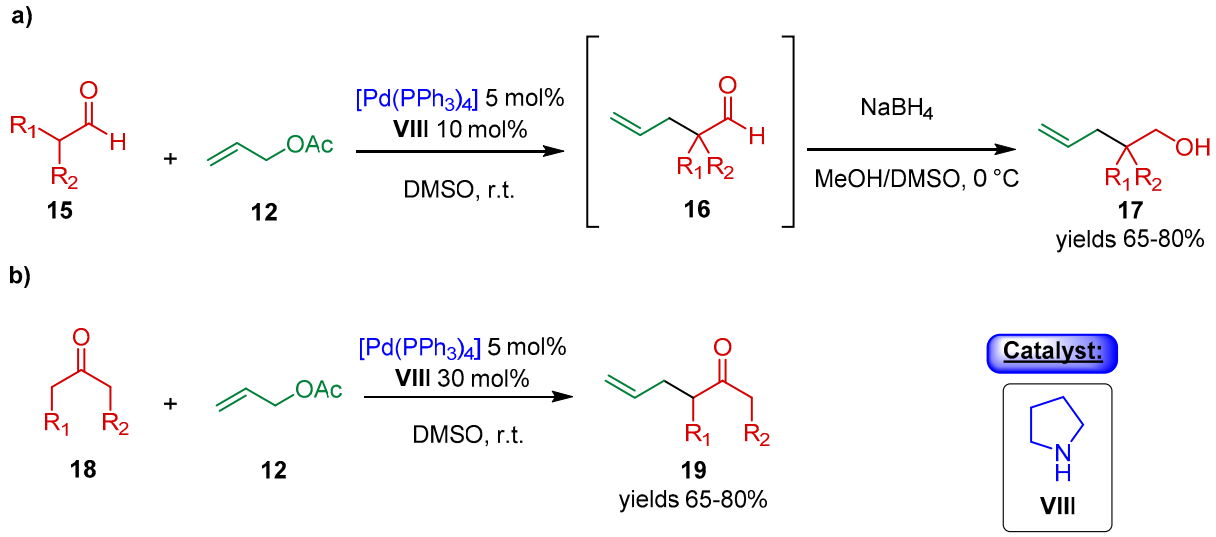
Scheme 4. Synergistic catalysis mediated by palladium and pyrrolidine.

Merging two powerful catalytic cycles enables both electrophilic and nucleophilic activation. As depicted in Scheme 5, the C–C bond formation is allowed by the catalytic enamine intermediate **11a** generated in situ, which attacks the catalytically generated electrophilic palladium π-allyl complexes **12a**. Reductive elimination and subsequent hydrolysis of the iminium intermediate regenerates the Pd(0) and the amine catalyst **VIII**, and yields the α-allylic alkylated aldehyde **13**.



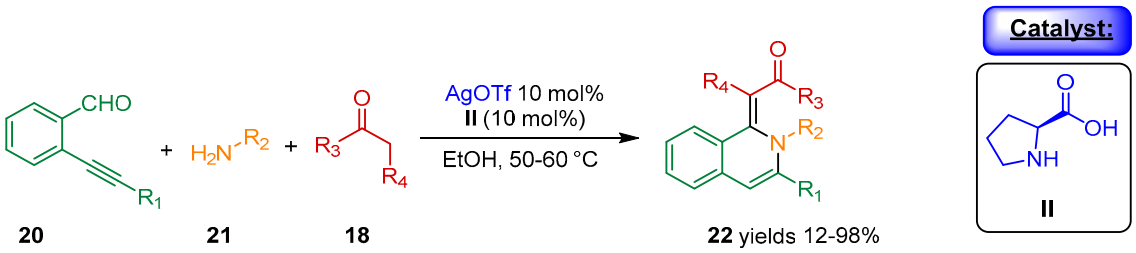
Scheme 5. Mechanistic insight in synergistic palladium and pyrrolidine-based catalysis.

The reaction proved to work smoothly with a range of aldehydes **15** (Scheme 6a) and ketones **18** (Scheme 6b) with high chemoselectivity. Unfortunately, the catalytic asymmetric variant provided the α-allylic alkylated alcohol **17** or ketone **19** with high enantioselectivity, but in moderate yields (yields 25% and 20%, *ee* 74% and 88%, respectively).



Scheme 6. General α-allylation of aldehydes (**a**) or ketones (**b**) via synergistic catalysis mediated by palladium and pyrrolidine.

Since then, several synergistic catalytic approaches based on transition metal catalysis and aminocatalysis were developed. Prompted by the great results obtained through synergistic catalysis and their growing interest in natural product-like compound synthesis [24–26]. Wu et al. described a novel and promising one-pot combination of silver triflate and proline catalysis provided an efficient route for the synthesis of 1,2-dihydroisoquinoline derivatives **22** via multicomponent reactions of 2-alkynylbenzaldehydes **20**, amines **21**, and ketones **18** [27] (Scheme 7).

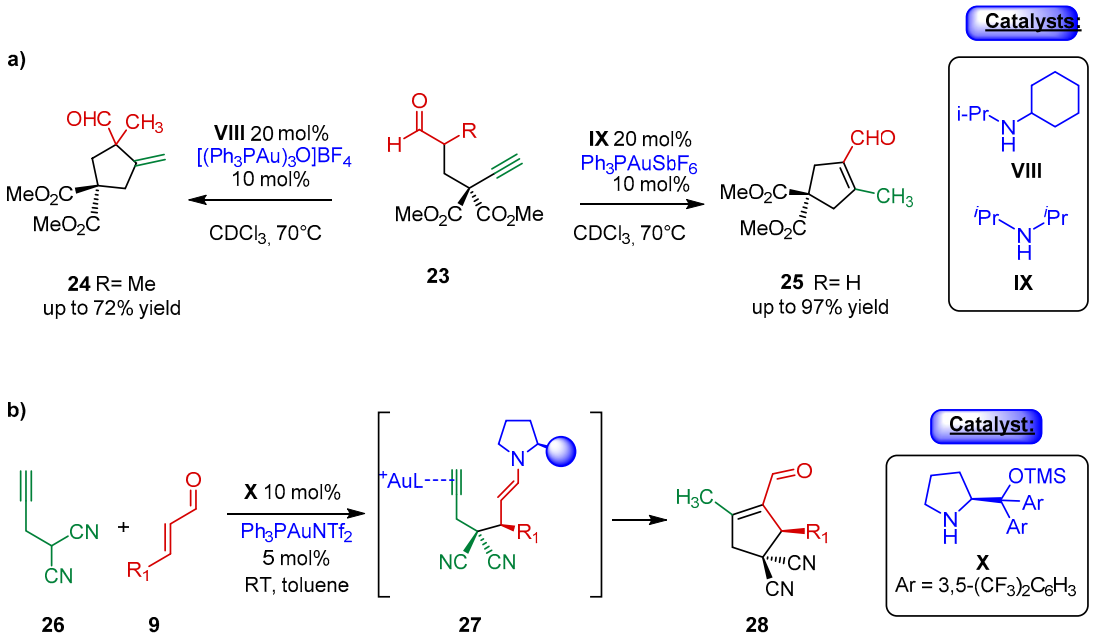


Scheme 7. Synergistic catalysis mediated by silver-based and proline catalysis.

Merging two powerful catalytic cycles enables both electrophilic and nucleophilic activation. The mild metal Lewis acids tested, such as silver, coordinate the triple bond of the starting 2-alkynylbenzaldehyde **20**, making it more electrophilic, while proline simultaneously generates the nucleophilic enamine intermediate.

Together with silver, gold was used as the metal partner. The first example of Au(I)-enamine synergistic catalysis was reported in 2008 by Kirsh et al. [28]. The authors performed a cyclisation of the alkyne aldehydes **23** to **24** or **25** providing racemic products with excellent yields (Scheme 8a). The proposed mechanism features a simultaneous enamine formation at the terminal aldehyde and a π-acid activation at the triple bond. This protocol, however, comes with an inherent challenge: If R is H, the Au(I)-catalysed cyclisation results in an exocyclic terminal alkene after protodeauration, which spontaneously isomerizes to the thermodynamically more stable compound **25**. This isomerization removes the new stereogenic center created during the carbon-carbon bond formation step. If R is a methyl group, a quaternary stereocenter bearing product **24** is created in up to 72% yield. An enantioselective version of this reaction was later reported by Jørgensen et al. (Scheme 8b) [29]. They exploited the sterically bulky Jørgensen-Hayashi catalyst **X** to induce the attack of **26** to an α,β-unsaturated aldehyde **9** via iminium-ion activation. The first Michael addition creates

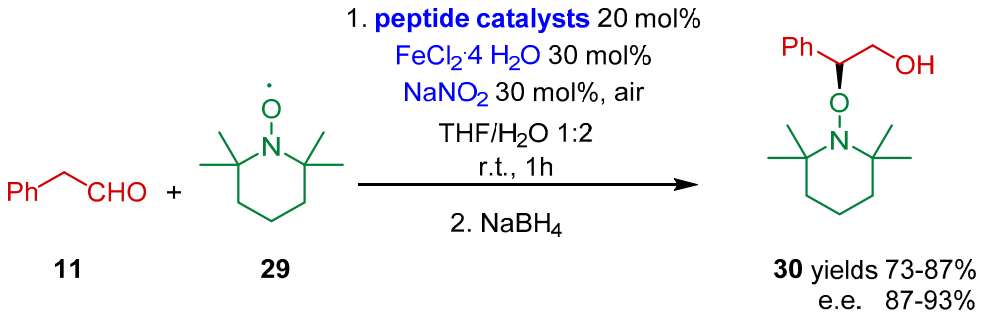
an intermediate, which undergoes synergistic enamine/Au(I) catalysis to obtain the carbocyclisation reaction with high enantio-enrichment of **28** in good to excellent yields.



Scheme 8. General α-allylation of aldehydes (**a**) or ketones (**b**) via synergistic catalysis mediated by palladium and pyrrolidine.

Inspired by metal-associated enzymes, Kudo's research group designed a biomimetic catalysis, exploiting the cooperation of a resin-supported peptide catalyst and Fe-based metal catalyst.

The combination of the peptide containing polyleucine and $FeCl_2$ in two catalytic cycles was highly efficient to allow the asymmetric oxyamination of aldehydes in aqueous media [30] (Scheme 9).



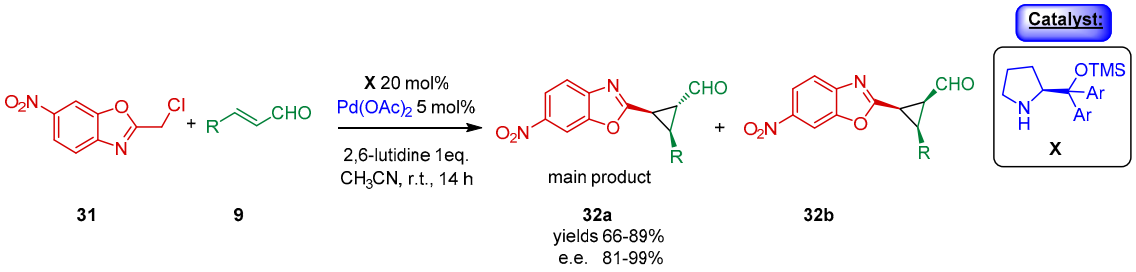
Scheme 9. Synergistic iron- and peptide-mediated catalysis.

The oxyamination of 3-phenylpropanal **11** is performed with TEMPO **29** using iron(III) chloride in the presence of the peptide catalyst. The reaction is carried out in THF/H_2O 1/2 (*v*/*v*) at room temperature; increasing the amount of water in the system THF/H_2O from 1/1 to 1/2 increases the hydrophobic effect and causes an acceleration of the desired product formation. The best results were obtained by introducing a polyleucine chain between the terminal prolyl residue of peptide catalyst and its support. This structural change enhances the reaction rate and increases the enantioselectivity [31].

Following studies showed that the amount of iron(III) chloride could be decreased to catalytic amount using dioxygen as the oxidant [32]. The best improvement is achieved by performing the reaction with iron(II) chloride under an air atmosphere; the oxyaminated product is obtained within 1 h, without using an oxidazing agent. This reaction system proved to be efficient enough that the loading

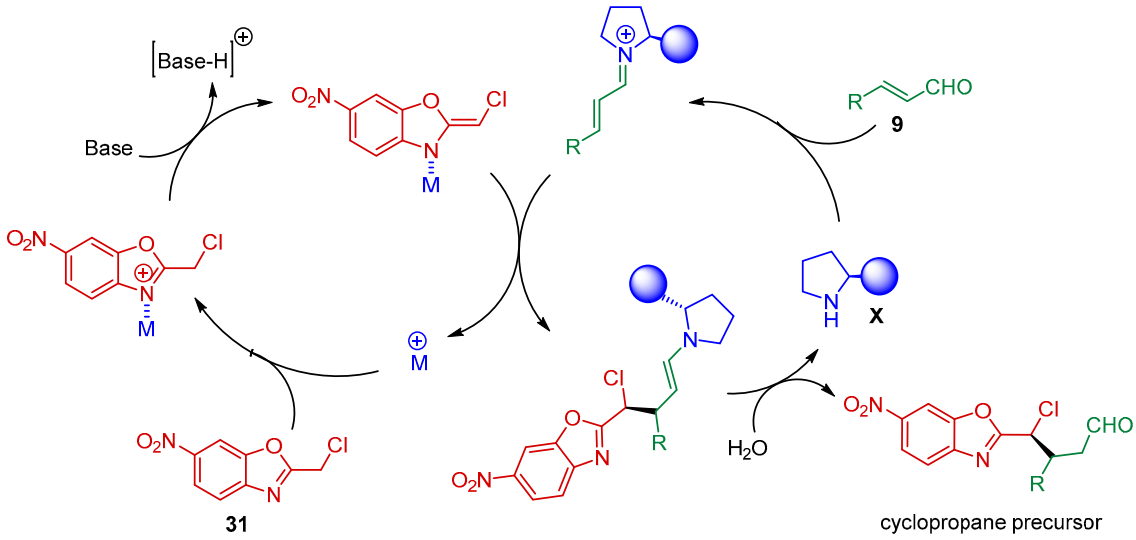
of the peptide catalyst could be reduced to 3 mol% without any loss in yield and enantioselectivity, by increasing the reaction time.

Based on this concept, in 2018 Rios et al. reported the first synergistic organocascade reaction for the synthesis of cyclopropanes **32** with an unusual cis configuration between the benzoxazole and the substituted phenyl ring with good yields and steroselectivities [33] (Scheme 10).



Scheme 10. Synergistic catalysis mediated by palladium and Jørgensen-Hayashi catalyst.

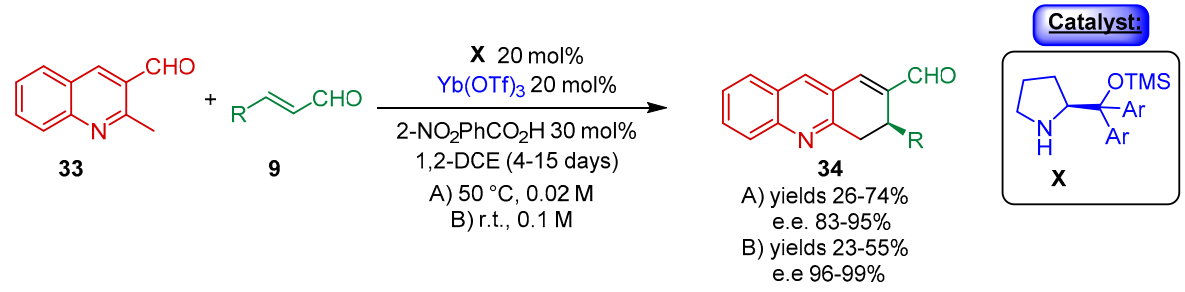
The reaction proceeds via a simultaneous organocatalytic activation of enals with a secondary amine catalyst and the metal Lewis acid-based activation of benzoxazoles; the stereocontrol in this protocol is imparted by the chiral organocatalyst, thus avoiding the need of expensive chiral ligands for the metal. The palladium catalyst coordinates to the nitrogen atom of the heterocycle, increasing the acidity of the adjacent alkyl chain, while the Jørgensen-Hayashi catalyst **X** activates the enals, generating an electrophilic iminium-ion intermediate; these two species can then react rapidly to generate a new C–C bond in the cyclopropane precursor (Scheme 11).



Scheme 11. Mechanistic insight in the synthesis of the cyclopropane precursor to compounds **32a** and **32b**.

The same research group reported another interesting example by merging organocatalysis via iminium-ion with ytterbium-based metal catalysis to prepare dihydroacridines [34]. The reaction proceeds via the activation of quinolines derivatives **33** with $Yb(OTf)_3$ and the concurrent enals activation via iminium-ion by the TMS-protected diaryl prolinol **X** (Scheme 12).

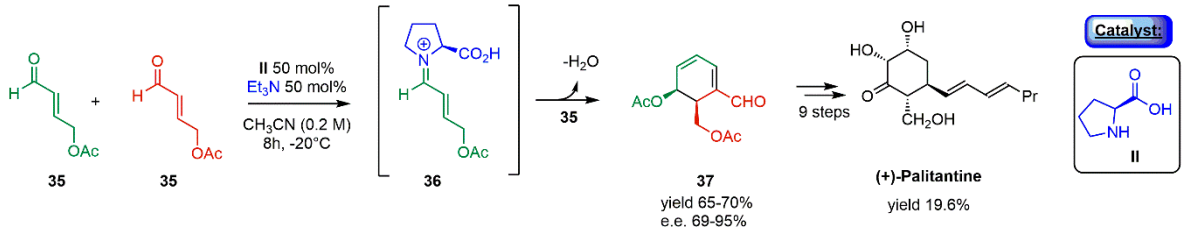
The metal Lewis acid coordinates the aromatic nitrogen and increases the nucleophilicity of the α-methylene that can react with the iminium-ion generated from the enal. The formed enolate intermediate undergoes an intramolecular aldol reaction with the carbaldehyde. The subsequent 6-exo-trig cyclisation, followed by a dehydration, yields the desired dihydroacridine **34**.



Scheme 12. Merging organocatalysis via iminium-ion with ytterbium-based metal catalysis.

2.1.2. Combination with Other Organocatalysts

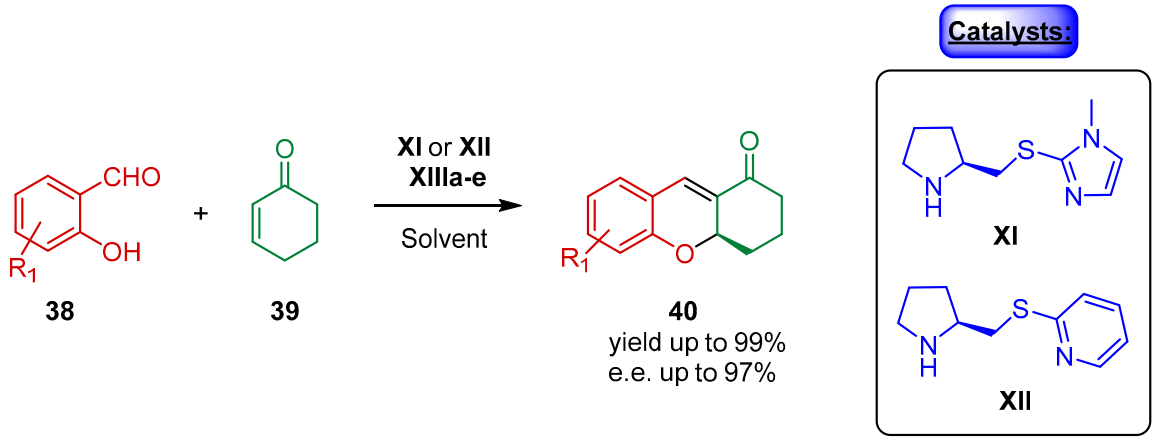
In 2007, Hong et al. reported an interesting method to access a precursor employed in the total synthesis of (+)-palitantine (Scheme 13) [35].



Scheme 13. Formation of new C–C bonds mediated by proline and triethylamine.

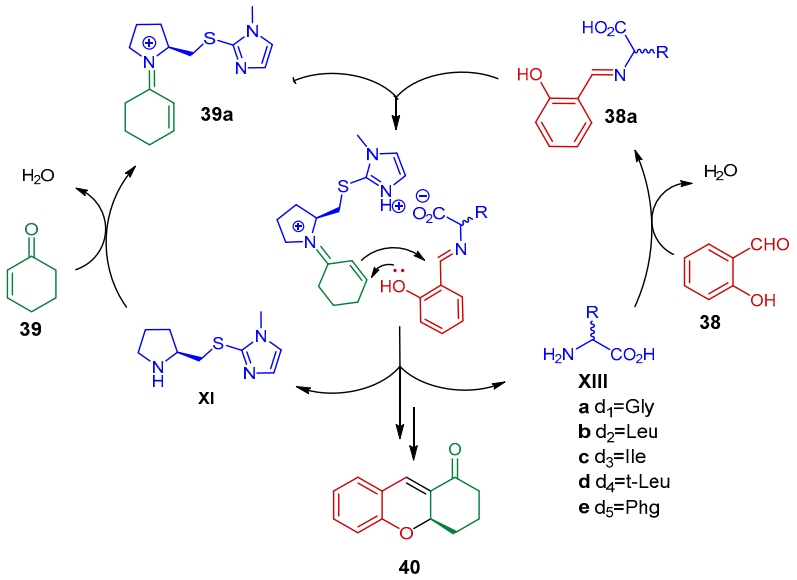
The reaction is a formal self-dimerization [4 + 2] addition of (*E*)-4-acetoxycrotonaldehyde activated by *L*-proline in presence of a trialkyl amine as a co-catalyst. Given the type of reaction, the pathway can only evolve if the reagent is activated in two different ways by the same catalyst. This is, fortunately, the case, given the complementary types of activation that proline can effect. While one aldehyde is activated via an electrophilic iminium-ion intermediate, the other one proceeds through a nucleophilic dienamine intermediate. At this point, the electronic rearrangement will produce the intermediate compound **37** with the formation of two new C–C bonds. Triethylamine was added as a co-catalyst to improve the reaction time and the yield; this way, the reaction could be carried out at a lower temperature, providing a higher enantiomeric excess.

While Hong presented a synergistic activation using the same catalyst to activate the two reaction partners, Xu et al. reported an enantioselective domino oxa-Michael-Mannich reaction between salicylaldehyde **38** and cyclohexenones **39**, activating the reaction partners with a combination of a primary and a secondary chiral amine (Scheme 14) [36].



Scheme 14. Synergistic catalysis based on a primary and a secondary amines activation.

The amino acid, a primary amine, condenses with salicylaldehyde **38** to form imine **38a**. A proline derivative **XI** generates an iminium-ion intermediate reacting with cyclohexenones **39** (Scheme 15). The intermediates formed with the two different catalysts can then react via an oxa-Michael-Mannich reaction. The depicted transition state was confirmed by Fourier-transform ion cyclotron resonance mass spectroscopy.



Scheme 15. Mechanistic insight in the enantioselective domino oxa-Michael-Mannich reaction.

2.1.3. Combination with Photocatalysts

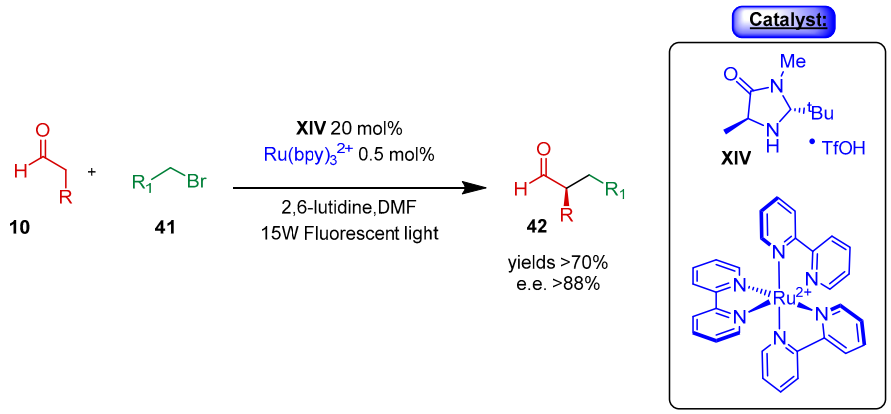
Photochemical reactions, together with enzymatically catalysed reactions, are generally considered as the beginning of the green chemistry concept for synthetic chemistry [37]. Solar light is undoubtedly the cleanest source of energy and the photon is considered a traceless regent [38]. Photocatalysis with visible light [39] is undoubtedly one of the emerging strategies to meet the increasing demand for more sustainable chemical processes.

A number of powerful methods has been recently developed applying organometallic complexes such as $[Ru(bpy)_3]^{2+}$ and $[Ir(ppy)_2(dtb\text{-}bpy)]^{+}$ where bpy = 2,2′-bipyridine, ppy = 2-phenylpyridine and dtb-bpy = 4,4′-di-tertbutyl-2,2′-bipyridine [40,41]. The redox potential of the metal complexes can be readily fine-tuned by ligand modification.

However, due to the high cost and potential toxicity of the ruthenium and iridium salts, as well as their limited availability, organic dyes could also be successfully used in photoredox catalysis instead of a metal catalyst [42].

Of particular note is the cooperative combination of photocatalysis with an organocatalytic cycle, offering catalytic methods for the enantioselective α-alkylation [41], α-perfluoroalkylation [43] or α-benzylation [44] of aldehydes (Scheme 16).

In the first case, in particular, the authors proposed two interwoven catalytic cycles that simultaneously generate an electron-rich enamine from the condensation of an aldehyde with the chiral amine catalyst and an electron-deficient alkyl radical via reduction of an alkyl bromide with a Ru(II) photoredox catalyst. It is well known that $[Ru(bpy)_3]^{2+}$ will readily accept a photon from a light source to populate the $^*[Ru(bpy)_3]^{2+}$ metal to ligand charge transfer (MLCT) excited states. These high energy intermediates remove a single electron from a sacrificial quantity of enamine to form Ru(I) that react via single-electron transfer with the α-bromocarbonyl substrate to furnish the reactive alkyl radical (and Ru(II)) able to react with the enamine formed in the complementary organocatalytic cycle.

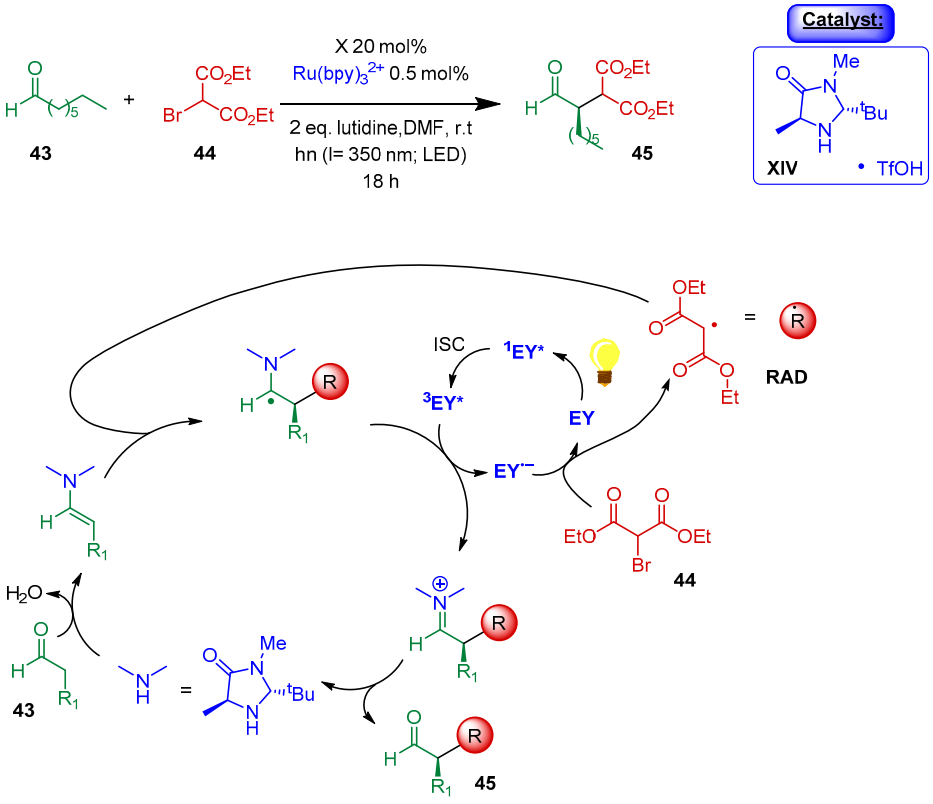


Scheme 16. Synergistic catalysis of proline derivative working in combination with photocatalysis performed by the MacMillan research group.

The same reaction of α-alkylation of aldehydes was proposed by Zeitler et al. in 2011, using a metal-free cooperative asymmetric organophotoredox catalysis approach mediated by luminescent organic dyes [42].

$[Ru(bpy)_3]^{2+}$ has been replaced with eosin **EY** that acts as a photoredox catalyst. After its excitation with visible light and the population of its more stable triplet state (^{3}**EY***), the eosin excited state follows a reductive quenching. The oxidation of a catalytic amount of enamine occurs to form **EY**$^{\cdot-}$, which subsequently reacts via single-electron transfer (SET) with alkyl halide to provide the electron-deficient alkyl radical (**RAD**).

The addition of this radical to the electron-rich olefin of the enamine that is simultaneously generated within the organocatalytic cycle merges both activation pathways. In the catalytic cycle, the subsequent oxidation of the amino radical to the iminium species provides the electron for the reductive quenching of the dye excited state ^{3}**EY*** (Scheme 17).

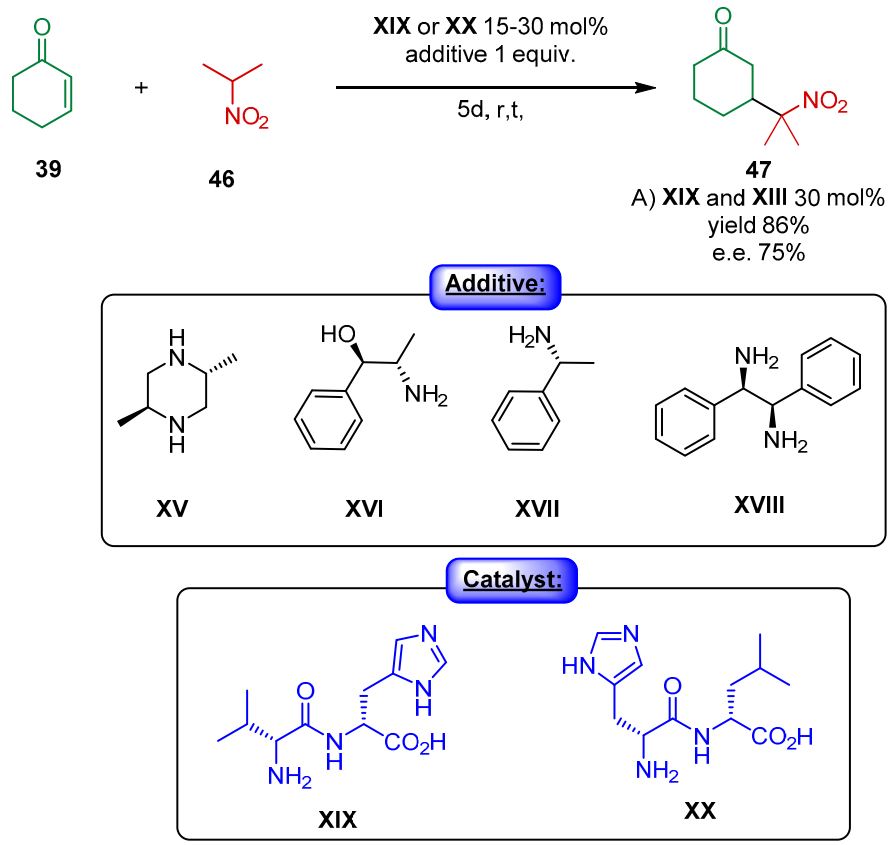


Scheme 17. Mechanistic insight in the reported proline and photo-synergistic catalysis.

3. Hydrogen Bonding Catalysis

Hydrogen bonding is an electrostatic interaction, so the typical value of bond energy between the catalyst and a substrate is around 10–30 kJ/mol. Asymmetric catalysts that can form hydrogen bonds are able to orient reagents, since the hydrogen bond is extremely directional. Moreover, by exalting acidity of the reaction partner, these kinds of catalyst affect the reactivity of the chemical species which they coordinate. In 1990, Kelly reported a reactivity study based on the Diels-Alder reaction between an α,β-unsaturated aldehyde as a dienophile, and different dienes. Bis-phenol derivatives act as catalysts and establish a double hydrogen bond with the oxygen on the dienophile; this implies that the gap in energy between the HOMO-LUMO orbitals decreases and, therefore, the speed of the desired reaction increases [45].

Usually a catalyst that exploits only hydrogen bonds to activate the reagents is not enough to establish the required stereocontrol; in fact, in general, an additional chiral catalyst or a bifunctional catalyst is needed. For example, Tsogoeva et al. reported the use of chiral diamino-compounds (**XV**–**XVIII**) as stoichiometric additives, besides a dipeptide catalyst (**XIX**–**XX**), to increase the efficiency of a conjugate addition of 2-nitropropane **46** to 2-cyclohexen-1-one **39** (Scheme 18).

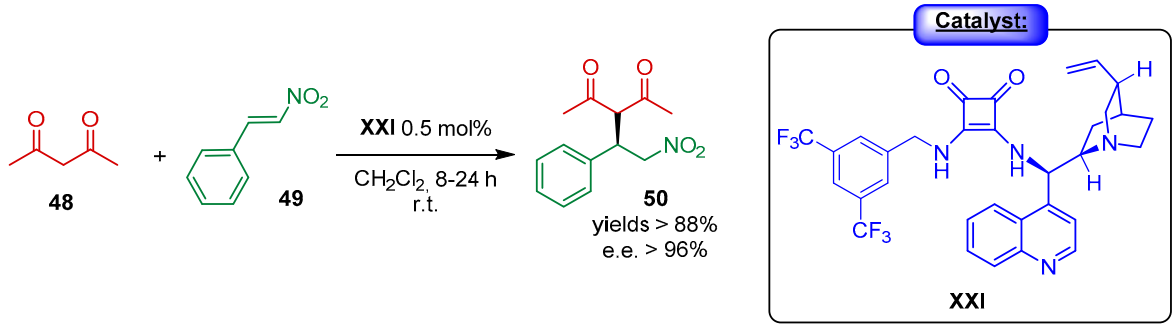


Scheme 18. Chiral diamino-compounds as stoichiometric additive to a dipeptide catalyst.

Bifunctional catalysts tend to be widely used since the spatial proximity of the catalytic units, generating two types of interaction with the reagents, may promote a controlled transition state giving rise to high enantioselectivity. Jacobsen et al. reported ground-breaking examples in the area, with chiral thiourea bifunctional catalysts [9]; it was established that the presence of two *m*-CF_3 groups on the aromatic ring improves the efficiency of the reaction [8,12,46].

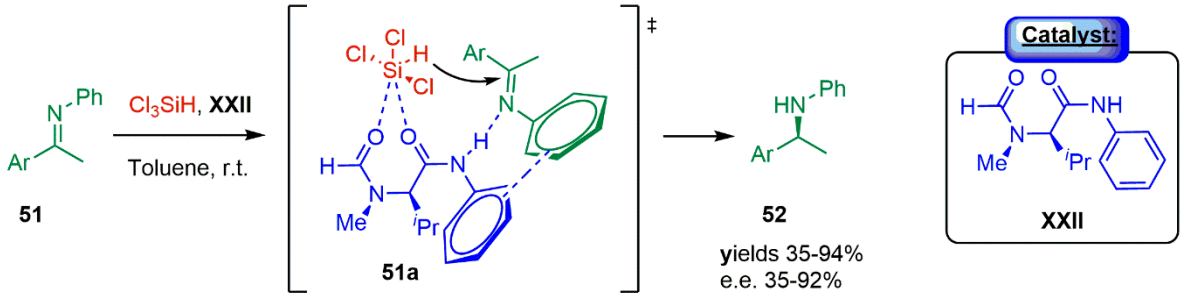
A related group of bifunctional catalysts is the squaramide-derived one, introduced by Rawal. Thanks to the higher efficiency shown, this type of catalyst is proving increasingly successful

(Scheme 19) [47]. Moreover, thiosquaramides show superior performance compared to thioureas, as described by Wheeler and et al. [48].



Scheme 19. The addition to nitrostyrene catalyzed of squaramide-derived catalyst, introduced by Rawal.

Hydrogen bonding is very relevant in biological systems for several reasons; indeed, the architecture of hydrogen bonding bifunctional catalysts is inspired by the interactions within the cavity of enzymes. For example, Malkov reported an interesting study about the activation of two reagents by dipeptide-derivatives **XXII** in an enantioselective reaction of ketimines **51** using trichlorosilane. The complementarity between the reagents and the "catalytic site", along with the weak interaction established, recalls an enzyme. In the transition state **51a**, three non-covalent contacts are established between the catalyst and the two reagents, two hydrogen bonds and one π-π interaction (Scheme 20), thus emphasizing the importance of non-covalent bonds [49]. Therefore, synergistic activations that exploit the hydrogen bond can help when weak interactions are not enough for successful activation.

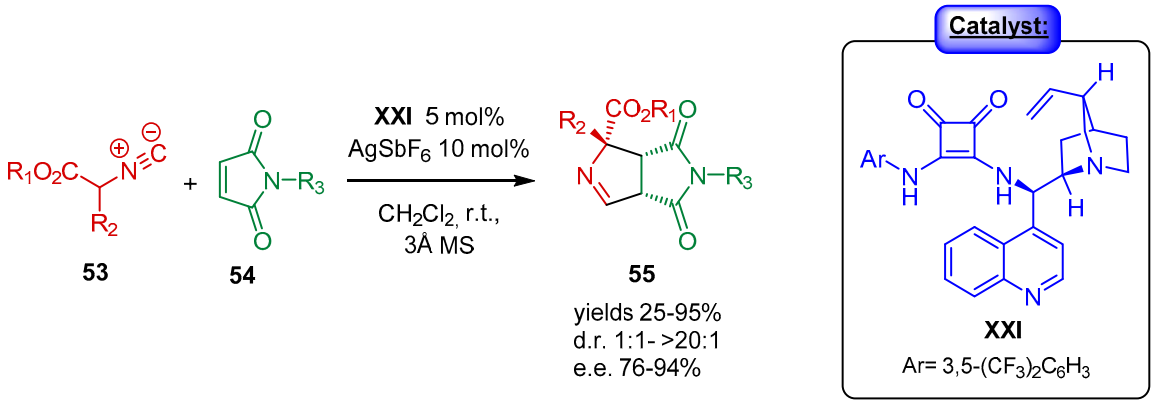


Scheme 20. Enantioselective reduction of ketimines to the corresponding secondary amines with a dipeptide-derived catalyst.

3.1. Synergistic Catalysis with Hydrogen Bonding Catalysts

3.1.1. Combination with Transition Metal-Based Catalysts

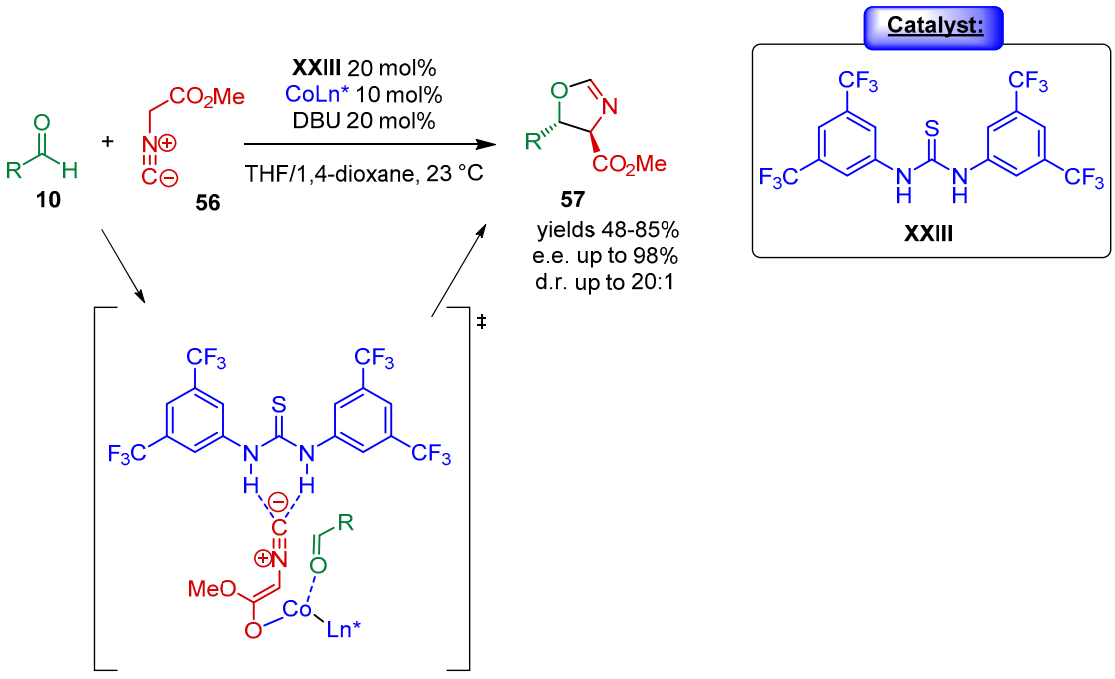
A catalytic system, combining *Cinchona* alkaloid-derived squaramide-based catalyst with $AgSbF_6$ was reported by Zhao, Shi et al. to perform a highly diastereo- and enantio-selective formal [3 + 2] cycloaddition of α-aryl isocyanoacetates **52** with *N*-aryl-substituted maleimides **54** (Scheme 21) [50].



Scheme 21. Synergistic catalysis combining a *Cinchona* alkaloid-derived squaramide-based catalyst with $AgSbF_6$.

The high stereocontrol is provided by the synergistic catalytic system, in which one carbonyl group of the maleimide is hydrogen-bonded to the squaramide motif; at the same time, Ag(I) chelates to the terminal carbon of the isocyano group, enhancing the acidity of the isocyanoacetate proton that can, therefore, be deprotonated by the quinuclidine nitrogen of the *Cinchona* catalyst. This multifunctional, well-designed, transitional state orients the isocyanoacetate enolate to attack the maleimide; subsequently, a 5-endo-dig cyclisation takes place, forming the product **55** with a third stereocentre.

Oh and Kim developed a domino aldol-cyclisation reaction between aldehydes **10** and methyl α-isocyanoacetate **56** [51]. This synergistic catalysis exploits a chiral cobalt complex, which works in concert with an achiral thiourea (Scheme 22).

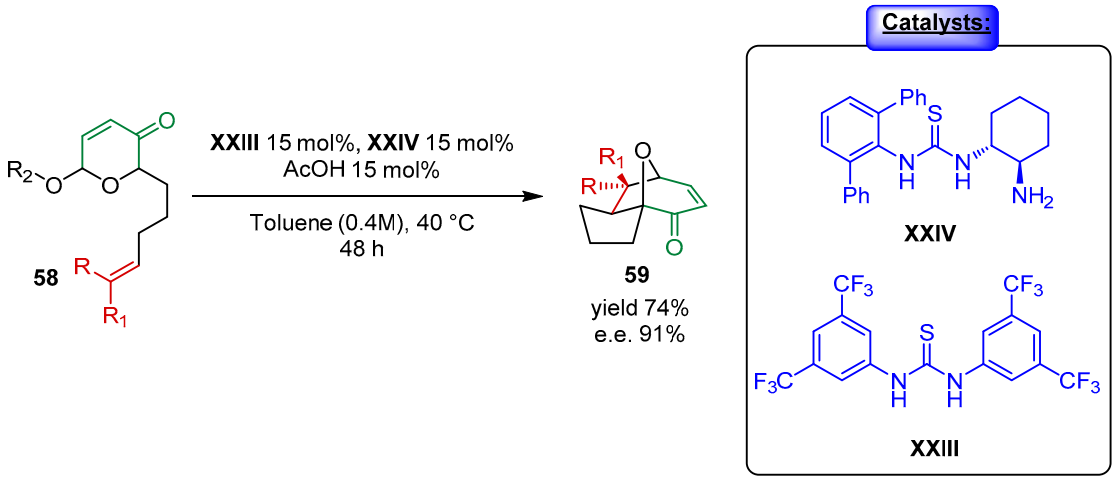


Scheme 22. Domino aldol-cyclisation reaction between aldehydes **9** and methyl α-isocyanoacetate **56** catalysed by cobalt and thiourea catalysts.

3.1.2. Combination with Other Organocatalysts

In 2011, Jacobsen reported a novel and elegant synergistic strategy to obtain tricyclic structures by [5 + 2] dipolar cycloaddition using a dual catalytic system [52].

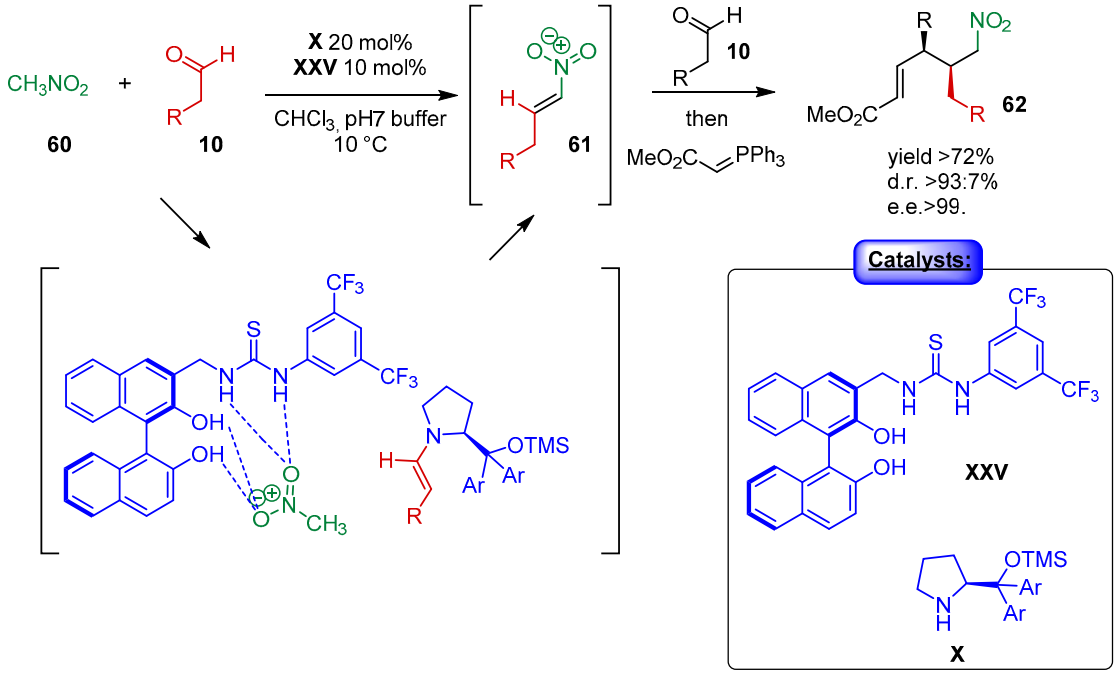
The system consists of two different types of thiourea-based catalysts; while **XXIV** exploits the primary amino group for enamine activation, **XXIII** activates the other reaction partner via a H-bond. The synergistic catalysis was demonstrated with a series of reactions run with different bifunctional chiral catalysts in the presence and absence of **XXIII**; this way, a clear and dramatic cooperative effect was observed (Scheme 23).



Scheme 23. Synergistic catalysis mediated by two different thiourea-based catalysts.

The authors propose that **XXIII** induce ionization to the pyrylium ion and acts as a carboxylate-binding agent to generate, cooperatively with **XXIV** whose amine condenses with the ketone to yield dienamine after tautomerisation, the reactive ion pair that undergoes intramolecular cycloaddition. The initial substrate condensation with the primary amine function present on catalyst **XXIV** generates an electron delocalization, which involves a C–C bond breaking, also leaving a positive charge on the oxygen atom. The second catalyst **XXIII**, by forming a hydrogen bond, assists the leaving group on the substrate. In this regard, the dipolarophile cycloaddition may occur.

Pihko developed a three-component reaction yielding a β,γ-functionalized aldehyde exploiting the synergy of a chiral secondary amine catalyst and a multiple-hydrogen-bond catalyst. This synthesis is a versatile strategy to avoid self-condensation of aldehydes and the whole study exemplifies the importance of evaluating the reactivity of each reaction partner during the synthesis design [53]. During the first reaction step, an aliphatic aldehyde **10**, activated as iminium-ion by the amine catalyst, undergoes condensation with nitromethane **60**, activated by the multiple H-bond donor catalyst **XXV**, providing a nitro-olefin **61**. The nitro-olefin can then be activated by the H-bond catalyst and reacts with the nucleophilic aldehyde activated via enamine by the secondary amine catalyst, to yield the β,γ-functionalised aldehyde **62** (Scheme 24).



Scheme 24. Synergistic catalysis mediated by a chiral secondary amine catalyst and a multiple hydrogen bond thiourea-based catalyst.

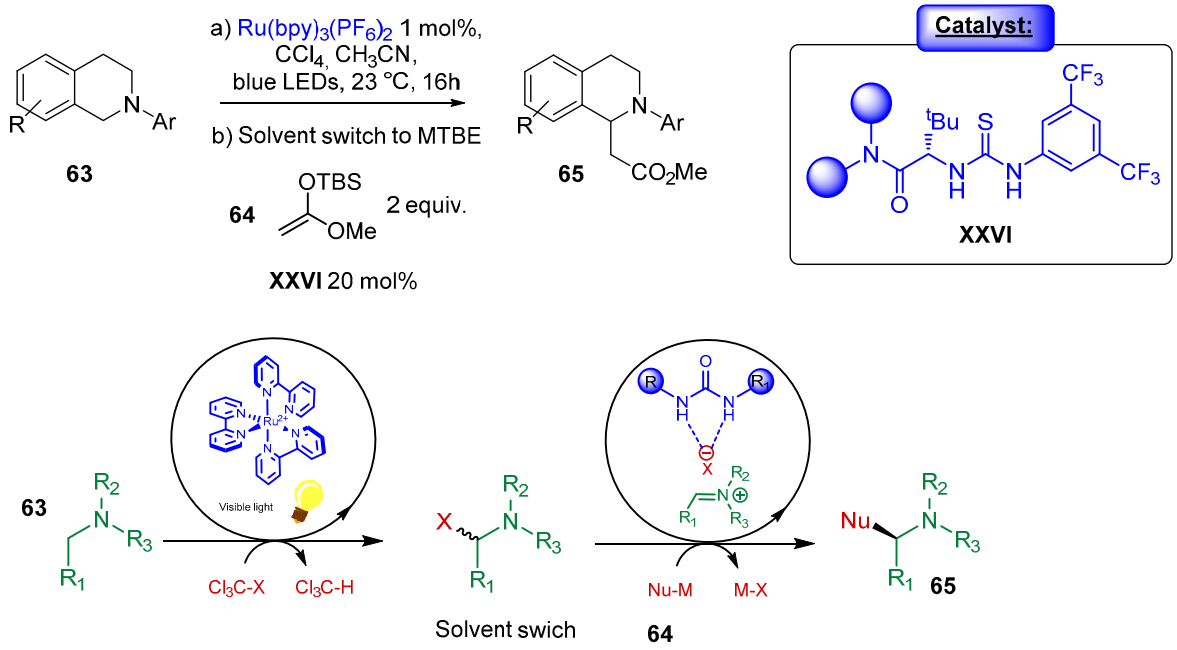
3.1.3. Combination with Photocatalyst

Photoredox catalysis has emerged recently as a powerful tool for the generation of synthetically useful high-energy organic intermediates such as free radicals [54] and radical anions and cations [55,56]. Successful efforts to induce enantioselective catalytic control in such photocatalysed processes have relied, thus far, on covalent organocatalysis, and only recently on chiral anion-binding catalysts [57].

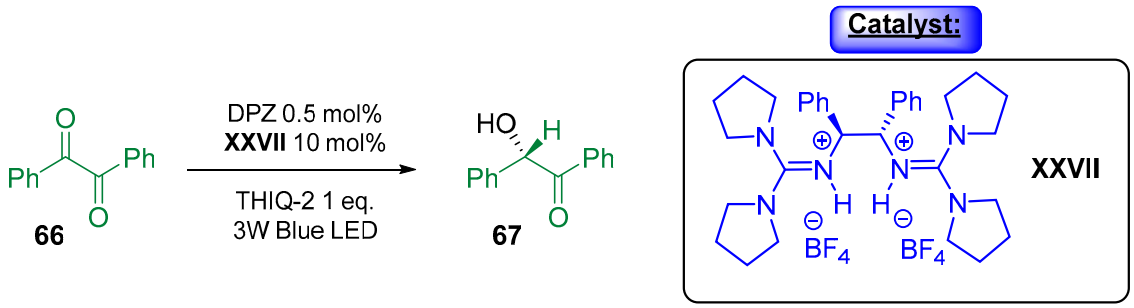
Stephenson et al. describe the successful development of a dual catalyst strategy with a chiral H-bond donor catalyst **XXVI** in combination with $[Ru(bpy)_3]^{2+}$, for the enantioselective oxidative alkylation of tetrahydroisoquinolines **63** with silyl ketene acetals **64** via enantioselective oxidative Mannich reactions, to yield tetrahydroisoquinoline-derived β-amino esters **65** [58].

An accurate screening of the reaction conditions, suitable for both transformations, allowed the combination of two very different methodologies for obtaining products with high enantiomeric excess in good yields (Scheme 25).

The asymmetric reduction of 1,2-diketones provides enantiomerically enriched α-hydroxy ketones, which are very useful as organic frameworks building blocks and as important intermediates in the pharmaceutical industry [59]. Based on the first work of Knowles et al. [60], where the presence of a hydrogen-bonding interaction between a Brønsted acid catalyst **XXVII** and the ketyl intermediate was verified, Jiang et al. reported the first example of asymmetric photoredox reduction of 1,2-diketones through a dual catalysis platform using a H-bonding organocatalyst [61]. In an attempt to work without using metals as catalysts, they tested a dicyanopyrazine-derived chromophore (DPZ) as the photoredox catalyst instead of ruthenium derivatives. The reaction worked with 0.5 mol% of DPZ, 1.0 equiv of THIQ-2 (2-naphthyl *N*-substituted tetrahydroisoquinolines), 10 mol% guanidinium salt **XXVII** and 10 mol% of NaBArF in PhCl solvent at 0 °C and under irradiation with a 3 W blue LED, giving chiral secondary alcohols **67**. All tested 1,2-diketones react completely, providing optically active α-hydroxy ketones in 60%–99% yields with 80%–98% *ee* (Scheme 26).



Scheme 25. Synergistic catalysis mediated by hydrogen bond thiourea-based catalyst and Ru-based photocatalyst.



Scheme 26. Hydrogen-bond based catalyst working in concert with photocatalysis [60].

The possibility to select a chiral Brønsted acid for proton shuttle permits two distinct reductions, through highly enantioselective protonation, and allows the synthesis of diverse and valuable chiral α-hydroxy ketones with high *ee* values.

4. *Cinchona* Alkaloids Organocatalysis

Cinchona alkaloids are a complex mixture of organic compounds derived from the bark of *Cinchona* and used for the treatment of malaria fever. This class of compounds presents five chiral centers and two different heterocycles, quinuclidine and a quinolinic one. (Figure 3)

Cinchona alkaloids are bifunctional catalysts (Figure 4); the nitrogen atom in the quinuclidinic ring works as a base activator site which can deprotonate and activate through a base-catalyzed mechanism a nucleophile having a pK_a = up to 10–11. After deprotonation, a tight ion pair is formed between the protonated catalyst and the deprotonated nucleophile, enabling a better enantiocontrol thanks to the steric hindrance. The 9-OH acts as a H-bond donor activating the electrophilic species [62] (Figure 4).

Cinchona alkaloids can be functionalized on the 9-OH with a range of functional groups, to obtain modular catalysts according to operative needs. In addition, their versatility derives from the fact that they can be easily functionalized as required in other positions, for example on the C5′ position, [63] or the nitrogen atom of the quinuclidinic portion can be quaternized to provide, for example, PTC catalysts that enable the activation of nucleophilic substrates with a pK_a values between 11 and 21 (Scheme 27).

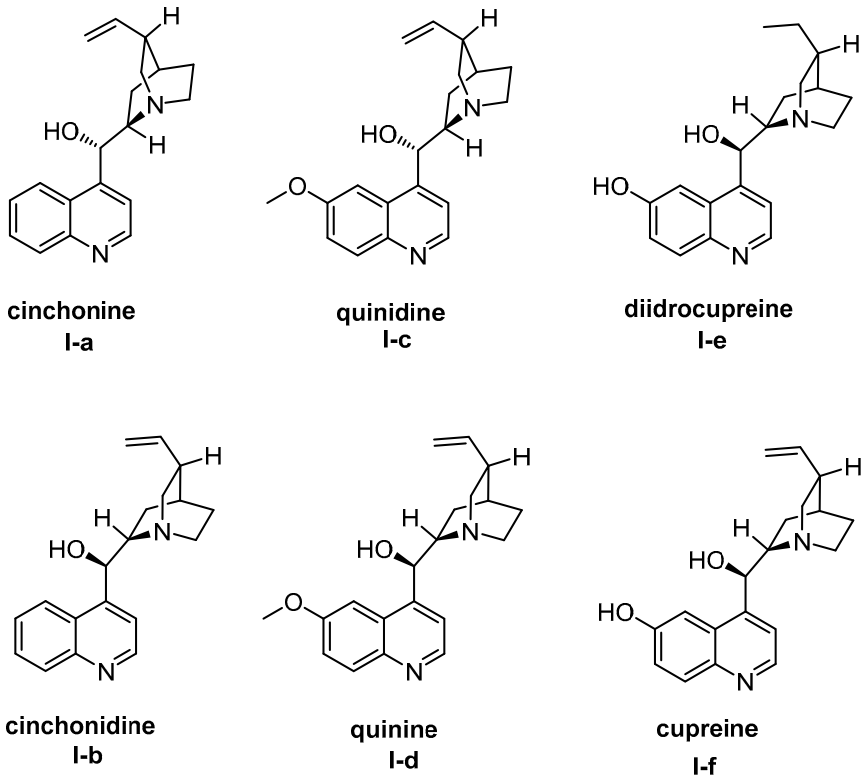


Figure 3. *Cinchona* alkaloids.

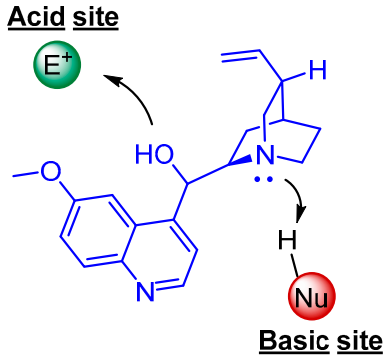
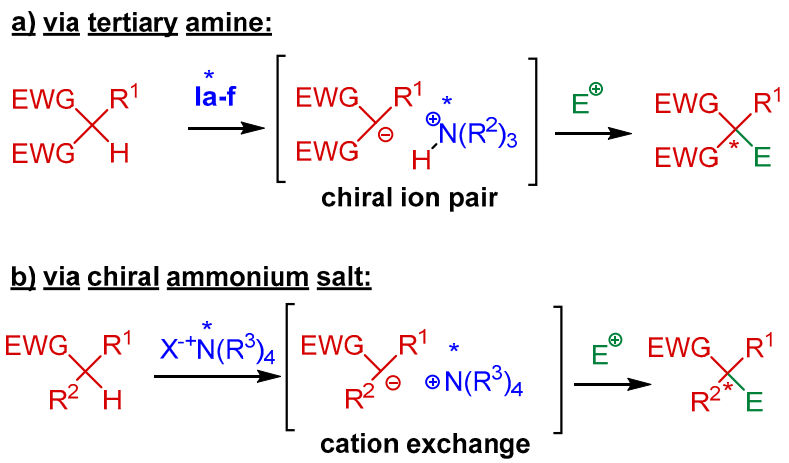
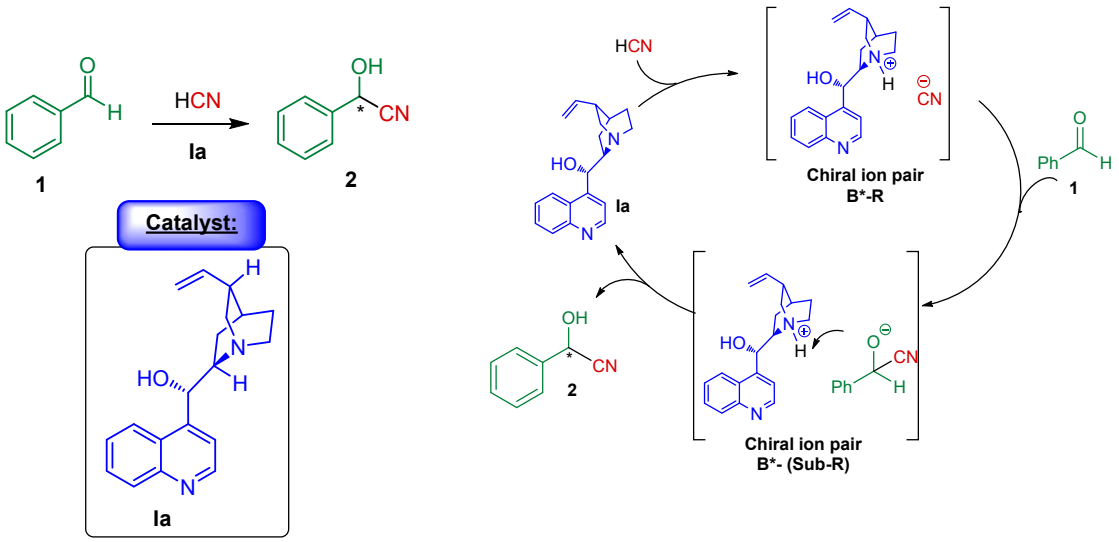


Figure 4. *Cinchona* alkaloids as bifunctional catalysts.



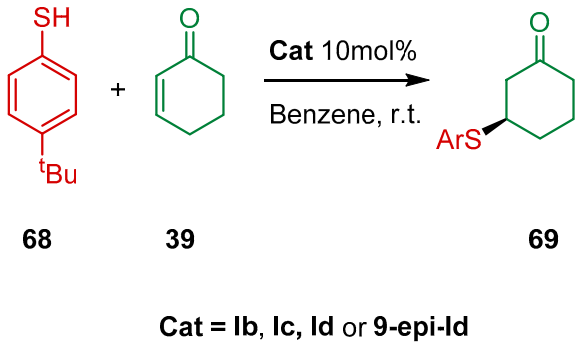
Scheme 27. Quinuclidinic proton quaternarization.

Cinchona alkaloids were first employed in organic chemistry in 1859 as a chiral auxiliary by Pasteur for the resolution of the racemate of tartaric acid [64]. The first asymmetric reaction employing *Cinchona* alkaloids was reported in 1912 by Bredig and Fiske [1]. Cinchonine **Ia** deprotonates HCN, forming a tight chiral ion pair that directs the attack of cyanide onto the benzaldehyde enantioselectively (Scheme 28).



Scheme 28. First asymmetric reaction employing cinchonine **Ia** as catalysts.

Furthermore, Wynberg and Hiemstra developed, in 1981, an enantioselective 1,4-addition of thiols to unsaturated ketones [65,66] (Scheme 29).



Scheme 29. Enantioselective 1,4-addition of thiols to unsaturated ketones.

Since then, *Cinchona* alkaloids have been used extensively in organocatalysis. The most common derivatives are functionalized at the C9 position, with either bulky groups, H-bonding moieties, or primary amines able to condense with carbonyls (Figure 5) [67,68].

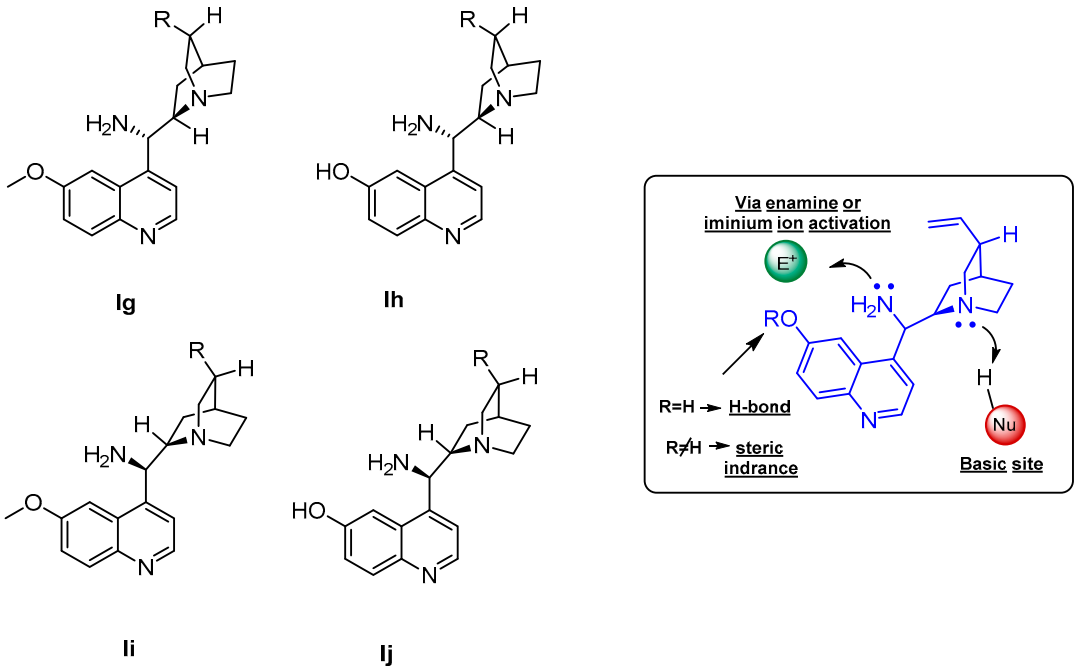
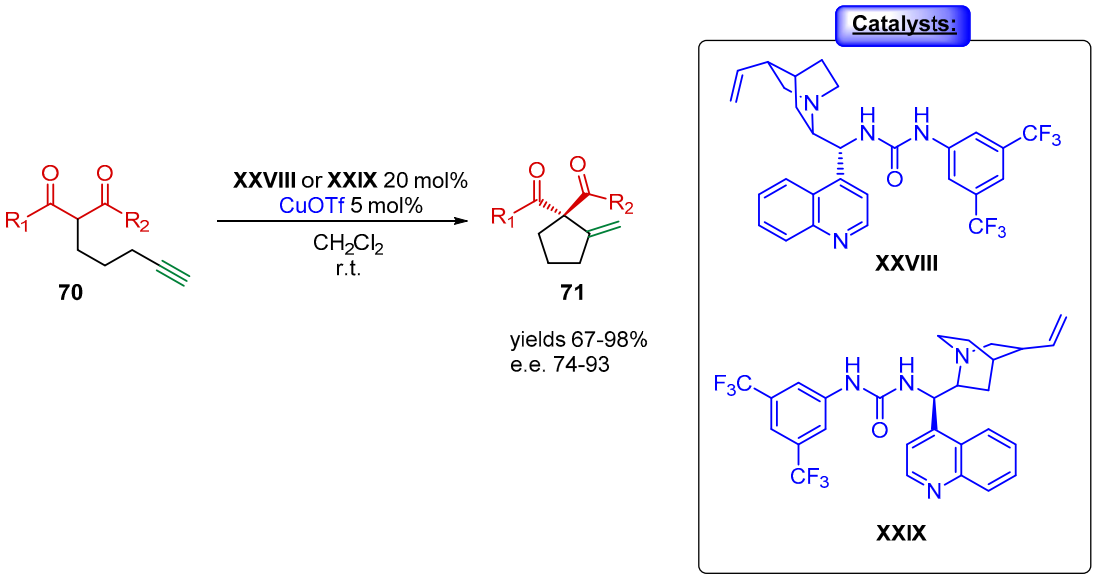


Figure 5. *Cinchona* alkaloids derivatives functionalized at the C9 position.

4.1. Synergistic Catalysis with Cinchona Alkaloids

4.1.1. Combination with Transition Metal-Based Catalysts

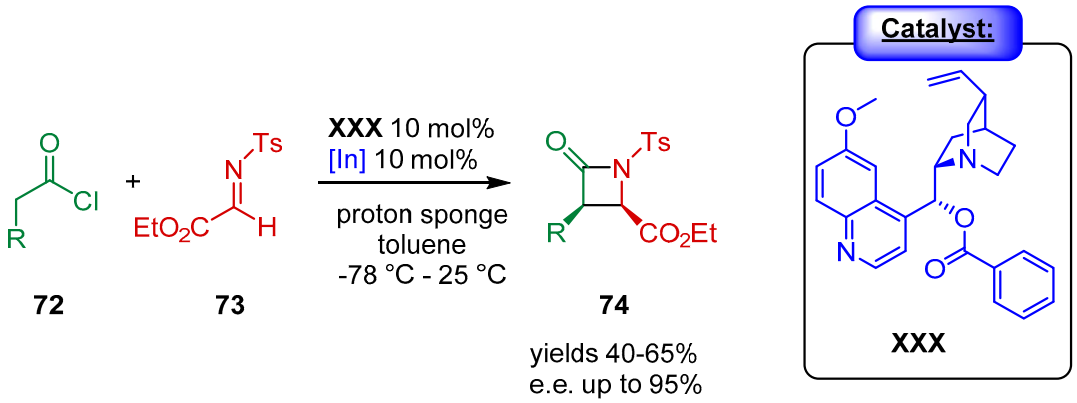
A remarkable example of *Cinchona*-derived bifunctional catalysts in combination with metal-catalysts exploits copper(I) triflate to perform an asymmetric Conia-ene reaction of β-ketoesters **70** [69] (Scheme 30).



Scheme 30. Synergistic catalysis mediated by *Cinchona*-derived bifunctional catalysts in combination with copper(I) triflate.

The organocatalyst acts as a Brønsted base and as a ligand for the copper enolate, imparting high levels of enantiocontrol. In a preliminary study, the thiourea-based organocatalysts derived from 9-amino-9-deoxyepicinchonidine were tested in synergy with transition-metal ions [70–72].

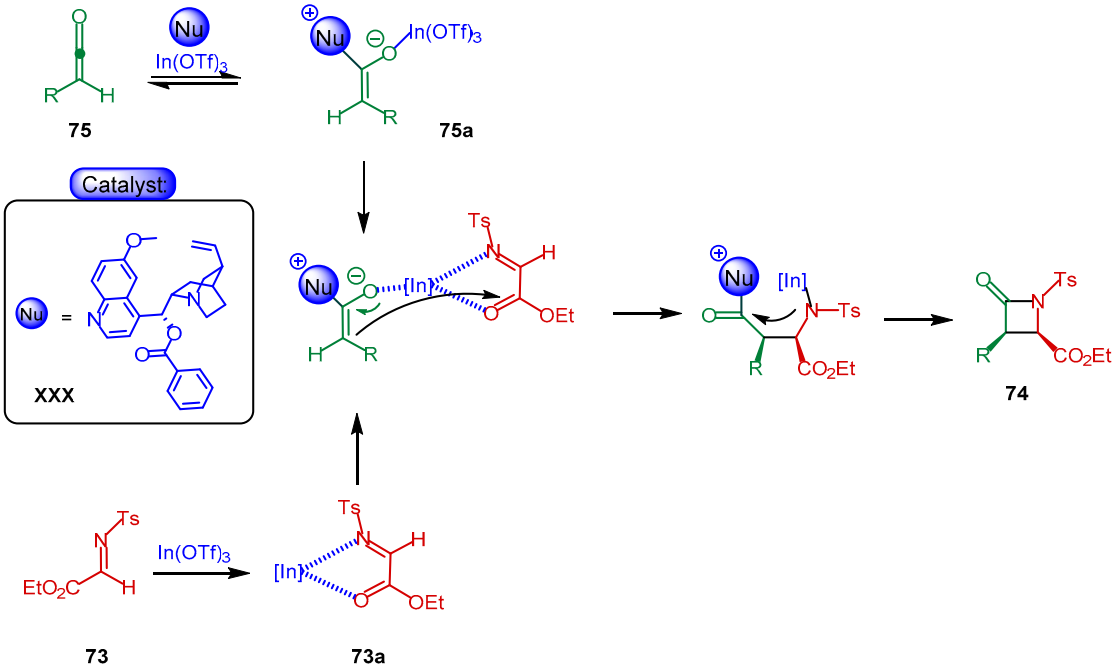
Lectka et al. reported a high-yielding diastero- and enantio-selective synthesis of β-lactam products exploiting a synergistic catalytic system, in which a chiral nucleophile organic molecule works in concert with an achiral Lewis acidic metal salt [73–78] (Scheme 31).



Scheme 31. β-lactams synthesis thanks to benzoylquinine and indium cooperative catalysis.

According to their mechanistic studies, the pure organocatalytic pathway with *Cinchona* catalyst activates acyl chlorides, providing ketene-derived zwitterionic enolates that subsequently add to electrophilic imines **73**, giving rise to β-lactam four-members rings **74** with excellent enantiomeric excess (over 95%), albeit in modest yields from 40% to 65%.

Aiming to improve the yields and suppressing the formation of undesired by-products, they proposed the addition of a Lewis acid catalyst to activate the imine. The combination of $In(OTf)_3$, as a Lewis acid, and benzoylquinine **XXX**, as a Brønsted base, proved to be the optimal one for the synthesis of β-lactams, using a powerful synergistic strategy maintaining high levels of diastero- and enantio-selectivity, while improving the yields (Scheme 32).

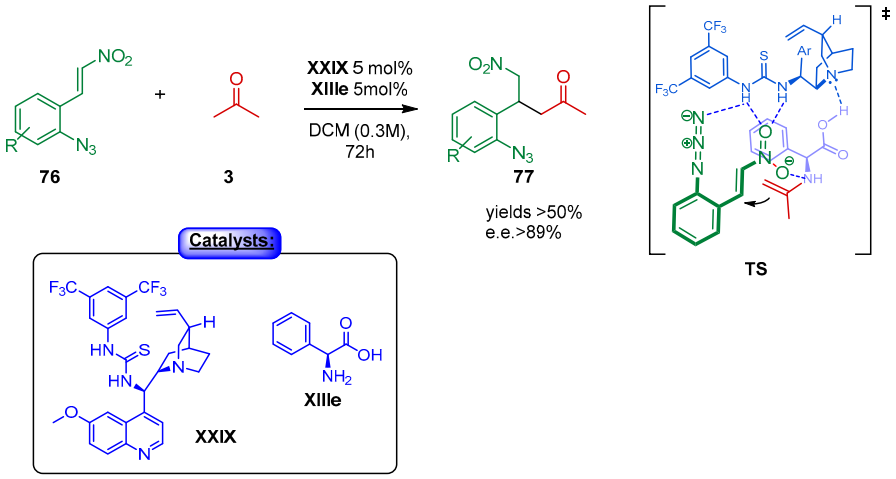


Scheme 32. Mechanistic insight in the β-lactams synthesis exploiting synergistic catalysis.

4.1.2. Combination with Other Organocatalysts

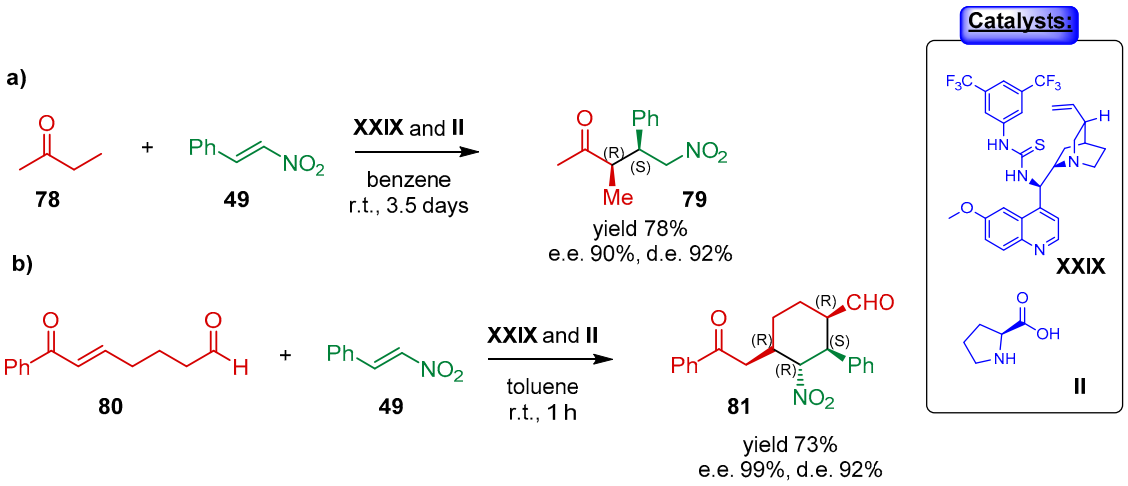
An asymmetric Michael reaction between 1-azido-2-(2-nitrovinyl)benzene **76** and acetone **3**, catalyzed by a combination of an amino acid with a *Cinchona*-derived bifunctional catalyst **XXIX**, was reported by Ramachary [79].

As depicted in Scheme 33, the proposed transition state features a network of hydrogen bonds between the thiourea catalyst **XXIX** with the azido- and nitro-group on the electrophile **76**. Acetone **3**, on the other hand, is activated via enamine by the amino acid **XIIIe**, which is also part of the H-bond network with the quinuclidinic nitrogen. The proximal effect influenced the facial approach between both activated reagents.



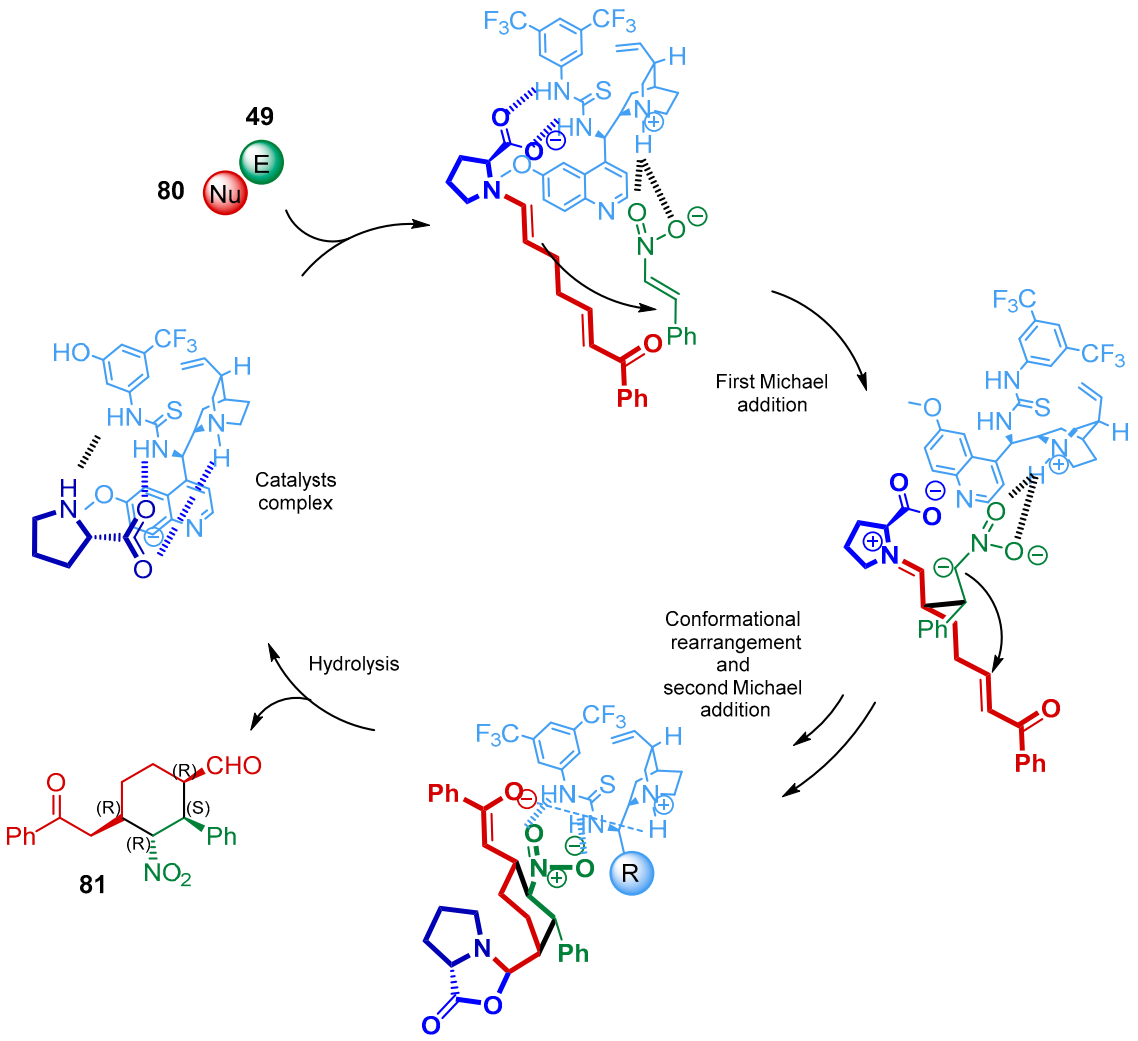
Scheme 33. Asymmetric Michael reaction catalyzed by a combination of amino acid **XIIIe** with the *Cinchona*-derived bifunctional catalyst **XXIX.**

Enantioselective additions of aldehydes to nitro-olefins, catalyzed by a combination of proline and a quinidine-thiourea catalyst and developed by Zhao (Scheme 34) [80,81], were recently further investigated by Sunoj [82]. The two original research papers are a Michael addition of butanone **78** to nitrostyrene **49** and a tandem Michael-Michael cascade reaction. The proline condenses with the aldehyde **80** to form a nucleophilic enamine, while the *Cinchona* alkaloid activates the nitro-olefin via a H-bond network. In the tandem cascade reaction, the condensation of proline occurs more rapidly with the aldehyde than with the ketone, given the difference in reactivity (Scheme 34).



Scheme 34. Michael addition reaction between nitrostyrene and ketone **78** (**a**) or α,β-unsaturated dicarbonylic compound **80** (**b**).

The *Cinchona* catalyst **XXIX** establishes a tight H-bond network, with a well-defined geometry; the thiourea coordinates with the proline carboxylate group while the protonated quinuclidinic ring with the nitrostyrene. Following the first Michael addition, and several rearrangements of hydrogen bonds, the intermediate is oriented in such a way that the electronic deficiency on the carbon adjacent to the nitro-group is near the electrophilic position, so that a new Michael addition can occur to yield the cyclic product **81** after hydrolysis (Scheme 35).



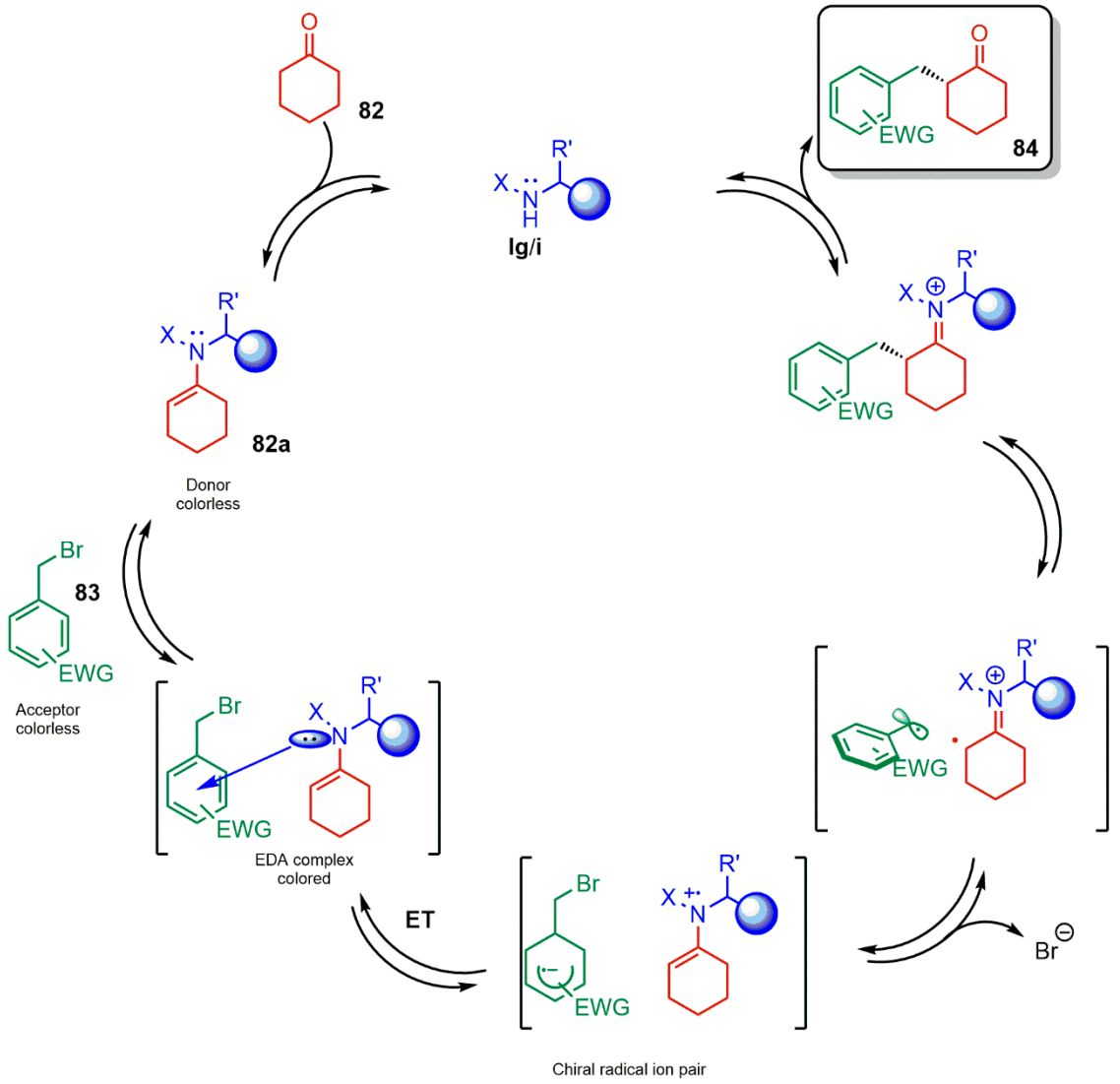
Scheme 35. Mechanistic insights in the enantioselective addition of aldehydes to nitro-olefins.

4.1.3. Combination with Photocatalysts

Asymmetric alkylation of cyclic ketones with alkyl bromides, to obtain of α-alkylated products, has been studied by Melchiorre et al., with high levels of regio-, diastereo-, and enantioselectivity [83]. Cyclohexanone derivatives **82** were reacted with substituted benzyl bromide **83** using quinine-derived primary amines **Ig** or **Ii** as catalyst.

The process is confirmed as photochemical since it requires light in order to proceed. The experiments were conducted using a household full-spectrum 23 W compact fluorescent lightbulb (CFL). The electron-rich enamine **82a**, formed from the condensation of ketones **82** (or aldehydes) with a chiral secondary amine **Ig/I** (*Cinchona*-based catalyst), and the electron-accepting alkyl bromide **83** form the coloured EDA complexes by means of molecular aggregations, which occur in the ground state of both compounds [84]. Light irradiation induced an electron transfer from the enamine to the bromide and a facile radical fragmentation of the latter. The ion pair radical puts the two reagents into

a geometrically restricted chiral space and into very close proximity. This condition facilitated a stereo controlled radical combination within the solvent cage to form a new carbon–carbon bond and the α-carbonyl stereogenic centre of the final product **84** (Scheme 36).



Scheme 36. Mechanistic insights in the intermolecular asymmetric alkylation of cyclic ketones with alkyl bromides, mediated by *Cinchona* alkaloids-based catalysis merged with photocatalysis.

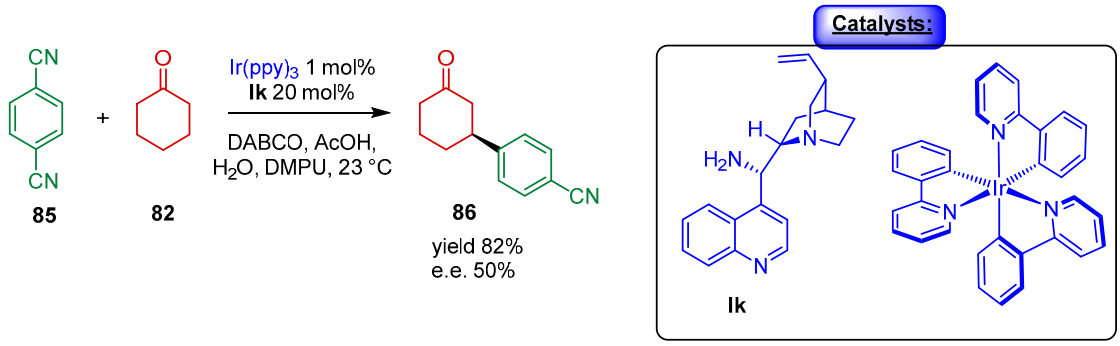
In this, the photocatalyst is not present but the photochemically reactive species is the adduct formed by molecular aggregation of the two reagents with the chiral catalyst.

Another example of synergistic photoredox activation for the direct β-arylation of ketones in combination with *Cinchona* alkaloids is presented by MacMillan [85]. The authors showed the use of [Ir(ppy)$_3$] as a photocatalyst to promote a single-electron transfer with 1,4-dicyanobenzene **85** to afford the corresponding arene radical anion. Iridium complexes have a strong absorption in the visible range, allowing them to accept a photon from a variety of light sources to populate the *Ir(ppy)$_3$ metal-to-ligand charge transfer excited state, which has strong reductant properties.

In combination with this photoredox step, cyclohexanone **82** should condense with the amine group of a *Cinchona*-derived organocatalyst **Ik** to form the electron-rich enamine.

At this juncture the photoredox and organocatalytic cycles would merge, as the electron-deficient Ir^{IV}(ppy)$_3$ intermediate should readily accept an electron, via SET, from the electron-rich enamine to generate the corresponding radical cation and subsequent β-enamine radical formation,

eventually giving the β-arylation product **86** with promising levels of enantioselectivity (82% yield, 50% *ee*) (Scheme 37).



Scheme 37. Enantioselective β-arylation of cyclohexanone exploiting synergistic catalysis of *Cinchona* alkaloids and photocatalyst.

5. Phosphoric Acids Catalysis

A powerful class of chiral catalyst used in asymmetric synthesis is represented by BINOL-derived phosphoric acids used as Brønsted acids in electrophilic catalysis, imitating what nature does with enzymes. The phosphoric acid group can decrease the energy of the LUMO orbital of an electrophilic substrate through the formation of an intermolecular hydrogen bond. Thanks to the high steric hindered substituents, substrates are confined to an extremely limited space, enabling stereocontrol. Thanks to the Brønsted acid and Lewis base sites, and to the potential steric hindrance, BINOL derivatives can have multiple modes of activation (Figure 6).

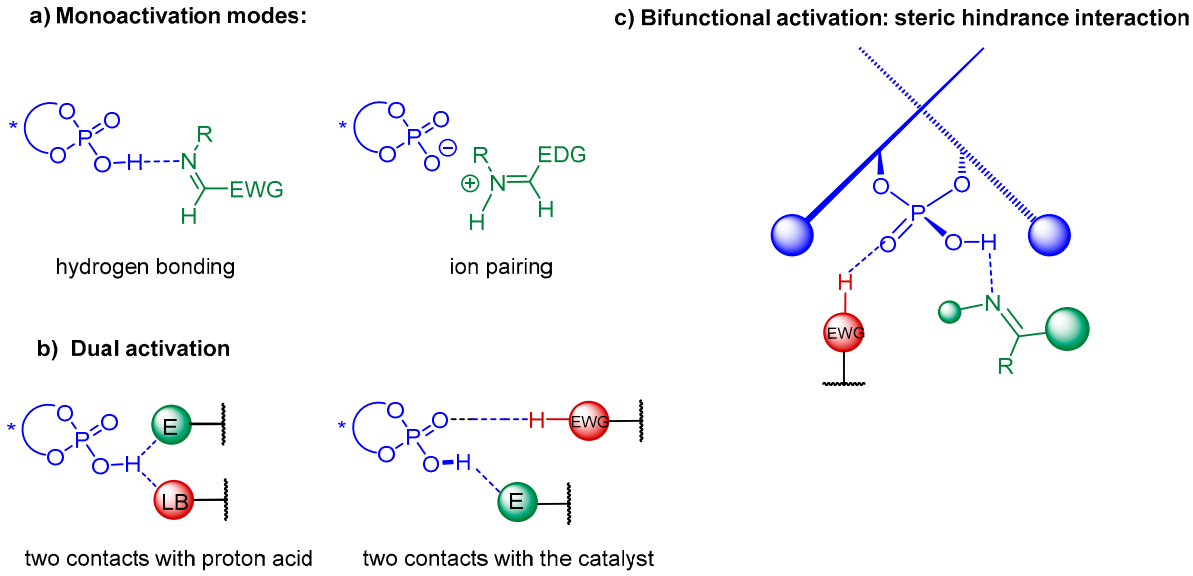
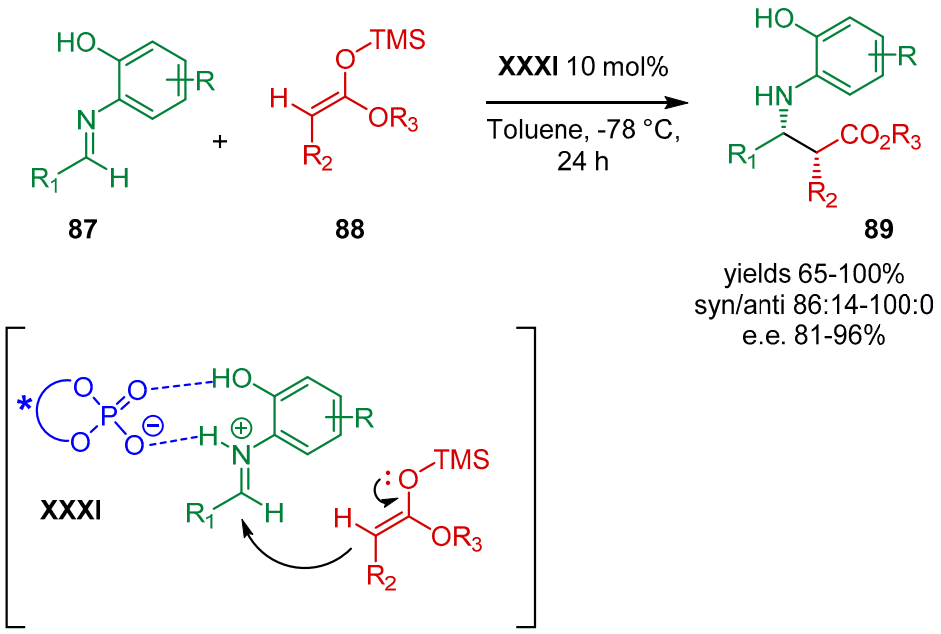


Figure 6. Activation modes of substrates by phosphoric acids.

In 1975, Cornforth used a similar catalyst derived from phosphinic acid for the hydration reaction of alkenes, paving the way for the study of chiral phosphoric catalyst [86,87]. Despite the early reports by Cornforth, it was only several decades later that chiral phosphoric acids were used as catalysts; in 2004, Akiyama [88] and Terada [89] simultaneously developed a Mannich reaction using two different BINOL-derived catalysts, a phosphoric acid and a phosphoramide, respectively [90] (Scheme 38).

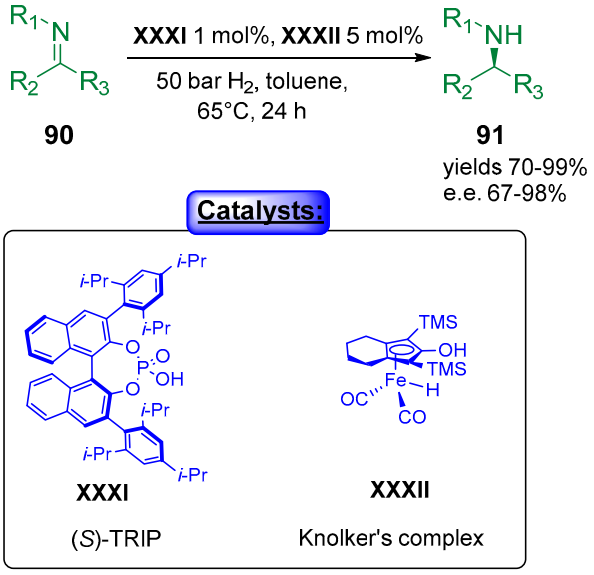


Scheme 38. Mannich reaction performed using BINOL-derived catalysts.

5.1. Synergistic Catalysis with Phosphoric Acids

5.1.1. Combination with Transition Metal-Based Catalysts

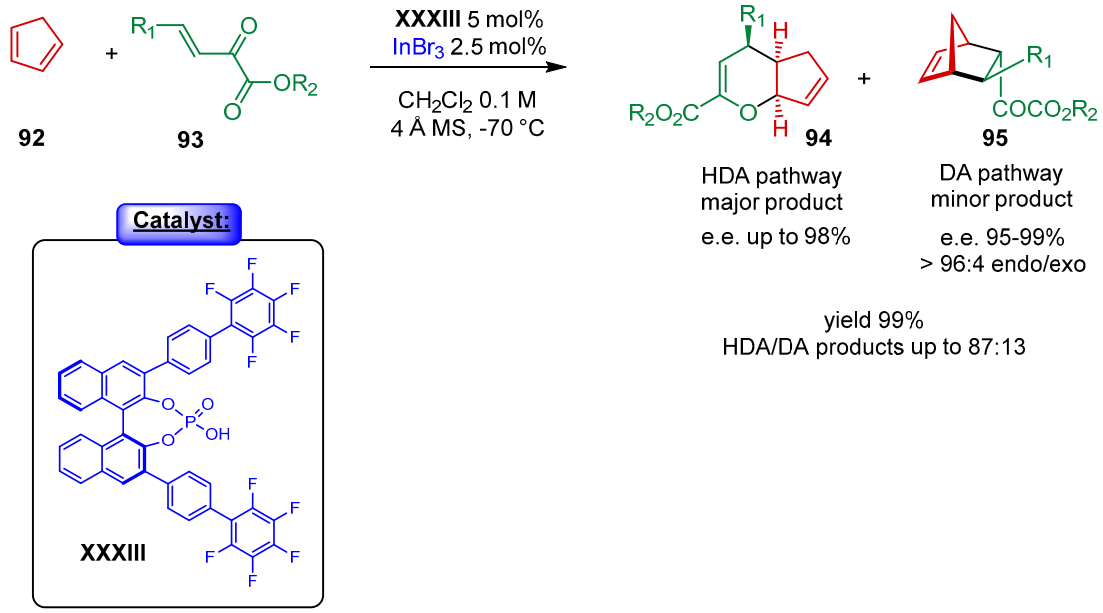
Beller et al. developed an asymmetric hydrogenation of imines, using an inexpensive metal catalyst and ligand in combination with TRIP [91], mimicking well-known biocatalysts, such as iron-based hydrogenases [92]. The iron complex catalyst **XXXII** and chiral acid **XXXI** work synergistically in a cooperative manner, enabling enantioselective hydrogenation (Scheme 39).



Scheme 39. Asymmetric hydrogenation of imines using iron-based catalyst **XXXII** synergistically with TRIP **XXXI.**

The Brønsted acid (*S*)-TRIP protonates the starting imine to form the corresponding chiral ion-pair. This intermediate accepts the hydride from Knölker complex, producing enantioenriched secondary amines.

Luo et al. developed the first regio- and enantio-selective hetero-Diels-Alder reaction of cyclopentadienes employing a chiral phosphoric acid/$InBr_3$ catalytic system (Scheme 40) [93].



Scheme 40. Enantioselective hetero-Diels–Alder reaction of cyclopentadienes exploiting a chiral phosphoric acid/$InBr_3$ catalytic system.

The chiral phosphoric acid **XXXIII** proved to be unable to catalyse the reaction; by combining it with a transition metal Lewis acid, the synergistic catalytic system is competent in activating the reaction partners towards the hetero-Diels-Alder pathway with good results in terms of both reactivity (99% yield) and enantioselectivity (*ee* 99%). It was shown that the free $InBr_3$ favours the DA pathway rather than HDA, demonstrating that the synergistic combinations of phosphoric acid and metal Lewis acid was needed for effective catalysis.

5.1.2. Combination with other Organocatalysts

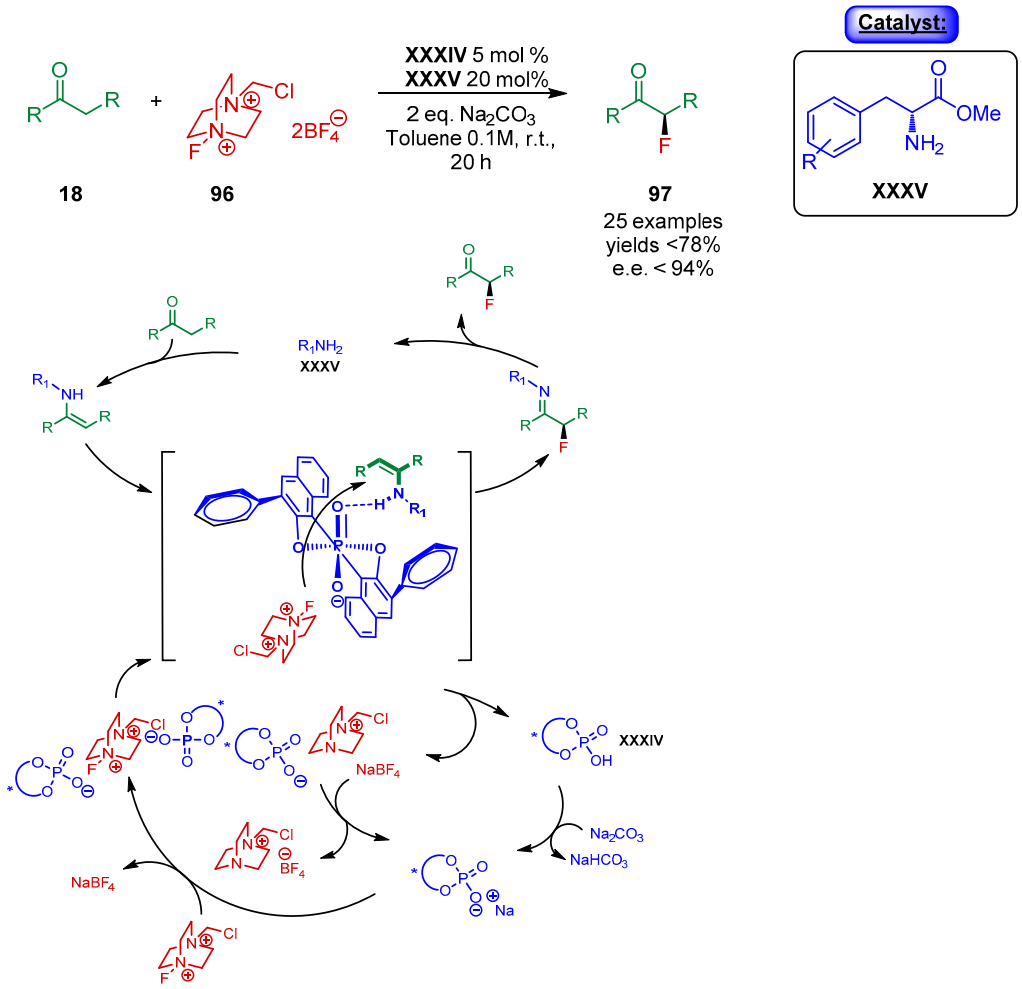
An elegant asymmetric fluorination of carbonyl compounds, carried out in a biphasic system, was reported by Toste [94].

The sodium salt of the chiral phosphoric acid **XXXIV** acts as a PTC, transporting Selectfluor **96** as a double chiral ionic pair, at the interphase; the carbonyl compound present in the organic phase is activated via enamine by the primary amine function of aminoacid derived **XXXV**. The two activated substrates can then react at the interphase, where an additional weak interaction is established between the amino group and one of the oxygens of **XXXIV** (Scheme 41).

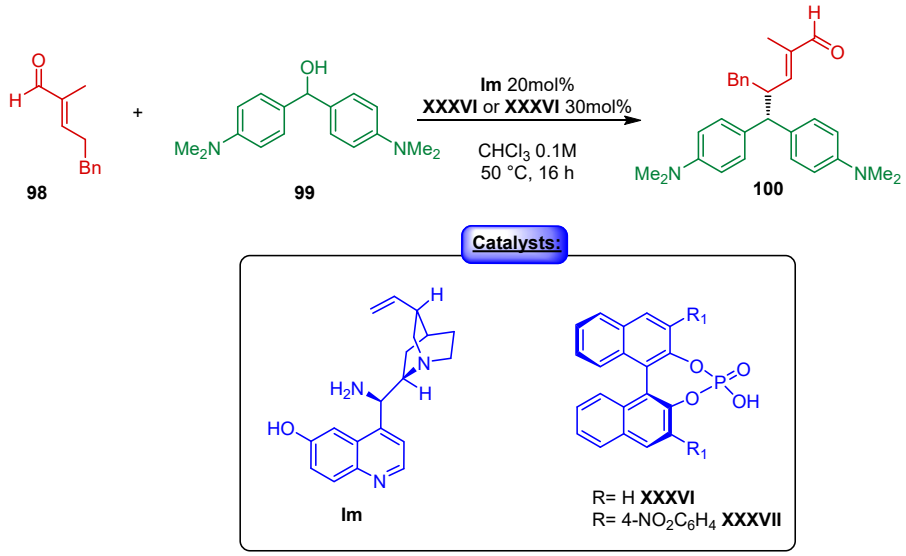
To avoid disrupting the well-balanced H-bond network, it was necessary to protect the carboxylic moiety of the amino acid.

A direct asymmetric γ-alkylation of α-substituted linear α,β-unsaturated aldehydes **98** with secondary alcohols **99** was reported by Melchiorre (Scheme 42) [95].

The reaction is formally a S_N1 reaction that proceeds through nucleophile attack of the activated **98** compound to the carbocation generated from **99**. The activate-nucleophile species is the dienamine, generated from the condensation between 6′-hydroxy-9-amino-9-deoxy-epiquinidine and the α,β-unsaturated aldehyde. The phosphoric acid protonates the pro-electrophile generating a stabilized carbocation that can be intercepted by the dienamine. A complex mechanistic model is proposed where the *Cinchona* catalyst coordinates with two phosphoric acids, on one hand via the 6′-OH and on the other hand with the protonated quinuclidinic nitrogen. The mechanistic model is supported by the fact that a 6′-OH group is needed for high enantiomeric excess.



Scheme 41. Asymmetric fluorination of α-branched cyclohexanones exploiting the combination of chiral anion phase-transfer and enamine catalysis.



Scheme 42. Asymmetric γ-alkylation of α-substituted linear α,β-unsaturated aldehydes with secondary alcohols.

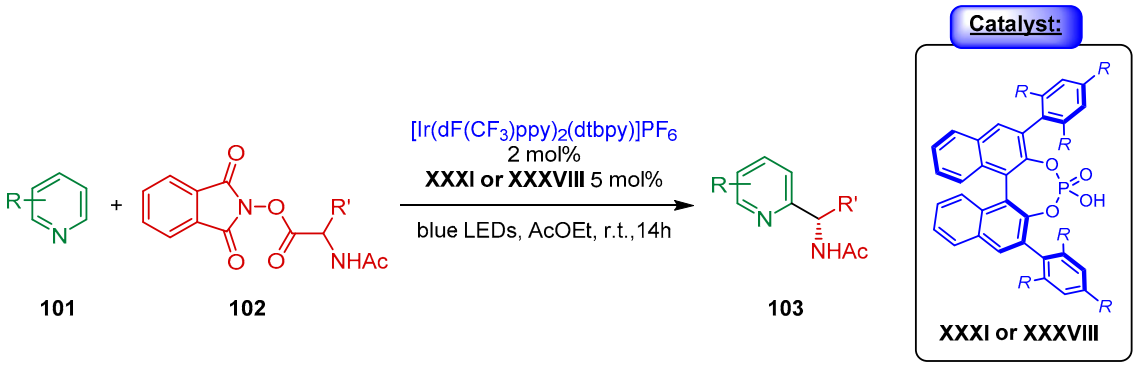
5.1.3. Combination with Photocatalysts

Stereocontrol in light-driven photochemical reactions still remains one of the most ambitious goals [96]. To achieve this goal, many dual catalytic systems based on the contemporary use of transition-metal photosensitizers and stereocontrollers have been successfully introduced, leading to the establishment of highly stereoselective protocols for the assembly of chiral molecules [60,97].

Phipps et al. disclose the direct Minisci-type addition of α-amino alkyl radicals **102** to the 2-position of basic heteroarenes **101**, with excellent control of both enantioselectivity and regioselectivity, by virtue of a combination of asymmetric Brønsted acid catalysis and photoredox catalysis [98].

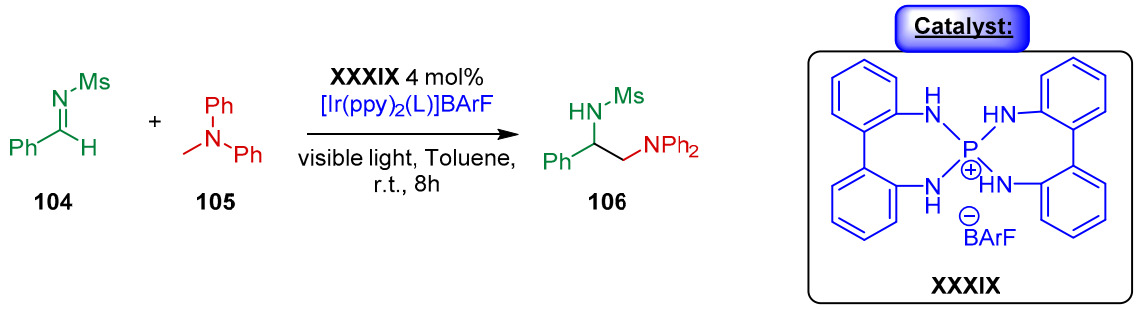
Protonation significantly reduces the energy of the LUMO of the heteroarene, and the conjugate anion of the chiral acid remain associated with the pyridinium cation through electrostatic and hydrogen-bonding interactions. Therefore, the substrate is activated by a chiral environment.

They use RAEs (Redox Active Ester), as precursors to N-acyl α-amino alkyl radicals, which are prochiral and nucleophilic radicals that possess hydrogen bond donor functionality. Breaking into several fragments of the RAE is induced via electron transfer from an Ir(II) species generated after irradiation of photocatalyst $[Ir(dF(CF_3)ppy)_2(dtbpy)]PF_6$, with $dF(CF_3)ppy$ = 2-(2,4-difluorophenyl)-5-(trifluoromethyl)-pyridinyl and dtbpy = 4,4′-bis(tert-butyl)-bipyridine, with blue LEDs. The chiral Brønsted acid were (*R*)-TRIP **XXXI** or (*R*)-TCYP **XXXVIII** (Scheme 43).



Scheme 43. Minisci-type addition of α-amino alkyl radicals to the 2-position of basic heteroarenes performed thanks to a combination of Brønsted acid catalysis and photoredox catalysis.

Ooi et al., instead, developed a highly enantioselective α-coupling of *N*-arylaminomethanes **105** with *N*-sulfonyl aldimines **104** using a chiral tetraaminophosphonium ion **XXXIX** and Ir-centred photosensitizer with visible light irradiation [99]. They adopted *N*-sulfonyl imines as the precursors of anion radicals due to their affinity to the hydrogen-bond donor catalyst (Scheme 44).



Scheme 44. Enantioselective α-coupling of N-arylaminomethanes catalyzed by chiral tetraaminophosphonium ion and Ir-centred photosensitizer.

The iridium complex $[Ir(ppy)_2(bpy)]BArF$ (where Hppy = 2-phenylpyridine, bpy = 2,2′-bipyridine, HBArF = tetrakis [3,5-bis(trifluoromethyl)phenyl]-borate) was reversibly promoted to its excited state, under visible light irradiation. Subsequent reductive quenching of the *Ir(III) species with **105** lead to the formation of electronically neutral Ir(II) complex and the cation-radical of **105** in presence of the counterion $BArF^-$. The Ir(II) complex gives an electron to the imine **104** to form the corresponding anion-radical that should be spontaneously paired with the positively charged of the Ir(III) complex.

This complex would undergo prompt ion exchange with the catalysis, to afford the parent photosensitizer and the adduct between the imine anion-radical and the Brønsted acid **XXXIX**.

At the same time, an aminomethyl radical is formed via deprotonation of the Ph_2NMe cation-radical by a basic species. Then, a coupling reaction between the imine anion-radical and the aminomethyl radical take place by means of the chiral catalyst to enantioselectively produce the 1,2-diamine derivatives **106**.

6. Conclusions

Synergistic catalysis evolved from organocatalysis combined with other types of catalysis to access new activation modes. As discussed, there is a range of different combinations that have been discovered and many more that still need to be designed. We believe that this relatively new field of catalysis holds high potential and will greatly contribute to synthetic chemistry, both in academia and in industry.

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