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Carbon–Carbon Bond Formation *via* Enantioselective Multicatalysis

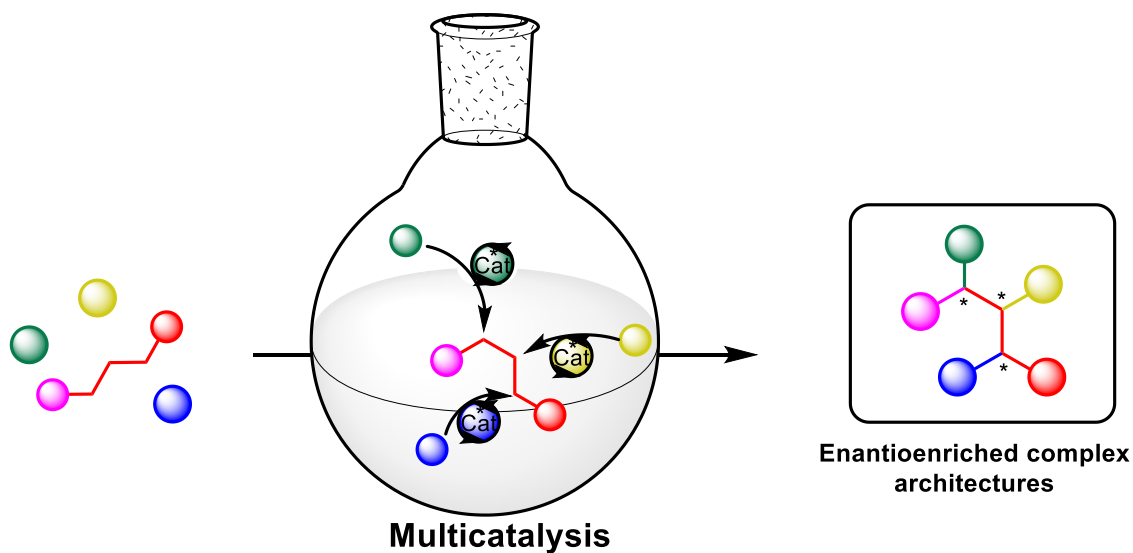
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Abstract:

Since the last two decades, the development of multicatalytic transformations has seen a tremendous growth. The combination of two or more catalysts enables to take the best from different worlds to activate molecules in an orthogonal and complementary manner. These multicatalytic combinations offer unique opportunities for the discovery of new synthetic pathways notably in the enantioselective creation of carbon–carbon bonds, which are illustrated in this chapter. Based on different multicatalytic types such as synergistic activation or relay cascades, combination between two metal complexes, two organocatalysts or finally metal- and organo-catalysis provides a broad array of transformations of great synthetic utility. In these methods, the control of the stereochemistry on the new products by one or more catalysts, usually provides excellent levels of stereocontrol, making of multicatalysis an approach of choice for the creation of complex chiral scaffolds.



Keywords

Multicatalysis; metal catalysis; organocatalysis; C–C bond formation; enantioselective; cascade

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Key points

- Multicatalysis is the combination between two distinct catalysts.
- By combining several catalysts, selective activation of the reaction components can be achieved with excellent efficiency.
- Several types of organocatalytic transformations exist, such as synergistic activation, relay cascades, merged-relay transformations and potential combination of these principles.
- Metal-metal, organocatalyst-organocatalyst and metal-organocatalyst combinations can be implemented.
- Thanks to multicatalysis, new synthetic pathways can be achieved directly creating complex enantioenriched scaffolds.

I. Introduction

a) Why multicatalysis?

As society keeps relying on increasingly complex technologies (drugs, materials, ...), it is crucial for synthetic chemists to keep moving forward by providing shorter and greener access to the molecular objects behind these technologies.¹ In order to prepare more rapidly and selectively molecules of high complexity while decreasing costs and waste generation, it is mandatory to take advantage at the best of catalytic transformations. Suitable catalysts can enable the required decrease in energy to assemble simple materials into the desired molecules. Moreover, given the predominance of chirality in all the living world, as well as in other fields such as materials, application of chiral catalysts can trigger the straightforward generation of the desired enantiomeric scaffold. For such purposes, decades of intense research have provided organic chemists with a broad array of organocatalysts or metal complexes of optimized efficiency. However, inherent to the use of a single catalyst activating the organic scaffolds in a single manner, limitations rapidly arise in terms of reactivity and resulting complexity or selectivity.

In order to activate the substrates with improved efficiency and in a better-defined manner, as in natural enzymes, it is desirable to activate them through multiple positions or functions. This could be achieved in a multicatalytic manner, trying to take the best from different catalysts combined in order to provide optimal reaction sequences and access to chiral molecules with the best possible enantiocontrol.²

While for years, the number of multicatalytic transformations developed had been rather limited, the last 15 years saw an exponential interest on the topic. It now represents an extraordinary rich field with over 2000 publications which refer to multicatalysis by the end of 2021. Given the diversity of multicatalytic reactions, in this chapter, we will try to highlight to the reader all the potential of multicatalytic approaches through selected examples, providing the reader with an overview of the field and the most successful and common approaches.

b) Multicatalytic strategies and challenges

Multicatalytic strategies are diverse and can encompass a myriad of approaches. At the fundamental level, multicatalysis is based on transformations where distinct active sites are located on different catalysts, in contrast with multifunctional catalysts where the active sites are located on the same catalyst (Figure 1.a). Similarly, strategies where the second species present in the system act exclusively as ligands for metal complexes cannot be considered as multicatalytic.

Multicatalysis can be divided into three major different pathways (Figure 1). In synergistic catalysis, two different catalysts (or more) activate separately the reactants to decrease the energy barrier required in a transition state for the creation of a new chemical bond (Figure 1.b). In relay catalysis, a first catalyst generates an intermediate, subsequently reacting thanks to a second catalyst to generate the final product (Figure 1.c). These relay multicatalyzed transformations can be in one-pot if one reactant and/or catalyst is added sequentially or in cascade if all chemical species of the system are present at the onset. The interest of such strategy is not only to avoid operations and waste notably arising from the isolation of the intermediates, but at the fundamental level, it provides unique opportunities when unstable or volatile intermediates are generated and directly derivatized in-situ. Distinct from this last approach, merged-relay catalysis combines two catalytic cycles in one big one with catalytic intermediates crossing from one sub-catalytic cycle to the other (Figure 1.d).³

These three approaches constitute the basis of multicatalysis and can be combined in complex sequences. As will be seen during this chapter, a reaction can encompass a complex merged-relay sequence involving for example an additional synergistic catalysis assembling different reactants.

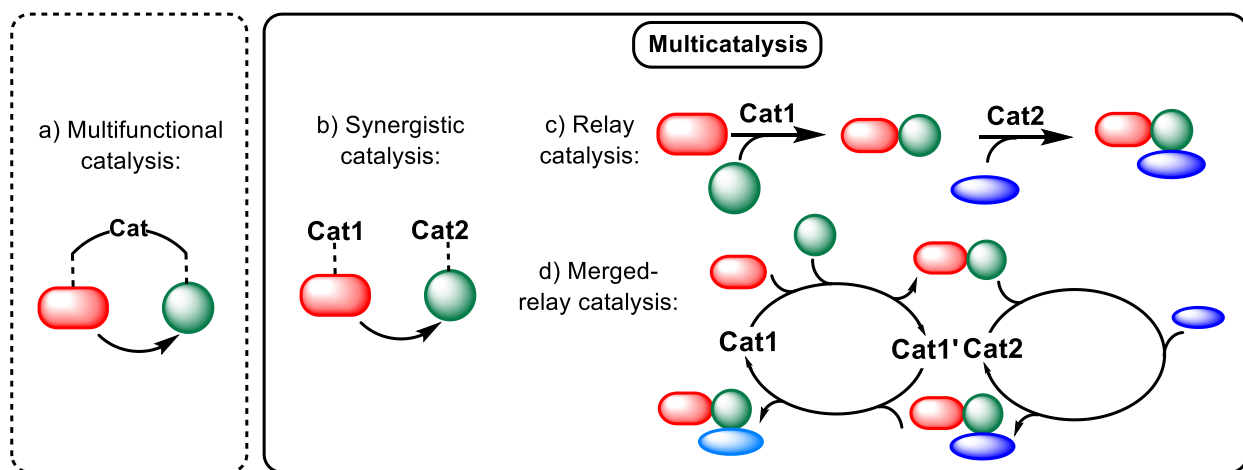


Figure 1: Principles multicatalytic strategies and comparison with multifunctional catalysis

All these approaches face multiple challenges in their development. At first, the compatibility between the different reactants/products and all the catalytic species involved must be optimal. For example, when a metal is mixed with an organocatalyst, potential interactions might be detrimental to the reactivity inhibiting both catalysts activity.

A broad range of advantages can be obtained thanks to the unique reactivities one can obtain from the use of multiple catalysts. Most importantly, it can unlock the rapid assembly of different reactants that would otherwise be totally unreactive, unravelling new synthetic connectivities. In parallel, it can provide

access to previously inconceivable unstable intermediates in-situ derivatizable to the desired products. As already mentioned, as a consequence, the new synthetic schemes can result in considerable synthetic economies, such as step-, atom- or redox-economies.¹ Finally, the catalysts can also control independently different stereogenic centers, facilitating the access at will to the desired stereoisomers notably through diastereodivergent catalysis.

The multicatalytic combinations can be as diverse as chemists imagination, taking advantage of all the reactivity encountered in the three pillars of catalysis, namely enzymatic catalysis,⁴ metal catalysis and organocatalysis. In this chapter, we will highlight progress achieved during the last two decades in the enantioselective construction of C-C bonds through 1) metal-metal multicatalysis; 2) organo-organocatalysis; 3) metal-organocatalysis. In all these combinations, the scientists have tried to take the best from two complementary worlds to potentially obtain optimal reaction profiles, pushing forwards the limit of organic synthesis.

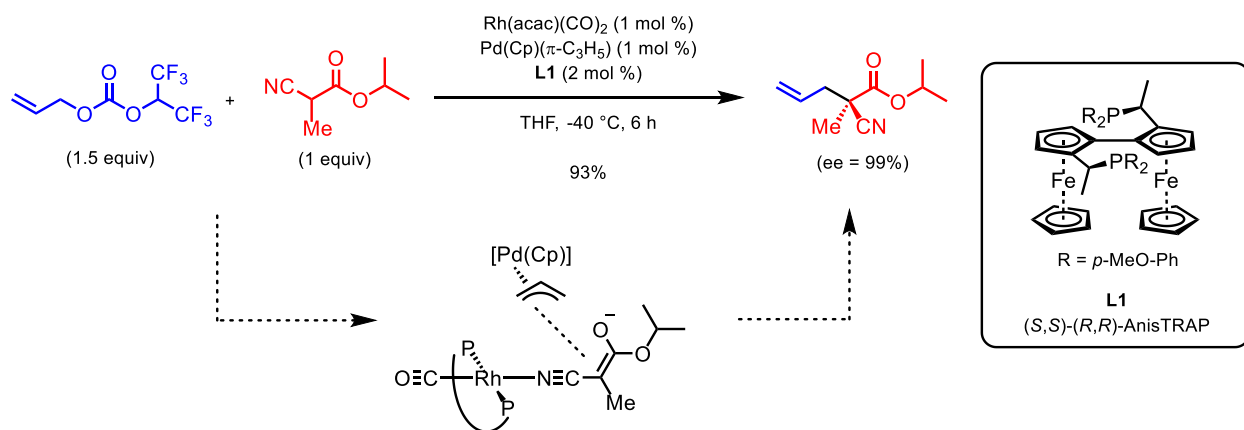
II. Metal/Metal catalysis

Enantioselective metal catalysis has dominated the world of organic synthesis notably until the end of the 20th century and the advent of organocatalysis.⁵ As a consequence, it is not surprising that the first examples of successful enantioselective multicatalytic transformations were based on the combination between different metal complexes.

a) Synergistic activation of pro-electrophiles through π -allyl formation

Enantioselective nucleophilic addition on metal π -allyl known as the Tsuji-Trost reaction is one of the best ways to create and control the stereochemistry of a new C–C bond at an allylic position. Given the potential to selectively activate in a distinct manner both electrophilic and nucleophilic partners, it is not surprising that metal π -allyl formation notably based on the use of palladium complexes has been widely applied in multicatalysis.

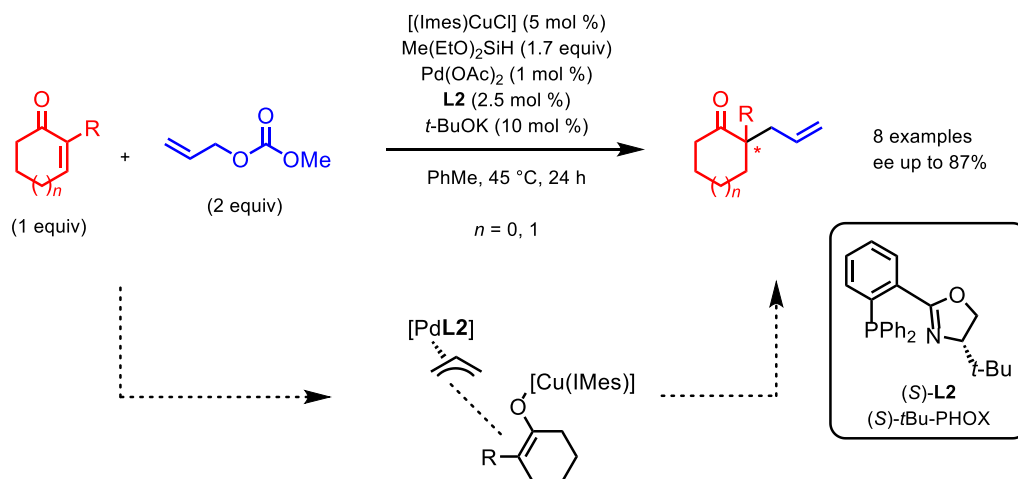
In this context, the first historical examples were developed in 1996 by the group of Sawamura and Ito based on the enantioselective allylation of α -cyano esters (Scheme 1).⁶ In order to develop an enantioselective version of this transformation, they successfully combined chiral rhodium and palladium complexes in a synergistic catalysis. The rhodium complex selectively activates the pro-nucleophile (cyano-ester) while the palladium complex selectively activates the pro-electrophile generating the reactive allyl partner. Thanks to this combination, the desired adduct can be obtained in excellent 99% *ee*. Of utmost importance, in control experiments, when removing one of the catalysts from the reaction mixture, a total loss in reactivity or selectivity is obtained resulting either in the lack of product formation in the absence of the palladium complex or 0% *ee* in the absence of the chiral rhodium complex. This clearly demonstrates the synergistic pathway and the implication of both catalysts in the enantioselective transition state of the transformation.



Scheme 1: First example of enantioselective synergistic metal-metal catalysis involving addition on a Pd- π -allyl complex

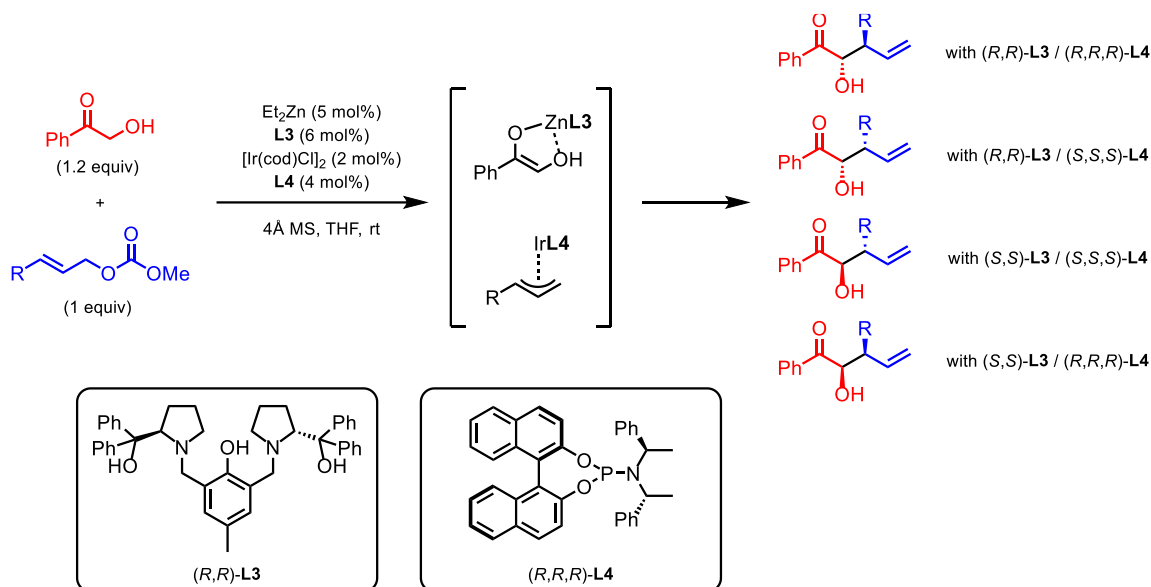
Taking advantage of such strategy, a broad array of transformations enabling the fast and enantioselective construction of diverse scaffolds of interest have subsequently been developed, combining different pronucleophiles activated by one metal complex such as copper or cobalt complexes, with π -allyl donors activated by another metal complex based either on Pd or Ir.⁷ For example, these transformations involved Schiff base, keto-esters or oxindoles as nucleophiles adding to various π -allyl acceptors.

Aside from these single synergistic events, the transformations can be complexified through incorporation in complex relay catalysis cascades. For example, a copper-catalyzed hydride 1,4-addition on enones could generate a reactive copper enolate, suitable for the enantioselective condensation on a chiral palladium π -allyl complex, the chiral phosphine ligand **L2** controlling the stereochemistry during the allylation (Scheme 2).⁸ This represents at the same time a cascade reaction with a hydride addition and a subsequent synergistic trapping of the generated enolate. It enables to go in a straightforward manner from enones to ketones possessing controlled quaternary stereocenters, without issues related to the regioselectivity of the enolate formation, a major advance in the field of site-selective enolate generation.



Scheme 2: Cascade 1,4-hydride addition/synergistic enolate allylation

One of the main advantages of synergistic catalysis is the potential to simultaneously control in a diastereodivergent manner two stereogenic centers. This means that both catalysts involved will govern independently each new created stereocenter. The concept, known for relay transformations, was first applied to synergistic catalysis in 2013 by the group of Carreira (metal/organocatalysis, *vide infra*). Taking advantage of this principle, in 2016, the group of Zhang discovered that the appropriate synergistic combination between chiral Iridium and zinc chiral complexes could promote the enantioselective allylation of hydroxy-ketones (Scheme 3).⁹ The zinc-**L3** prophenol ligand complex selectively activates the hydroxy-ketone controlling the stereochemistry arising from the enolate face addition. On the other side, the iridium-**L4** phosphoramidite complex controls the enantiofacial addition on the π -allyl. As a consequence, the stereocontrol on the two contiguous stereocenters is independently performed by each metal complex. If one changes the stereochemistry of one ligand, this inverts the stereocontrol on the associated stereocenter resulting in the possibility to access with equal efficiency (>6:1 dr and >98% ee) all 4 stereoisomers through the four chiral complex combinations.

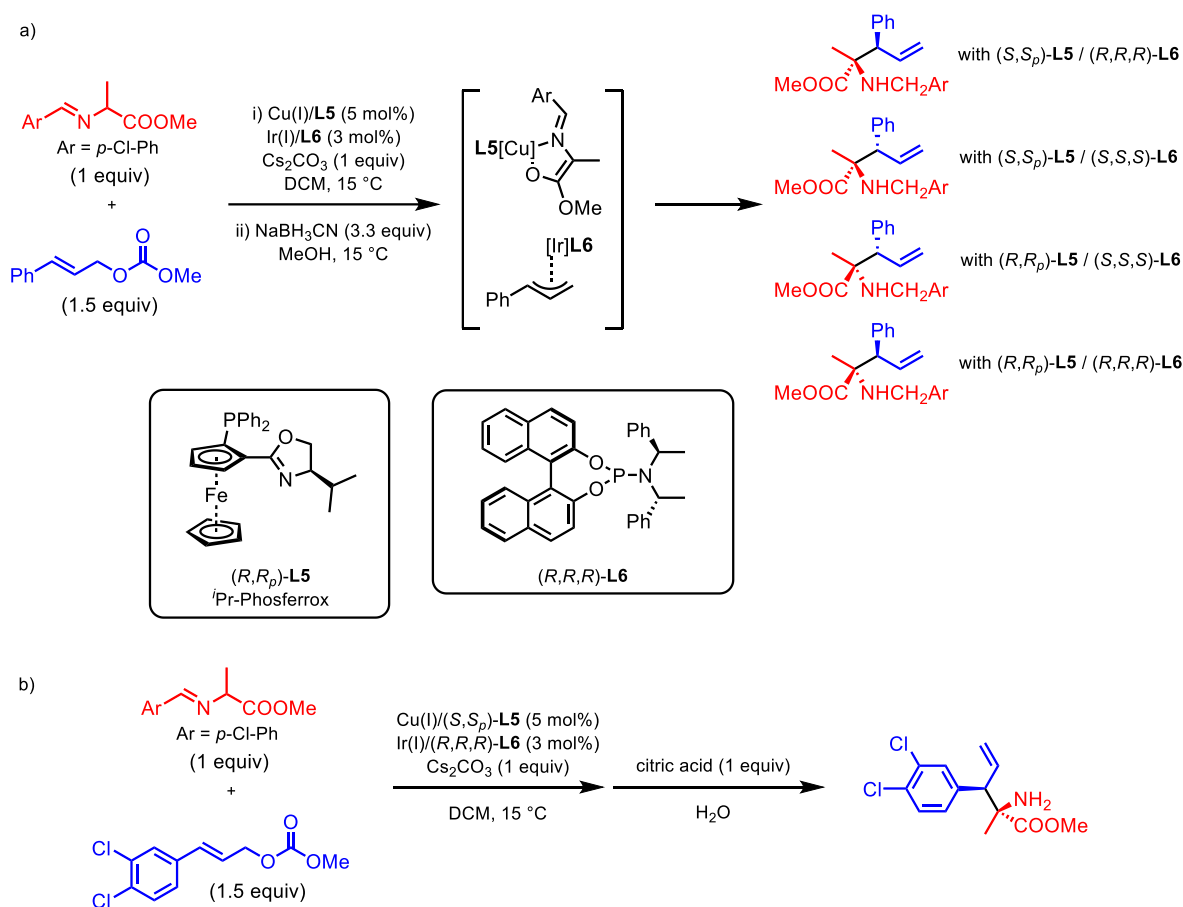


Scheme 3: Diastereodivergent Zn-Ir allylation of hydroxy-ketones

Following this strategy, a broad series of stereodivergent synergistic condensations were reported, enabling the elaboration of a wide array of useful scaffolds.¹⁰ This was illustrated in the synthesis of structurally different unnatural amino acids. These strategies not only rely on allyl carbonates as pro-nucleophiles but also dienes, allenes, and allyl-epoxides in order to generate the desired metal- π -allyl complexes. Thanks to the appropriate combination between the two chiral complexes, in all these cases, the two stereogenic centers were independently controlled in a modular fashion.

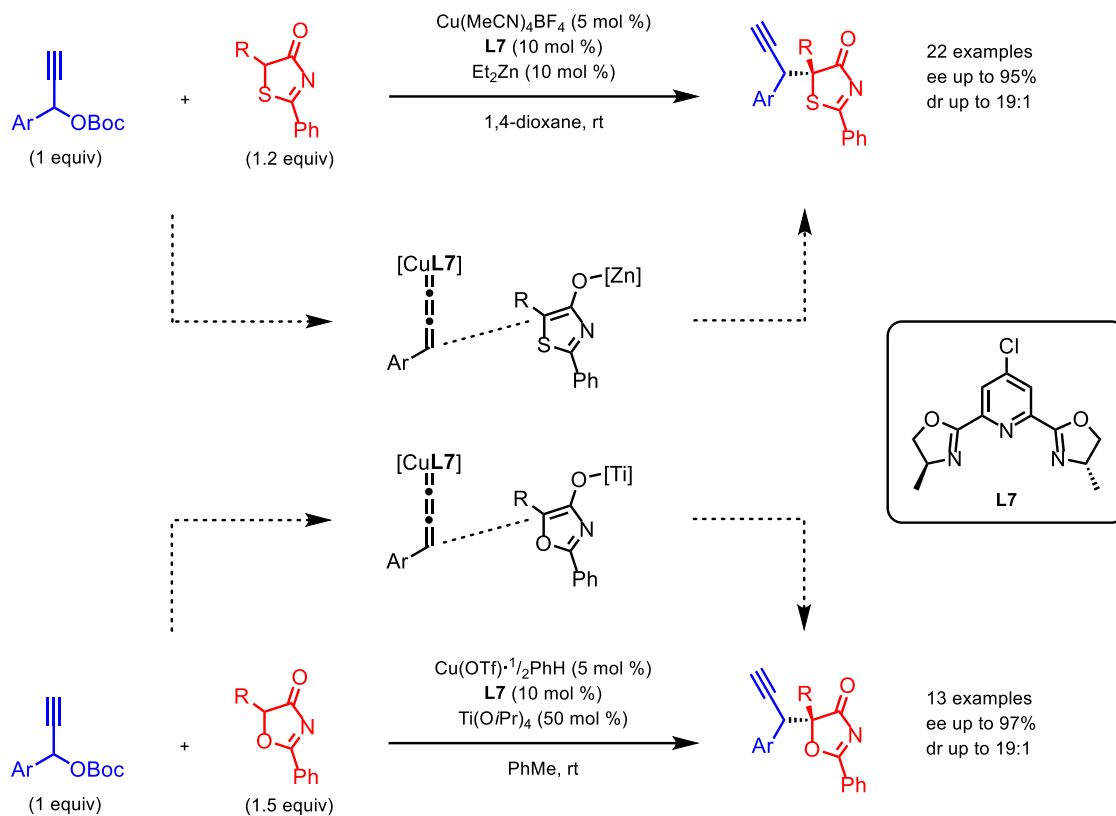
Illustrating this concept, the group of Wang reported the diastereodivergent allylation of aldimine esters (Scheme 4a).¹¹ In this synergistic multicatalysis, a chiral copper complex controls the stereochemistry on the ester pro-nucleophile while the iridium complex controls the enantiofacial addition on the allyl donor, enabling once again the modular access to all 4 stereoisomers with equal efficiency. As in other metal-metal multicatalyzed diastereodivergent processes, the challenge in such transformation is to find the

appropriate ligand for the selective complexation to only one of the two metals. Herein, the authors used a mixed phosphine-oxazolidine ferrocene ligand **L5** for the copper complex while a phosphoramidite ligand **L6** stabilized the iridium complex. Such a strategy is highly useful for the synthesis of otherwise inaccessible unnatural α,α -disubstituted α -amino acids, as illustrated in Scheme 4b.



Scheme 4: Diastereodivergent Cu-Ir condensation of allylation of aldimine esters

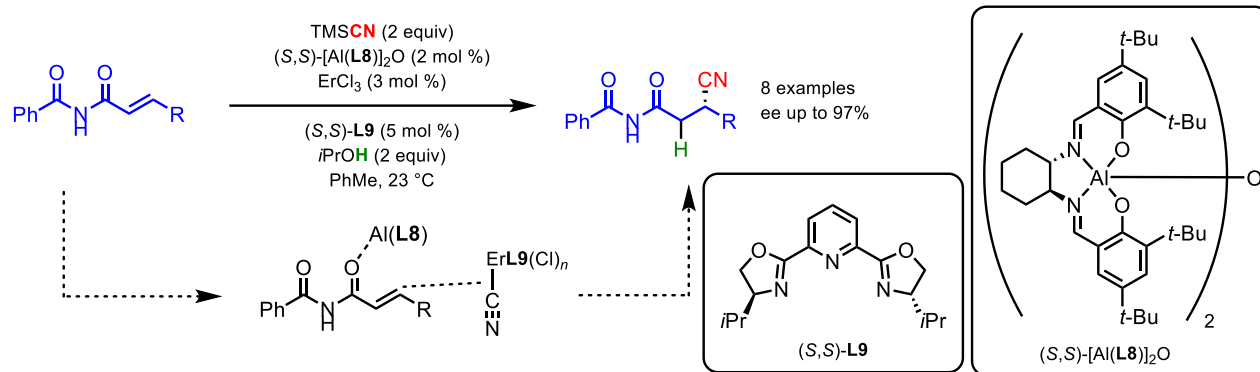
Alternatively to π -allyl formation, propargylation of pro-nucleophiles can be performed through the formation of reactive copper allenylidene intermediates (Scheme 5).¹² Starting from propargylic carbonates, the chiral copper complex enables the formation of this highly reactive intermediate. On the other side, 5*H*-thiazol-4-ones activated by a zinc Lewis acid or 5*H*-oxazol-4-ones activated by a titanium Lewis acid can perform the nucleophilic addition. The synergistic combination between chiral copper catalyst and the Lewis acid activating both partners once again enable to obtain optimal reactivity and selectivity in the formation of the two contiguous stereocenters. In this case, as a limitation, the stereochemistry is controlled by the same ligand coordinating both on the copper complex and the Lewis acid (Ti or Zn), precluding any possible stereodivergency of the process.



Scheme 5: Cu/Zn and Cu/Ti stereoselective propargylic substitution

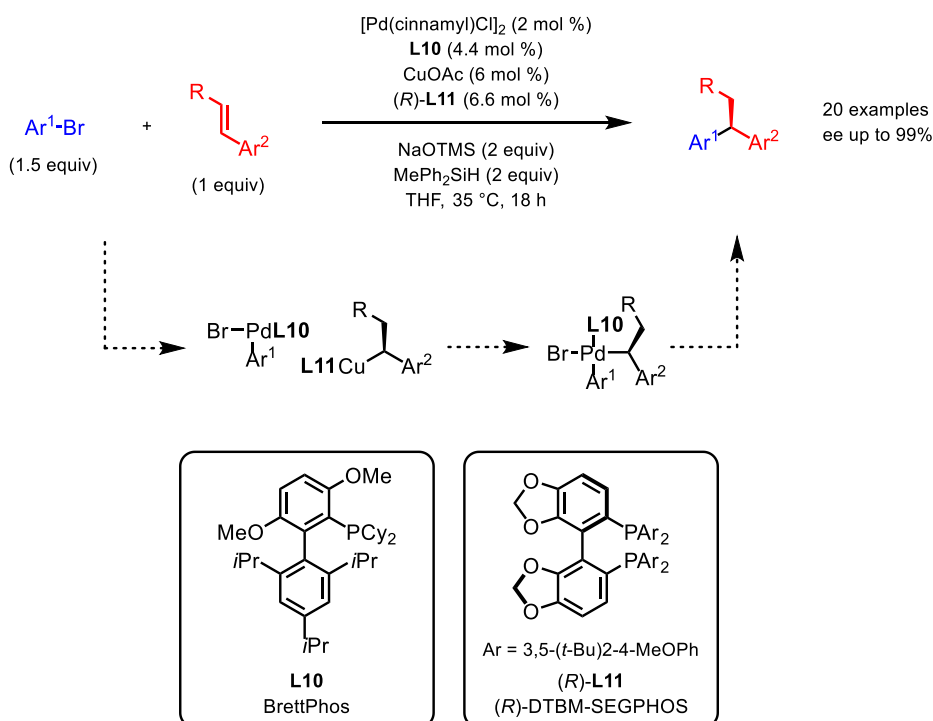
b) Other synergistic activation by metal/metal multicatalysis

Aside from the well-studied generation of electrophilic π -allyls, metal-metal multicatalysis has also been applied with success in other processes. Historically, in 2004 the group of Jacobsen discovered that combination between an aluminum Salen **L8** and an erbium Pybox **L9** complex, could promote the enantioselective conjugate cyanide addition to unsaturated imides (Scheme 6).¹³ This synergistic multicatalysis where the aluminum complex activates the electrophile and the erbium complex the nucleophile, enables to obtain optimal reactivity (>80% yield) and enantioselectivity (>90% ee). Once again, the dual role of both complex is crucial in this synergistic pathway and removing either complex totally shuts down the reactivity (<3% yield).



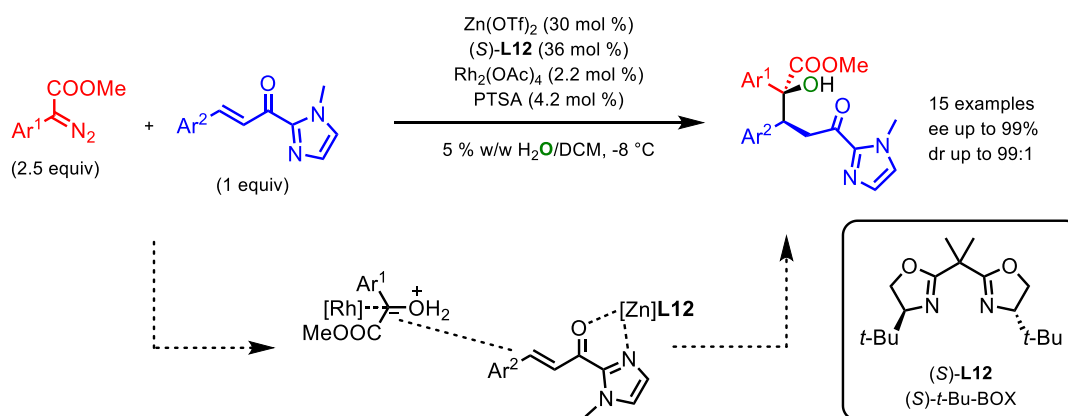
Scheme 6: Synergistic addition of cyanide to unsaturated imides

The group of Buchwald has been interested in the catalytic generation of reactive copper organometallic complexes through insertion of copper hydride on unsaturated compounds and their subsequent trapping on a broad range of electrophiles. Taking advantage of such approach, they have demonstrated that the copper organometallic complexes could react in a synergistic mechanism with a palladium organometallic complex (Scheme 7).¹⁴ In this transformation, a catalytic copper-hydride generated using 1 equivalent of a silyl-hydride donor can insert in an olefin to afford the desired chiral alkyl-copper organometallic complex with good stereocontrol. On the other side, after oxidative addition, stereospecific transmetalation with the achiral palladium-**L10** complex generates after reductive elimination the desired adduct. Overall, thanks to the application of the suitable chiral biphenyl ligand **L11** on the copper metal center, such a strategy enables the direct enantioselective hydroarylation of olefins usually with excellent enantiocontrol. It has then been extended to the aryloborylation of olefins through a bis-functionalization of the alkenes.¹⁵



Scheme 7: Synergistic Cu/Pd enantioselective hydroarylation of alkenes

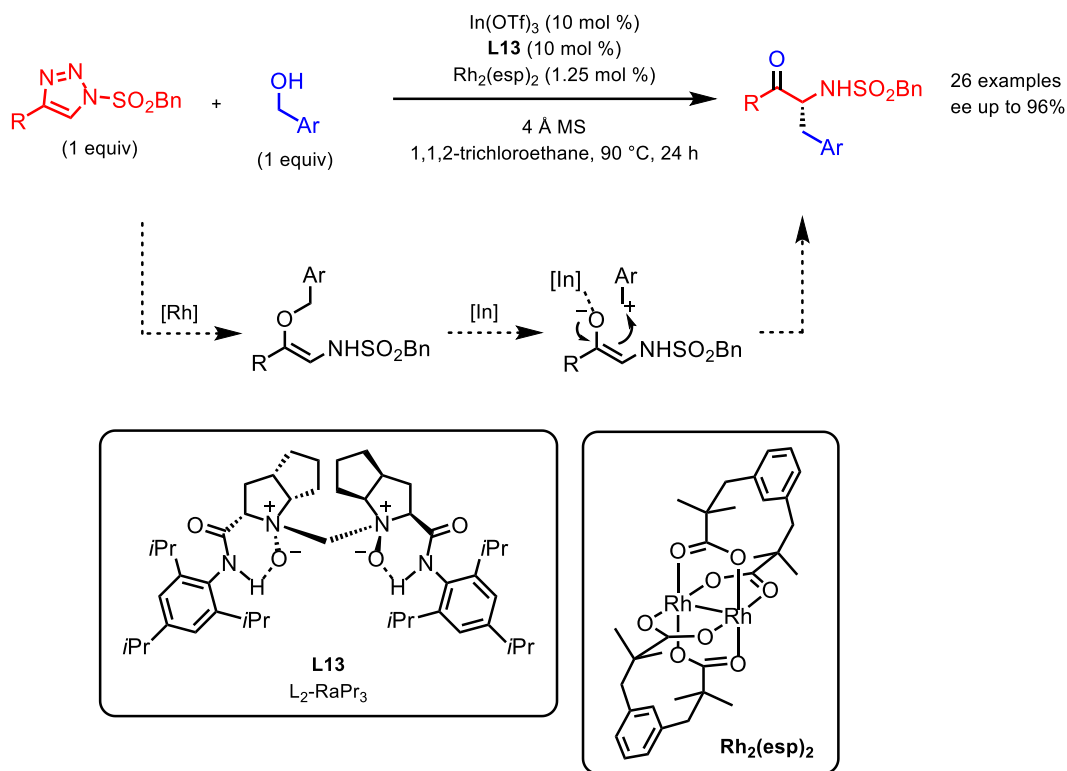
Rhodium complexes are well known to generate rapidly and selectively carbene complexes through insertion in diazo compounds. On the other side, zinc complexes can act as excellent Lewis acids for the activation of unsaturated compounds. By combining these two worlds, the group of Hu disclosed a multicomponent reaction involving a carbene formation, water addition generating a rhodium reactive anion subsequently adding to the activated Michael acceptor (Scheme 8).¹⁶ The stereochemistry on the final product is controlled during the Michael addition thanks to the use of the chiral zinc-**L12** complex, coordinated to the Michael acceptor to increase its electrophilicity. Of interest, it must be highlighted that the different metal catalysts involved in this transformation are perfectly tolerating the presence of large amount of water in this transformation.



Scheme 8: Synergistic Rh/Zn multicomponent transformation

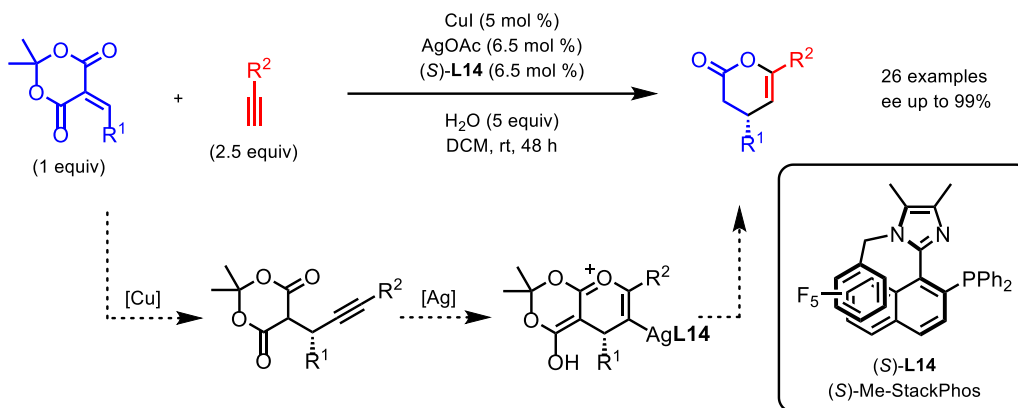
c) Relay metal-metal multicatalysis

Aside from synergistic systems, metal/metal catalysis can also advantageously be applied in relay transformations, where the product of a first catalytic cycle is transformed directly in cascade by a second catalyst. Following the strategy of rhodium carbene formation/electrophilic trapping, one can avoid starting from hard to prepare and unstable diazo compounds (Scheme 9).¹⁷ This can be achieved through the use of triazoles able to undergo a rhodium-catalyzed retro-cycloaddition directly furnishing the reactive enolate able to add to the electrophile. In this case, a benzylic alcohol furnishes the reactive cation upon indium catalysis, leading to the alkylation of the enolate (stabilized either by the rhodium or the indium complex), generating a chiral ketone in excellent enantiocontrol.



Scheme 9: Rh/In cascade condensation of triazoles and benzylic alcohols

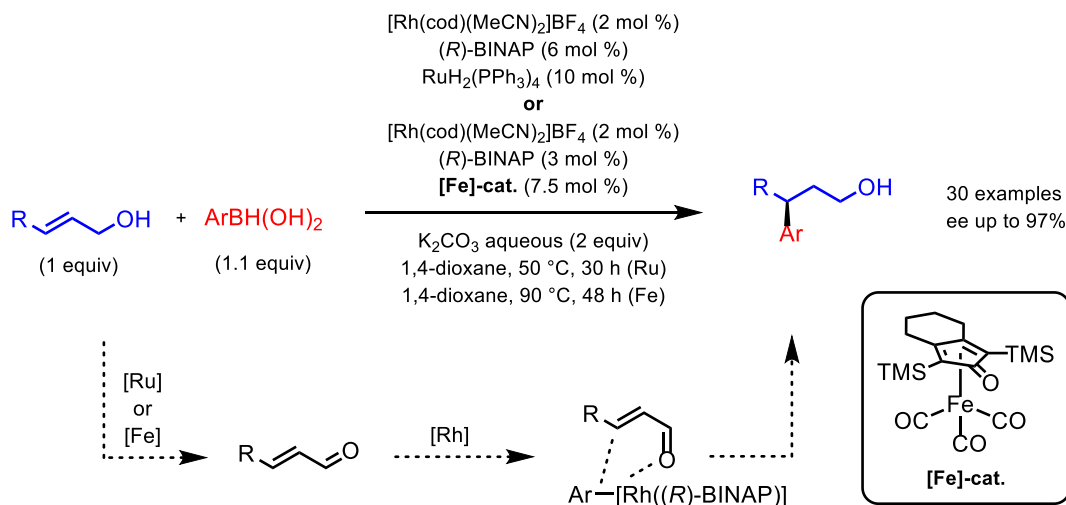
In 2019, the group of Aponick reported a typical example of relay transformation involving the formation of an intermediate through a first metal catalyzed cycle, directly derivatized in another product through another catalytic cycle involving another metal.¹⁸ This strategy involves the use of a compatible copper complex stabilized by a chiral phosphine ligand **L14** and a silver salt (Scheme 10). The copper complex catalyzes the alkynylation of the Meldrum acid via an enantioselective 1,4-addition. From the Michael adduct, the silver salt catalyzes the 6-endo-cyclization, liberating after decarboxylation and release of CO₂ and acetone, the desired lactone. Of interest, once again, the metal catalysts used are compatible with the 5 equivalents of water required for this process, demonstrating the tolerance of such metal catalytic systems, a water tolerance not limited only to organocatalytic transformations.



Scheme 10: Cu/Ag relay synthesis of δ -lactones

d) Merged-relay metal/metal multicatalysis

As mentioned in the introduction, two distinct catalytic pathways can be intertwined in a single one, through merged-relay catalysis. In 2013, our group reported the first example of multicatalytic enantioselective borrowing hydrogen based on the merging of two catalytic cycles, one based on a metal the other on an organocatalyst (Vide infra). In 2019, applying such approach to a metal-metal multicatalysis, the group of Dydio reported a combination between a borrowing hydrogen complex (Ru or Fe) able to reversibly activate alcohols to aldehydes and a chiral Rhodium complex enabling an enantioselective Michael addition on the in-situ generated unsaturated aldehyde (Scheme 11).¹⁹ Here, merging the two catalytic systems in one enables to directly go from allylic alcohols to chiral aliphatic alcohols by avoiding the stoichiometric steps associated with the oxidation to the reactive aldehyde and its reduction.

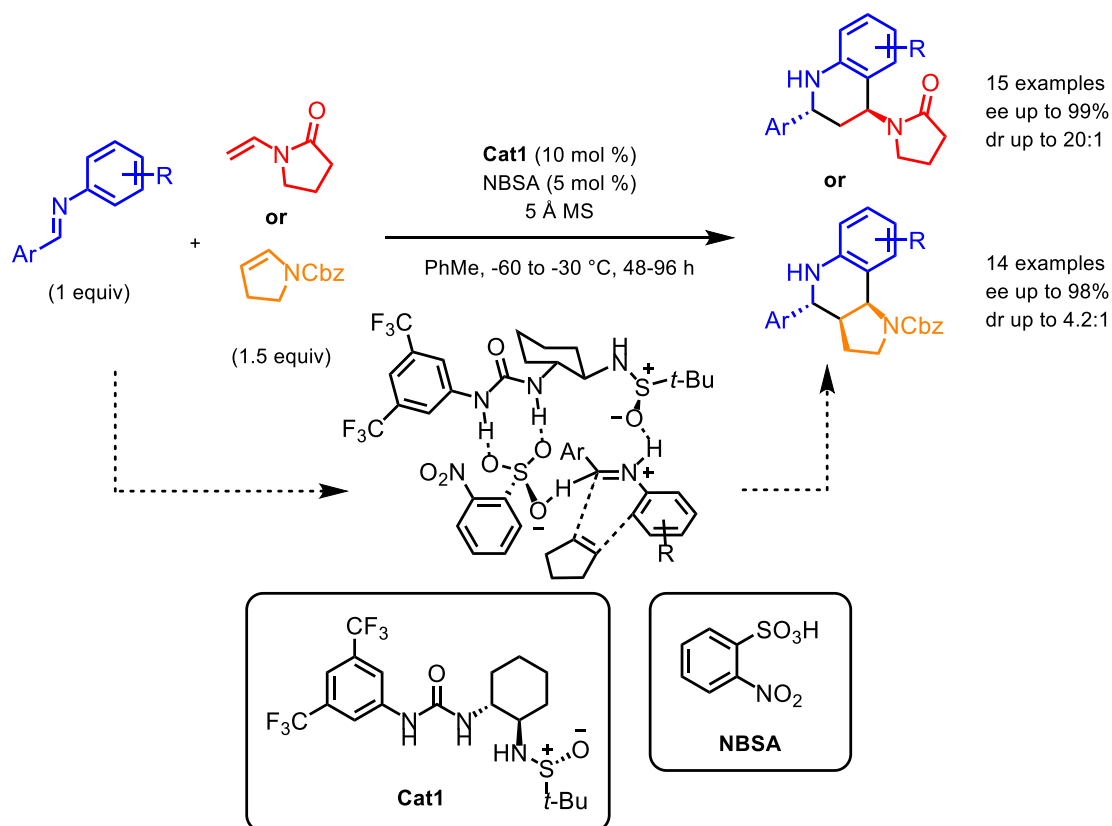


Scheme 11: Metal-Metal enantioselective borrowing hydrogen

III. Organo-/Organo-catalysis

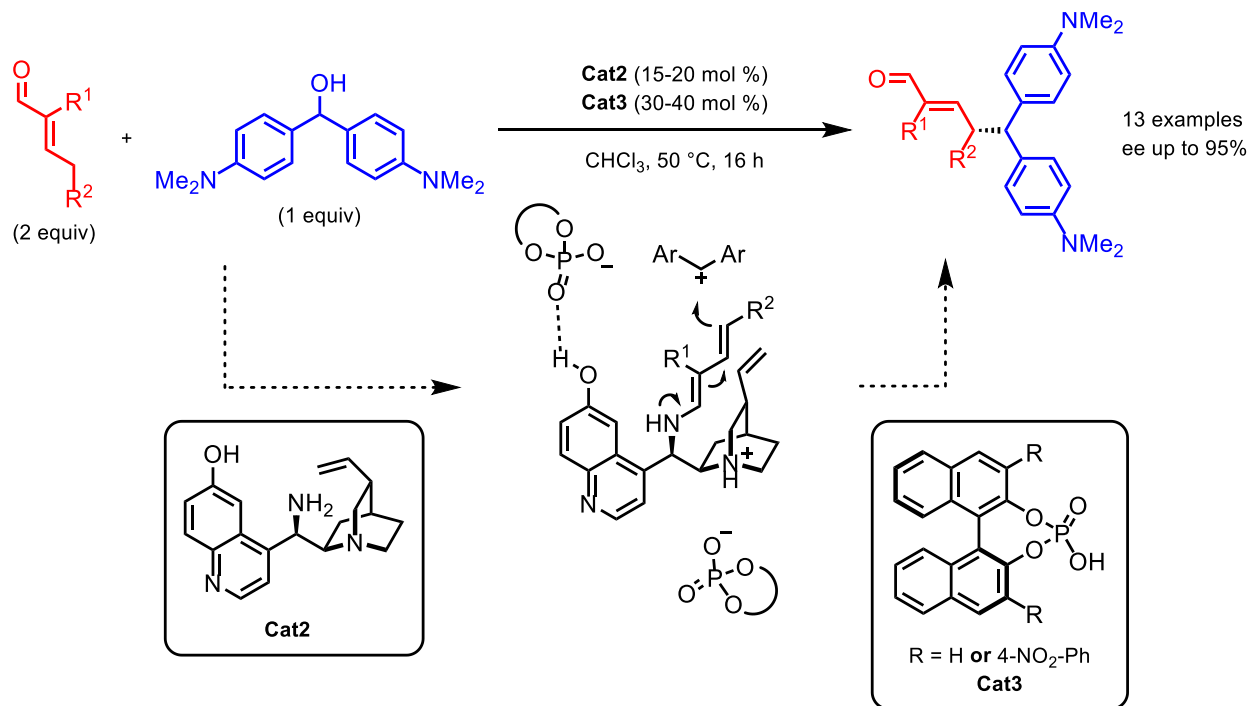
a) Synergistic organo-/organo-catalysis

With the advent of organocatalysis enabling the activation of organic molecules in a complementary way to metal catalysis, synthetic chemists have tried to take advantage of the orthogonality between different organocatalysts to induce different multicatalytic pathways. The concept of synergistic activation of two reaction partners taking advantage of two complementary activation modes also found applications in the field of organo-/organo-catalysis. For example, in 2010, the team of Jacobsen discovered that a chiral urea **Cat1** can be combined with ortho-nitrobenzenesulfonic acid acting as a Brønsted acid in a Povarov reaction (scheme 12).²⁰ Synergistic activation of both reaction partners through multiple stabilization enables the enantioselective addition of electron rich alkenes such as 2,3-dihydrofuran or enamides to imines. The reaction is general and provides valuable nitrogen containing heterocycles with once again, typically above 90% *ee*.



Scheme 12: Synergistic Povarov reaction

Synergistic multiple activation of different reaction partners can also be applied to the alkylation of unsaturated aldehydes via a S_N1 type transformation. For example, a chiral primary amine cinchona derived catalyst can efficiently activate these carbonyl compounds for an enantioselective γ -functionalization based on a dienamine activation. In parallel, bis-benzylic alcohols can be activated towards a S_N1 reaction by chiral phosphoric acids, forming the reactive cations (Scheme 13).²¹ Synergistic addition of the dienamine on the generated cation afford the desired alkylated aldehydes. Once again, a considerable match/mismatch effect is obtained when combining the two organocatalysts. Indeed, going from the optimal combination to the mismatch one drops the reactivity to less than 30% conversion and the selectivity to 21% *ee*, thus confirming the synergistic nature of the multicatalytic process.

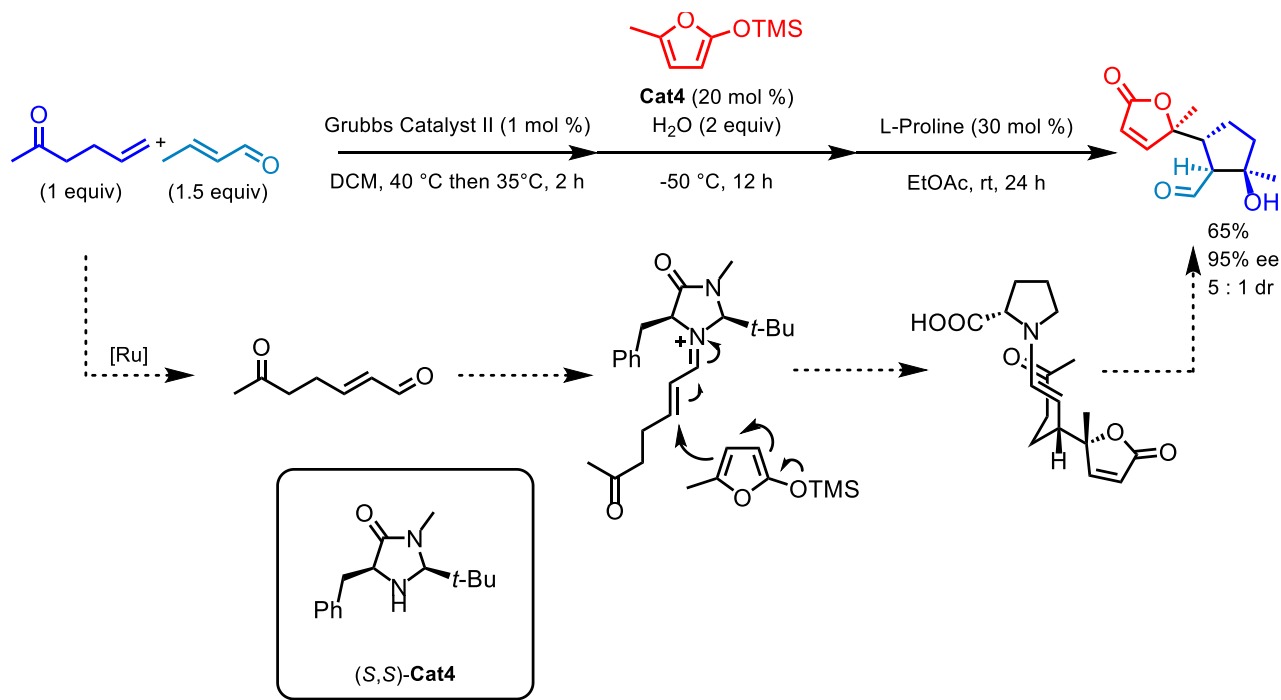


Scheme 13: Synergistic S_N1 functionalization of unsaturated aldehydes

b) Relay organo-/organo-catalysis

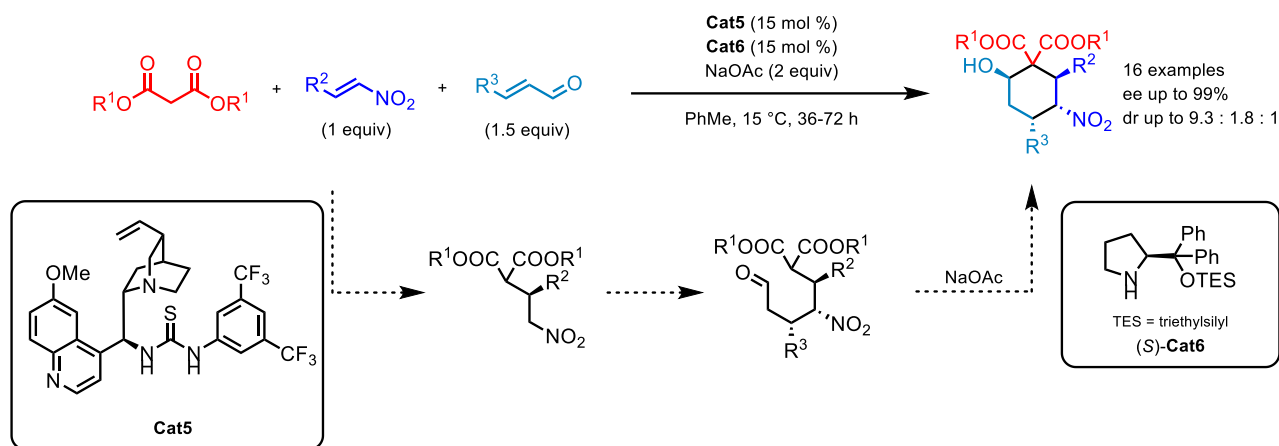
The use of secondary amines as organocatalysts could provide two different sets of activation of aldehydes, either through iminium or enamine catalysis. In 2009, the group of MacMillan took advantage of these complementary modes to promote relay multicatalytic transformations called “organocascades” (Scheme 14).²² These relay transformations take advantage of the complementary reactivity of two secondary amines, each one promoting a particular step of the process (either iminium or enamine activation). In this example, a chiral imidazolidinone first induces the Michael addition on the unsaturated aldehyde via iminium catalysis, while Proline subsequently selectively functionalizes the aliphatic aldehyde through enamine catalysis. Since the two stereocenters are independently governed by each catalyst, this diastereodivergent multicatalysis can be modified at will to obtain either the *syn*- or *anti*-adducts. Of interest, combining such an approach with an additional metal catalyzed cross metathesis in a relay sequence, could trigger the straightforward generation of the core structure of the natural product

aromadendranediol. Upon the cross metathesis, the generated unsaturated aldehyde reacts in a Mukaiyama type Michael addition with a silyl enol ether. Upon one-pot addition of L-Proline, intramolecular aldol reaction creates the complex natural product core with four controlled contiguous stereogenic centers.



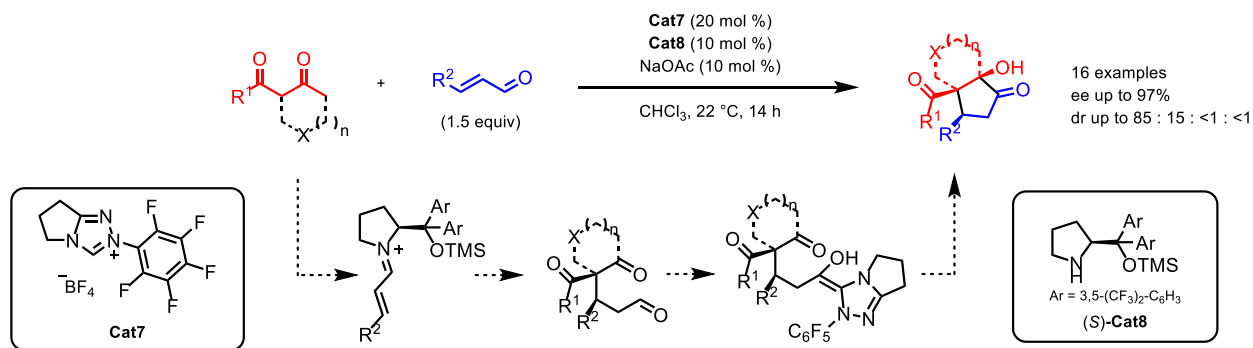
Scheme 14: Organocascade functionalization of unsaturated aldehydes

Such multicatalytic organocascades have been applied with great success in the elaboration of other complex scaffolds. It must be pointed out that the cascade adducts are usually obtained with high levels of enantiocontrol through an amplification of chirality arising from the successive stereoselective events. In 2009, the groups of Xu and Dixon combined an organocascade with a synergistic multiple organocatalytic transformation (Scheme 15).²³ This multicomponent transformation involves an enantioselective organocatalyzed 1,4-addition of dialkyl-malonates to a nitroolefin followed by trapping of the in-situ generated enolate by a 1,4-addition to an unsaturated aldehyde promoted by iminium catalysis by the secondary amine, ultimately followed by the ring closure through intramolecular aldolization. In this multicomponent assembly, the quinine-thiourea derivative **Cat5** activates both diester and the nitro group, while the secondary amine **Cat6** activates the aldehyde in the second Michael addition. Thanks to the application of these two catalysts, the generated molecules possess 4 controlled stereogenic centers obtained with excellent levels of stereocontrol (typically > 75% of the major dia and >98% ee).



Scheme 15: Organocascade synthesis of substituted cyclohexanes

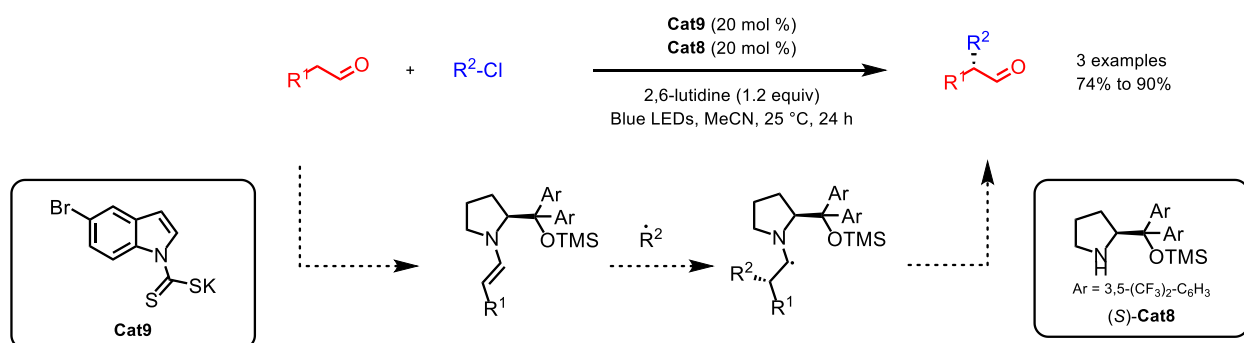
The same year, the team of Rovis reported an organocascade taking advantage of another activation mode. By combining a chiral pyrrolidine together with the achiral NHC **Cat7**, a cascade consisting of an enantioselective 1,4-Michael addition of a 1,3-dicarbonyl compound followed by a NHC-catalyzed intramolecular benzoin condensation was developed (Scheme 16).²⁴ During the Michael addition, by virtue of the control by the chiral pyrrolidine catalyst **Cat8** through iminium activation, the Michael adducts are obtained with good levels of enantiocontrol (>85% *ee*). This Michael adduct is directly transformed by the NHC through the benzoin condensation. Demonstrating the interest of such relay multicatalytic sequences, performing the reaction in a sequential manner, the adduct was isolated with a marked decrease in enantiocontrol (58% *ee*) together with a reduced yield. This is due to the instability of the Michael adduct, notably rapidly racemizing under the reaction conditions. As a result, directly intercepting this aldehyde in an organocascade through the NHC catalyzed cyclization triggers the formation of the desired product prior to racemization of the intermediate aldehyde.



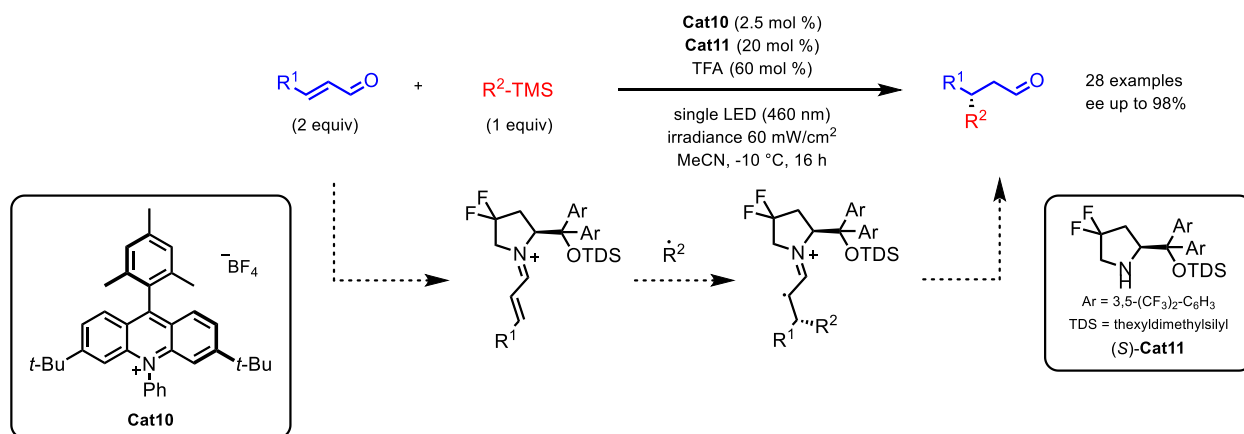
Scheme 16: Relay chiral iminium / NHC catalysis

Relay catalysis can also be applied in photoredox organo/organo-catalysis. In 2019, the team of Melchiorre found that a dithiocarbamate catalyst could induce Single Electron Transfer (SET) under light to activate benzyl chlorides and generate the corresponding nucleophilic radicals. This reactive radical can be intercepted in parallel by a chiral enamine catalytic cycle, providing a final alkylation of aldehyde

(Scheme 17).²⁵ Thanks to the use of a chiral pyrrolidine catalyst **Cat8** for the enamine activation, the desired aldehydes are obtained with decent levels of enantiocontrol (74-90% *ee*). This approach triggers the enantioselective alkylation of aldehydes, a transformation impossible to accomplish by other means. Following this principle, the conjugate addition to unsaturated aldehydes can be achieved through the combination between an organocatalyzed iminium activation and a photoredox catalytic cycle (Scheme 18).²⁶ This involves use of alkyl-silyl pronucleophiles generating upon a SET the desired reactive alkyl radicals. In this case, use of fluorinated pyrrolidine organocatalyst is crucial to avoid catalyst decomposition under those reaction conditions and to ensure optimal enantiocontrol.



Scheme 17: Photoredox catalytic enantioselective alkylation of aldehydes



Scheme 18: Photoredox catalytic enantioselective conjugate addition

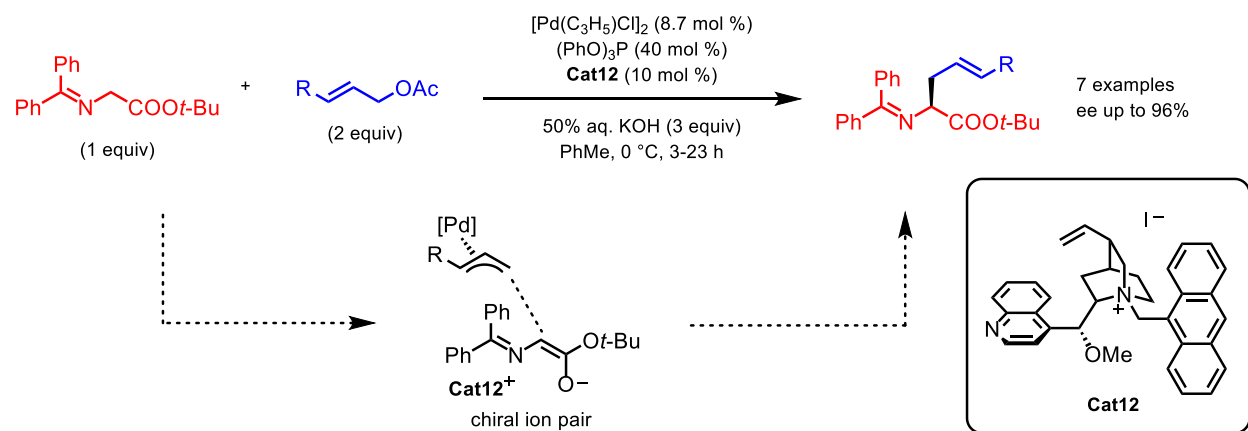
IV. Metal/Organo-catalysis

One of the major advances in the field of mult catalysis arose from the combination between metal complexes and organocatalysts. Indeed, given the extraordinary complementarity between these two fields, combining them in mult catalysis enables to merge the best from these two different worlds. However, as a drawback, developing metal/organo-catalytic transformations requires to solve the

challenge of the potential negative interactions between the metal center and the potentially coordinating organocatalysts. These interactions can be positive if the organocatalyst acts as a beneficial ligand for the metal, which cannot be considered as multicatalysis and as a result will not be discussed in this chapter.²⁷ On the other side, the organocatalyst might also be able to shut down the reactivity of the metal. As a consequence, finding the appropriate compatible catalytic species represents one of the main challenges in the field.

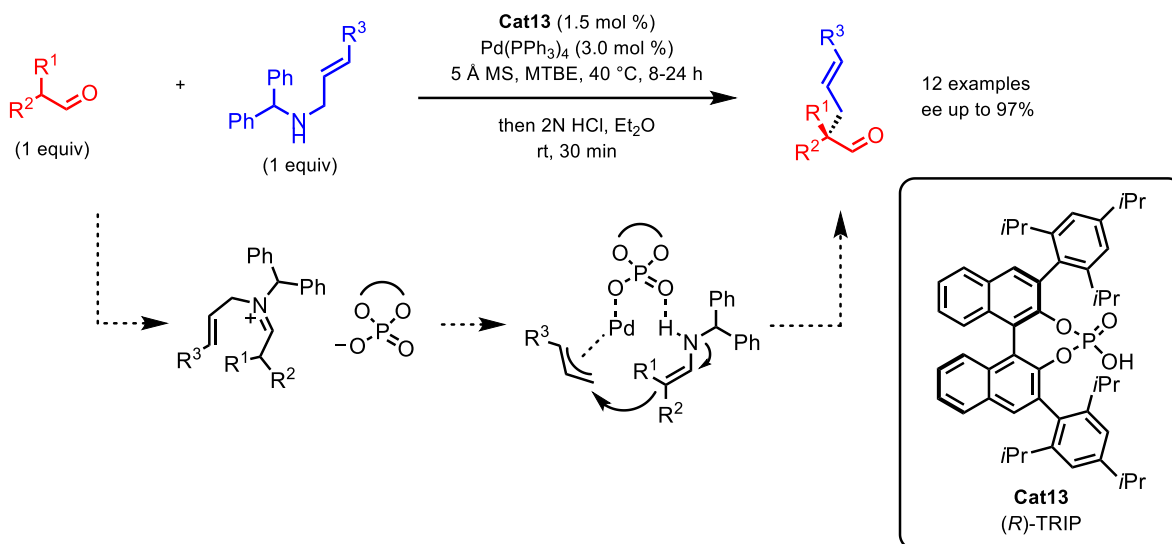
a) Synergistic activation of pro-electrophiles through π -allyl formation

As for metal/metal catalysis, metal π -allyl formation has been widely applied for the activation of pro-electrophiles in metal/organo-catalysis. One of the historical examples of multicatalytic transformations was based on such principle. In 2001, the teams of Takemoto, Gong and Mi independently developed enantioselective allylations transformations based on multicatalysis (Scheme 19)²⁸. Quinine-derived Phase Transfer Catalysts were well known for their propensity to activate pro-nucleophiles such as Schiff bases, promoting their enantioselective alkylation. Combining this approach with a palladium catalyzed π -allyl formation, the allylation of glycine derived iminoesters proceeded with *ee*'s above 90%, demonstrating for the first time, all the potential of enantioselective metal/organo-catalysis.



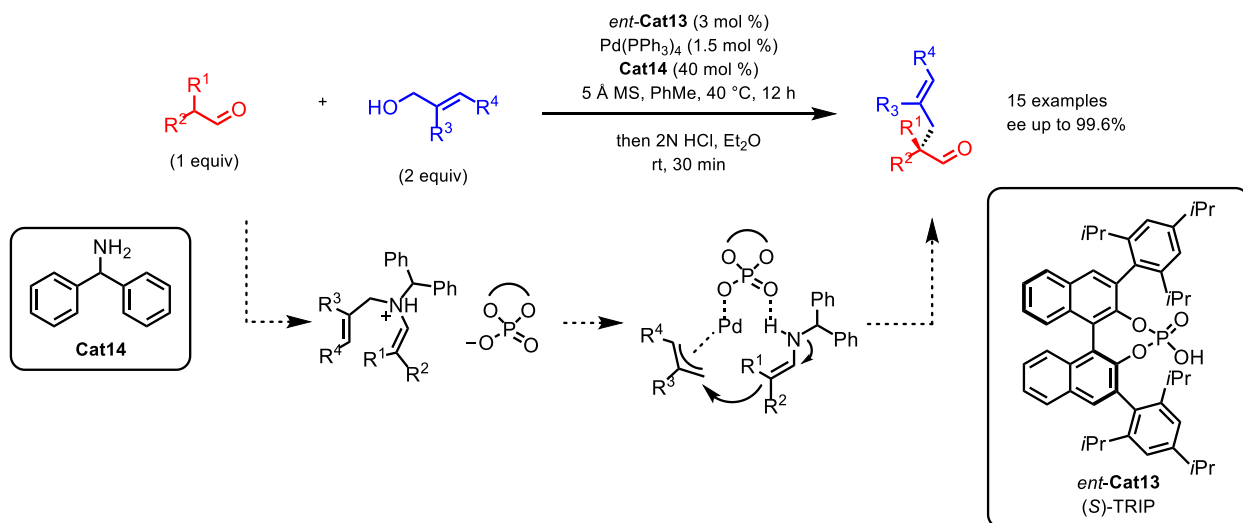
Scheme 19: PTC/Pd multicatalytic allylation of Schiff bases

Following these reports, a diversity of organocatalysts have been applied to activate different pro-nucleophiles towards trapping with a palladium π -allyl complex, such as for example the intramolecular allylation of aldehydes.²⁹ In 2007, the group of List reported an alternative strategy for intermolecular aldehyde allylation based on the use of chiral counterions (Scheme 20).³⁰ This approach relied on the condensation of aliphatic aldehydes with stoichiometric amines. In the presence of the chiral phosphoric acid organocatalyst, a chiral enamine is generated. The palladium complex triggers the formation of the π -allyl, thus allylating the enamine. The intermediate corresponding anion generated is then hydrolyzed back to the enantioenriched aldehyde after treatment under acidic conditions. In this transformation, the chirality on the generated adduct is exclusively controlled by the chiral phosphoric acid.



Scheme 20: Counterion directed allylation of aldehydes

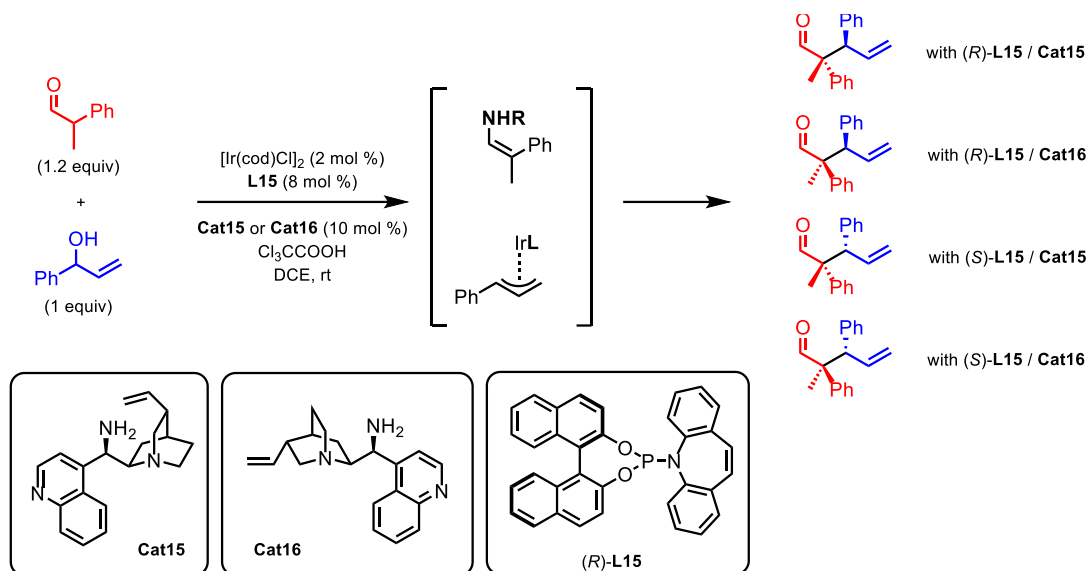
Following this report, the same group found that the process could be catalyzed by a primary amine to promote the allylation starting from allylic alcohols (Scheme 21).³¹ This transformation involves the palladium complex for the π -allyl formation, the chiral phosphoric acid helping in the allylic alcohol metalation and directing the enantioselective addition in the allylation transition state and finally the amine generating the nucleophilic enamine. Thanks to this successful combination between three distinct catalysts, a broad range of allylated aldehydes possessing challenging quaternary stereogenic centers could be prepared in typically more than 90% ee. Of interest, such strategy could be further extended to the allylation starting from terminal alkenes through a relay allylic C-H activation.³²



Scheme 21: Triple-catalyzed allylation of aldehydes

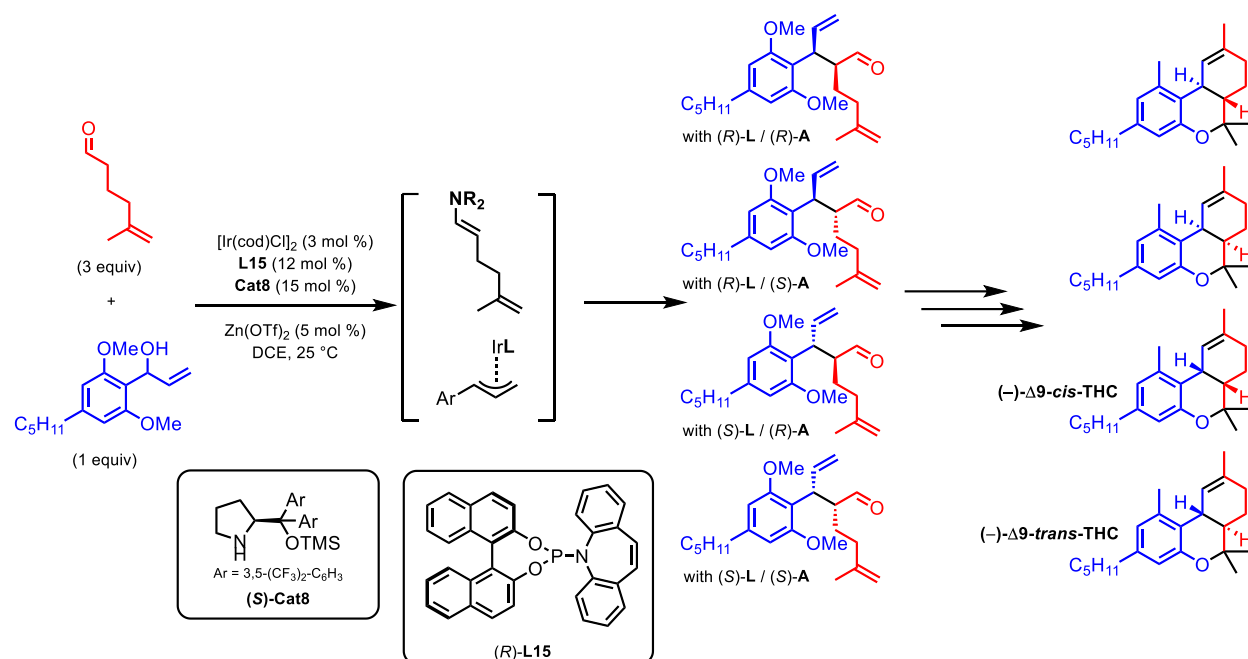
One of the main advances in the field consisted in adding a chiral phosphoramidite ligand to a metal iridium complex. By appropriately combining a chiral secondary amine organocatalyst **Cat15** derived from

quinine or its pseudo-enantiomer **Cat16** with the generated chiral iridium complex, a fully stereodivergent process could be obtained, where each stereocenter is independently controlled with equal efficiency (Scheme 22).³³ The organocatalyst generating the reactive enamine is responsible for the control of the stereocenter from the pro-nucleophile while the iridium complex controls the enantiofacial addition on the π -allyl. As a result of this synergistic approach, all four stereoisomers of the product containing a challenging quaternary stereocenter could be generated in a stereodivergent manner in more than 14:1 *dr* and 99% *ee*.



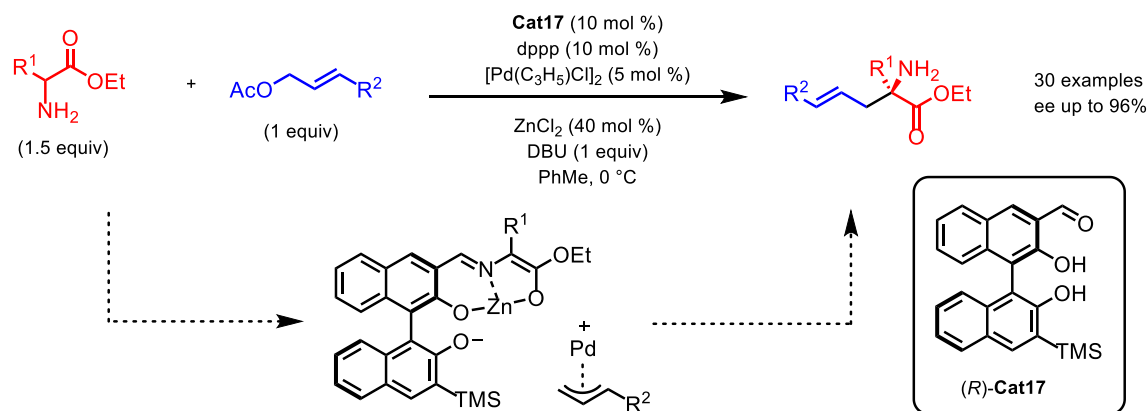
Scheme 22: Diastereodivergent allylation of aldehydes

Applying the same strategy to linear aldehydes using secondary amine chiral organocatalysts could notably be applied in the concise synthesis of Δ^9 -tetrahydrocannabinols (Scheme 23).³⁴ This synthesis required the activation of a linear aldehyde. In order to proceed, the authors applied a chiral secondary amine organocatalyst, controlling the stereochemistry during the enamine addition. Once again, the phosphine ligand on the metal center independently controls the stereochemistry on the π -allyl. As a consequence of the stereodivergence of this process, all four stereoisomers of Δ^9 -tetrahydrocannabinols could be efficiently prepared with excellent diastereo- and enantio-control.



Scheme 23: Diastereodivergent allylation of aldehydes for the stereodivergent synthesis of Δ^9 -tetrahydrocannabinols

Finally, in 2019, the group of Guo reported an alternative system where an amine pro-nucleophile is activated by a chiral aldehyde as organocatalyst in combination with a zinc salt (Scheme 24).³⁵ This complementary strategy allows the condensation of *N*-unprotected amino acid esters with allyl acetates directly affording α,α -disubstituted α -amino acid esters. Upon condensation of the aldehyde catalyst **Cat17** with the imine, the process involves the generation of a reactive stabilized zinc enolate, reacting with the palladium π -allyl. Use of a chiral BINOL derivative as organocatalyst provides excellent enantiocontrol during the synergistic transition state, affording the allylated products with enantiomeric excesses typically between 80-90% and up to 96%.

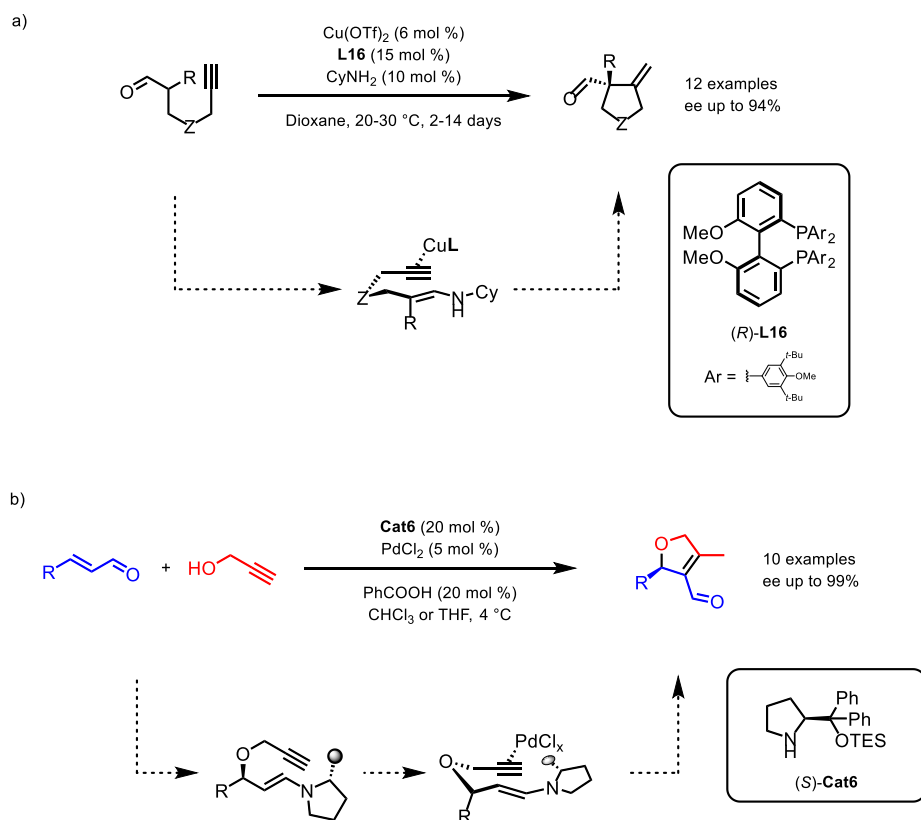


Scheme 24: Multicatalytic allylation through aldehyde catalysis

b) Synergistic activation through metal catalyzed activation of the pro-electrophile

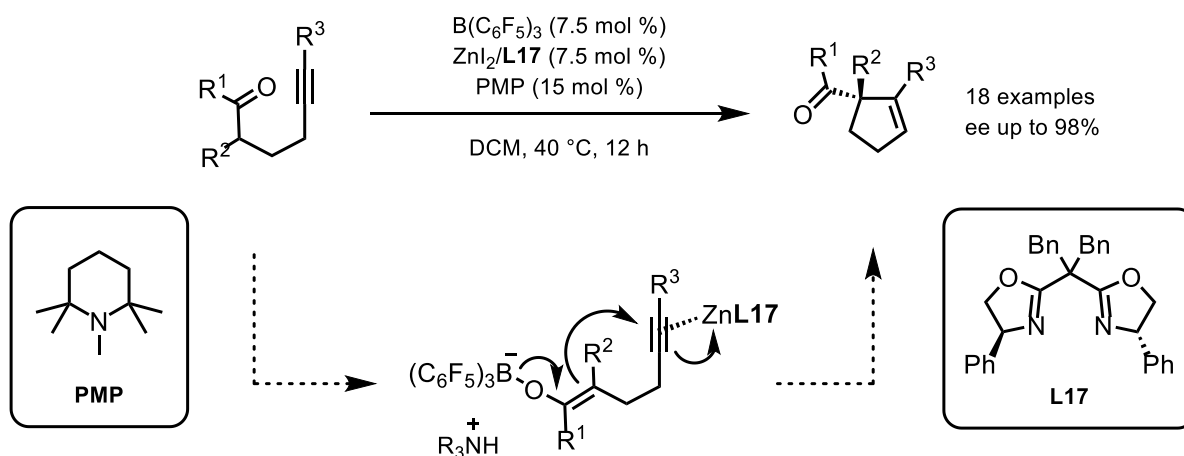
Given the lack of reactivity of some of the intermediates generated through organocatalytic activation, researchers have developed different multicatalytic synergistic transformations where the metal co-catalyst enhances the reactivity of one of the reaction partners. In addition, by providing better defined transition states, such strategy could also considerably improve the levels of stereocontrol.

Lewis acids are efficient to activate alkynes towards addition of various classes of nucleophiles such as enolate derivatives in a Conia-Ene type transformation. Taking advantage of such reactivity, the team of Michelet and Ratovelomanana-Vidal reported a multicatalytic Conia-Ene type cyclization (Scheme 25a).³⁶ Starting from an α -disubstituted aldehyde, use of an achiral primary amine organocatalyst generates the required reactive nucleophilic enamine. On the other side, a chiral copper complex, activates the alkyne through π -coordination favoring the enantioselective addition of the enamine. By applying chiral diphosphine ligand **L16**, the chiral cyclopentanes generated are obtained in modest to excellent enantiocontrol depending on the substitution pattern (36-94% *ee*). The challenge in developing such Conia-Ene multicatalytic transformations lies in the required compatibility between a Lewis base prompt to rapidly coordinate with the Lewis acid, potentially strongly impacting both reactivity and selectivity.³⁷ In this context, chiral sterically demanding secondary amines organocatalysts are compatible with a large number of Lewis acids which found applications in the synthesis of various cyclopentanes, spiro-oxindoles, dihydrofuryls or dihydrofurans (scheme 25b).³⁸



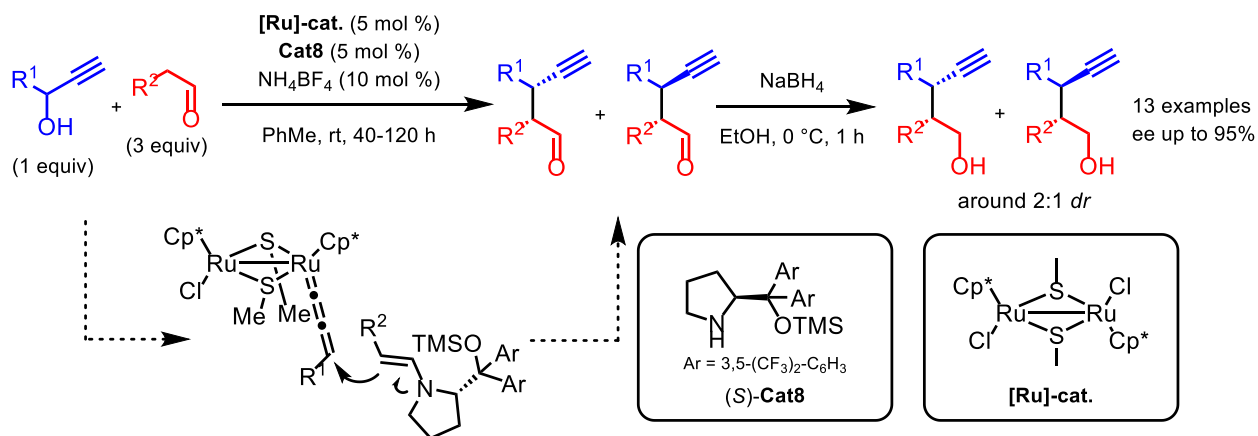
Scheme 25: Conia-Ene synergistic transformations

Aside from transformations catalyzed by primary or secondary amines, more recently, a strategy based on the cooperative use of a frustrated Lewis pair was applied for an intramolecular enantioselective cyclization (Scheme 26).³⁹ This strategy implies the use of three distinct catalysts. The chiral zinc complex activates the alkynes towards the addition of the boron enolate generated through the cooperative use of $B(C_6F_5)_3$ and a tertiary amine organocatalyst. As a result of the unique reactivity provided by these three catalysts, ketones can participate in such enantioselective cyclization which is complementary to the above mentioned scope obtained with aldehydes using secondary amines organocatalysts. Most interestingly, given the relatively mild conditions not involving the use of strong bases, in the obtained final cyclopentenones, the ketones and the alkenes do not conjugate, preserving the stereogenic center obtained in excellent enantiocontrol (typically >94% *ee*).



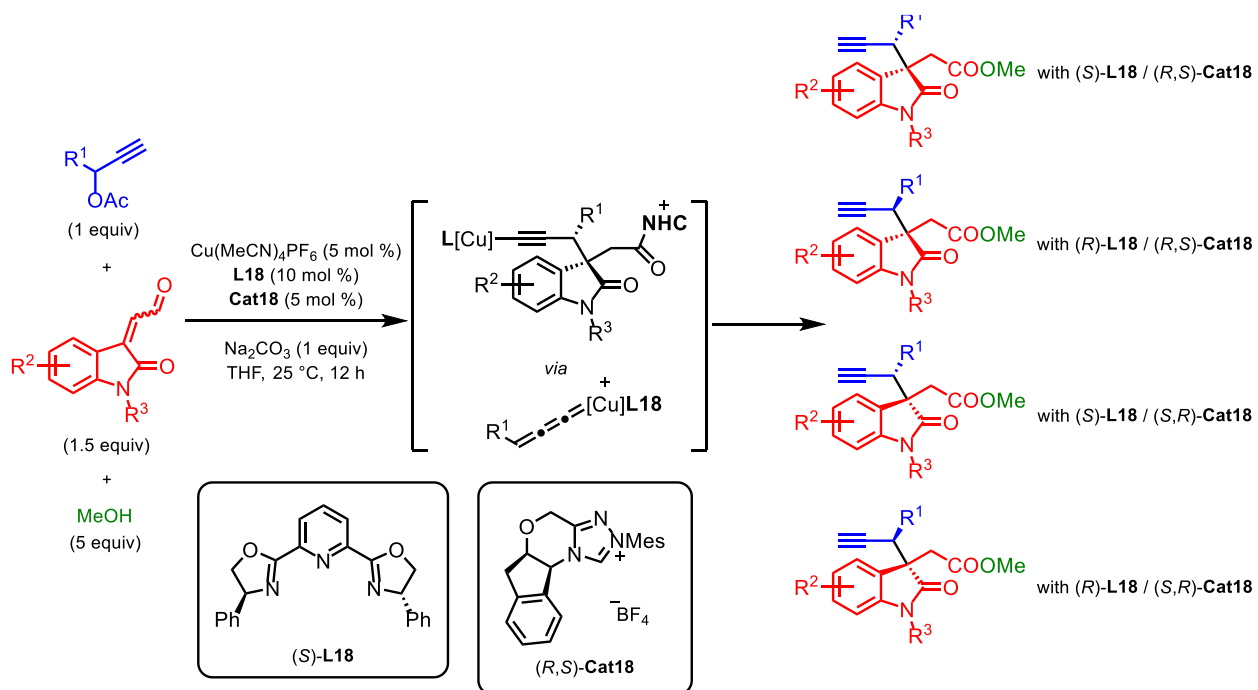
Scheme 26: Triple catalyzed intramolecular Conia-Ene type cyclization

Aside from the direct activation of alkynes, Lewis acids can also be used in mult catalysis for the formation of reactive allenylidenes. For example, alkylation of propargylic alcohols with aldehydes could be mediated by selectively combining a ruthenium complex with a chiral pyrrolidine secondary amine organocatalyst (Scheme 27).⁴⁰ As for the above-mentioned examples, the secondary amine generates the reactive nucleophilic enamine and on the other side, the ruthenium complex activates the electrophile by generating an electrophilic ruthenium–allenylidene complex. As a consequence of this dual activation, the C–C bond is efficiently generated with excellent enantiocontrol (>90% *ee*). However, the geometry around the electrophile is poorly controlled, resulting in moderate diastereoselectivity (around 2:1 *dr*). This moderate diastereocontrol can be explained by the use of an achiral ruthenium complex, the enamine-type catalysts not controlling the stereodifferentiation on the allenylidene.



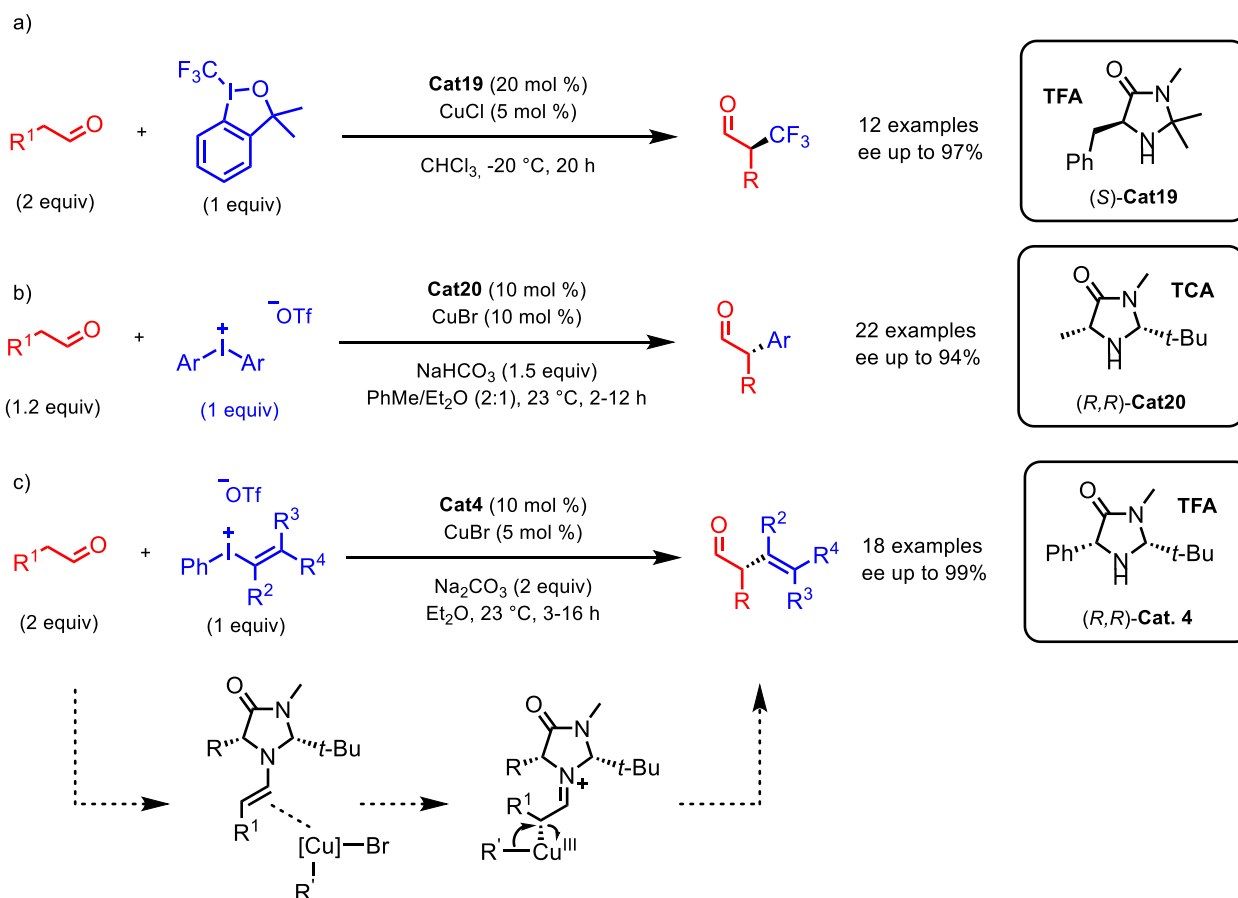
Scheme 27: Addition of enamines to ruthenium–allenylidene complexes

In order to provide better diastereocontrol, recently, such combinations were extended to the use of a chiral *N*-heterocyclic carbene (NHC) acting as organocatalyst for the activation of unsaturated aldehydes in combination with a chiral copper complex activating the pro-electrophile (Scheme 28).⁴¹ The NHC triggers the functionalization of the aldehyde at the oxindole position, through addition of the generated dienolate with the formed chiral copper–allenylidene complex. Even though NHCs are known as potential ligands for metal complexes, what is remarkable is the excellent compatibility between the two chiral catalysts used, enabling a fully stereodivergent process. Indeed, switching the chirality on the two catalysts can independently direct at will the formation with equal efficiency of the four possible stereoisomers of the product.



Scheme 28: Diastereodivergent addition of enamines to copper–allenylidene complexes

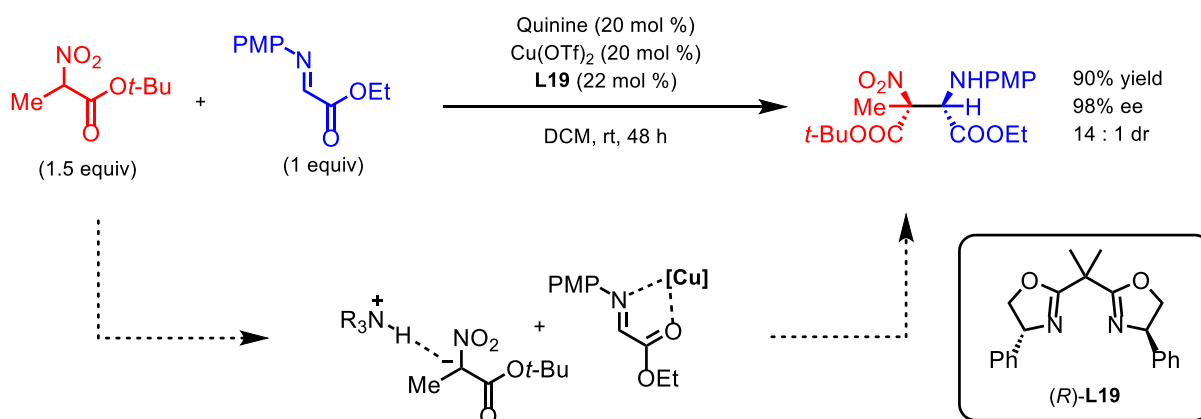
A considerable advance in the field of multicatalysis also came from the combination between enamine catalysis with the activation of hypervalent iodine reagents by copper catalysts. Such triggers the functionalization of aldehydes with a wide variety of carbon electrophiles (Scheme 29). In a seminal report, the team of MacMillan found that Togni's reagent, in the presence of 5 mol% of a copper salt, could convert to a reactive electrophile towards addition of a chiral enamine (Scheme 29.a).⁴² Such a transformation afforded the enantioselective α -trifluoromethylation of aldehydes with excellent levels of enantiocontrol (>90% *ee*). Starting from diaryliodonium triflates, the enantioselective α -arylation of aldehydes could also be performed once again with excellent enantioselectivity (Scheme 29.b),⁴³ while using vinyl iodonium triflates could generate α -vinyl aldehydes of great synthetic value (Scheme 29.c).⁴⁴ Mechanistic studies shed light on the reaction pathway of this synergistic multicatalytic transformation. From the iodonium salt, oxidative addition of the copper (I) catalyst generates the electrophilic R–Cu(III) complex. In parallel, the aldehyde reacts with the secondary amine organocatalyst generating the nucleophilic enamine. In the synergistic transition state, the enamine adds to the Cu center, forming a copper organometallic complex, leading to the final product after reductive elimination and organocatalyst liberation.



Scheme 29: α -functionalization of aldehydes using synergistic Cu/enamine catalysis.

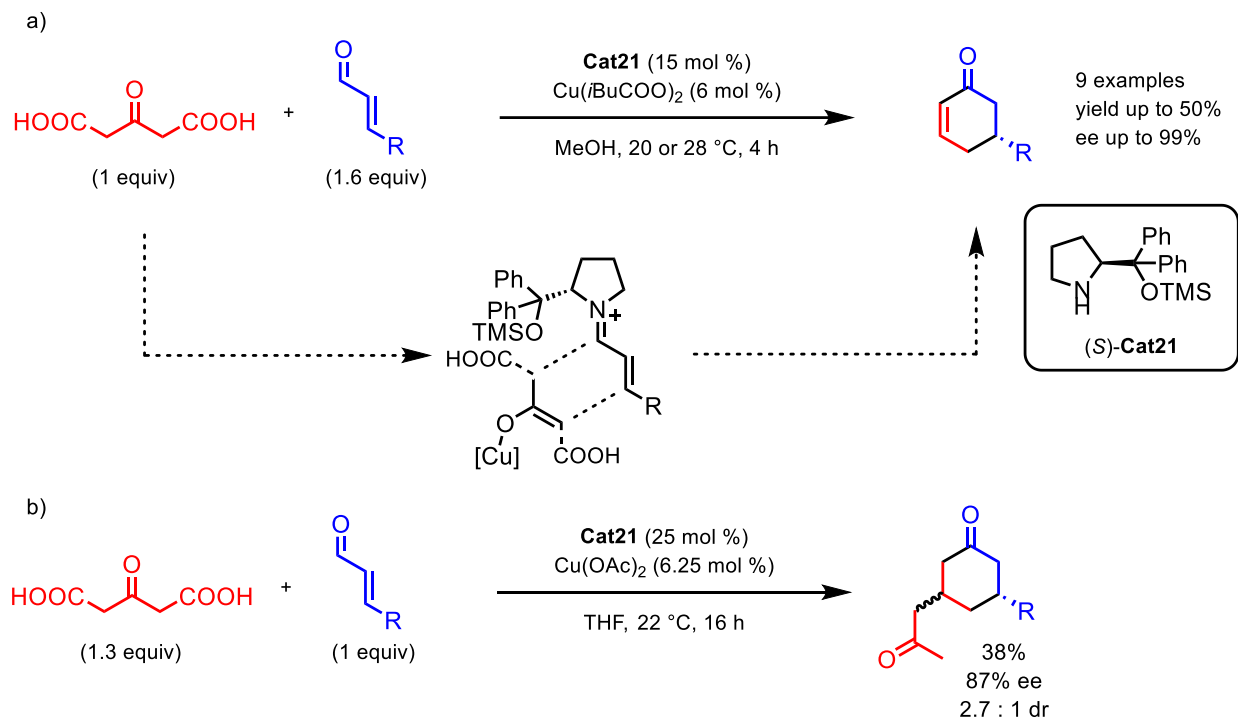
c) Synergistic activation through metal catalyzed activation of the pro-nucleophile

Aside from appropriately activating pro-electrophiles, Lewis acids have also been used in order to activate pro-nucleophiles. Illustrating this principle, in an early example, in 2005, the group of Jørgensen reported a synergistic aza-Henry reaction (Scheme 30).⁴⁵ When independently applying a copper(II) bisoxazoline complex or quinine alone in the addition of nitro-esters to imines, modest yield and stereocontrol were achieved. However, when appropriately mixing them, the desired Mannich adduct was obtained in an optimized 90% yield, 14:1 *dr* and 98% *ee*. This demonstrated that on one side, the electrophile was selectively activated by the Lewis acid (copper salt) while on the other side the organocatalyst activated the nitro-esters by deprotonation. Altogether, the presence of both catalysts in the transition state, provides a well-defined geometry for the stereocontrolled C–C bond forming event, generating two contiguous stereocenters, one being a tetrasubstituted carbon.



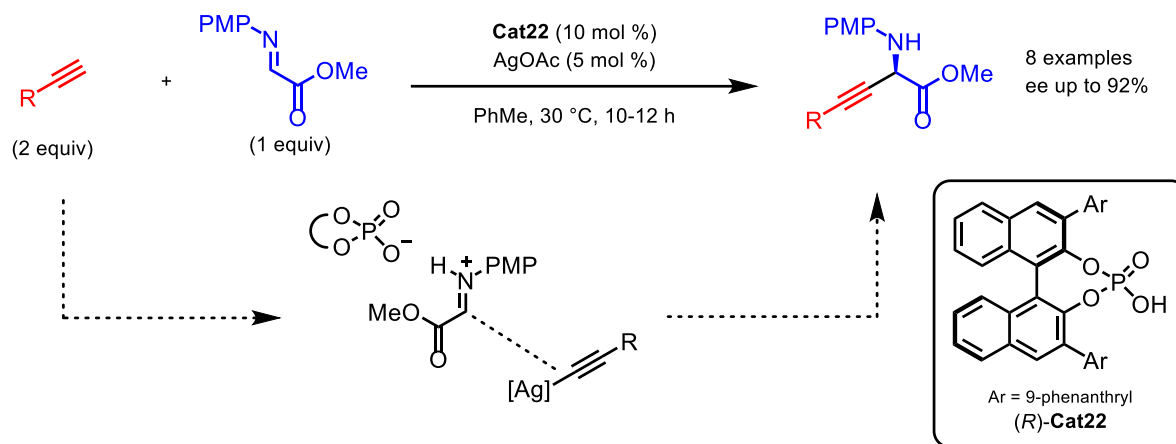
Scheme 30: Synergistic Cu/quinine multicatalytic aza-Henry reaction

Enhancement of reactivity and selectivity was also achieved in a multicatalytic generation of chiral cyclohexenones reported by our group (Scheme 31).⁴⁶ This transformation involved the application of 1,3-acetonedicarboxylic acid as a reactive acetone surrogate performing a cascade di-decarboxylative Michael/aldol/dehydration sequence. First attempts implied the activation of the unsaturated aldehyde with a secondary amine chiral organocatalyst through iminium activation. However, the desired adduct was generated in a low 12% yield and 90% *ee*. Simply adding 6 mol% of Cu(*i*-BuCOO)₂ enhanced the yield to 50% and most importantly the *ee* to 98%. The increase in enantiocontrol indicates a synergistic role of the copper complex, implied in the dual activation of the keto-acid through formation of the corresponding enolate. This cascade could be applied to access structurally diverse cyclohexenones of great synthetic interest. In addition, modifying the conditions notably by using an excess of keto-diacid, an additional cascade Michael addition on the cyclohexenone was observed, generating a chiral 1,5-diketone in 87% *ee*.



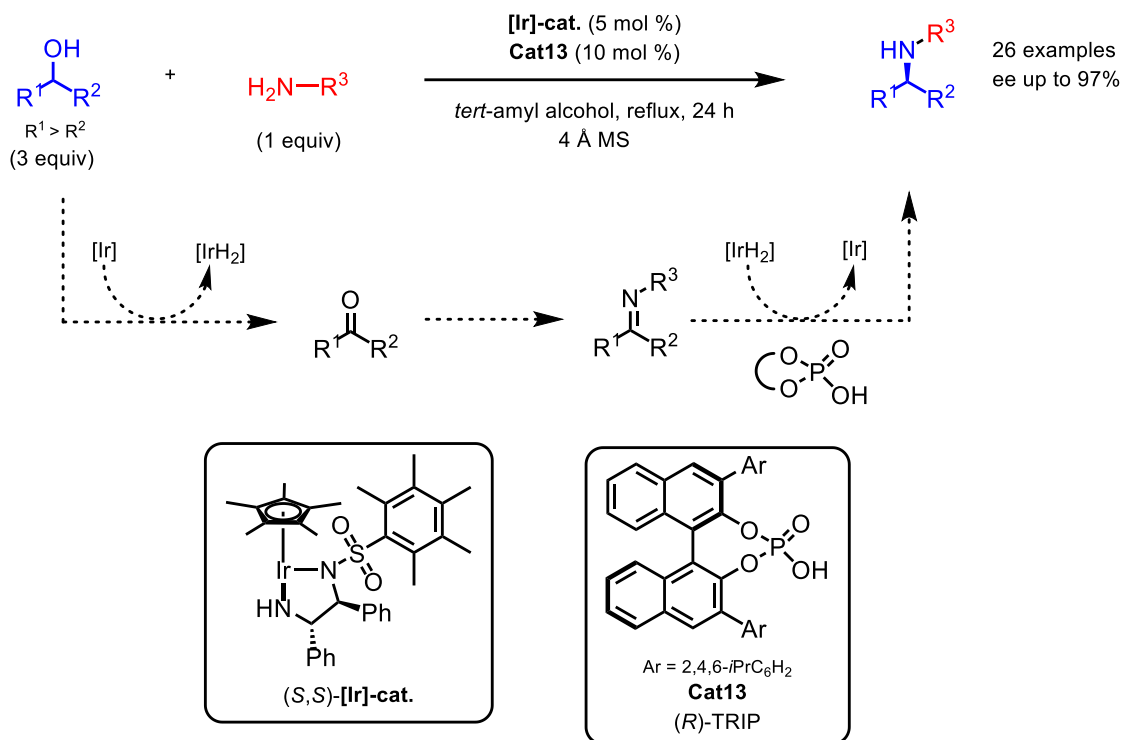
Scheme 31: Cascade di-decarboxylative Michael/aldol/dehydration synthesis of cyclohexenones

Carboxylic or phosphoric acids are well known for their propensity to activate a wide variety of scaffolds containing a basic nitrogen atom via the formation of the corresponding more electrophilic protonated species.⁴⁷ In 2007, the group of Rueping took advantage of such property to activate an imine towards the enantioselective addition of an organometallic specie (Scheme 32).⁴⁸ The application of a chiral phosphoric acid provides the appropriate chiral environment around the protonated imine to enable the enantioselective addition of the silver alkynide complex to this chiral ion pair. The resulting generated amino-esters are obtained in more than 86% *ee*, demonstrating the potential of such multicatalytic approach in the control of the addition around an *in-situ* generated charged intermediates.



Scheme 32: Chiral phosphoric acid / AgOAc synergistic catalysis

The notion that a chiral phosphoric acid can control the chiral environment around a charged nitrogen atom activating an electrophile towards the enantioselective addition of an organometallic nucleophile has found numerous applications since then. For example, enantioselective hydrogenation of imines was found to be efficient through such a multicatalytic combination.⁴⁹ Aside from classical hydrogenation, applying this principle, the team of Zhao reported the valuable first efficient enantioselective amination of alcohols proceeding through a borrowing hydrogen (Scheme 33).⁵⁰ In this approach, a chiral iridium complex performs a reversible alcohol dehydrogenation to a carbonyl compound, liberating an iridium hydride. By applying a chiral phosphoric acid co-catalyst, a chiral iminium ion is generated upon condensation of the amine on the in-situ generated aldehyde. Addition of the iridium hydride to the iminium provides the final chiral amine in excellent enantiocontrol (>90% ee). This strategy is based at the same time on a merged-relay mechanism with two intertwined catalytic cycles (reversible dehydrogenation and phosphoric acid catalyzed protonation) and on a synergistic transition state, involving a simultaneous control by the two catalysts of the incoming nucleophile (hydride) on the electrophile (iminium). Of interest, this strategy could be expanded to the dynamic kinetic resolution of alcohols possessing adjacent stereogenic centers.⁵¹

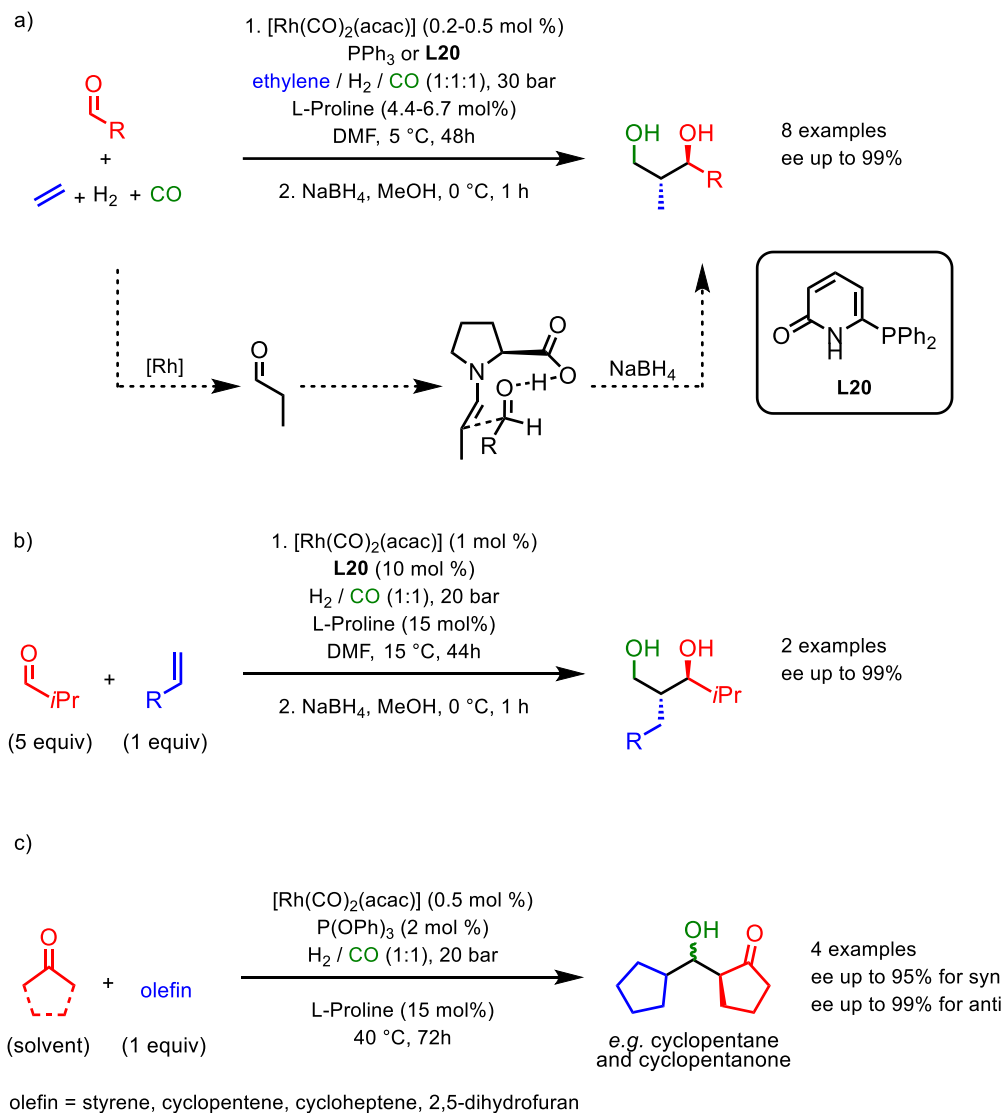


Scheme 33: Alcohol amination by hydrogen borrowing / chiral phosphoric acid catalysis

d) Relay cascades

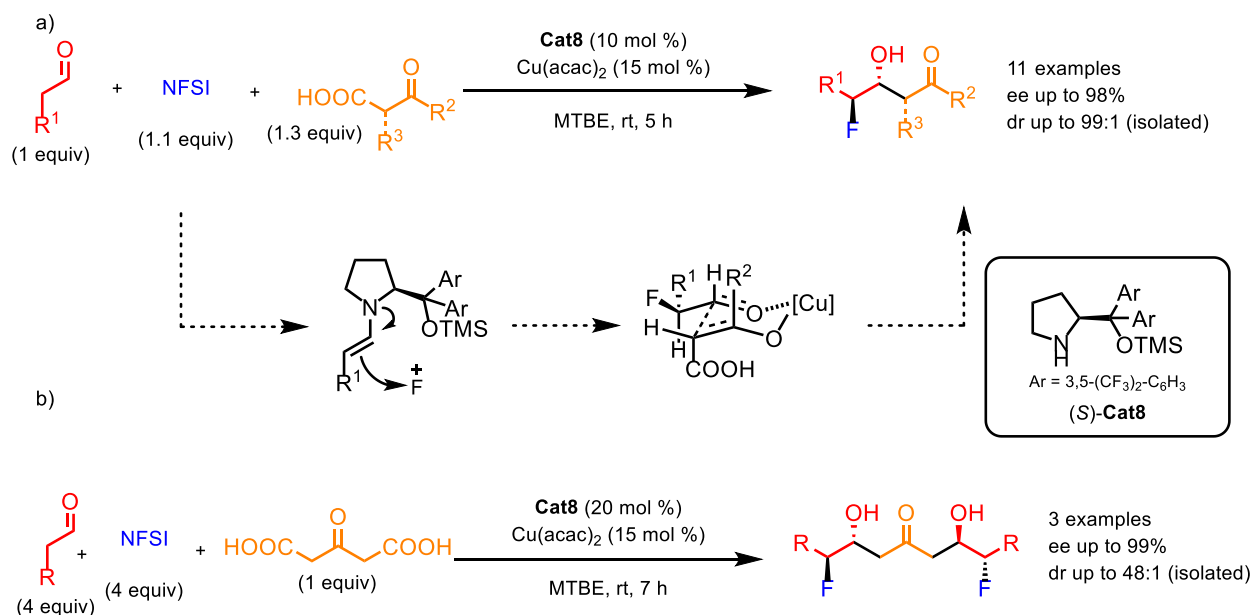
Aside from synergistic catalysis, organo/metal multicatalysis based on relay transformations have also changed our vision of organic synthesis. As mentioned in the introduction, relay reactions can be in one-pot if different reagents/catalysts are sequentially added to the reaction mixture or in cascade if all of them are present at the onset. These strategies enable considerable synthetic economies by reducing the number of operations and most importantly, can unlock innovative reactions through the in-situ generation and derivatization of unstable intermediates.

In 2007, the group of Breit reported a typical example of relay-cascade directly converting simple substrates thanks to a metal catalyst, into a reactive carbonyl intermediate directly derivatized in a subsequent organocatalytic step (Scheme 34).⁵² Rhodium-catalyzed hydroformylation was applied to convert widely available alkenes such as ethylene into the corresponding pro-nucleophilic linear aldehydes, directly reacting in a proline catalyzed enantioselective aldol reaction with another electrophilic aldehyde, generating the *anti*-aldol adducts in more than 90% *ee* (Scheme 34.a). Of interest, applying ethylene, propionaldehyde is *in-situ* generated in the reaction mixture and directly reacts with the other aldehyde in a cross-aldol transformation. Given the propensity of propionaldehyde to self-condense, slowly releasing it in the reaction media increases the selectivity towards the cross-aldolization, demonstrating the interest of this multicatalytic relay cascade. The strategy was also simultaneously applied by the group of Eilbracht to the *in-situ* generation of electrophilic aldehyde in the presence of acetone acting as the pro-nucleophile (Scheme 34.c).⁵³



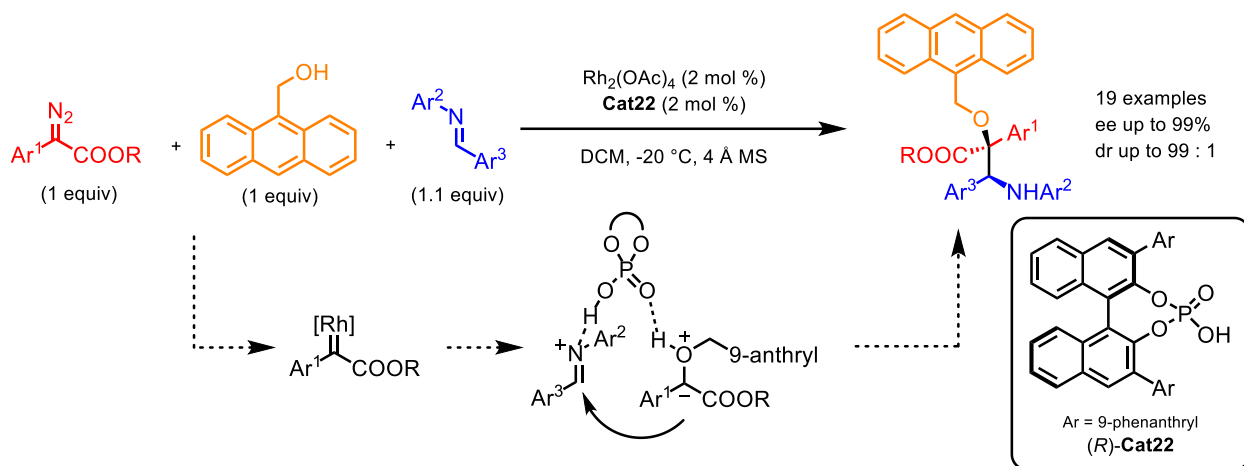
Scheme 34: Relay rhodium catalyzed hydroformylation/proline catalyzed aldol reaction

Relay-multicatalysis can also be applied to in-situ generate and derivatize other classes of unstable and volatile aldehydes. In 2017, our group reported that enantioenriched fluorinated aldehydes prone to undergo rapid racemization and decomposition, could be in-situ produced through an enamine organocatalyzed aldehyde fluorination (Scheme 35).⁵⁴ In the presence of a pro-nucleophilic keto-acid and a copper catalyst, the fluorinated aldehydes were transformed in a diastereoselective aldolization prior to racemization, affording the aldol adducts with excellent diastereo- and enantio-control (>95% ee). Of great interest, the strategy can be applied from simple keto-acids or from inexpensive keto-diacid, directly leading to complex keto-diols possessing 4 controlled stereogenic centers and key precursors of 1,3,5-triols.⁵⁵ This strategy implying an organocatalytic aldehyde functionalization followed by a copper catalyzed aldol reaction could be further applied to the synthesis of other fluorinated building blocks or in natural product synthesis.⁵⁶



Scheme 35: Relay organocatalytic aldehyde fluorination/copper catalyzed aldol reaction

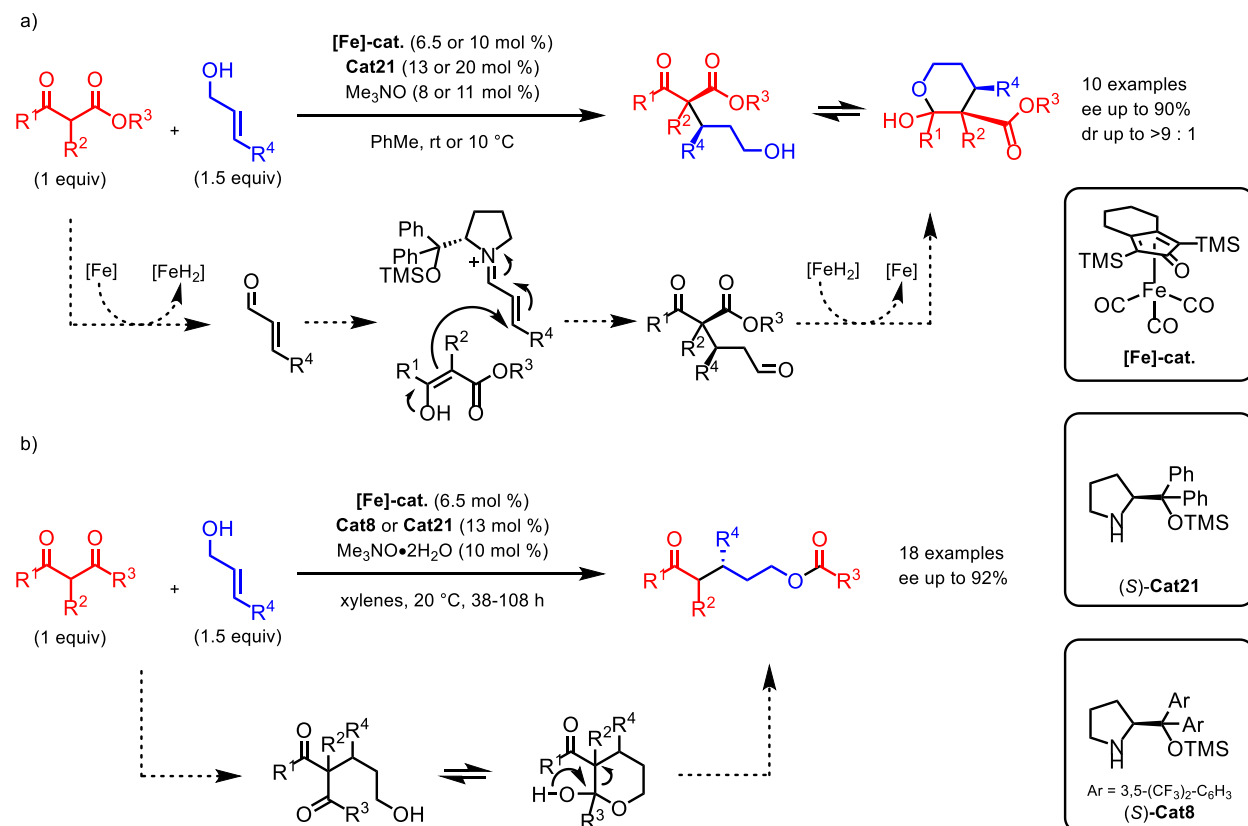
Applying the principle of control around a protonated imine via the use of a chiral phosphoric acid presented in scheme 32, the group of Gong reported another type of relay multicomponent coupling between a diazo-ester, an alcohol and an imine (Scheme 36).⁵⁷ In this strategy, the rhodium complex activates the diazo compound through generation of the corresponding metal carbenoid. The alcohol subsequently adds generating a reactive enolate. This enolate can add to the protonated imine, while the chiral ion pair generated thanks to the use of the phosphoric acid controls the enantiofacial addition, generating complex scaffolds with two controlled stereogenic centers with excellent dia- and enantio-control.



Scheme 36: Multicomponent assembly catalyzed by a chiral phosphoric acid and a rhodium complex

e) Merged-relay metal/organo-catalysis

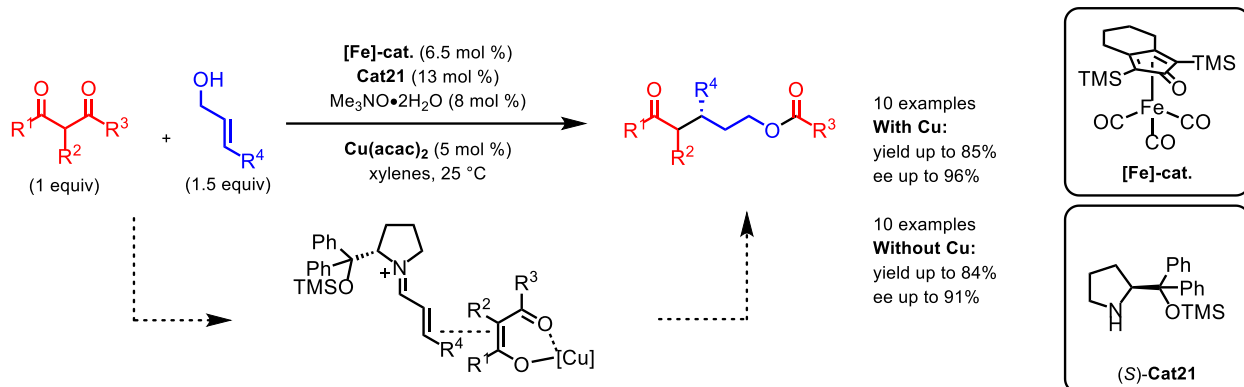
As mentioned in the introduction, merged-relay transformations are fundamentally different from relay reactions and involve the merging of two catalytic cycles in a bigger one, with species generated in a catalytic amount crossing between the two cycles. In 2013, our group reported a typical example of such process for the enantioselective addition of keto-esters to allylic alcohols (Scheme 37.a).⁵⁸ This enantioselective transformation implies the merging of an iron catalyzed borrowing hydrogen and an aminocatalyzed Michael addition. The iron catalyst can activate in a reversible and temporary manner alcohols to reactive carbonyl compounds such as aldehydes.⁵⁹ At the aldehyde level, the chiral secondary amine catalyst generates the electrophilic iminium ion, enabling the stereocontrolled addition of the keto-ester. Reduction of the chiral aldehyde by the iron hydride closes the catalytic cycle and liberates the desired alcohol. As a consequence of the combination between two catalytic cycles and of the use of a chiral secondary amine organocatalyst, the chiral alcohols can be obtained in up to 90% *ee* directly from allylic alcohols by avoiding the traditional oxidation and reduction steps associated with such transformation. Of interest, when starting from diketones, an additional cascade was observed directly affording ketones of great interest for natural product synthesis (Scheme 37.b). This cascade involves lactol formation from the generated alcohol, evolving through a Claisen-type fragmentation to liberate on side the mono-ketone and the other one a protected alcohol.⁶⁰



Scheme 37: Enantioselective multicatalytic borrowing hydrogen and application in a cascade Claisen fragmentation

Based on a detailed mechanistic study, we discovered that adding a third catalyst to the system greatly improved both reactivity and selectivity in these transformations (Scheme 38).⁶¹ This copper salt activates

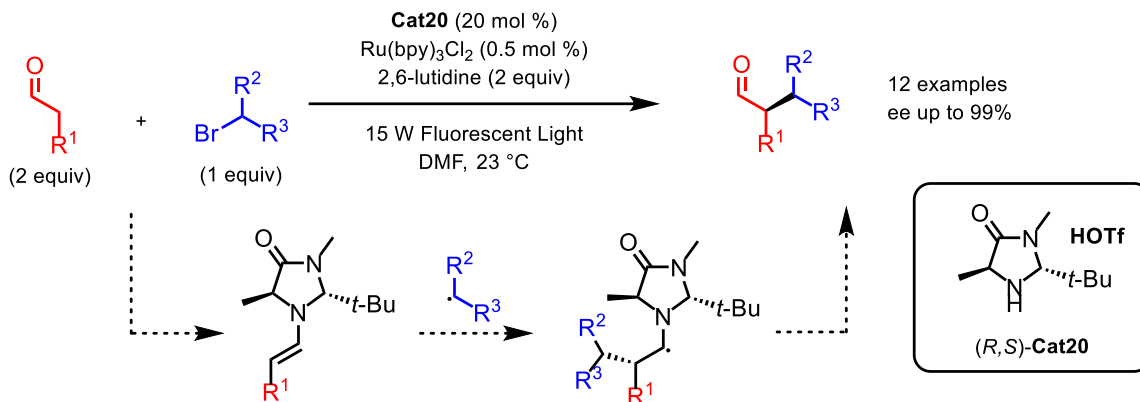
in a synergistic manner the pro-nucleophile during the Michael addition. As a result, the products are obtained in higher yields, enantioselectivities (typically around 90% *ee*) and the scope could be extended to other substrates such as keto-sulfones or nitro-esters.



Scheme 38: triple catalysis for improved enantioselective borrowing hydrogen

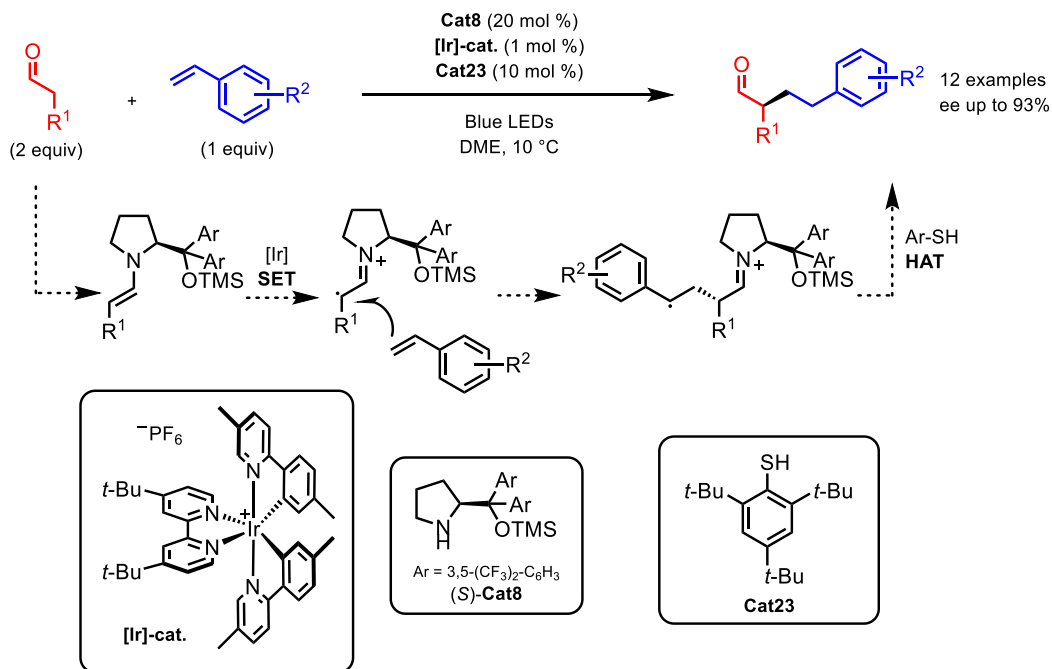
f) Photoredox metal/organo-catalysis

In 2008, the group of MacMillan discovered that photoredox activation could be induced through multicyclic transformations involving a photoredox metal catalyst and a chiral organocatalyst. This initial discovery opened an all-new world for organic chemists with innovative potential disconnections, leading to an extraordinary rich field in only one decade. Typical photoredox transformations imply a particular merged relay multicyclic mechanism where two catalytic cycles are interlocked, one involving a metal complex able to absorb light and trigger the radical formation and the organocatalyst, controlling the stereochemistry during the addition to the reactive radical intermediates. In the initial report, it was found that aldehydes could be alkylated with bromocarbonyl compounds, a long-standing challenge in the field of aminocatalysis (Scheme 39).⁶² This multicyclic reaction implied a ruthenium photocatalyst $\text{Ru}(\text{bpy})_3^{2+}$, generating the reactive electron deficient alkyl radical upon photon absorption. On the other side the secondary amine catalyst forms the electron rich enamine, reacting with this alkylating reagent generating a radical intermediate. Single electron transfer with the $^*\text{Ru}(\text{bpy})_3^{2+}$ liberates back again the free amine and affords the alkylated aldehyde, obtained with excellent enantiocontrol (88-99% *ee*).



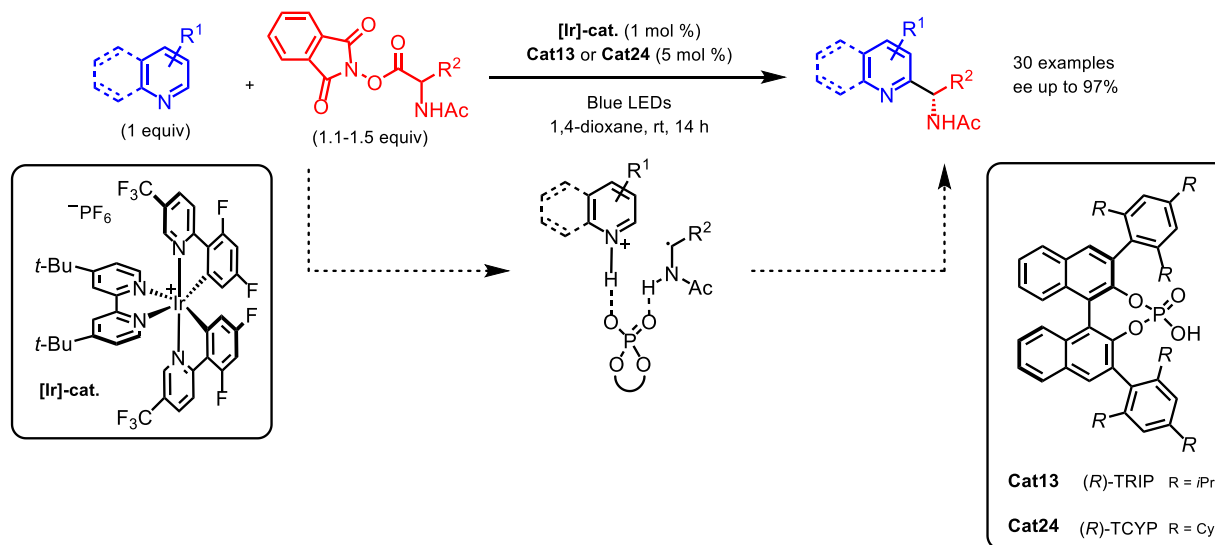
Scheme 39: Initial report of photoredox enantioselective aldehydes alkylation.

Complementary to this transformation, in 2017, the same team found that simple and widely available alkenes could be engaged in aldehyde alkylation (Scheme 40).⁶³ In order to proceed, this valuable photoredox transformation involves three merged catalytic cycles. Upon photoactivation, the iridium photocatalyst reacts with the chiral enamine formed from reaction of the aldehyde with the secondary amine catalyst, to generate an electrophilic radical. Enantioselective C-C bond formation by reaction with the alkene generates a new radical. In order to liberate the product and the organocatalyst, a third catalytic cycle involves hydrogen atom transfer with a thiol catalyst. As a result of this complex catalytic cycle, simple substrates can be easily coupled in an enantioenriched manner, demonstrating all the potential of mult catalysis to achieve otherwise impossible transformations.



Scheme 40: triple catalyzed aldehyde alkylation with alkenes

Aside from aminocatalyzed transformations, photoredox mult catalysis has found applications using other activation modes. For example, in 2018, the team of Phipps found that combining an iridium photocatalyst and a chiral phosphoric acid catalyst could induce the first Minisci-type addition to pyridines and quinolines (Scheme 41).⁶⁴ Upon photoactivation of the iridium complex, an activated amino-ester generates the reactive alkyl-radical. This radical can add to the heteroarene activated through hydrogen bonding by the organocatalyst controlling the stereochemistry on the final product. Proton-transfer and re-oxidation liberates the functionalized heteroarenes with excellent levels of enantioselectivity (typically >90% *ee*). Given the mild conditions, the reaction is quite general and a broad array of useful chiral heteroarenes can be obtained easily through this approach.



Scheme 41: Photoredox mult catalysis with chiral phosphoric acid

V. Conclusion

Since the early days of mult catalysis it was quite clear that such synthetic methodologies had the potential to afford complex molecular scaffolds with high selectivity and wide scope once the associated challenges are overcome. It represents an approach of choice notably as soon as the enantioselective creation of valuable C-C bond is required. The examples presented herein represent a small fraction of what is possible by exploiting the advantages of two or more catalytic systems. The main implications for the synthetic chemist are the possibility to construct complex architectures in a limited number of synthetic operations, working with stable and easy-to-handle substrates, and avoiding the waste associated with multi-step synthesis, waste arising from purification of intermediates, and stoichiometric by-products among others.

At the fundamental level, different mult catalytic strategies can be developed, based on a synergistic transition states, relay, or merged-relay cascades. Given the diversity of catalytic activation modes that were already known, researchers have fully exploited both metal and organocatalysis to develop a broad array of mult catalytic transformations leading rapidly to enantioenriched complex scaffolds of interest. These strategies could involve metal/metal, organo/organo, or metal/organo-catalysis.

With the success achieved in the creation of structurally complex scaffolds in only less than two decades, the future should see an exponential expansion of the field of mult catalysis. Given the diversity of the possible catalyst combinations with the potential to activate as diverse substrates as can a chemist imagine, the potential of mult catalysis seems only limited to the chemists' imagination.

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