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Combining transition metal catalysis and organocatalysis – an update

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The combination of transition metal catalysis and organocatalysis as a new and exciting research area has attracted increasing attention as it can enable the development of unprecedented transformations that is not possible by use of either of the catalytic systems alone, and can improve the reactivity, efficiency and stereocontrol of existing chemical transformations. In this review, we summarize recent remarkable progress in the field of combined transition metal catalysis and organocatalysis, further highlighting the potential of this new and exciting research area and the many challenges that still remain for the future.

1. Introduction

Catalysis has been established as one of the most useful and powerful tools for identifying or engineering new chemical reactions. Historically, catalytic organic synthesis has been dominated by transition metal catalysis.[1] Since 2000, organocatalysis has grown explosively to become one of the most exciting research areas in current organic chemistry.[2] Organocatalysts can promote various organic transformations through distinct activation modes.[3–12] In recent years, the combination of transition metal catalysts and organocatalysts has emerged as a new and powerful strategy for developing new and valuable reactions, and has attracted increasing attention[13,14] as it can enable the development of unprecedented transformations that is not possible by

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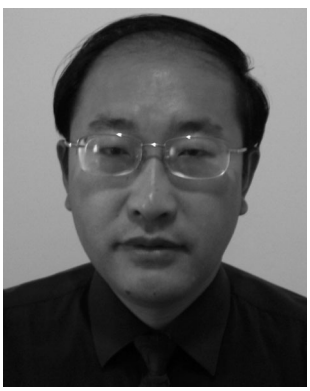

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use of either of the catalytic systems alone. Since our first review on this topic appeared in 2009,[13a] reports on combined transition metal catalysis and organocatalysis including new types of catalyst combinations and new reaction types have increased so fast that an update review on this topic is overdue. This review examines and highlights recent impressive developments and advances in combined organo- and transition metal catalysis. Only articles after 2009 are considered and older reports are only mentioned if there is a close relationship to the publications within this review. For a better understanding, at the beginning we provide a general taxonomy of combining organo- and transition metal catalysis. The advantages of combining both catalytic forms and their challenges are then explained. Subsequently, a literature survey of reported organo-/transition metal catalyst combinations is classified based on the mode of organocatalytic activation, and reaction types are discussed in different types of catalyst combinations.

2. Taxonomy of combining organo- and transition metal catalysis

The combination of organo- and transition metal catalysis is not simply mixing two different catalysts. To reflect the state of the art of this important field, we provide a general classification. For simplicity, we schematically depict the catalytic cycles for a general reaction of two substrates (A and B) affording a product (P).

The first type of catalysis is cooperative catalysis, wherein both the organocatalyst and the transition metal catalyst are directly involved in the same catalytic cycle, working cooperatively to form a product (Fig. 1A).

Different from cooperative catalysis, the second type of catalysis is defined as synergistic catalysis[15] wherein both the organocatalyst and the transition metal catalyst simultaneously activate substrates A and B in two directly coupled catalytic cycles, leading to the formation of a product (Fig. 1B).

As depicted in Fig. 1C, the third type of catalysis is known as sequential or relay catalysis, which requires both the organocatalyst and the transition metal catalyst to perform two distinct catalytic cycles for the consecutive reactions, whereby the substrates (A and B) first react to form an intermediate (**INT I**) in the first catalytic cycle, which can either be the organocatalytic cycle or the transition metal catalytic cycle. Subsequently, this intermediate is converted to the final product (P) by another independent catalyst.

3. Advantages and challenges of combining organo- and transition metal catalysis

While transition metal and organocatalysis individually will have their own place in modern organic chemistry, the combination of transition metal and organocatalysis is particularly attractive as this concept has shown the following unique advantages: (1) It can enable the development of new, previously unattainable transformations by use of either of the catalytic systems alone as the combined catalysis can lead to new types of reactivities. (2) It can create or improve the enantioselectivity where stereochemical control was previously absent or challenging. The combination of transition metal and organocatalysis provides more possibilities to render a reaction enantioselective than testing a single chiral catalyst. By using appropriate combinations of an organocatalyst and an achiral or chiral transition metal catalyst, facile ways for reaction optimization can be achieved. On the other hand, if a metal catalyst and an organocatalyst are able to initiate reactions individually, an asymmetric relay catalytic reaction may be realized with either or both chiral catalysts controlling the stereochemistry. (3) It can improve the efficiency and broaden the substrate scope of existing transformations through the cooperative effect of two or more catalysts.

Despite these stark-obvious advantages, there are some perceived challenges facing this concept. The main challenge in the development of combined transition metal and organocatalyzed transformations is to ensure compatibility of catalysts, substrates, intermediates and solvents throughout the

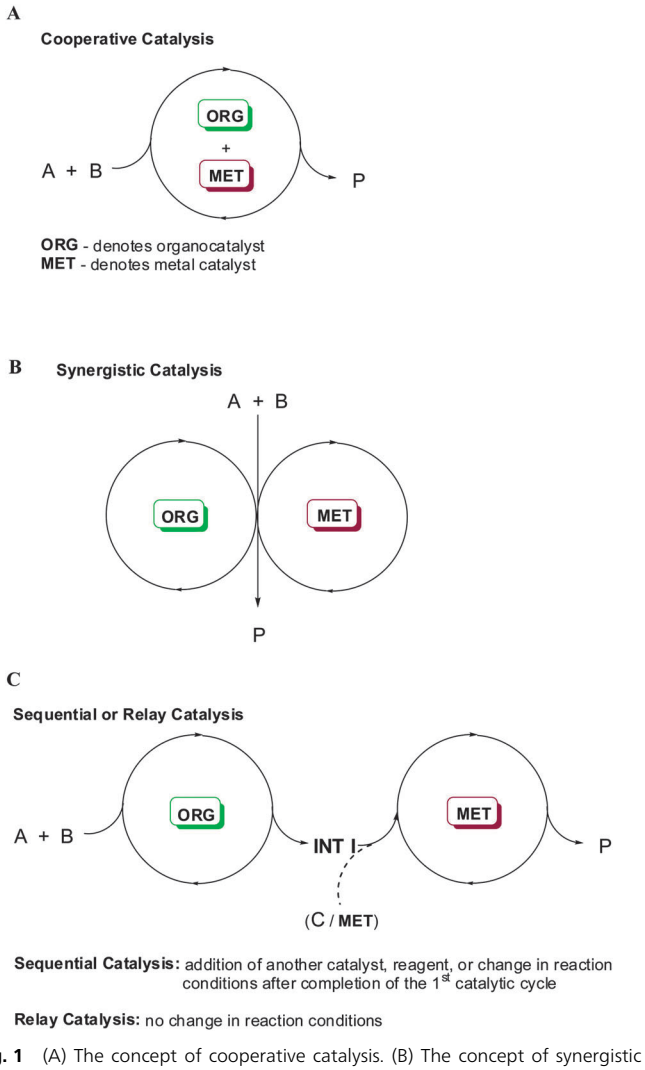


Fig. 1 (A) The concept of cooperative catalysis. (B) The concept of synergistic catalysis. (C) The concept of sequential or relay catalysis.

whole reaction sequence. The key to overcoming this challenge is the judicious selection of appropriate catalyst combinations. Often combining a hard Lewis acid with a soft Lewis base or a soft Lewis acid with a hard Lewis base will avoid the deactivation of catalysts. In addition, the following strategies have also been adopted: the use of the site isolation or phase separation techniques, and sequential addition of catalysts and substrates.

4. Catalysts used in combining organo- and transition metal catalysis

Transition metal catalysts have been combined with the following types of organocatalysts: (a) aminocatalysts including secondary amines and more recent primary amines; (b) Brønsted acid catalysts, especially phosphoric acids based on the chiral BINOL scaffold; (c) hydrogen-bonding catalysts such as thioureas; (d) Brønsted base catalysts; (e) Lewis base (nucleophilic) catalysts; (f) chiral phase transfer catalysts; and (g) *N*-heterocyclic carbene catalysts. The catalyst combinations almost cover all types of organocatalysts. Among them, the combination of amine- and transition metal catalysts as well as the combination of Brønsted acid- and transition metal catalysts have been most intensively investigated in the past several years. Recently, the combination of *N*-heterocyclic carbene and metal catalysis has opened new directions in the area of combined catalysis. On the other hand, with respect to transition metals, the following metals have been employed in the combined organo- and transition metal catalysis: Pd, Rh, Ru, Cu, Ni, Zn, Fe, Ir, Co, Mn, Ti, Y, In, Nb, Au, Ag, Pt, V. Among them, the combination of gold catalysis and organocatalysis has developed quite rapidly in the past four years.[13c] Due to versatile reactivity patterns of transition metals in various transformations,[1] new exciting discoveries could be made through the combination of organocatalysts with different transition metal catalysts.

5. Combining amine and transition metal catalysis

Amine catalysis including secondary amine catalysis and more recent primary amine catalysis plays a crucial role in the course of the development of organocatalysis.[3] Generally, aminocatalysts catalyze organic reactions through two types of activation modes: enamine activation[4] and iminium activation[7] (Scheme 1(A) and (B)). This ability also makes a catalyst ideal for application in tandem reactions *via* iminium–enamine activation (Scheme 1(C)).

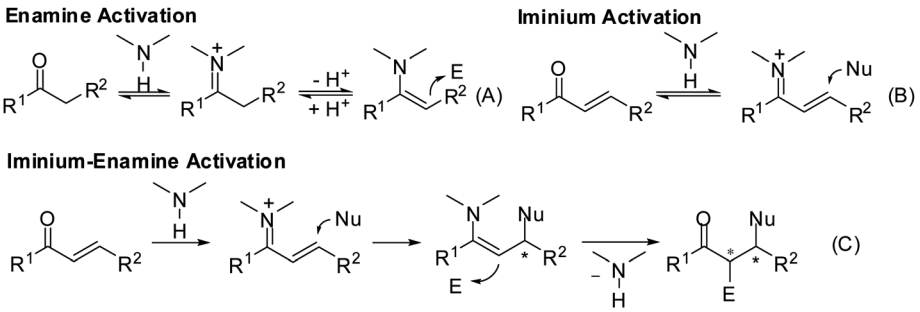
While amine catalysis has been explored by several leading experts since 2000, the first example of combined amine and transition metal catalysis was not reported by Córdova and Ibrahem until 2006.[16] A major challenge is to avoid the deactivation effects of the two catalytic cycles. This breakthrough work has bridged more traditional transition metal catalysis with the newly established prosperous area of aminocatalysis. In the following section, we summarize recent developments on amine-/transition metal catalyst combinations classified based on the mode of aminocatalytic activation: enamine, iminium and iminium–enamine activation. In the corresponding subsection reaction types are discussed and highlighted.

5.1 Combining enamine and transition metal catalysis

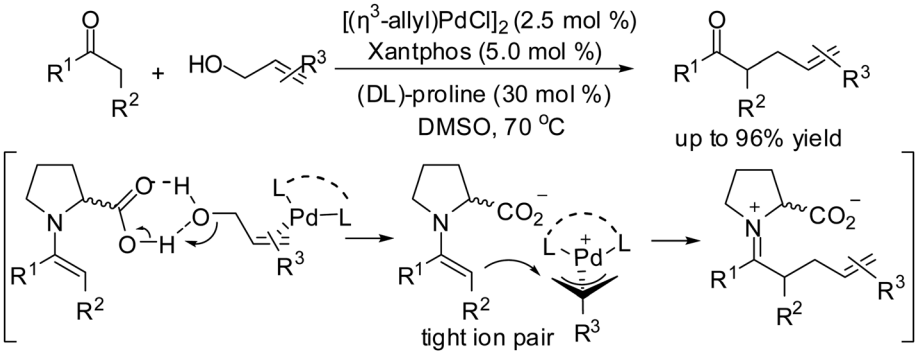
α-Alkylation, α-arylation and α-vinylation of carbonyls. Since the research group of Córdova disclosed the first example of combined transition metal and enamine catalysis for the direct catalytic intermolecular α-allylic alkylation of ketones and aldehydes,[16] remarkable advances have been made in the α-allylic alkylation of ketones and aldehydes.

In 2009, Breit's group reported a novel direct catalytic intermolecular α-allylic alkylation of enolizable ketones and aldehydes with allylic alcohols by combining enamine catalysis and palladium catalysis (Scheme 2).[17] In this report, allylic alcohols were used directly as the substrates, and the proline/palladium/Xantphos combination was identified as the best catalytic system for the allylation process. Control experiments showed that the presence of a carboxylic acid group in the secondary amine catalyst played a crucial role in the catalytic efficacy. However, employing enantiomerically pure proline did not result in any enantiomeric excess in this transformation.

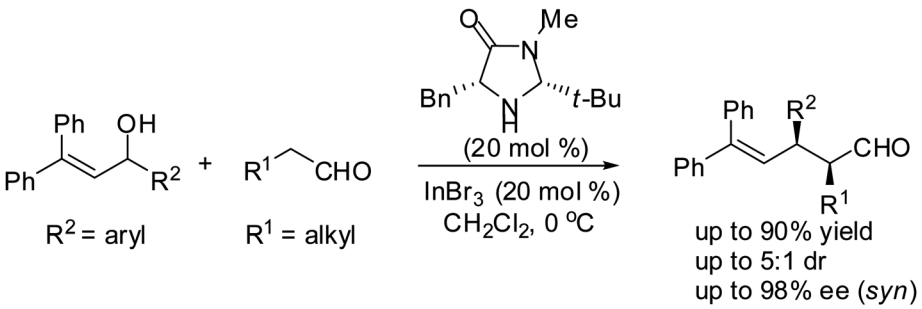
To effect combined amine and transition metal catalyzed asymmetric intermolecular allylation with allylic alcohols, Cozzi and co-workers developed a new catalyst combination consisting of metal Lewis acid $InBr_3$ and MacMillan catalyst (Scheme 3).[18] Mechanistically, this allylation process is different from Breit's protocol. In the Lewis acid catalysis, allylic alcohols produced *in situ* allylic carbocations instead of π-allyl palladium electrophiles, which reacted with *in situ* generated



Scheme 1 Enamine, iminium and iminium–enamine activation.



Scheme 2 Breit's catalytic intermolecular α-allylic alkylation of aldehydes and ketones with allylic alcohols.



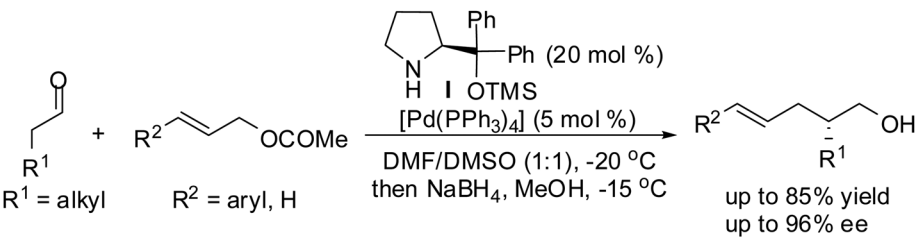
Scheme 3 Cozzi's catalytic asymmetric intermolecular allylation of aldehydes with allylic alcohols.

chiral enamine intermediates to afford the corresponding chiral α-allylated carbonyl products. While the enantioselectivities of this allylation process were high, the diastereoselectivities were generally moderate (2 : 1–5 : 1 dr). Interestingly, it was found that there was a relationship between the diastereoselectivities and the substitution patterns of the R^2 aromatic group of the allylic substrates. With an R^2 group in which the two substituents in position 2 and 6 of the aryl were different, the allylation became more diastereoselective. While various aldehydes were examined in this asymmetric allylation process, the reaction information with ketones as the carbonyl substrates remains unknown.

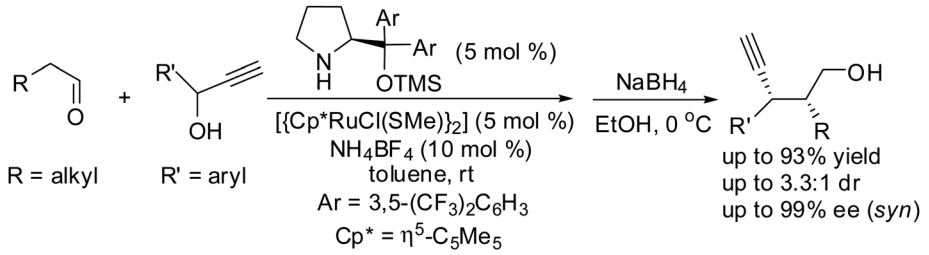
Very recently Córdova and co-workers reported a different asymmetric α-allylic alkylation of aldehydes promoted by $[Pd(PPh_3)_4]$ and Jørgensen–Hayashi chiral secondary amine catalyst **I**, in which allyl acetates were used as the substrates (Scheme 4).[19] Interestingly, in their report published in 2006,[16] the authors already investigated the enantioselective variant of this α-allylic alkylation with the same catalyst combination ($[Pd(PPh_3)_4]$/chiral secondary amine catalyst **I**), however, this catalyst combination in DMSO at room temperature just provided 25% yield and 77% ee. In the current investigation, the authors found that the solvents and temperature played very important roles in achieving high conversion and enantioselectivity. The optimization studies showed that the highest reactivity was achieved in DMSO and the highest enantioselectivity in DMF, respectively. Thus a mixed solvent of DMF/DMSO (1 : 1) was used. Additionally, decreasing the reaction temperature significantly improved the enantioselectivity of the products.

In addition to allylation reactions outlined above, the strategy of combining enamine and transition metal catalysis has also been applied to the propargylation,[20] which is one of the most important fundamental reactions in organic synthesis.

By combining enamine and transition metal catalysis, the Nishibayashi group developed the first enantioselective propargylic



Scheme 4 Córdova's catalytic asymmetric α-allylic alkylation of linear aldehydes with allyl acetates.

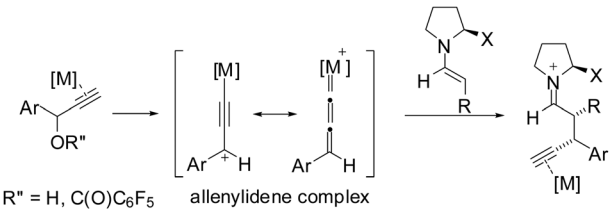


Scheme 5 Asymmetric propargylic alkylation of aldehydes with propargylic alcohols *via* transition metal and enamine catalysis.

alkylation of aldehydes with propargylic alcohols.[21] In the presence of a catalytic amount of a chiral secondary amine and a ruthenium complex, the propargylation with a variety of enolizable aldehydes proceeded smoothly to afford the corresponding propargylic alkylated products in excellent yields with moderate diastereoselectivities and high enantioselectivities (Scheme 5). The propargylation protocol is effective for a wide range of aromatic propargylic alcohols (R′ = aryl). However, no reaction occurred when aliphatic propargylic alcohol was used as a substrate under the same reaction conditions. These results indicate that the presence of an aryl moiety at the propargylic position of propargylic substrates is necessary for the catalytic reaction to take place.

To avoid the use of expensive ruthenium complexes, the Nishibayashi group developed a new enantioselective variant of propargylic alkylation of aldehydes using propargylic esters as the propargylation reagents (Scheme 6).[22] In this case, a copper complex bearing racemic BINAP was utilized as the transition metal catalyst. The stereochemistry of BINAP did not affect the enantioselectivity of the propargylic alkylated product. The asymmetric induction of this propargylic alkylation was thought to result from the chiral organocatalyst. One drawback of this protocol is that high catalyst loading is required to achieve reasonable chemical yields. Additionally, the use of propargylic esters is not atom economic. Interestingly, the nature of the ester group in propargylic esters was found to play a critical role in promoting the catalytic alkylation. Only 1-(1-naphthyl)-2-propynyl 2,3,4,5,6-pentafluorobenzoate (R′ = 1-naphthyl, R″ = C_6F_5) afforded the desired products in acceptable yields. Comparatively, it seems that ruthenium provides the propargylic alkylated products in higher yields,[21] while copper delivers higher selectivities.[22]

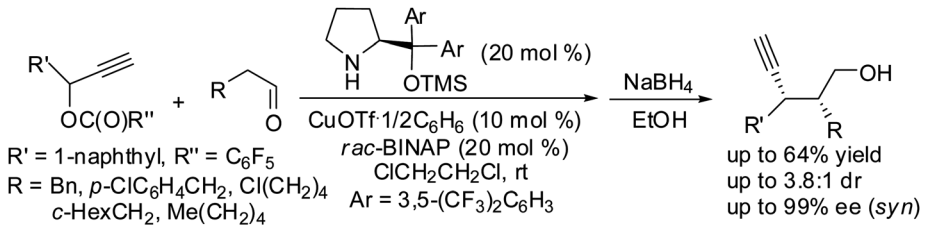
These two catalytic reactions are considered to provide a new type of enantioselective propargylic substitution, where the enamines generated *in situ* from aldehydes enantioselectively attack the γ-carbon atom of the ruthenium–allenylidene complexes (Scheme 7).



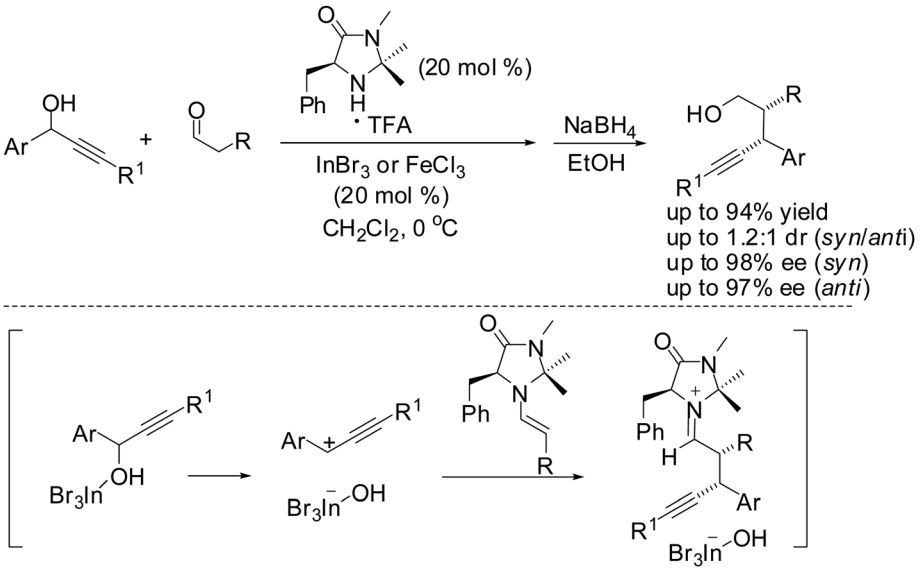
Scheme 7 Mechanism of enantioselective α-propargylation of aldehydes using terminal alkynes.

While the above two propargylation reactions[21,22] are effective for terminal alkynes, these protocols cannot be extended to internal alkynes as the corresponding allenylidene intermediates cannot be formed with internal alkynes. In order to circumvent this substrate limitation, Nishibayashi and co-workers developed a new method to activate propargylic alcohols, enabling the propargylic alkylation of aldehydes with internal alkynes (Scheme 8).[23] In this report, a metal Lewis acid ($InBr_3$ or $FeCl_3$), was used in combination with MacMillan catalyst. Mechanistically, this propargylic alkylation was considered to proceed *via* propargylic cations as reactive intermediates (Scheme 8). Further studies also supported the proposed mechanism. The presence of an electron-donating group such as a dimethylamino or methoxy moiety on the propargylic benzene ring dramatically promoted the propargylic alkylation. In contrast, no reaction occurred at all when a less electron-donating group such as a methyl moiety was introduced onto the propargylic benzene ring. Shortly after this report,[23] the Cozzi group reported the same transformation in water using a similar dual catalyst system consisting of $In(OTf)_3$ and MacMillan catalyst.[24]

The above catalyst combination consisting of a chiral enamine and metal Lewis acid catalysts was not only effective for allylic



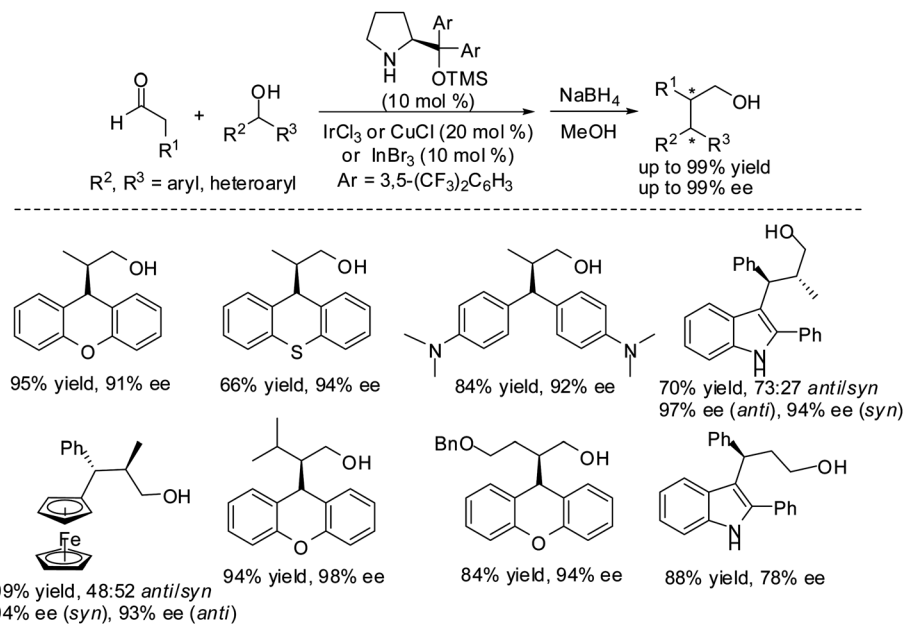
Scheme 6 Asymmetric propargylic alkylation of aldehydes with propargylic esters *via* transition metal and enamine catalysis.



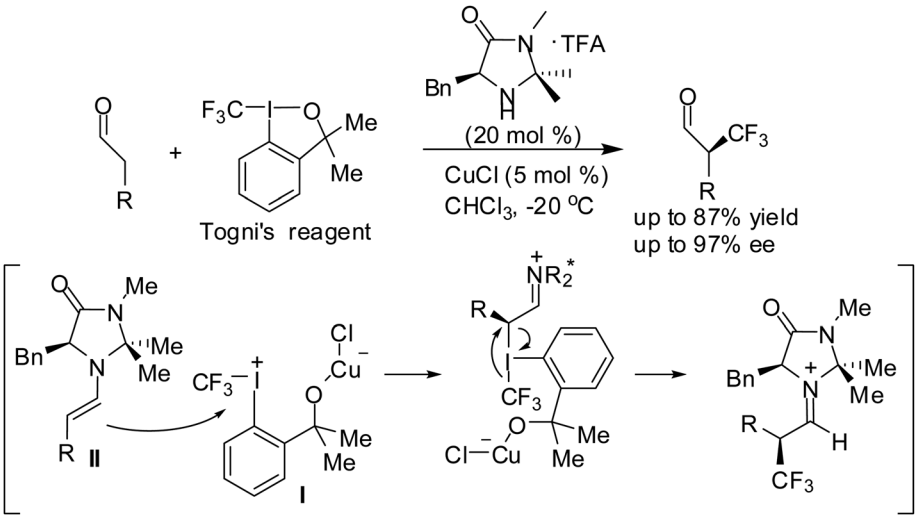
Scheme 8 Enantioselective α-propargylation of aldehydes using internal alkynes *via* transition metal and enamine catalysis.

alcohols[18] and propargylic alcohols,[23,24] but also for other types of alcohol substrates. Recently, Xiao found that the combined catalytic systems involving a diarylprolinol silyl ether and metal Lewis acids CuCl, $IrCl_3$, or $InBr_3$ efficiently catalyzed enantioselective intermolecular α-alkylation of aldehydes with the alcohols which are not active in previous combined enamine and transition metal catalysis (Scheme 9).[25] A variety of activated alcohols, such as xanthydrol, 9*H*-thioxanthen-9-ol, bis(4-(dimethylamino)-phenyl)-methanol, ferrocenyl(phenyl)methanol, and phenyl(2-phenyl-1*H*-indol-3-yl)methanol worked well to afford the corresponding products in high yields and high levels of stereochemical control. With regard to aldehydes, both linear and bulky aldehydes, as well as aldehydes bearing an oxygen atom, were suitable substrates for this enantioselective α-alkylation. Notably, problematic acetaldehyde in enamine catalysis also served as a good partner for this alkylation. While this protocol displays a broad substrate scope, the substrates used are still activated alcohols which can produce relatively stable carbocations in the presence of metal Lewis acid catalysts. Given the versatility of metal Lewis acids in electrophilic activation, we believe that new asymmetric reactions involving unactivated alcohols could be achieved through metal Lewis acid/enamine catalysis in the future.

In all the examples outlined above, activated alcohols and their esters were used as the coupling substrates. Interestingly,



Scheme 9 Asymmetric intermolecular α-alkylation of aldehydes with alcohols by merging a diarylprolinol silyl ether with $IrCl_3$, CuCl or $InBr_3$.



Scheme 10 Enantioselective α-trifluoromethylation of aldehydes using Togni's reagent *via* the combination of copper and imidazolidinone catalysts.

synthetic useful hypervalent iodine reagents have not yet been examined as new coupling partners in combined amine and transition metal catalysis. Due to their low toxicity, ready availability, and ease of handling, hypervalent iodine reagents have found extensive use in synthetic organic chemistry as new coupling partners.[26] Recently their applications in combined metal and enaminecatalysis have been explored by MacMillan and co-workers.

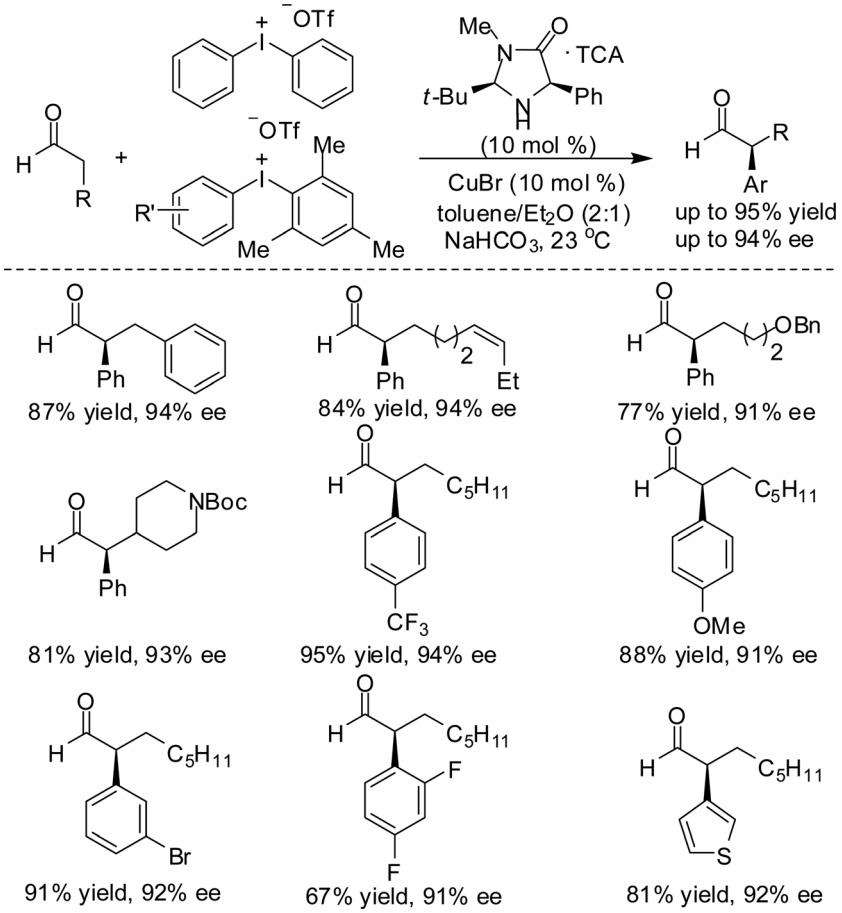
Utilizing Togni's hypervalent iodine reagent as the coupling partner, MacMillan and co-workers developed a nice enantioselective α-trifluoromethylation of aldehydes (Scheme 10).[27] In the presence of copper and imidazolidinone catalysts, various α-trifluoromethylated aldehydes were obtained in good yields with excellent enantioselectivities. While this α-trifluoromethylation protocol exhibits broad scope of the aldehydic component and wide functional group tolerance, it requires high catalyst loading (of 20 mol% of imidazolidinone catalyst). The synergistic use of a Lewis acid in combination with an imidazolidinone catalyst was found to be crucial for high reaction conversion. In the absence of a Lewis acid catalyst, the α-trifluoromethylation reaction with the imidazolidinone catalyst led to low yield (14% yield, 92% ee). Thus, it was reasoned that a Lewis acid should facilitate cleavage of the I–O bond and create active electrophilic iodonium intermediate **I** for nucleophilic attack by the enamine intermediate **II**.

Inspired by the success of the enantioselective α-trifluoromethylation of aldehydes using Togni's hypervalent iodine reagent,[27] MacMillan and co-workers have recently explored the enantioselective direct α-arylation of aldehydes using diaryliodonium salts as an arylation partner and a combination of copper and imidazolidinone catalysts (Scheme 11).[28] This α-arylation protocol displays remarkable substrate scope and functional group tolerance. Various aldehydes that incorporate a wide range of functional groups, including arenes and olefins as well as ethers, esters, and carbamates reacted with diphenyliodonium triflate to afford the desired products in good yields with high enantioselectivity. With regard to diaryliodonium salts, a variety of *para*-, *meta*- and *ortho* substituted aryl rings with diverse steric and electronic properties can be enantioselectively coupled with aldehydes in this α-arylation reaction. Moreover, heteroaromatics of an electron-rich or electron-poor nature were also suitable coupling partners.

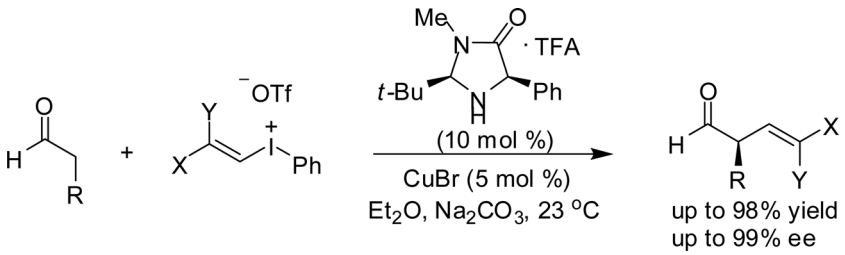
Recognizing the generality of this strategy, MacMillan and co-workers turned to vinyl iodonium salts, and accomplished an enantioselective α-vinylation of aldehydes *via* the combination of copper and enamine catalysis (Scheme 12).[29] This protocol provides a direct route for the enantioselective construction of enolizable α-formyl vinylic stereocenters without racemization or olefin transposition.

In the examples discussed above, both amine and transition metal catalysts have been directly involved in the key bond forming step. Recently, MacMillan and co-workers developed a mechanistically different strategy wherein a catalyst induced the formation of a reactive intermediate, but was not involved in the actual coupling event.[30] Utilizing this strategy of combining enamine catalysis with organometallic photoredox catalysis, MacMillan and co-workers accomplished the enantioselective α-benzylic alkylation of aldehydes, an important yet challenging reaction (Scheme 13).[31] Notably, previous direct organocatalytic methods to form α-benzylated aldehydes require multiple and/or electron-rich aryl rings on the electrophilic coupling partner to stabilize intermediate benzylic carbocations. This combined catalysis strategy enables electron-deficient aryl and heteroaryl methylene bromides to be used as the electrophilic coupling partner(s).

α-Oxyamination of aldehydes. In 2007, Sibi and Hasegawa reported an enantioselective α-oxyamination of aldehydes using $FeCl_3$ and a chiral secondary amine catalyst.[32] The enantioselectivity becomes somewhat lower when the reaction is performed at room temperature. In an effort to circumvent this problem, Kudo and co-workers designed a new combined catalyst system for the same asymmetric α-oxyamination of aldehydes (Scheme 14).[33] This protocol used a resin-supported peptide as the organocatalyst. Notably, the new catalyst system



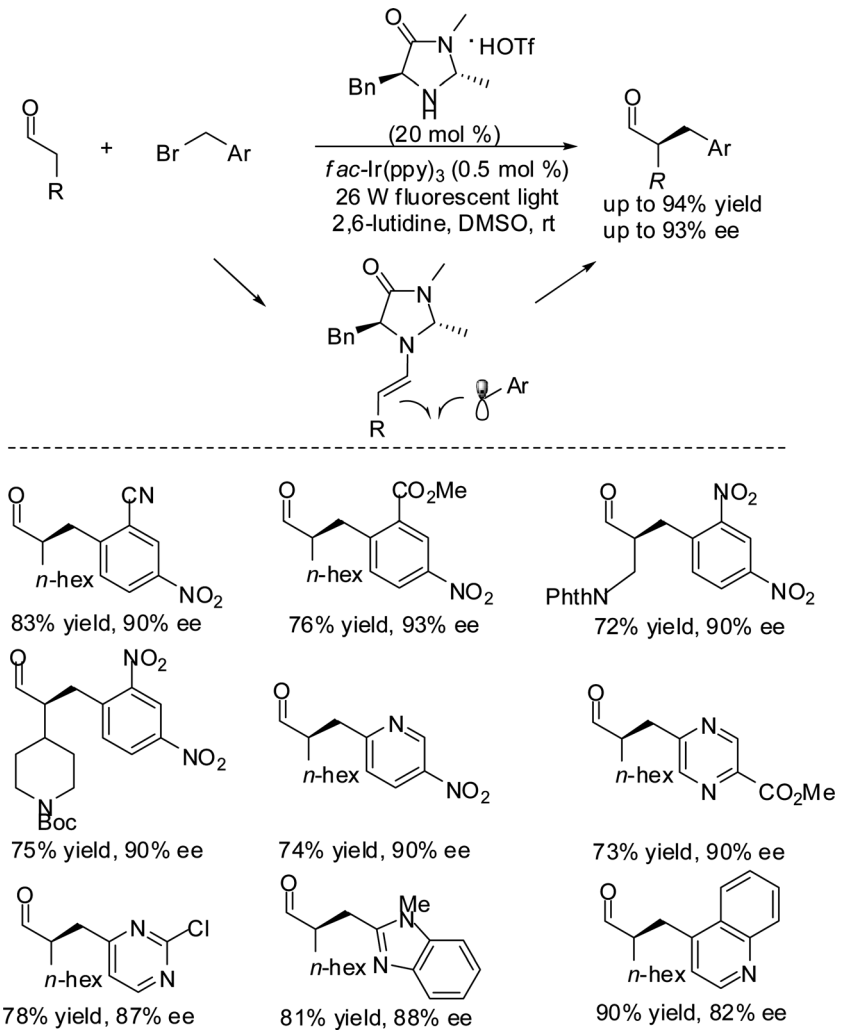
Scheme 11 Enantioselective α-arylation of aldehydes using diaryliodonium salts *via* the combination of copper and imidazolidinone catalysts.



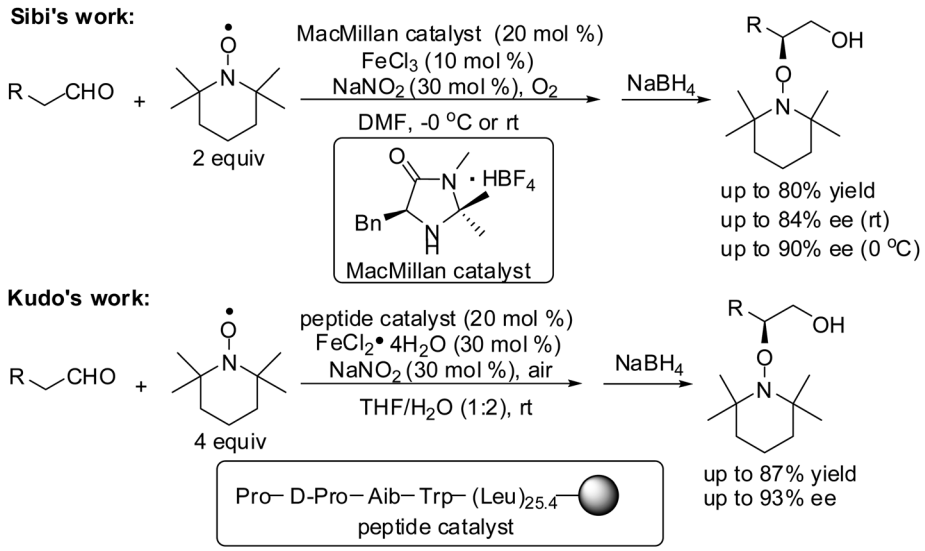
Scheme 12 Enantioselective α-vinylation of aldehydes using vinyl iodonium salts *via* the combination of copper and imidazolidinone catalysts.

allowed the highly enantioselective α-oxyamination to take place not only at room temperature but also in aqueous media. It was found that the condition under dioxygen atmosphere was not necessary, and the reaction completed under air within 1 h. Iron(III) chloride was also effective for this reaction, however, the use of iron(II) chloride gave superior results. Interestingly, different from Sibi's reaction system, the α-oxyamination reactions with Kudo's catalyst system in organic solvents (DMF, THF) resulted in poor yields. As an extension of this work, a one-pot sequential alcohol oxidation and asymmetric α-oxyamination in aqueous media was developed.[34] The newly developed procedure avoids the necessary purification step associated with the use of aldehydes. In addition, the resin-supported peptide catalyst can be reused seven times without substantial loss in both yields and enantioselectivity.

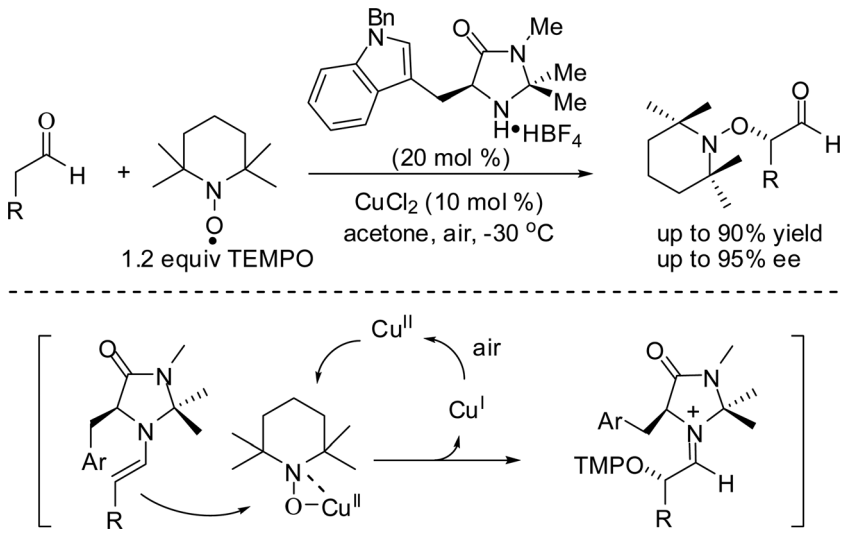
While the mechanism of amine-catalyzed α-oxyamination of aldehydes is well known, the mechanism of the above α-oxyamination reactions remains unknown. Interestingly, Sibi and Hasegawa originally proposed that their α-oxyamination reaction proceeded *via* a SOMO-activation[6] pathway in which an outer-sphere single electron oxidation of a transiently generated enamine using $FeCl_3$ produced a radical cation, which trapped the oxygen radical at the α-position. Recently, MacMillan and co-workers published a paper posing a question for the mechanism proposed by Sibi and Hasegawa.



Scheme 13 Enantioselective α-benzylation of aldehydes with electron-deficient aryl and heteroaryl substrates.



Scheme 14 Eantioselective α-oxyamination of aldehydes by Sibi and Kudo.



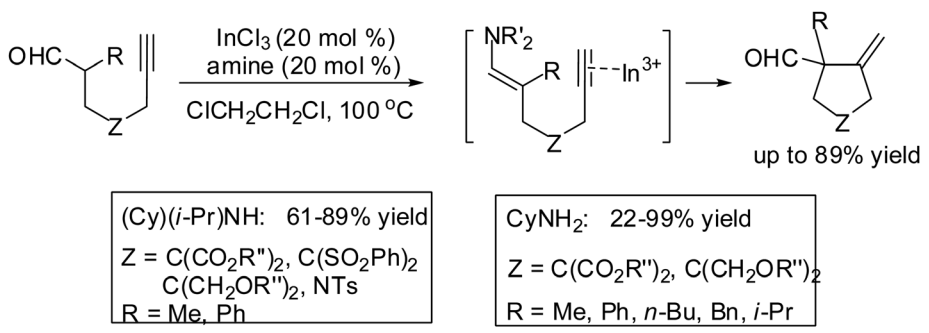
Scheme 15 MacMillan's enantioselective α-oxyamination of aldehydes.

They considered that this transformation most likely proceeded *via* synergistic catalysis wherein the metal catalyst employed in the Sibi studies does not participate as an oxidant, but as a coordinating metal, creating an iron–TEMPO complex that is electrophilic at oxygen and therefore activates towards enamine addition.[35]

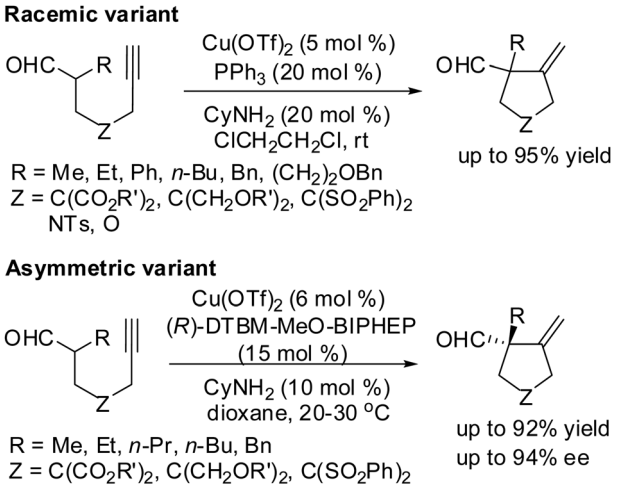
On the basis of this mechanistic insight and the hypothesization that the use of alternative metal salts, which are known to form stable complexes with TEMPO, could lead to a more general and highly enantioselective method for the α-oxyamination of aldehydes, MacMillan and co-workers developed a new enantioselective α-oxyamination of aldehydes that combines imidazolidinones and $CuCl_2$ in a synergistic catalysis transform (Scheme 15).[36] The air was used as a stoichiometric oxidant in this new protocol which is environmentally or economically advantageous. Moreover, the new protocol broadened the functional group tolerance of the reaction and increased both yields and enantioselectivities. In contrast to existing methods, a broad range of heteroatoms, olefins, arenes, and steric environments are tolerated to provide α-oxyamination products in high yields and with excellent enantioselectivity.

Direct carbocyclization of formyl alkynes. The first combined enamine and transition metal catalyzed carbocyclization of formyl alkynes was reported by Kirsch *et al.* in 2008.[37] In this report, both the Au(I) and the achiral secondary amine were used as the catalysts. This methodology gave the products in good to excellent yields. However, the scope described for this catalytic system in the case of α-methyl-substituted formyl aldehydes was very limited. To expand the substrate scope of the carbocyclization reaction, a new dual catalytic system consisting of a secondary amine, (Cy)(i-Pr)NH, and an indium salt, $InCl_3$, was developed by Michelet and Ratovelomanana-Vidal in 2010 for the direct carbocyclization of α-disubstituted formyl alkynes (Scheme 16).[38a] This dual catalytic system was effective for various α-methyl and α-phenyl substrates; however, for the corresponding substrates of *n*-butyl, benzyl, or i-propyl, the catalytic use of less sterically demanding primary amine catalyst, $CyNH_2$, in combination with $InCl_3$ was required to obtain efficient transformation.[38b]

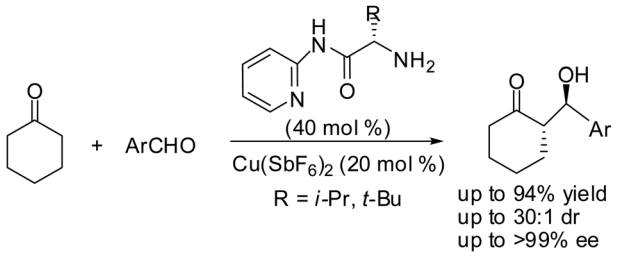
While the above combined catalytic systems were effective for various formyl alkynes, they still required rather elevated temperature (70 to 100 °C). To solve this issue, Michelet and Ratovelomanana-Vidal recently developed an efficient Cu(I)/amine catalytic system for the direct carbocyclization of α-disubstituted formyl alkynes (Scheme 17).[39a,b] This novel cooperative catalytic system allows the cyclization of a broad range of α-disubstituted formyl alkynes to proceed at room temperature, providing a



Scheme 16 Cooperative indium(III) and amine catalyzed direct carbocyclization of α-disubstituted formyl alkynes.



Scheme 17 Cooperative copper(I) and primary amine catalyzed direct carbocyclization of α-disubstituted formyl alkynes.



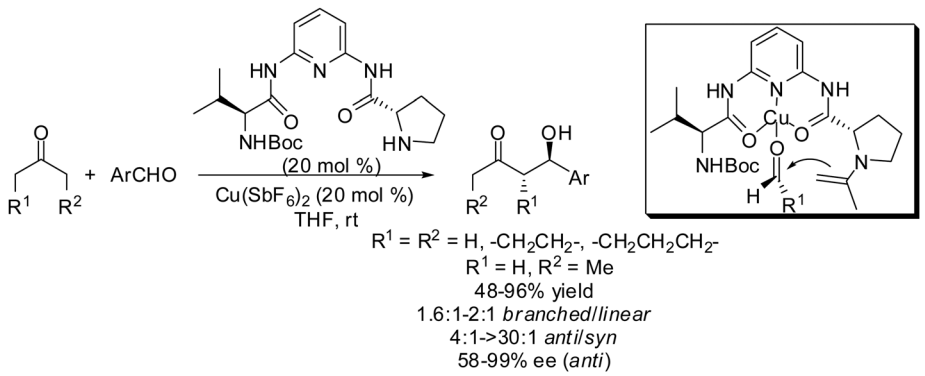
Scheme 19 Direct asymmetric aldol reactions of ketones by primary amine–metal Lewis acid bifunctional catalysts based on bidentate ligands.

high variety of 5-membered cyclic skeletons including cyclopentanes, indanes, pyrrolidines and tetrahydrofuran, in good to excellent yields. Notably, this combined catalyst system provides the possibility to render the carbocyclization enantioselective. Employing a chiral copper(I) complex in combination with a primary amine catalyst ($CyNH_2$), they successfully accomplished an enantioselective variant of the direct carbocyclization reaction with moderate to excellent enantioselectivities (Scheme 17).[40] This represents the first enantioselective carbocyclization of formyl alkynes catalyzed by the merger of enamine and transition metal.

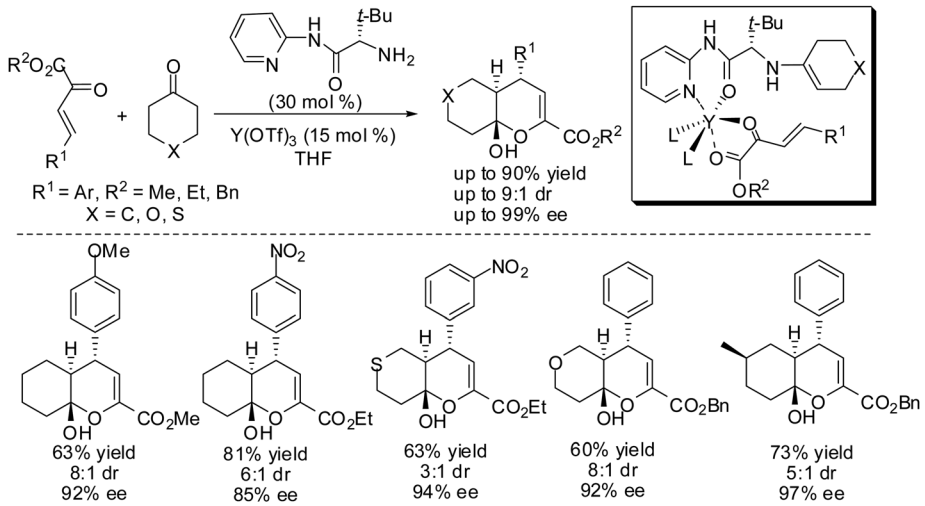
Aldol reaction. The direct catalytic asymmetric aldol reactions[41] promoted by chiral enamine catalysts are one of the most studied chemical reactions in organocatalysis. However, the merger of an enamine and a metal Lewis acid for the direct asymmetric aldol reaction was not reported until 2009. The major challenge in developing Lewis acid–Lewis base bifunctional catalysts lies in the acid–base self-quenching, leading to catalyst-inactivation. To solve this problem, Wang and co-workers developed a tridentate-ligand-tethered secondary amine as a bifunctional catalyst to maximize the compatibility of a Lewis basic secondary amine and a Lewis acidic transition metal for the direct asymmetric aldol reaction of ketones with aryl aldehydes (Scheme 18).[42] $Cu(SbF_6)_2$ was found to be the optimal metal choice for the best reactivity and stereoselectivity. Most of the examined aldehyde acceptors are electron-poor species, and the donors include acetone, cyclopentanone, cyclohexanone and 2-butanone. The regioselectivity in the case of 2-butanone is poor, though the diastereoselectivity and enantioselectivity in such cases is high.

To extend this bifunctional catalysis strategy,[43] the same group has recently developed a new class of primary amine–metal Lewis acid cooperative bifunctional catalysts using simple bidentate ligands (Scheme 19).[44] These catalysts catalyzed the direct asymmetric aldol reactions of cyclohexanone and aryl aldehydes efficiently, offering higher enantioselectivities than those based on tridentate ligands. Moreover, the catalysts were compatible with water.

Inverse-electron-demand hetero-Diels–Alder reaction. Asymmetric inverse-electron-demand hetero-Diels–Alder reaction between cyclic ketones and β,γ-unsaturated-α-ketoesters (activated enones) represents a challenging reaction in traditional organocatalysis as it has been reported that the same reactants in the presence of different proline-derived catalysts can lead to a highly enantioselective aldol reaction[45] or an asymmetric formal [3+3] annulation reaction.[46] To offer a convenient and viable approach to meet the long-standing challenge, Wang and co-workers introduced the concept of enamine/metal Lewis acid bifunctional catalysis to the hetero-Diels–Alder (HDA) reaction of cyclic ketones and β,γ-unsaturated-α-ketoesters (Scheme 20).[47] The strong activation of the activated enones through chelation to the metal and the intramolecular nature of the bifunctional catalyst was considered to contribute



Scheme 18 Direct asymmetric aldol reactions of ketones by enamine–metal Lewis acid bifunctional catalysts.



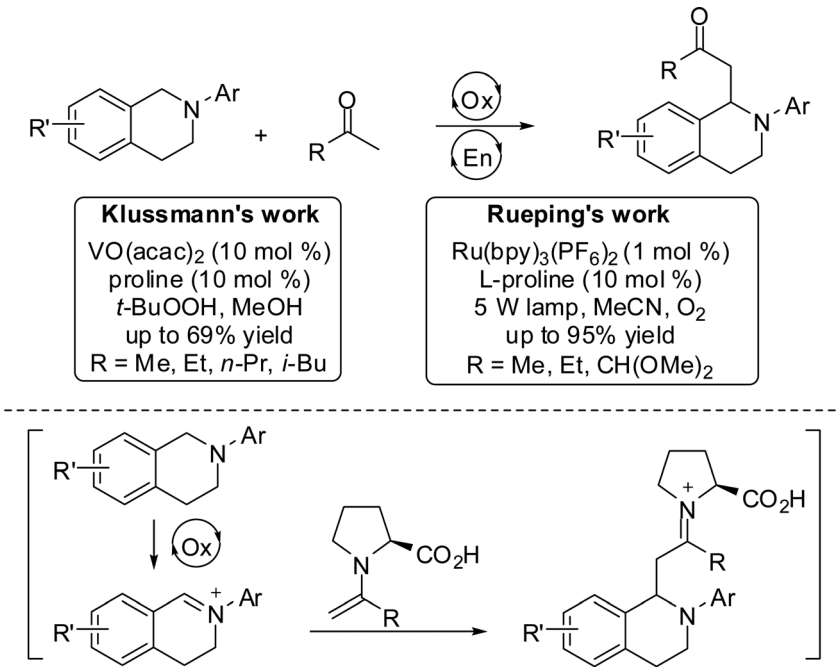
Scheme 20 Asymmetric HDA reaction of cyclic ketones by enamine/metal Lewis acid bifunctional catalysis.

to the high activity and stereoselectivity of the HDA reactions. A wide range of β,γ-unsaturated-α-ketoesters with both electron-donating and electron-withdrawing aromatic substituents at the γ-position reacted smoothly with various six-membered cyclic ketones, affording the chiral dihydropyran derivatives with up to four stereogenic centers in excellent chemo- and enantioselectivities.

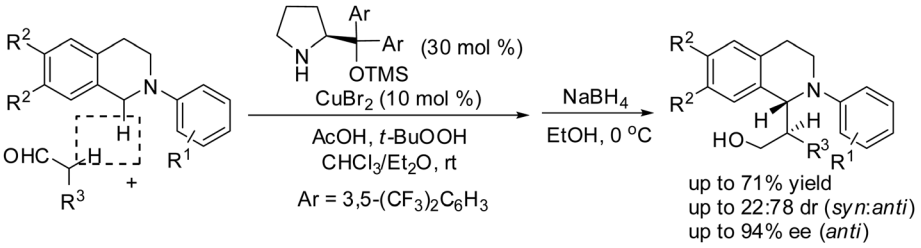
Cross-dehydrogenative coupling reactions. The direct oxidative cross-dehydrogenative coupling (CDC) of two C–H bonds represents an atom-economical and environmentally friendly strategy for C–C bond formation.[48] Recently CDC reactions attracted increasing interest in combined transition metal and amine catalysis.

In 2009, Klussmann and co-workers reported a CDC reaction of cyclic tertiary amines with non-activated ketones (methyl ketones) using a combination of vanadium and proline as the catalyst (Scheme 21).[49] Two years later, the same oxidative coupling reaction using a combination of ruthenium and proline was reported by the Rueping group (Scheme 21).[50] Instead of using catalytic $VO(acac)_2$ and *t*-BuOOH to generate the intermediate iminium ions, this protocol used photocatalytic oxidation with $Ru(bpy)_3(PF_6)_2$ to generate the intermediate iminium ions. As with Klussmann's protocol, Rueping's photoredox oxidative coupling with enantiomerically pure L-proline also resulted in nearly racemic products (7–8% ee).

Recently, Chi and co-workers disclosed an enantioselective oxidative CDC of tertiary amines with aldehydes using a chiral secondary amine in combination with $CuBr_2$ as a dual catalytic



Scheme 21 Oxidative CDC of tertiary amines and ketones reported by Klussmann and Rueping.



Scheme 22 Chi's oxidative cross-dehydrogenative coupling of tertiary amines and aldehydes.

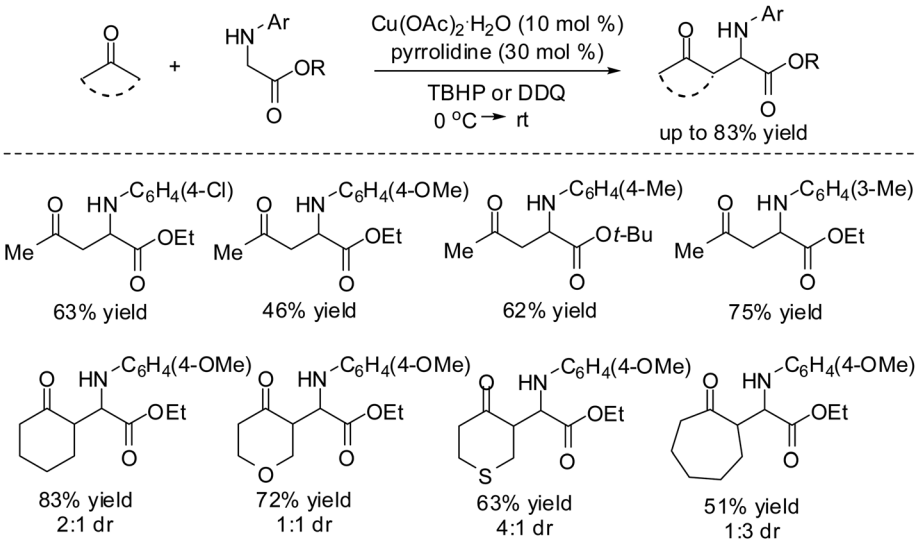
system (Scheme 22).[51] This oxidative CDC allows optically active β-amino alcohols that contain tetrahydroisoquinoline units to be synthesized efficiently. The protocol was effective for a variety of *N*-aryl-tetrahydroisoquinolines with both electron-withdrawing and donating R^1 substituents on the *N*-aryl ring. The R^2 substituents on the tetrahydroisoquinoline ring did not influence the reaction outcomes. In addition to propionaldehyde, other aldehydes such as *n*-butyraldehyde, *n*-valeraldehyde and 3-phenylpropionaldehyde provided the desired products with good enantioselectivity, albeit in lower yields. While the diastereoselectivity of this CDC is still modest, it represents the first highly enantioselective oxidative coupling reaction of tertiary amines and non-activated carbonyl compounds.

In the oxidative CDC reactions outlined above, the common tertiary amines have been used as the coupling substrates. Recently Huang and co-workers demonstrated a remarkable example of a CDC reaction in which less used secondary amines were used as coupling partners.[52] The coupling of *N*-aryl glycine esters with unmodified ketones (acetone and cycloketones) proceeded smoothly under the dual catalysis of $Cu(OAc)_2 \cdot H_2O$ and pyrrolidine in the presence of TBHP or DDQ to give the desired *N*-aryl amino acid derivatives in good yields (Scheme 23). Interestingly, when cycloketones were employed instead of acetone in this CDC reaction, TBHP (*tert*-butyl hydroperoxide) had to be replaced with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) as the oxidant. In addition, although various 6- and 7-membered cyclic alkanones were suitable substrates for this CDC, simple 5-membered cycloketone such as cyclopentanone has remained to be explored. Asymmetric catalysis was also investigated; however, low asymmetric induction ($\leq$15% ee) was observed with several chiral secondary amine catalysts.

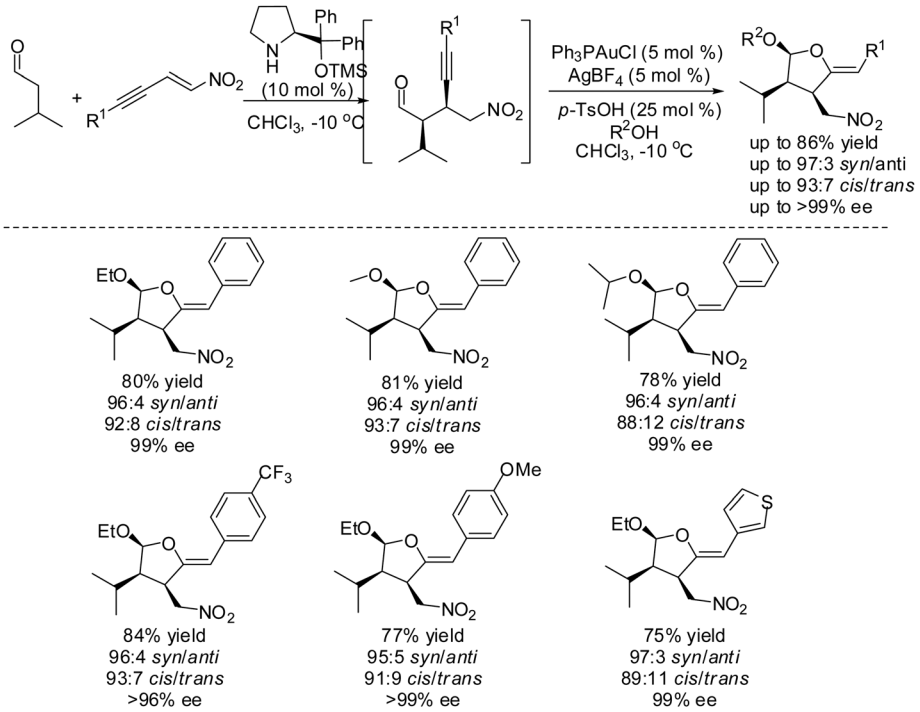
In spite of these exciting reports, an enantioselective oxidative CDC reaction with simple ketones still remains a significant challenge in this field.

Tandem reactions. Tandem reaction is one of the most powerful synthetic tools for accessing complex molecules rapidly and efficiently from relatively simple starting materials by enabling several bond-forming events to occur in the same reaction vessel.[53,54] In recent years, the combination of transition metal and enamine catalysis has been used for the development of new tandem transformations.

In 2009, Krause, Alexakis and co-workers reported an impressive enantioselective tandem Michael addition/acetalization/cyclization reaction (Scheme 24).[55] This tandem catalysis provided chiral nitrosubstituted tetrahydrofuranyl ethers in good yields with high diastereo- and enantioselectivities. The key to this methodology is the design of bifunctional alkyne-tethered nitroalkene substrates. In this report, the Au(I) catalyst was added sequentially to the reaction flask to effect acetalization/cyclization after the completion of the first amine-catalyzed asymmetric



Scheme 23 Huang's oxidative cross-dehydrogenative coupling of secondary amines and ketones.

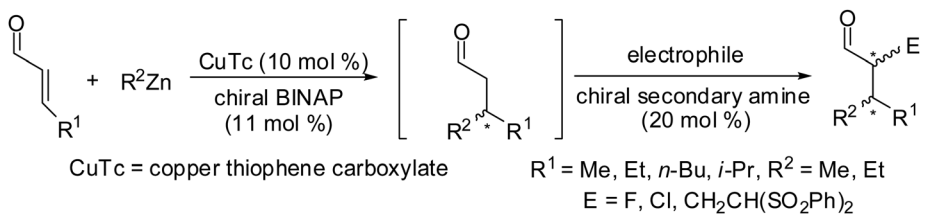


Scheme 24 Amine-catalyzed Michael addition/gold-catalyzed acetalization/cyclization.

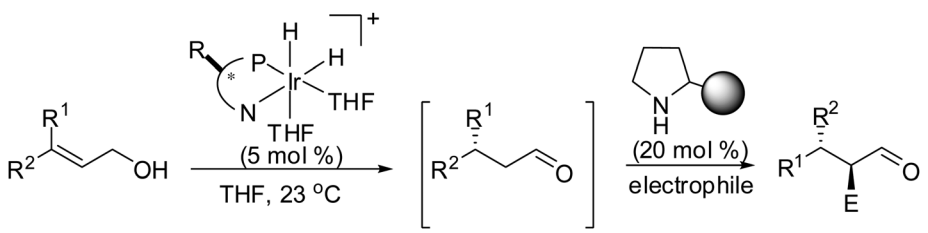
Michael addition. The authors also mentioned that *p*-TSA is crucial in ensuring that the Au(I) catalyst is not deactivated by the secondary amine catalyst.

Utilizing the sequential catalysis strategy, Alexakis and co-workers developed a highly enantioselective copper-catalyzed 1,4-addition/organocatalyzed α-functionalization of enals to produce the α,β-chiral aldehydes bearing two contiguous stereocenters (Scheme 25).[56] In this report, the chiral second amine catalyst was added sequentially to the reaction flask after the completion of the first copper-catalyzed enantioselective 1,4-addition. This methodology has been applied in the concise synthesis of (2*S*,3*S*) isomer of Valnoctamide®. The most attractive feature of this protocol is that any product enantiomer or diastereomer could be achieved by judicious catalyst selection (copper ligand/organocatalyst). This work represents the first example of combining an enantioselective copper-catalyzed step with an asymmetric organocatalytic step.

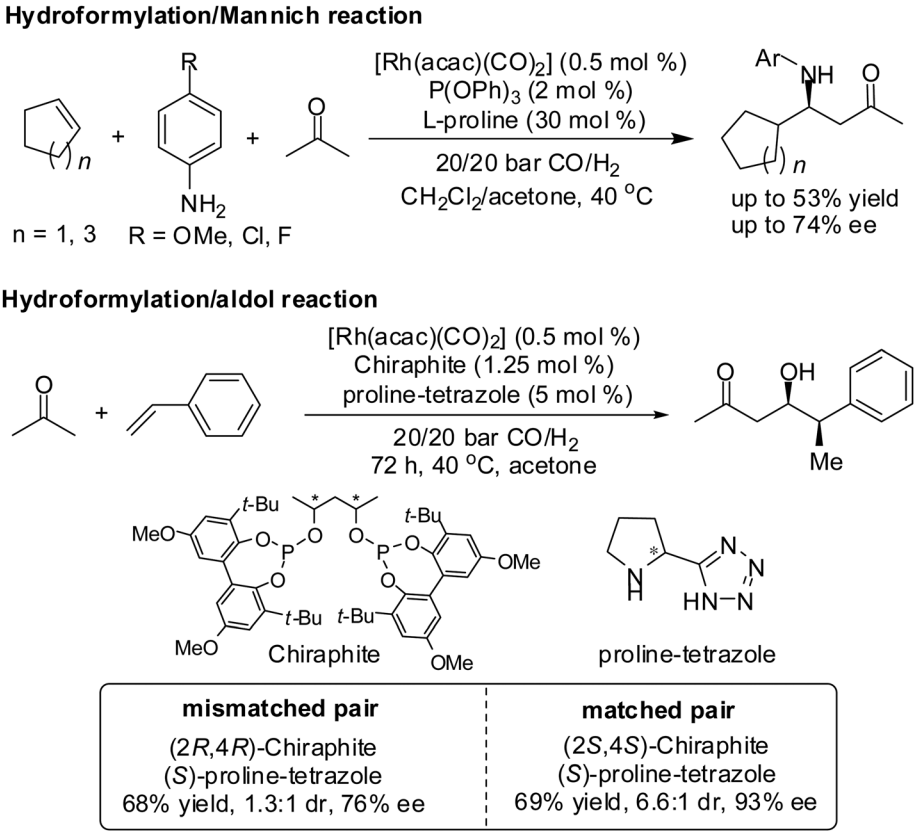
In a different light, Alexakis and Mazet developed a new highly stereoselective synthesis of α,β-chiral aldehydes.[57] The protocol involves a recently discovered iridium-catalyzed isomerization of 3,3-disubstituted primary allylic alcohols[58] followed by a well-established amine-catalyzed α-functionalization



Scheme 25 Copper-catalyzed 1,4-addition/amine-catalyzed α-substitution of enals.



Scheme 26 Asymmetric synthesis of α,β-chiral aldehydes from the alcohols by iridium/enamine catalysis.



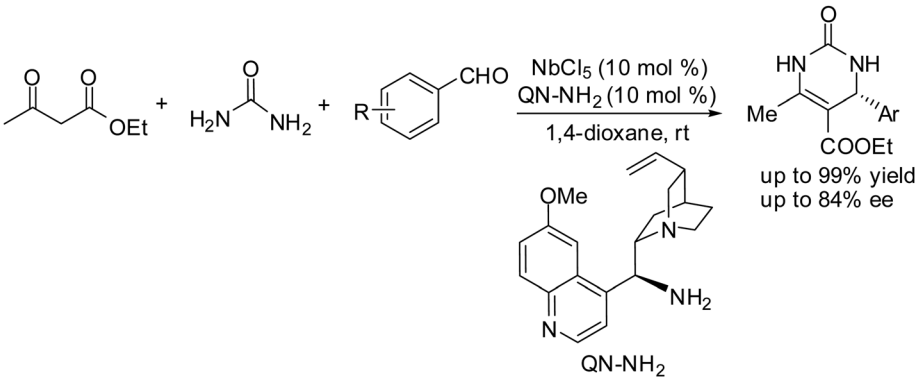
Scheme 27 Combination of Rh-catalyzed hydroformylation with enamine catalysis.

of aldehydes (Scheme 26). The use of a chiral iridium catalyst in combination with a chiral enamine catalyst was found to give excellent diastereo- and enantioselectivities. When compared with copper-catalyzed 1,4-addition/amine-catalyzed α-functionalization sequence,[56] this protocol generally gives the α,β-chiral aldehyde products in relatively moderate yields.

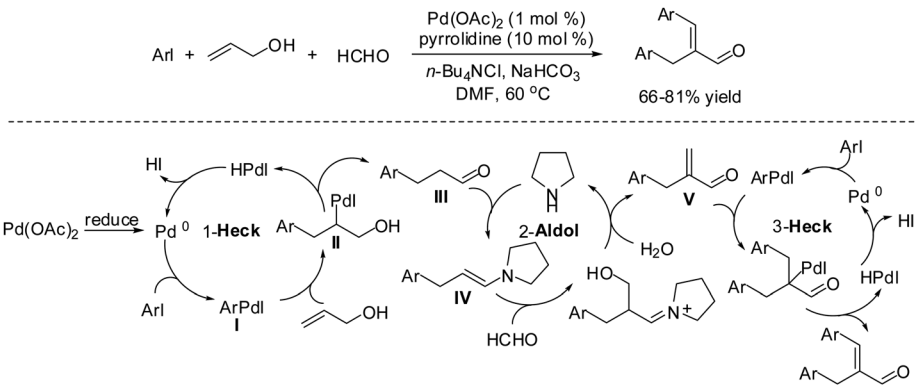
Hydroformylation of olefins has been established as an important industrial tool for the production of aldehydes and products derived therefrom. Recently rhodium-catalyzed hydroformylation has been combined with enamine catalysis for the development of new tandem reactions. Two recent examples are listed in Scheme 27. The first tandem protocol involves a rhodium-catalyzed hydroformylation and a subsequent proline-catalyzed enantioselective Mannich reaction.[59] Starting from simple alkenes, chiral β-amino ketones were obtained in a one-pot fashion. However, yields and enantioselectivities are moderate. The second tandem protocol involves a rhodium-catalyzed enantioselective hydroformylation and a subsequent proline-tetrazole catalyzed aldol reaction.[60] In this protocol, a chiral β-hydroxyl ketone was obtained in good yield with high dr and ee values. Additionally, two chiral catalysts were used in this instance, and match/mismatch effects were observed. It was found that the diastereoselectivity of this tandem reaction could be considerably increased by using a matched pair of catalysts, and decreased, but not inverted, by using a mismatched pair of catalysts. While some issues such as reactivity and stereoselectivity of the reactions still need to be addressed further, the work outlined here confirms the potential of combining rhodium-catalyzed hydroformylation with organocatalysis in the development of new types of tandem reactions.

The enamine-/transition metal dual catalysis has also been used in Biginelli reaction by Xu, Lai, and co-workers (Scheme 28).[61] In this instance, a transition metal Lewis acid/primary amine catalyst system, $NbCl_5$/QN-NH_2, was used. The authors proposed that $NbCl_5$ was responsible for the reactivity, and the chiral primary amine, QN-NH_2, introduced the stereoselectivity to this reaction. While the reaction enantioselectivity is still moderate, it provides a different way to this important transformation, and holds potential for further development.

The power of combined catalysis lies in its ability to develop unprecedented transformations not currently possible by use of either of the catalytic systems alone. By combining enamine and palladium(0) catalysis, Huang and co-workers recently developed an unprecedented Heck–Aldol–Heck cascade reaction in which two C–C single bonds and one C=C double bond were formed in one process.[62] The mechanism of this remarkable transformation is outlined in Scheme 29. At first, $Pd(OAc)_2$ is reduced to palladium(0) by alkene, amine, *etc.* in the reaction system to start the first catalytic cycle. Insertion of a C=C double bond of the allyl alcohol to organopalladium intermediate **I** leads to β-arylated intermediate **II** preferentially, rather than its α-arylated counterpart due to steric hindrance. β-Arylated propanal **III** as the product of the first cycle for Heck reaction enters into the second catalytic cycle for the aldol



Scheme 28 $NbCl_5$/primary amine catalyzed enantioselective Biginelli reaction.



Scheme 29 Heck–Aldol–Heck cascade reaction by combining palladium(0) catalysis and aminocatalysis.

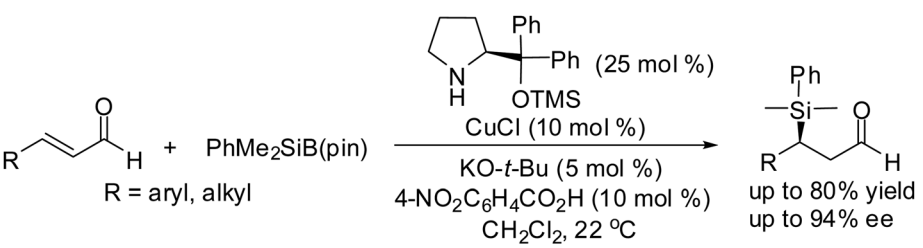
condensation catalyzed by pyrrolidine to afford disubstituted alkene **V**. Subsequently, **V** enters into the third catalytic cycle for the second Heck reaction to produce the desired trisubstituted alkene.

5.2 Combining iminium and transition metal catalysis

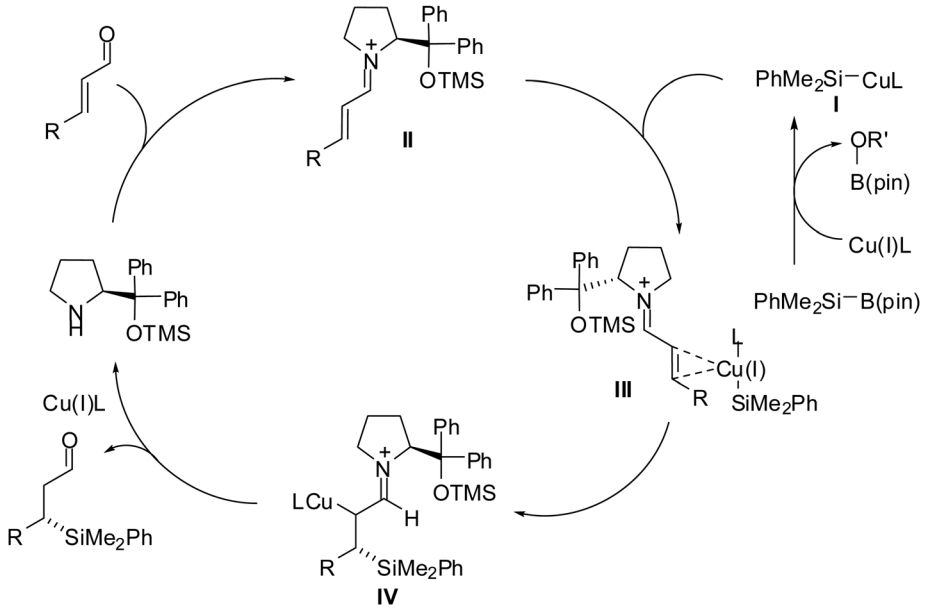
By merging iminium with transition metal catalysis, the Córdova group developed the first enantioselective silyl conjugate addition to α,β-unsaturated aldehydes using Me_2PhSi-B(pin), an unlikely nucleophile in traditional iminium catalysis (Scheme 30).[63] In the presence of 10 mol% CuCl and 25 mol% chiral secondary amine, chiral β-silyl aldehydes were obtained in good yields with high enantioselectivities. The silyl conjugate addition tolerated enals with either an aryl substituent or an aliphatic moiety at the β-position. It seems that the catalytic β-silylation of cinnamic aldehydes bearing an electron-donating group gave a higher enantioselectivity than those with an electron-withdrawing group at the phenyl group.

This enantioselective conjugate silyl addition reaction was proposed to proceed through the following mechanism (Scheme 31). Me_2PhSi-B(pin) reacts with CuCl to form the nucleophilic Cu(I)-silane **I**. In parallel, a simple chiral amine condenses with α,β-unsaturated aldehyde to produce the iminium intermediate **II**. Then the Cu(I)-silane **I** reacts with the chiral iminium intermediate **II** *via* possible intermediate **III**. The resultant copper-bound β-silyl iminium ion **IV** hydrolyzes to provide the desired enantioenriched β-silyl aldehyde.

In addition to the enantioselective conjugate silyl addition, catalytic asymmetric borane conjugate addition has also been proved to be feasible *via* the merger of transition metal and



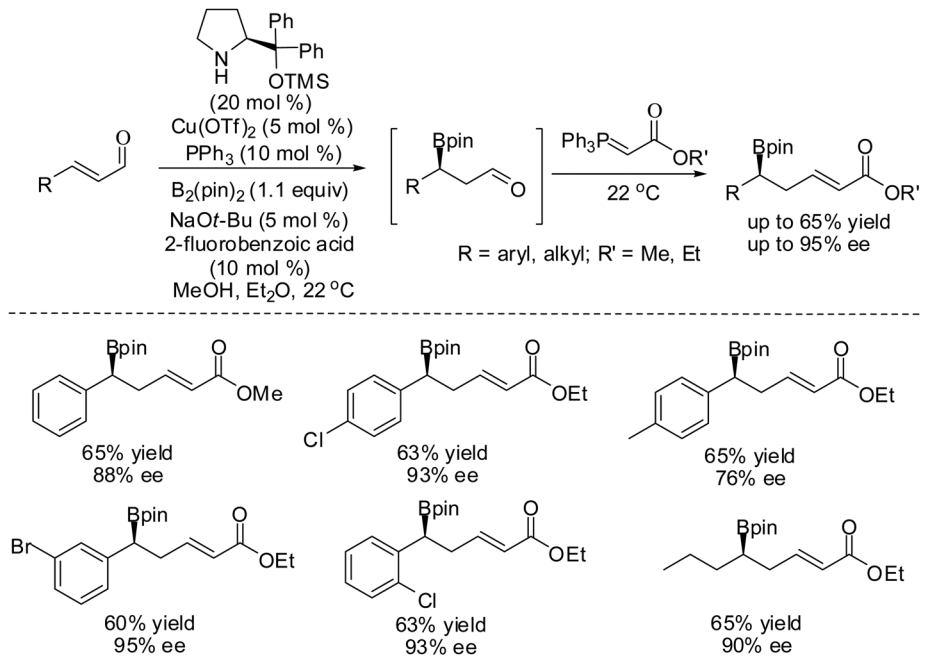
Scheme 30 Enantioselective conjugate silyl addition to α,β-unsaturated aldehydes *via* merger of copper and iminium catalysis.



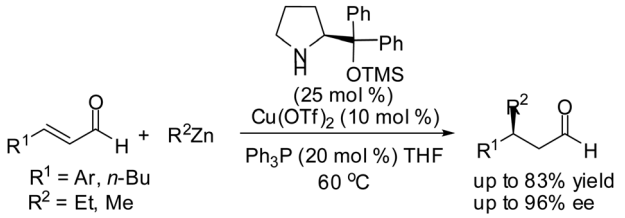
Scheme 31 Mechanism of enantioselective conjugate silyl addition to α,β-unsaturated aldehydes.

iminium catalysis. Recently the Córdova group developed a catalytic asymmetric borane conjugate addition that was trapped by Wittig reaction to afford chiral homoallylboronates (Scheme 32).[64] The protocol tolerated enals with both aryl and aliphatic substituents at the β position. Moreover, cinnamic enals with an electron-withdrawing group at the *para*, *ortho*, or *meta* position exhibit higher reactivity in the β-boration step. However, the enals bearing heterocyclic substituents at the β position were not suitable substrates for this three-component reaction.

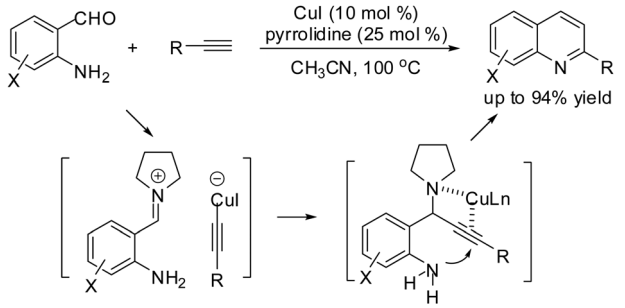
Recognizing the generality of this strategy, Córdova and co-workers turned to carbon nucleophiles, and developed a highly enantioselective conjugate addition of dialkylzinc reagents to α,β-unsaturated aldehydes (Scheme 33).[65] The direct transition-metal-catalyzed enantioselective 1,4-addition of an organometallic reagent to an α,β-unsaturated aldehyde in the presence of a chiral ligand is challenging due to a competing 1,2-addition reaction. By using a combination of transition metal and iminium catalysis, chiral β-alkyl aldehydes were obtained in moderate to good 1,4-regioselectivities with high



Scheme 32 Three-component enantioselective reaction between a diboron reagent, α,β-unsaturated aldehydes and 2-(triphenylphosphoranylidene) acetate esters.



Scheme 33 Catalytic enantioselective β-alkylation of α,β-unsaturated aldehydes by the combination of copper and iminium catalysis.



Scheme 34 Synthesis of 2-substituted quinolines by metal/amine dual catalysis.

enantioselectivity (up to 96% ee). This protocol did not require the use of a glove box. This novel conjugate addition has been utilized as the key step for the expeditious total synthesis of bisabolane sesquiterpenes.

In the above examples of combining transition metal with iminium catalysis, α,β-unsaturated aldehydes have been used as the iminium substrates. Recently aryl aldehydes have been proved to be effective partners in the merger of transition metal with iminium catalysis.[66,67]

The first example reported by Patil and Raut involves a tandem 1,2-addition/cycloisomerization between 2-aminobenzaldehydes and terminal alkynes. In this instance, a dual catalytic system consisting of CuI and pyrrolidine was utilized (Scheme 34).[66] The presence of both catalysts is necessary, and the use of either of the catalysts alone did not give any product. This protocol displays a wide substrate scope with respect to both 2-aminobenzaldehydes and terminal alkynes. Aromatic, heteroaromatic and aliphatic alkynes reacted efficiently to give the desired products in good yields. Interestingly, enynes were also good substrates for this tandem reaction. The tandem reaction with various functionalized 2-aminobenzaldehydes bearing *ortho*, *meta*, and *para* substitutions on the aryl ring proceeded smoothly to give the corresponding products in moderate to good yields.

Another recent example was demonstrated by Ramachary and co-workers for the multicomponent reaction of 2-ethynylbenzaldehyde, CH-acids and Hantzsch ester using L-proline/CuI/Cs_2CO_3 as the catalyst (Scheme 35).[67] This protocol provides a new process for the synthesis of substituted indenes.

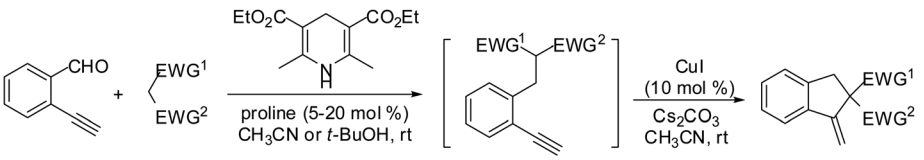
In the examples discussed above, the carbonyl compounds are directly used as starting substrates. Recently, a different strategy involving the combination of metal catalyzed oxidation and aminocatalysis has been developed by Rueping and co-workers for the development of new tandem transformations. In these reactions, allylic alcohols, the precursors of α,β-unsaturated aldehydes, were used directly as the substrates. The key to the implementation of this strategy is the development of suitable catalyst combinations to meet the requirements that the metal-catalyzed oxidation is adaptable to the catalytic cycle of the chiral amine catalyst, and the chiral amine catalyst is not oxidized.

The combination of tetrapropylammonium perruthenate/*N*-methylmorpholine *N*-oxide (TPAP/NMO) as the oxidant and diarylprolinol TMS-ether catalyst has been identified as the effective system for several catalytic asymmetric tandem reactions (Scheme 36).[68] The remarkable advantage of the combination of metal catalyzed oxidation and iminium catalysis is that the necessary purification or distillation step associated with the use of aldehydes in organocatalysis is avoided.

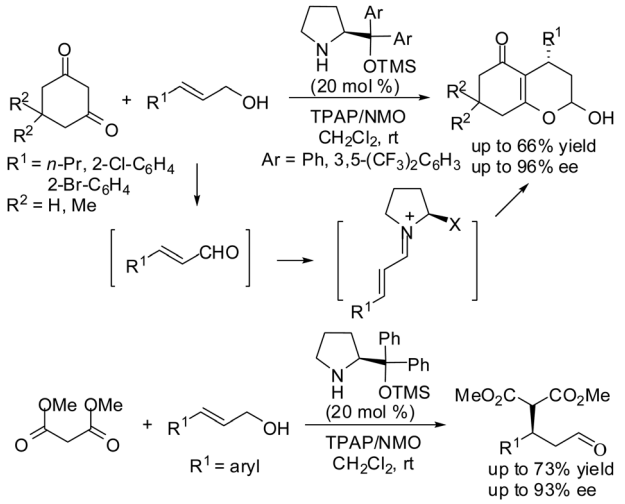
In order to develop a more simple and economic procedure, the Rueping group also examined cheap, non-toxic, heterogeneous oxidizing reagents as they could be easily separated by filtration. They found that MnO_2 could be used as a cheap and readily available heterogeneous oxidant in combination with chiral secondary amines (Scheme 37).[69]

In addition to allylic alcohols, this dual catalysis strategy has also been found to be effective for propargyl alcohol substrates. Using the TPAP/NMO in combination with a chiral secondary amine catalyst, Rueping and co-workers developed a nice tandem sequence involving a metal-catalyzed oxidation of propargyl alcohols to propargylic aldehydes followed by an iminium–allenamine cascade (Scheme 38).[70] This tandem asymmetric process provides comparable results to those reported by Wang and co-workers[71] in terms of yields and enantioselectivity. Advantageously, the preparation and purification steps associated with the use of propargylic aldehydes in Wang's work are avoided.

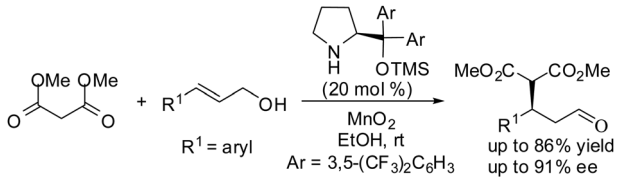
Here we would like to mention that Rueping's iminium–allenamine cascade[70] actually belongs to the catalog of combined iminium–enamine and transition metal catalysis; however, for a better understanding of the strategy of combining



Scheme 35 Synthesis of substituted indenes through the multicomponent reaction catalyzed by L-proline/CuI/Cs_2CO_3.



Scheme 36 Asymmetric oxidative iminium cascade by the combined system consisting of TPAP/NMO and chiral amine catalysts.



Scheme 37 Asymmetric oxidative iminium cascade by the combined system consisting of MnO_2 and chiral amine catalyst.

transition metal catalyzed oxidation and aminocatalysis, we have included this example in this subsection.

5.3 Combining iminium–enamine and transition metal catalysis

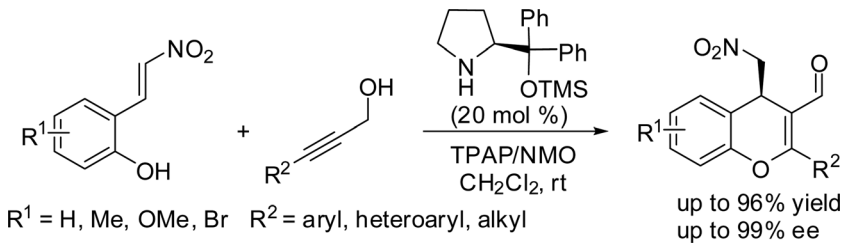
Inspired by Dixon's seminal work,[72] Córdova and co-workers developed a highly enantioselective dynamic kinetic asymmetric transformation (DYKAT) involving α,β-unsaturated aldehydes and propargylated carbon acids (Scheme 39).[73] In this asymmetric reaction, a chiral secondary amine was used in combination with the Pd(0) catalyst. The protocol exhibits a broad substrate scope. Notably, this protocol could be employed for the formation of cyclopentenes bearing all-carbon quaternary stereocenters with good diastereoselectivities and high enantioselectivities.

This DYKAT proceeds through amine catalyzed Michael addition followed by Pd(0)/enamine catalyzed cycloisomerization, giving access to functionalized cyclopentenes (Scheme 40). Although the Michael adducts **I** and **I′** are formed in equal amounts as the conjugate addition step is reversible, the intramolecular cycloisomerization constitutes an irreversible chemical transformation, which proceeds at distinct rates for different enamine diastereomers, thus leading to optically active functionalized cyclopentenes.

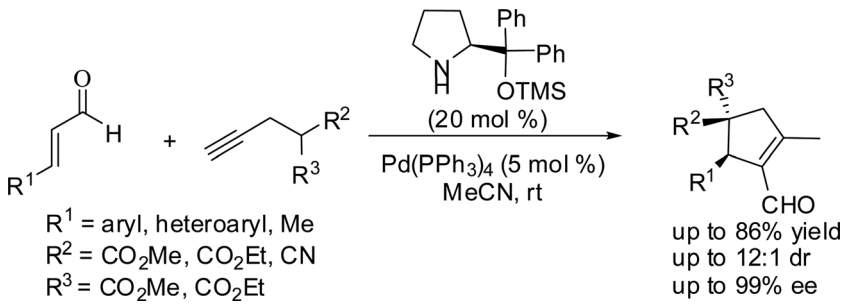
Almost concurrently, similar asymmetric cascade reactions were reported independently by Jørgensen[74] and Wang.[75]

Recognizing the generality of this strategy, Córdova and co-workers turned to propargylic alcohol substrates, oxygen nucleophiles, and developed an enantioselective oxa-Michael/carbocyclization reaction (Scheme 41).[76] Valuable dihydrofurans were obtained in good to high yields with excellent enantioselectivities.

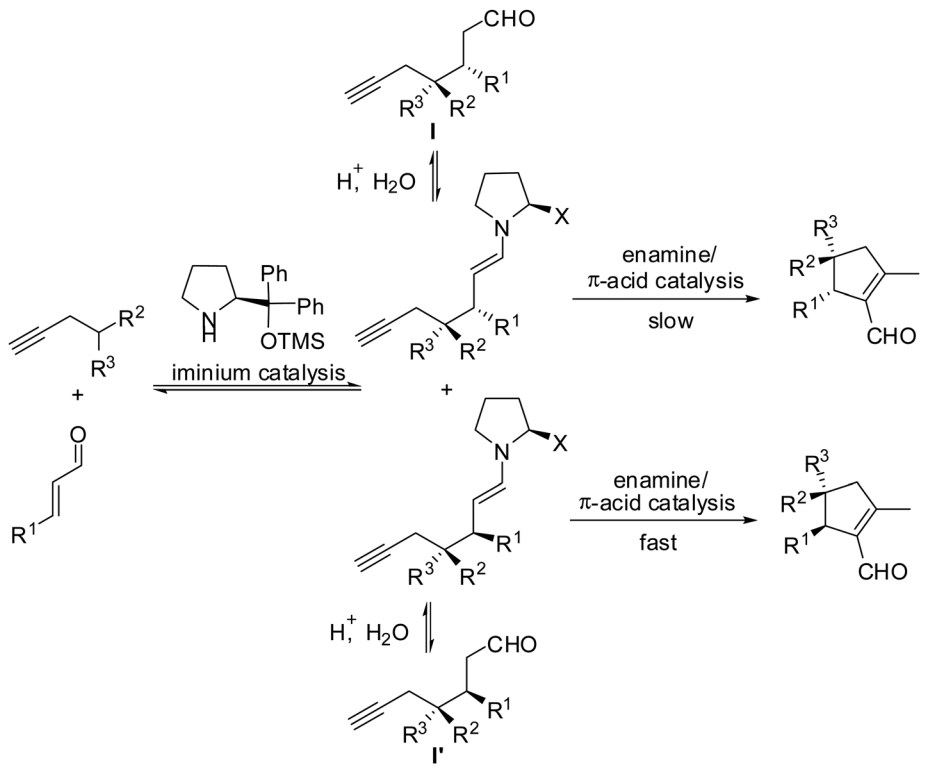
On the basis of the amine/metal dual catalysis strategy, Wang and co-workers recently reported an enantioselective aza-Michael/carbocyclization reaction of α,β-unsaturated aldehydes using *N*-tosyl propargylamines as nitrogen nucleophiles (Scheme 42).[77]



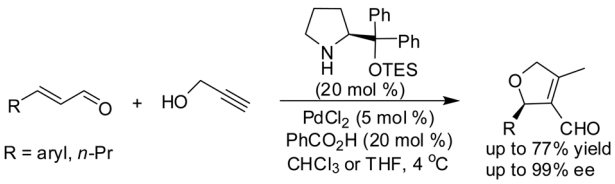
Scheme 38 Catalytic asymmetric synthesis of 4*H*-chromenes *via* oxidative iminium–allenamine cascade.



Scheme 39 DYKAT by combined amine- and transition metal-catalyzed enantioselective cycloisomerization.



Scheme 40 Mechanism of DYKAT by combined amine- and transition metal-catalyzed enantioselective cycloisomerization.



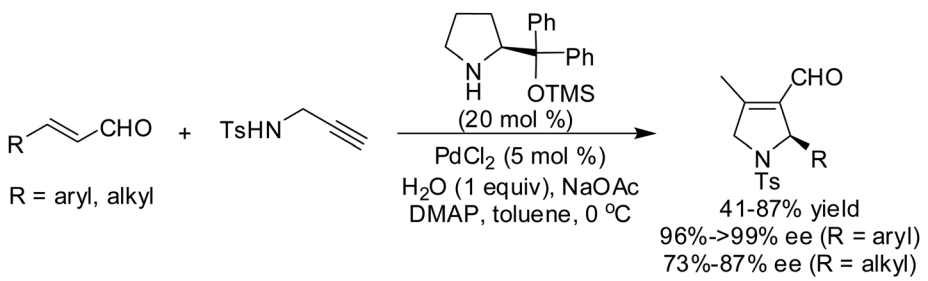
Scheme 41 Enantioselective oxa-Michael/carbocyclization by amine–metal dual catalysis.

This protocol provided multisubstituted chiral pyrrolines with excellent enantioselectivities in moderate to good yields. It seems that aromatic enals provided higher enantioselectivities than aliphatic enals.

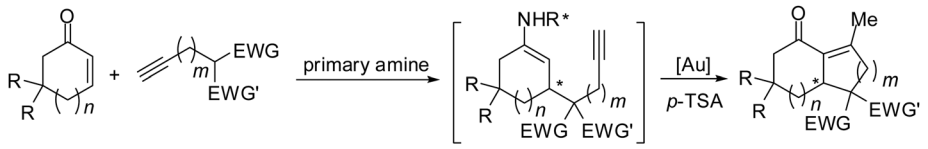
In view of the potential of this amine/metal dual catalysis, an enantioselective sulfur-Michael/carbocyclization reaction may be feasible in principle.

The strategy of combining π-acid catalysis with iminium–enamine catalysis has also been extended to utilize α,β-unsaturated ketones as Michael acceptors, producing highly functionalized bicyclic enones in good yields with high enantioselectivities (Scheme 43).[78] In this case, chiral primary amine[79] was used as the organocatalyst due to its known efficiency in activating enones, which is much less effective if a secondary amine is employed. Additionally, a *p*-TSA additive was required to ensure regeneration of catalytically active Au(I). This requirement might be explained by the presence of several nitrogen atoms of the cinchona scaffold, resulting in Au(I) deactivation.

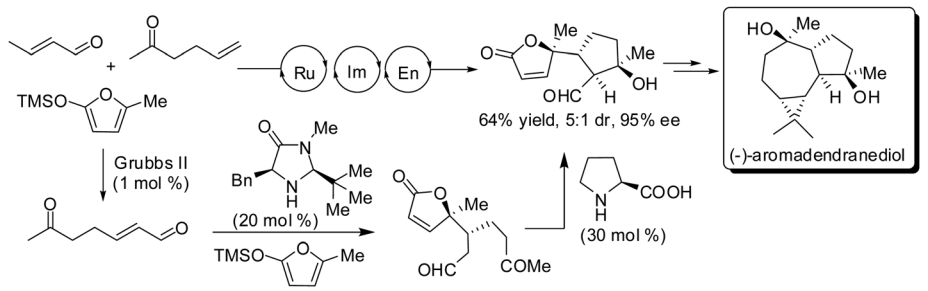
In the above examples of combining transition metal catalysis with iminium–enamine catalysis, a single chiral amine serves two roles: iminium catalyst and enamine catalyst. Recently MacMillan and co-workers developed an elegant triple-cascade catalysis consisting of ruthenium catalysis, iminium and enamine catalysis, in which two different secondary amines served as



Scheme 42 Enantioselective aza-Michael/carbocyclization reaction by amine/metal dual catalysis.



Scheme 43 Combined amine- and gold-catalyzed enantioselective Michael/carbocyclization involving α,β-unsaturated ketones.



Scheme 44 Triple-cascade catalysis consisting of cross-metathesis, iminium and enamine catalysis.

enamine catalyst and iminium catalyst, respectively.[80] In this case, the sequential addition of a Grubbs II catalyst, an imidazolidinone catalyst and proline together with the respective addition of 5-hexene-2-one, crotonaldehyde, and trimethylsilyloxyfuran afforded the desired cascade adduct in 64% yield, 95% ee, and with a 5 : 1 dr (Scheme 44). Taking advantage of this cascade product as the key building block, a concise total synthesis of (–)-aromadendranediol was accomplished in only 8 steps.

6. Combining Brønsted acid and transition metal catalysis

(Chiral) Brønsted acid catalysis represents another major research area in organocatalysis.[8] This field was initiated by the introduction of chiral BINOL-derived phosphoric acids in 2004 by Akiyama[81] and Terada.[82] Generally, Brønsted acids promote organocatalytic reactions through protonation to form a (chiral) ion pair (Fig. 2). Recently the combination of Brønsted acid and transition metal catalysis has emerged as another new strategy to carry out organic transformations.[83,84]

Before we discuss recently reported reactions, important features of chiral phosphoric acids (Fig. 3), the most intensively studied catalysts in Brønsted acid catalysis, have to be reviewed.

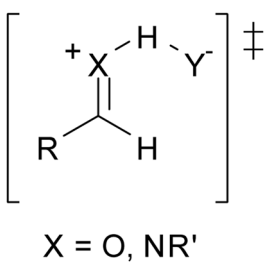


Fig. 2 Brønsted acid activation of a carbonyl or imine group.

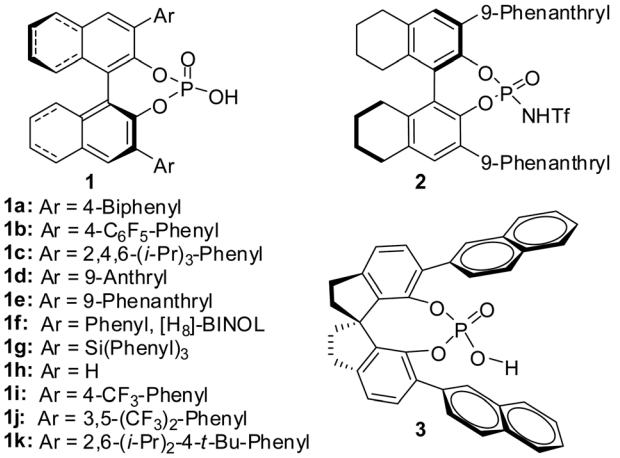


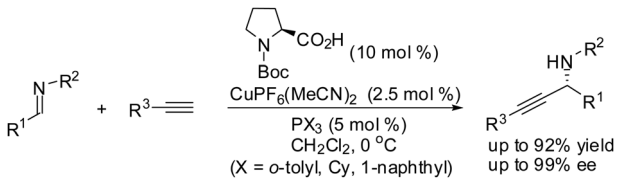
Fig. 3 Chiral phosphoric acids used in this review.

Phosphoric acid can either serve as a Brønsted acid catalyst or can act as an anion. Here we would like to mention that the asymmetric counteranion-directed transition-metal catalysis[85] wherein the deprotonated form of a chiral Brønsted acid is utilized as the counteranion of a transition-metal complex will not be included here as it may not fit into the topic of this review.

Asymmetric alkynylation of imines

The first combined Brønsted acid and transition metal catalyzed asymmetric alkynylation of imines was disclosed by Rueping and co-workers in 2007.[86] Recently, the asymmetric alkynylation reaction again attracted interest in transition metal/Brønsted acid dual catalysis.[87,88]

One recent example of transformations of this type was reported by Arndtsen and co-workers.[87] Simple and inexpensive amino acids are used as chiral catalysts which activate the imine substrates through hydrogen bonding while an achiral



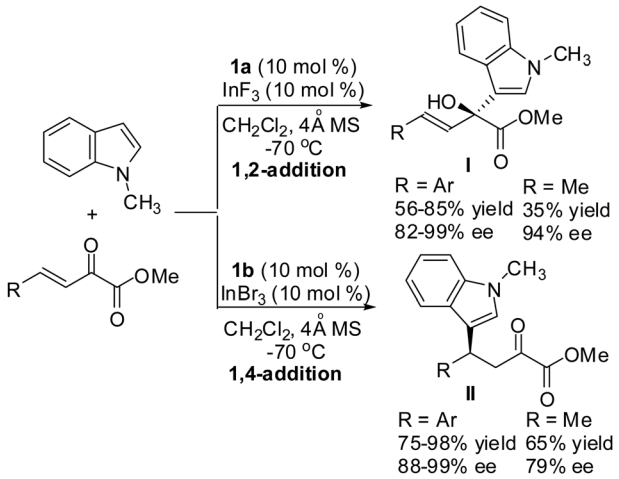
Scheme 45 Alkynylation of imines *via* the merger of Brønsted acid and transition metal catalysis.

Cu(I) complex bearing an easily variable monodentate phosphine ligand activates terminal alkynes (Scheme 45). The main advantage of this protocol is the flexibility and modularity of the catalyst system. While the primary chiral information is brought about by the α-amino acid, the steric bulk of the copper catalyst has also a significant influence on the enantioselectivity of the alkynylation reaction. In addition, the accelerating influence of the amino acid allows use of electron-rich *N*-alkylimines which have been reported to be uncreative toward alkynylation, likely because of their reduced electrophilicity.

Another recent example was reported by Maruoka and co-workers.[88] In this instance, C1-Substituted *C*,*N*-cyclic azomethine imines were utilized as substrates, and the combination consisting of copper(I)/pybox and an axially chiral dicarboxylic acid was used as the catalyst system. This protocol provides chiral tetrahydroisoquinolines bearing a quaternary center in excellent yields with good enantioselectivities (Scheme 46). A variety of aromatic and aliphatic terminal alkynes could be incorporated to generate a tetrasubstituted carbon center at the C1-position with high enantioselectivity. Notably, the chain length of the C1 substituent had only minimal impact on the reactivity and selectivity.

Friedel–Crafts alkylation

The chiral Brønsted acid catalyzed asymmetric Friedel–Crafts reaction is one of the most powerful methods to synthesize optically active aromatic compounds.[89] Recently, Luo and co-workers described a new strategy for the enantioselective Friedel–Crafts reaction of *N*-protected indoles with β,γ-unsaturated α-keto esters, in which chiral phosphoric acids were used in combination with indium halides (Scheme 47).[90] Interestingly, by simply changing the counteranions of indium(III) from fluoride to bromide, a switch of regioselectivity from 1,2- to 1,4-addition was achieved with excellent reactivity and



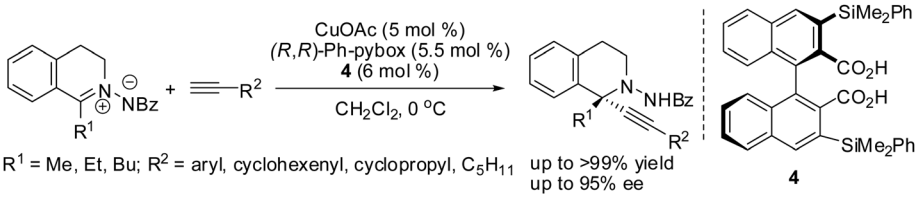
Scheme 47 Enantioselective Friedel–Crafts alkylation of indoles with β,γ-unsaturated α-keto esters catalyzed by combined phosphoric acids and InX_3.

enantioselectivity. The regioselectivity switch seems to be independent of the chiral phosphoric acids employed. Both 1,2- and 1,4-addition reactions worked well with a variety of β,γ-unsaturated α-keto esters bearing either γ-aromatic or aliphatic substituents. This work highlights the importance of counteranions in tuning both chemoselectivity and stereoselectivity, and thus a detailed mechanistic study is desirable.

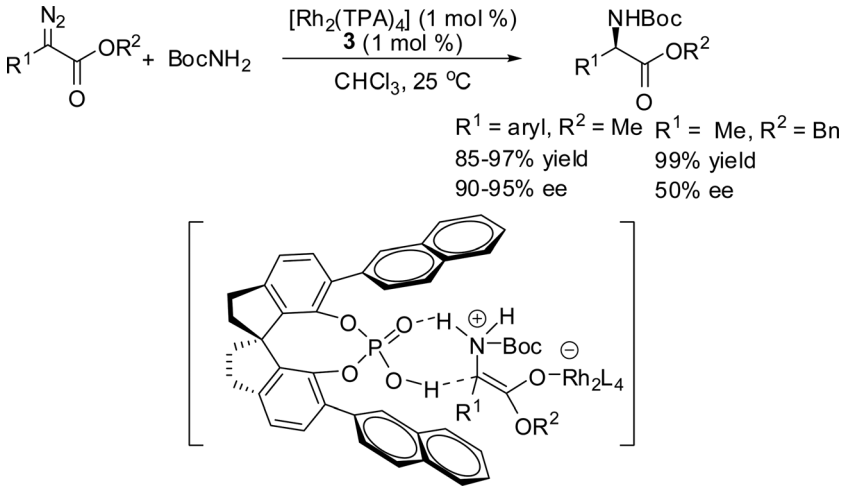
N–H bond insertion

Transition metal-catalyzed insertion of metal carbene into N–H bonds is one of the most effective approaches to construct carbon–nitrogen bonds, and the development of enantioselective versions of the N–H insertion reactions has attracted considerable attention.[91]

Recently, Zhou and Zhu developed a highly enantioselective N–H insertion reaction catalyzed by a dirhodium(II) carboxylate and a chiral spiro phosphoric acid (SPA) **3**.[92] While copper-catalyzed asymmetric N–H insertion reactions have been reported, these protocols require high catalyst loading (5–10 mol%) to achieve satisfactory yields and enantioselectivities. On the other hand, the activity of dirhodium(II) catalysts is usually superior to that of copper catalysts in nonenantioselective N–H insertion reactions; however, chiral dirhodium catalysts gave only low to modest enantioselectivities (<50% ee). Under the cooperative catalysis by dirhodium(II) complexes and chiral SPAs, excellent reactivity and high enantioselectivity (up to 95% ee) were achieved in the presence of 0.1 mol% of catalyst within 1 min. It is suggested that the chiral SPA acts as



Scheme 46 Catalytic asymmetric alkynylation of C1-substituted *C*,*N*-cyclic azomethine imines catalyzed by Cu(I)/Brønsted acid.



Scheme 48 Asymmetric N–H insertion catalyzed by rhodium and chiral spiro phosphoric acids.

a proton-transfer shuttle in this N–H insertion reaction, facilitating the proton transfer step *via* a seven-membered-ring transition state (Scheme 48). The formation of a chiral rhodium(II) phosphate species by a simple ligand exchange was ruled out through a mechanistic investigation with ^{31}P NMR. This protocol shows a broad substrate scope. Various α-aryl-diazoacetate substrates reacted smoothly with *tert*-butyl carbamate ($BocNH_2$) to provide the desired N–H insertion products in high yields with high enantioselectivities. α-Alkyl-diazoacetate substrate such as benzyl 2-diazopropanoate also worked well to afford the N–H insertion product almost quantitatively, albeit with moderate enantioselectivity.

Diels–Alder reaction

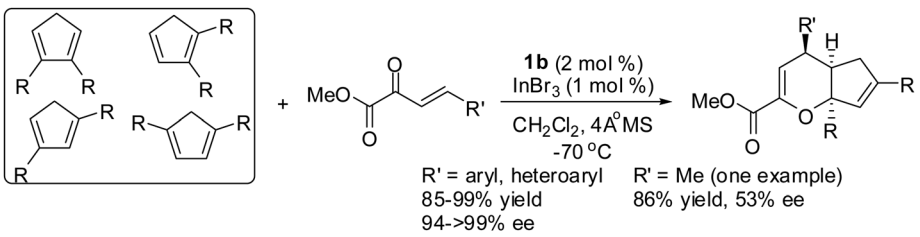
The catalytic asymmetric hetero-Diels–Alder reactions of bis-substituted cyclopentadienes remain a challenge in asymmetric catalysis. Recently, Luo and co-workers utilized the dual catalysis strategy to achieve this challenging reaction.[93] The key to this methodology is the identification of a highly active binary-acid catalyst system consisting of a chiral Brønsted acid and a metal Lewis acid (Scheme 49). This hetero-Diels–Alder reaction worked well with various aromatic and heteroaromatic-substituted ketoesters, offering high yields and selectivities. In contrast, the alkyl-substituted ketoester was less selective. The binary-acid catalyst system was also effective for the mono-substituted cyclopentadienes, cyclopentadiene and acyclic 1,3-dienes.

Asymmetric hydrogenation

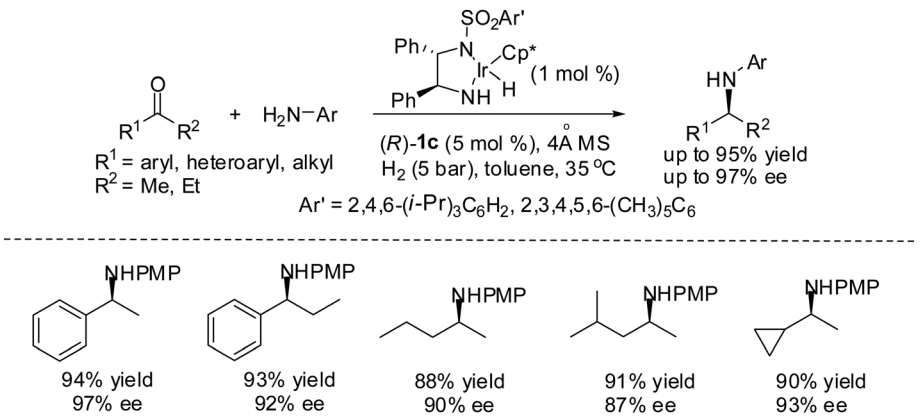
The asymmetric reduction of imines and nitrogen-containing heteroaromatic compounds is one of the most straightforward approaches for the synthesis of the chiral amines.[94]

The first combined Brønsted acid and transition metal catalyzed asymmetric hydrogenation (reductive amination of ketones) was disclosed by Xiao and co-workers in 2009 (Scheme 50).[95,96] In this protocol, a new dual catalytic system composed of a chiral Ir(III) complex and a chiral phosphoric acid was used as the catalyst combination. The reductive amination exhibits a remarkably broad substrate scope. Not only aryl methyl ketones but also more challenging substrates like aryl ethyl and dialkyl ketones can be used successfully. The phosphoric acid is suggested to fulfill three roles: as a Brønsted acid it catalyzes the formation of the imine, and it also serves as a chiral counteranion to the iridium catalyst and to the iminium ion.

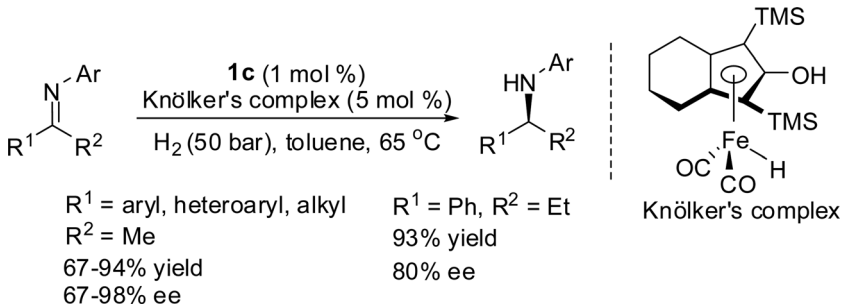
While Xiao's work is very impressive, it utilizes two chiral catalysts: chiral iridium complex and a chiral phosphoric acid. Recently the combination of an achiral transition metal catalyst and a chiral Brønsted acid was reported by Beller and co-workers for the asymmetric hydrogenation of imines.[97] In this report, Knölker's complex, a simple achiral iron hydrogenation catalyst, is used in combination with a chiral phosphoric acid (*S*)-TRIP **1c** to produce enantioenriched secondary amines from the corresponding acyclic imines (Scheme 51). Various aromatic ketimines were hydrogenated smoothly in



Scheme 49 Asymmetric hetero-Diels–Alder reaction of bis-substituted cyclopentadienes.



Scheme 50 Reductive amination catalyzed by a chiral iridium complex and a chiral phosphoric acid.



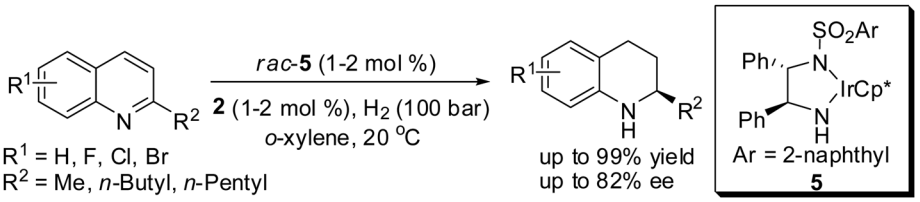
Scheme 51 Catalytic asymmetric hydrogenation of imines using an achiral iron catalyst and a chiral phosphoric acid.

high yields with excellent enantioselectivity. Both electron-donating and electron-withdrawing substituents on the aromatic rings at *meta* or *para* positions had little impact on the hydrogenation activity. Heteroaromatic imines and *N*-heteroaryl-substituted imines were also reduced with excellent enantioselectivity. Notably, the reduction of aliphatic imines occurred with high enantioselectivity. In spite of these excellent results, it remains to be seen if this combined catalytic system can be applied to the direct asymmetric reductive amination of ketones.

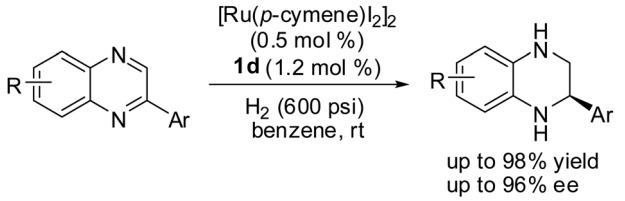
The concept of chiral Brønsted acid activated, transition metal catalysis has been further developed by Rueping and co-workers. Using the combination of a racemic iridium complex and *N*-triflylphosphoramide as the chiral Brønsted acid catalyst, they developed a Brønsted acid differentiated metal catalyzed asymmetric hydrogenation of quinolines by kinetic discrimination (Scheme 52).[98] A variety of 2-substituted quinolines were reduced to the corresponding tetrahydroquinolines in good yields with up to 82% ee. Combination of the corresponding enantiopure iridium catalysts with the same chiral Brønsted acid was also investigated. They found that the resulting diastereomeric combinations differed in their catalytic properties, and the matched-case provided higher reactivities and selectivities. This is the first example of more acidic *N*-triflylphosphoramides combined with transition metal complexes.

On the basis of a serendipitous disproportionation of dihydroquinoxaline, Zhou, Fan and co-workers developed an elegant transition metal/Brønsted acid relay catalysis system for the highly enantioselective hydrogenation of quinoxalines through convergent asymmetric disproportionation of dihydroquinoxalines (Scheme 53).[99]

The mechanism of this remarkable transformation is outlined in Scheme 54. Firstly, ruthenium(II)-catalyzed hydrogenation of quinoxalines **I** generates dihydroquinoxalines **II**. Subsequently,



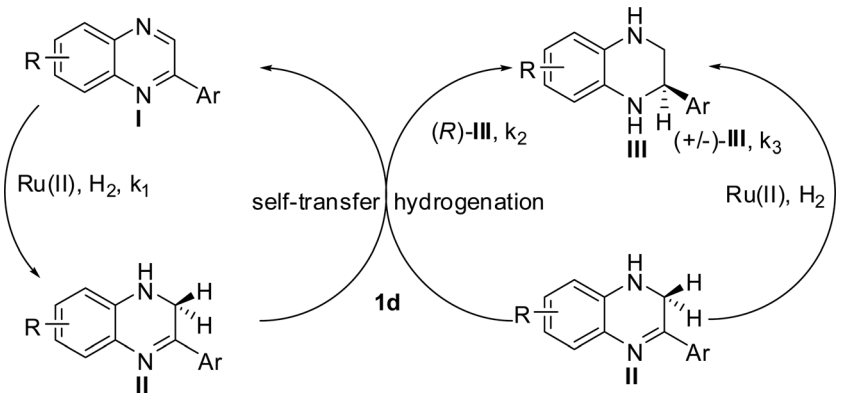
Scheme 52 Brønsted acid differentiated metal catalyzed asymmetric hydrogenation of quinolines.



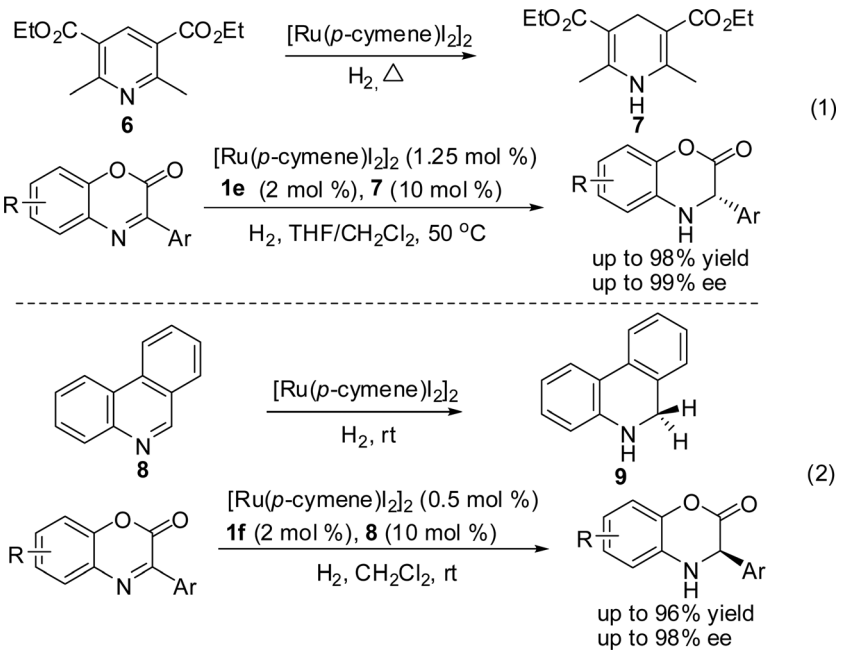
Scheme 53 Convergent asymmetric disproportionation of dihydroquinoxalines by metal/Brønsted acid relay catalysis.

the intermediates **II** undergo self-transfer hydrogenation to deliver primary starting materials **I** and the final products **III** in the presence of chiral Brønsted acid **1d**. The key to achieve excellent enantioselectivities in this transformation is that the reaction rate of this principal reaction k_2 is faster than that of the undesired side reaction k_3 ($k_2 > k_3$).

In a different light, the Zhou group recently developed two new impressive examples of biomimetic asymmetric hydrogenation promoted by metal/Brønsted acid relay catalysts.[100] In the first example,[100a] a catalytic amount of Hantzsch ester[101] regenerated *in situ* by Ru complexes under hydrogen gas has been employed for the chiral phosphoric acid promoted biomimetic asymmetric hydrogenation of benzoxazinones with up to 99% ee (Scheme 55). In the second example,[100b] a new and easily regenerable NAD(P)H model 9,10-dihydrophenanthridine (DHPD) has been designed for the biomimetic asymmetric hydrogenation, due to the fact that the regeneration of DHPD from phenanthridine can be easily performed under very mild conditions. Thus, the substrate scope is not limited to benzoxazinone substrates used in the first example.[100a] The biomimetic asymmetric hydrogenation of benzoxazines, quinoxalines and quinolines also proceeded smoothly to give excellent activities and enantioselectivities (Scheme 55).



Scheme 54 Proposed mechanism for the convergent asymmetric disproportionation of dihydroquinoxalines.



Scheme 55 Biomimetic asymmetric hydrogenation catalyzed by metal/Brønsted acid relay catalysis.

While a few asymmetric hydrogenation examples outlined above may belong to the catalog of tandem reactions, for a better understanding, we have included them in this asymmetric hydrogenation subsection.

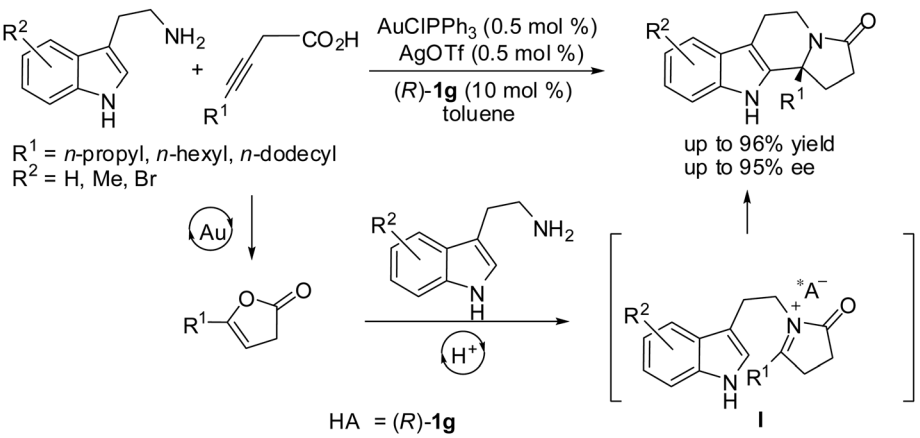
Tandem reactions. The strategy of combining Brønsted acid and transition metal catalysis has been applied to the development of tandem reactions. In this regard, Au(I) catalysts have played a prominent role.[102] The combined Brønsted acid and Au(I) catalysis was initiated by three seminal works in 2009 by Dixon,[103] Gong[104] and Che,[105] independently. One key concept underlying such systems is the fact that H^+ is isolobal to Au^+ and hence they share similar characteristics in terms of their electronic properties.[13c]

Dixon *et al.* described a Brønsted acid/Au(I) sequential catalysis in which propargylic acids catalyzed by Au(I) afforded enol lactones *via* a *5-endo-dig* cyclization. After the completion of the first cyclization, the chiral Brønsted acid catalyst was added sequentially to the reaction flask to effect the second cyclization *via* *N*-acyliminium intermediates **I** and form the enantioenriched the tetracyclic indole products (Scheme 56).[103]

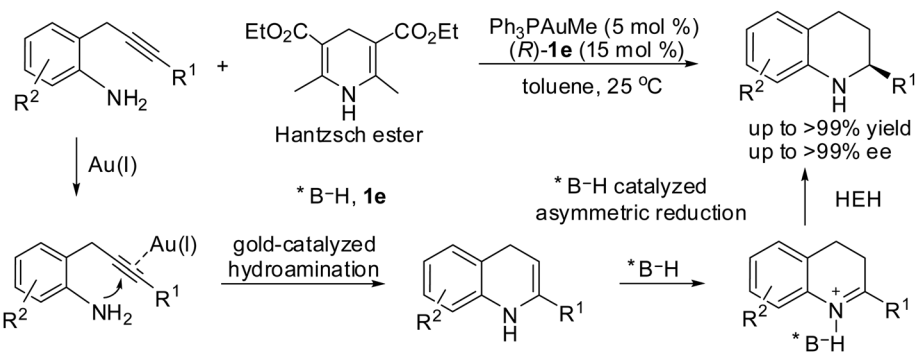
Then Gong and co-workers reported an interesting relay catalysis involving an intramolecular hydroamination/transfer hydrogenation sequence (Scheme 57).[104] In this relay catalysis, an achiral Au(I) complex, PPh_3AuMe, is employed to catalyze the first intramolecular hydroamination reaction to form 1,4-dihydroquinolines. Then the 1,4-dihydroquinolines are protonated to the dihydroquinolinium intermediates under the catalysis of a chiral phosphoric acid. The presence of an organohydride source, such as the Hantzsch ester, affected a subsequent asymmetric transfer hydrogenation to generate enantioenriched tetrahydroquinolines in one operation in excellent yields and enantioselectivities. This relay catalytic process tolerated a wide spectrum of 2-(2-propynyl)anilines bearing either aromatic or aliphatic substituents on the propynyl moiety. Notably, the variation of substituent on the aniline moiety was also tolerable. Various 2-(2-Propynyl)anilines with electron-withdrawing, neutral, or electron-donating substituents reacted well to provide tetrahydroquinoline derivatives in excellent yields and enantioselectivities.

Almost at the same time, Che's group disclosed a tandem intermolecular hydroamination/transfer hydrogenation of alkynes and anilines using a gold(I) complex and a chiral Brønsted acid.[105] In this instance, chiral secondary amines were obtained in good yields with excellent enantioselectivities. This reaction proceeds through a mechanism similar to Gong's reaction (Scheme 58).

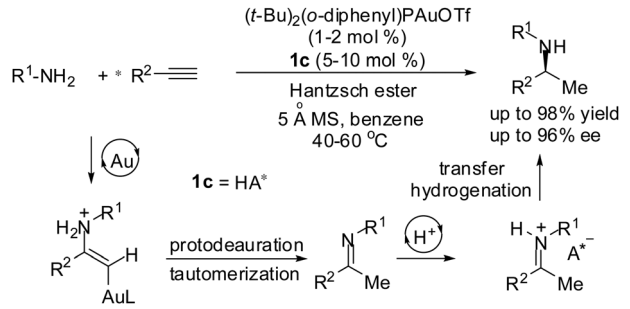
Taking advantage of gold (I)-catalyzed hydroamination combined with Brønsted acid catalyzed three-component Povarov reaction,



Scheme 56 Au(I)/Brønsted acid catalyzed *N*-acyliminium cyclization cascade.



Scheme 57 Gong's tandem hydroamination/transfer hydrogenation reaction.



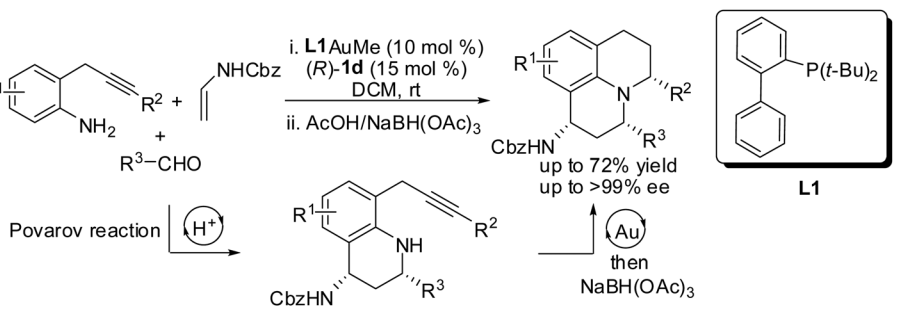
Scheme 58 Che's hydroamination/transfer hydrogenation.

Gong and co-workers developed a three-component cascade for the synthesis of structurally diverse julolidine derivatives (Scheme 59).[106] The methodology is effective for various electronically poor, neutral, or rich benzaldehydes. Moreover, 2-furancarbaldehyde and an aliphatic aldehyde also participated in the smooth relay catalytic three-component reaction to afford julolidine derivatives in high yields and excellent levels of enantioselectivity.

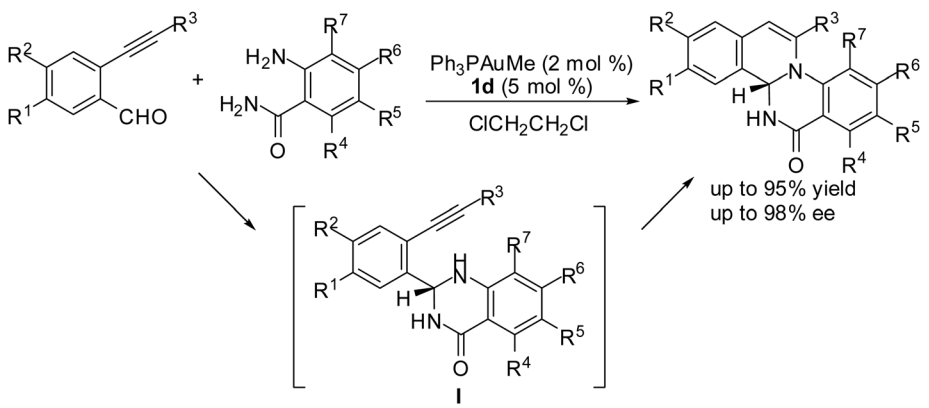
Gold(I)-catalyzed hydroamination has also been combined with chiral phosphoric acid-catalyzed enantioselective condensation between 2-alkynylbenzaldehydes and 2-aminobenzamides (Scheme 60).[107] The key to this methodology is to search for a suitable achiral gold(I) catalyst which should only catalyze hydroamination and should not take part in the enantioselective condensation process, resulting in racemization of relatively labile optically pure aminals **I**. The authors screened a variety of Au(I) complexes and found that Ph_3PAuMe was suitable for the asymmetric cascade reaction. Thus, the combination of Ph_3PAuMe with a chiral phosphoric acid catalyst afforded the optically pure fused 1,2-dihydroisoquinoline products with high ee's.

The combined catalysis based on gold(I)-catalyzed hydroamination has been further developed by Gong and co-workers. By utilizing a gold/palladium/Brønsted acid ternary system, a remarkable hydroamination/allylic alkylation reaction was achieved, providing pyrrolidine derivatives in high yields (Scheme 61).[108] In this reaction, the gold catalyst is responsible for the hydroamination while Brønsted acid and palladium cooperatively catalyze the allylic alkylation. Unfortunately, no asymmetric information is provided in this report. This may be due to difficult asymmetric control in the allylic alkylation step.

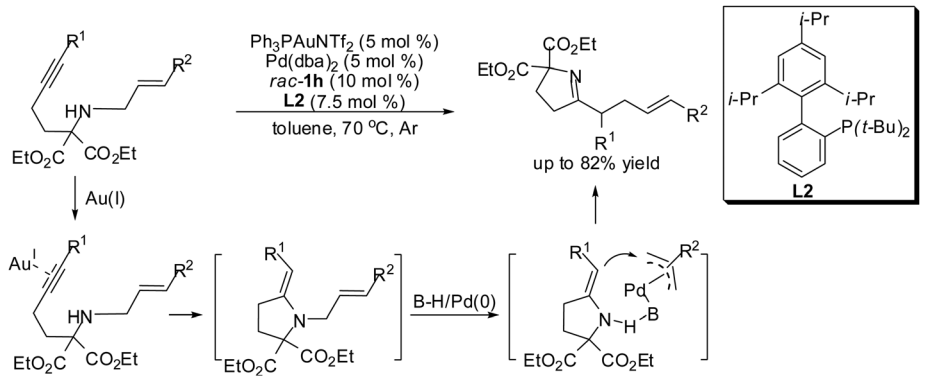
Another recent example of Au(I)/Brønsted acid dual catalysis was demonstrated by Gong *et al.* for the construction of structurally challenging vicinal quaternary centers (Scheme 62).[109] In this instance, a Au(I) catalyst was first employed to catalyze the hydroalkoxylation of alkynol to form cyclic enol ether, which was protonated to the corresponding oxonium ion upon the treatment with a chiral Brønsted acid. Then azlactone nucleophile attacked the electrophilic carbon of the oxonium ion to generate the final product *via* the proposed transition state **I**. The protocol is useful as it affords conformationally restricted



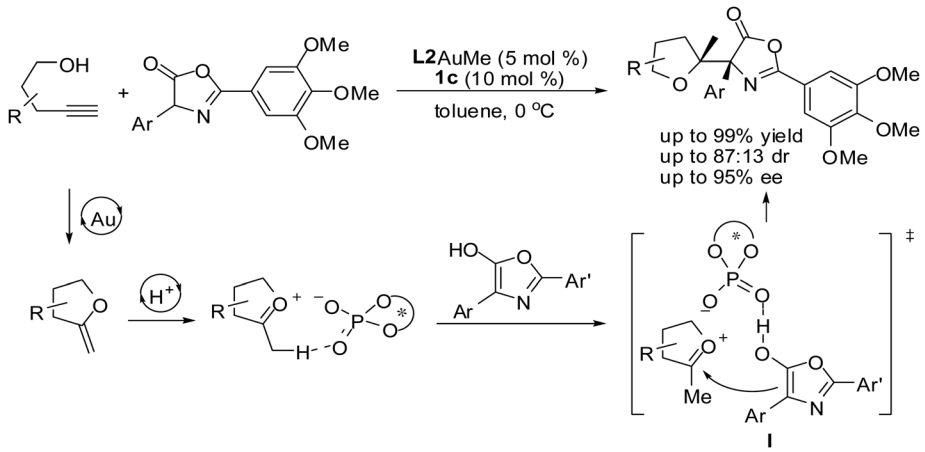
Scheme 59 Synthesis of julolidine derivatives by combined gold and Brønsted acid catalysis.



Scheme 60 Synthesis of optically pure fused 1,2-dihydroisoquinolines by Au(I)/chiral Brønsted acid dual catalysis.



Scheme 61 Hydroamination/allylic alkylation reaction catalyzed by a gold/palladium/Brønsted acid ternary system.



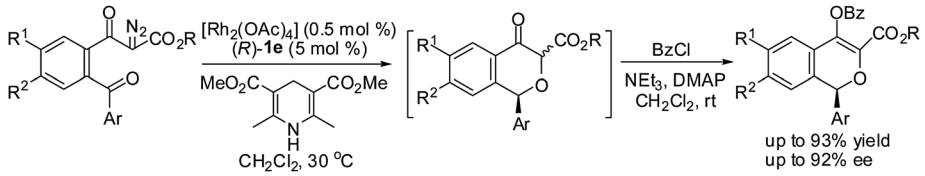
Scheme 62 Asymmetric cyclization of alkynols triggered addition of azlactones.

amino acid precursors in good yields and with high enantioselectivity. Regretfully, the diastereoselectivity is still moderate.

In addition to gold, transition metal rhodium has also played an important role in the development of combined Brønsted acid and transition metal catalyzed tandem reactions. Using a binary catalytic system consisting of a rhodium complex and a chiral phosphoric acid, Terada and Toda very recently developed an unprecedented relay catalysis involving a carbonyl ylide formation/enantioselective reduction sequence (Scheme 63).[110] Chiral isochromenes were obtained in good yields with high enantioselectivity. This relay catalysis was applicable to a variety of α-diazocarbonyl compounds. The substituent on the Ar group had little effect on the enantioselectivities irrespective of the electronic character and position of the substituent introduced on the phenyl ring. The α-diazocarbonyl compounds having substituents on the basal aromatic ring also underwent smoothly the consecutive transformation to afford the desired products. Mechanistic studies indicated that the chiral phosphoric acid was responsible for high enantioselectivity. The use of several chiral dirhodium(II) complexes yielded the racemic products in the absence of the chiral phosphoric acid.

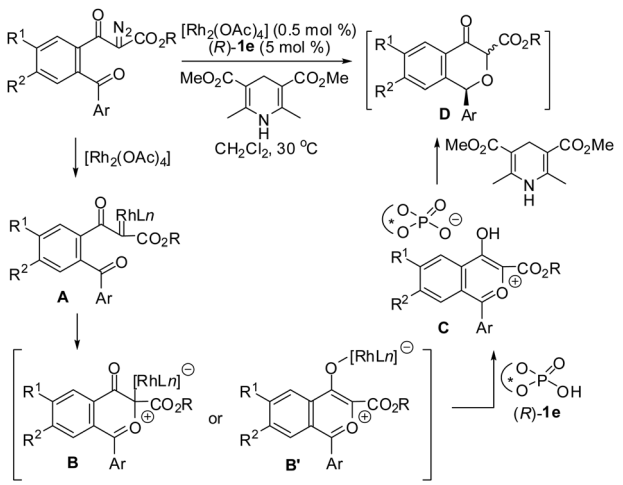
This relay catalysis was proposed to involve four consecutive reactions (Scheme 64). $Rh_2(OAc)_4$ catalyzed the decomposition of the α-diazocarbonyl compound to form a rhodium carbenoid **A**. Subsequently, the rhodium carbene complex **A** underwent intramolecular cyclization to yield the carbonyl ylide equivalent **B** which was tautomerized to the oxidopyrylium equivalent **B′**. The protonation of this transient species by the chiral phosphoric acid (*R*)-**1e** afforded ion pairs of the stable isobenzopyrylium ion **C** and the conjugate base of (*R*)-**1e**. Then, the isobenzopyrylium **C** underwent enantioselective reduction under the influence of the chiral conjugate base of (*R*)-**1e** to afford the product D.

In addition to relay catalytic reaction outlined above,[110] the synergistic catalysis of a Brønsted acid and a rhodium complex has been successfully applied in multicomponent tandem reactions. The first example of this type involving an enantioselective three-component reaction of aryldiazoacetates, alcohols and aldimines catalyzed by an achiral rhodium and a chiral chiral phosphoric acid was disclosed by Hu and co-workers in 2008.[111] This methodology has been utilized for the synthesis of Taxol side chain and (–)-*epi*-cytoxazone.[112] Recognizing the generality of this synergistic catalysis strategy, Hu and co-workers investigated other α-carbonyl diazo substrates and oxygen nucleophiles that have proven challenging under traditional rhodium catalysis. They found that in



Ar, R^1, R^2	yield (%)	ee (%)
Ar = 4-ClC_6H_4-, $R^1 = R^2 = H$	93	86
Ar = 4-$MeOC_6H_4$-, $R^1 = R^2 = H$	84	87
Ar = 4-MeC_6H_4-, $R^1 = R^2 = H$	90	89
Ar = 3-MeC_6H_4-, $R^1 = R^2 = H$	89	90
Ar = 2-MeC_6H_4-, $R^1 = R^2 = H$	92	88
Ar = Ph, $R^1 = H$, $R^2 = Br$	85	92
Ar = Ph, $R^1 = Cl$, $R^2 = Cl$	81	74

Scheme 63 Terada' relay catalysis using a dirhodium(II) tetracarboxylate/chiral phosphoric acid binary system for consecutive transformations.

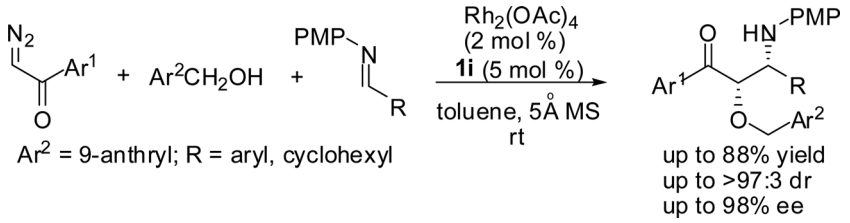


Scheme 64 Mechanism of Terada's relay catalysis using a dirhodium(II) tetracarboxylate/chiral phosphoric acid binary system.

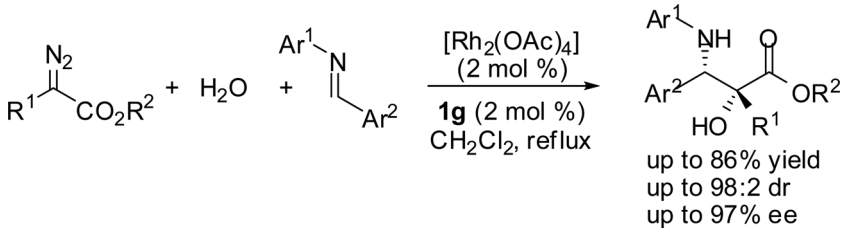
the presence of $Rh_2(OAc)_4$ and a chiral Brønsted acid catalyst, various diazoacetophenones reacted smoothly with an alcohol and imines in one-pot manner to afford optically active β-amino-α-hydroxyl ketones in good yields with excellent diastereo- and enantioselectivities (Scheme 65).[113] The three-component protocol was also effective for a variety of aldimines. The reactions with both electron-rich and electron-poor imines generally proceeded smoothly to afford the corresponding products with excellent dr and ee. The reaction is a little sensitive to the steric effects of the imines used. Notably, the alkylimine generated *in situ* from a cyclohexyl aldehyde was equally effective, providing the desired product in 68% yield with 93% ee.

This synergistic catalysis strategy was also extended to water as a nucleophile, producing *syn*-β-amino-α-hydroxyesters in good yields with excellent selectivities (Scheme 66).[114]

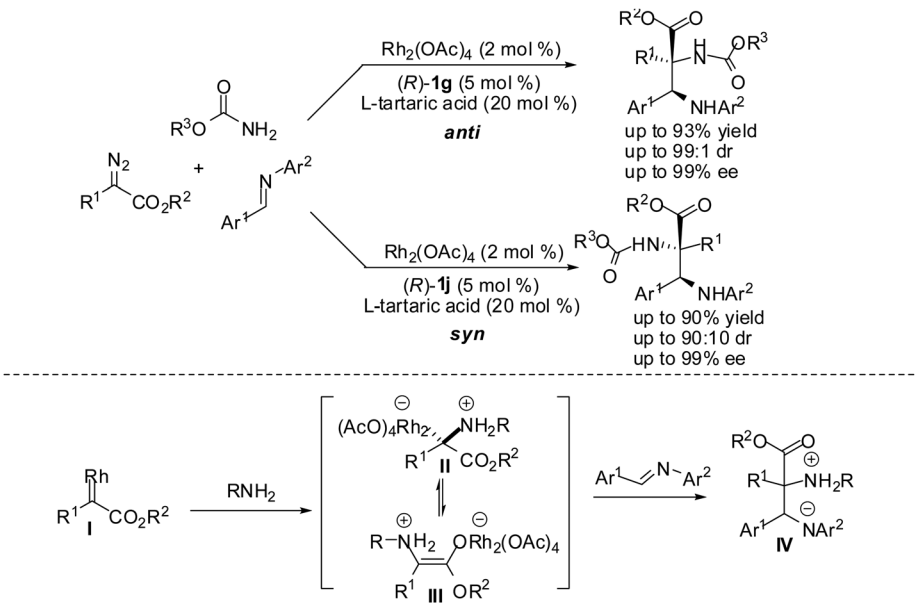
In the three-component reactions discussed above, the oxonium ylide generated *in situ* from a α-carbonyl diazo compound and an alcohol initiated by a rhodium complex is trapped by the imine electrophile. Recently, the highly reactive protic ammonium ylides were successfully trapped by imine electrophiles in a controlled manner, and an enantioselective three-component Mannich-type reaction of a diazo compound, a carbamate, and an imine was developed using a dual catalysis strategy (Scheme 67).[115] Notably, the diastereoselectivity of the three-component reaction was found to be switchable simply by changing the steric nature of the 3,3′-BINOL substituents. Both *syn*- and *anti*-α-substituted α,β-diamino acid derivatives with an α-quaternary carbon center



Scheme 65 Enantioselective three-component reaction of diazoacetophenones with alcohols and imines catalyzed by $Rh_2(OAc)_4$ and chiral Brønsted acids.



Scheme 66 Enantioselective three-component reaction of aryldiazoacetates, water and aldimines.



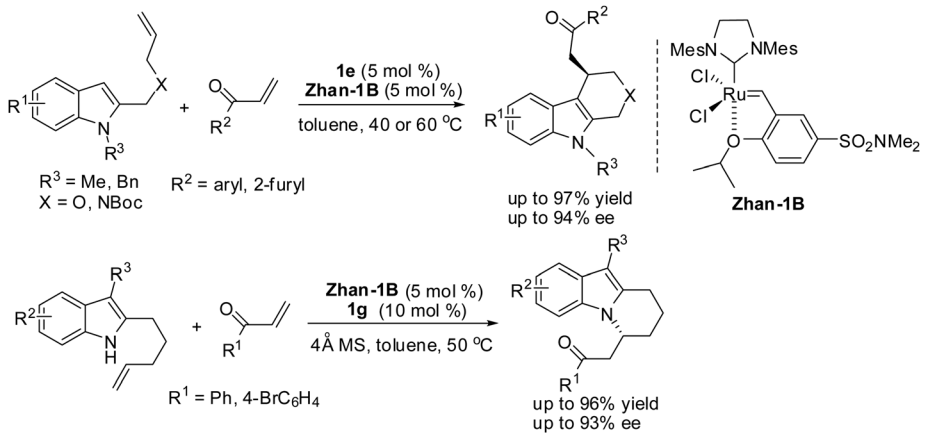
Scheme 67 Diastereoselectively switchable enantioselective three-component reaction of diazo compounds, carbamates and imines.

could be obtained in good yields with high diastereo- and enantioselectivity.

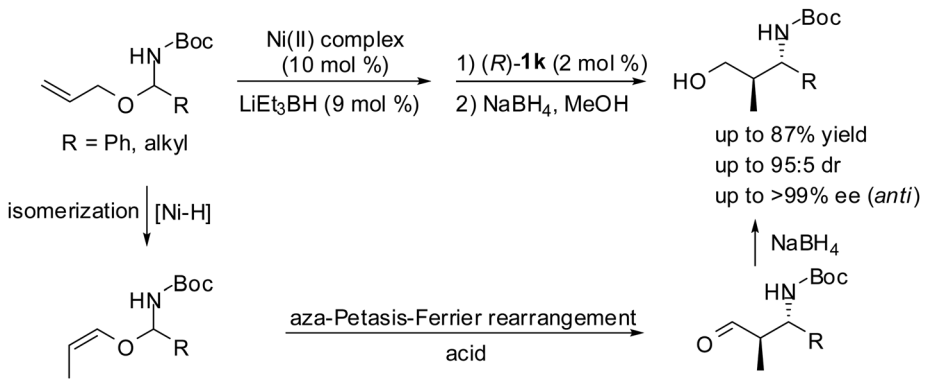
While rhodium catalysis has found extensive applications in modern organic synthesis, combined rhodium and organocatalyzed reactions are still limited. The substrates in these transformations generally involve α-diazocarbonyl compounds.

Ruthenium-catalyzed olefin cross-metathesis represents one of the most powerful tools for the formation of carbon–carbon double bonds.[116] Recently the combined utility of ruthenium-catalyzed olefin cross-metathesis with Brønsted acid catalysis has been demonstrated. Using an achiral ruthenium (**Zhan-1B** catalyst) and chiral Brønsted acid catalysts, the You group developed two elegant tandem enantioselective reactions: one involves olefin cross-metathesis and a subsequent intramolecular Friedel–Crafts alkylation, and another involves olefin cross-metathesis followed by an intramolecular aza-Michael addition (Scheme 68).[117] In these two protocols, two versatile alkene-tethered indoles were skillfully utilized together with enones. The olefin cross-metathesis step is catalyzed by the **Zhan-1B** catalyst while the intramolecular cyclization (intramolecular Friedel–Crafts alkylation or intramolecular aza-Michael addition) is the stereogenic step, where the chiral phosphoric acid was employed to effect the enantioselectivity. These protocols allow the use of readily available starting materials to construct synthetically valuable chiral *N*-containing heterocycles.

In addition to Au, Rh and Ru, transition metal nickel has also been combined with Brønsted acid catalysis for the development of new reactions. In 2009, Terada and co-workers reported a sequential isomerization/aza-Petasis-Ferrier rearrangement reaction by combining Ni(II) hydride complexes with a chiral phosphoric acid.[118] In this protocol, the Ni(II) hydride complexes, formed *in situ* from the corresponding NiI_2 complexes, isomerized hemiaminal allyl ethers to the *Z*-configured vinyl ethers. Subsequently, chiral Brønsted acid-catalyzed aza-Petasis-Ferrier rearrangement of the resulting vinyl ethers with consequent reduction of the formed chiral aldehydes provided the chiral β-amino alcohols (Scheme 69). Notably, these β-amino alcohols cannot be accessed by the typical Mannich reaction as aliphatic aldimines readily isomerize to the corresponding enamines. While this is the first combined use of Brønsted acid catalysis and Ni(II) catalysis, it demonstrates the feasibility and power of this type of catalyst combinations, and holds potential for further development.



Scheme 68 Metal/Brønsted acid catalyzed olefin cross-metathesis-based tandem reactions.

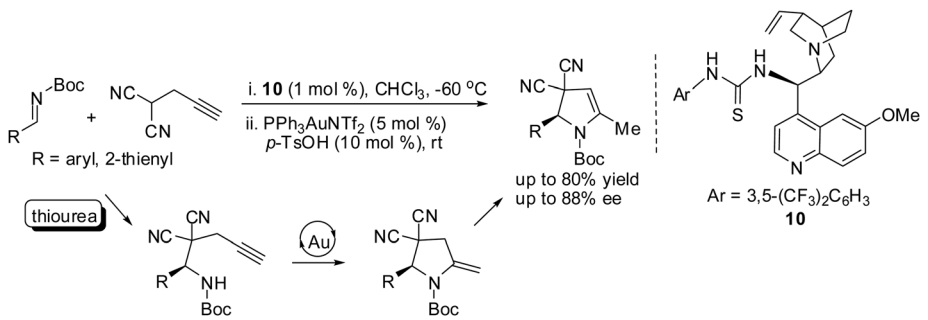


Scheme 69 Sequential isomerization/aza-Petasis-Ferrier rearrangement reaction.

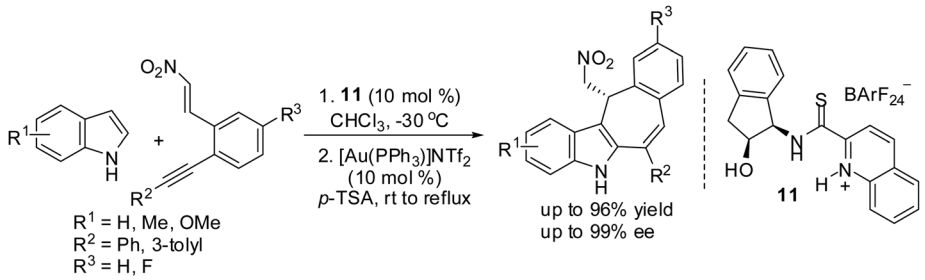
7. Combining hydrogen-bonding and transition metal catalysis

While the utility of amine/transition metal and Brønsted acid/transition metal dual catalytic systems has been extensively investigated, the combination of transition metal and hydrogen-bonding catalysis, such as the use of related thiourea derivatives is much less developed.

The first example of combining hydrogen-bonding catalysis and transition metal catalysis has been reported by Jørgensen and co-workers in a sequential enantioselective Mannich/hydroamination reaction (Scheme 70).[119] In this protocol, the versatile propargylated malononitrile and *N*-Boc-protected imines were utilized as the substrates. The cinchona alkaloid derived bifunctional tertiary amine-thiourea was employed to catalyze the enantioselective Mannich reaction *via* thorough hydrogen-bonding interaction, whereas the widely used $Ph_3PAuNTf_2$ was used to catalyze hydroamination reaction to form optically active 2,3-dihydropyrroles. The use of excess *p*-TsOH was crucial as it prevented deactivation of the Au(I) catalyst by protonating the basic quinuclidine and quinoline moieties of the organocatalyst. This indicates that the problem



Scheme 70 Thiourea Mannich-type reaction/gold-catalyzed alkyne hydroamination and isomerization.



Scheme 71 Sequential double Friedel–Crafts type reaction by combined thiourea and gold catalysis.

of catalyst deactivation still needs to be solved effectively in gold/tertiary amine–thiourea combination.

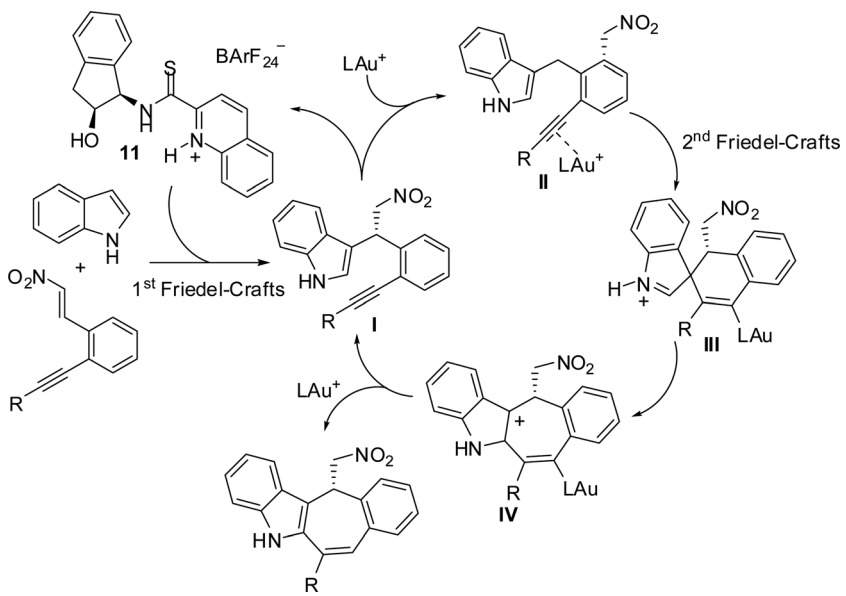
Recently, the combination of hydrogen-bonding catalysis and Au(I) catalysis has been demonstrated by Enders and co-workers to synthesize a seven-membered ring containing tetracyclic indole derivatives in good yields with excellent enantioselectivities (Scheme 71).[120] While the deactivation of the Au(I) catalyst occurred regardless of whether *p*-TSA was added, the addition of *p*-TSA was still necessary as it helped to regenerate the catalytically active Au(I) species to ensure that both the organocatalytic and Au(I) catalytic cycles could operate well in tandem.

This sequential transformation was proposed to proceed through the following mechanism (Scheme 72). The indole reacts with nitroalkene to form the chiral intermediate **I**. Then the C3-substituted intermediate **I** undergoes a second Friedel–Crafts type reaction with gold(I) activated alkyne to generate a spirocyclic intermediate **III**. The spirocyclic intermediate **III** rearranges through a 1,2-shift to effect an expansion from a six- to a seven-membered ring **IV**. Subsequent rearomatization and protodeauration lead to the final product.

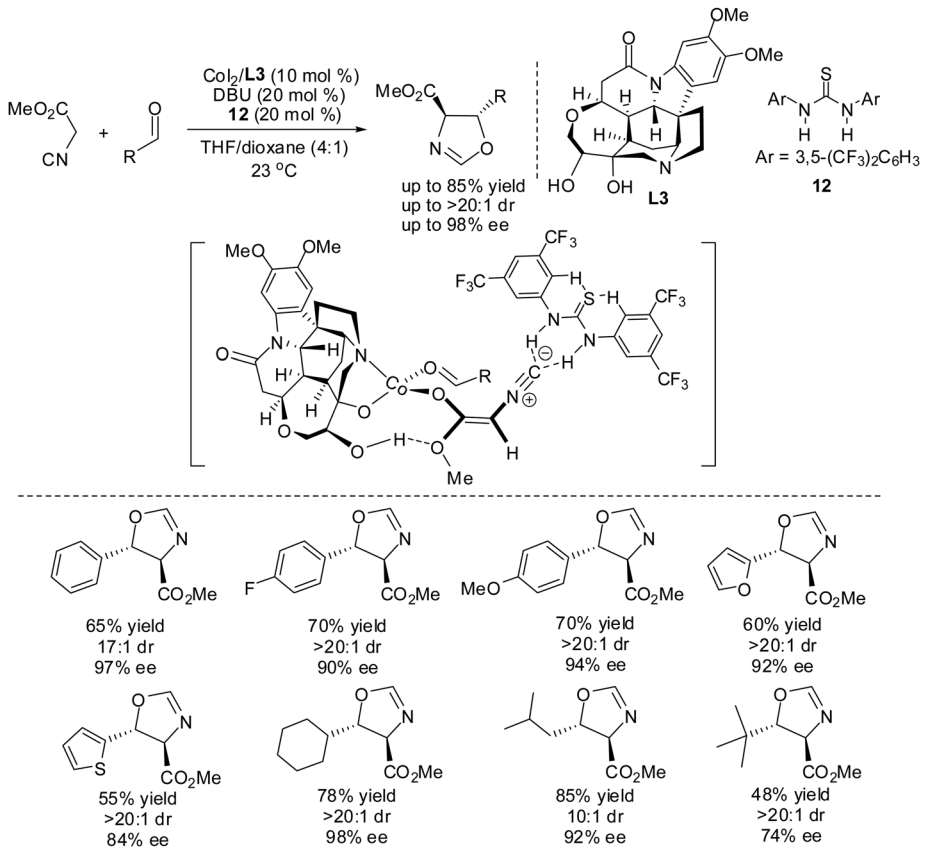
In addition to the combination of an achiral transition metal catalyst and a chiral hydrogen-bonding catalyst outlined above, the combined use of a chiral transition metal catalyst with an achiral hydrogen-bonding catalyst has also been demonstrated to be feasible. An elegant example has been recently demonstrated by Oh and Kim in a highly diastereo- and enantioselective catalytic aldol reaction of methyl α-isocyanoacetate (Scheme 73).[121] The anion-binding of the thiourea to isocyanides was considered to be responsible for high stereocontrol. The catalytic aldol reaction was applicable to a variety of aromatic, heteroaromatic, and aliphatic aldehydes. In general, excellent diastereo- and enantioselectivities (>20 : 1 dr, 90–98% ee's) were obtained at ambient temperature. The limitation of the current dual catalysis lies in *ortho*- and *meta*-substituted benzaldehydes, where low levels of enantioselectivity were obtained in the range of 20–50% ee but with excellent diastereoselectivities (>20 : 1 dr).

As demonstrated in these three examples,[119–121] by using appropriate combinations of an organocatalyst and an achiral or chiral transition metal catalyst, facile ways for reaction optimization can be achieved. This work further demonstrates the power of the combined catalysis in reaction optimization.

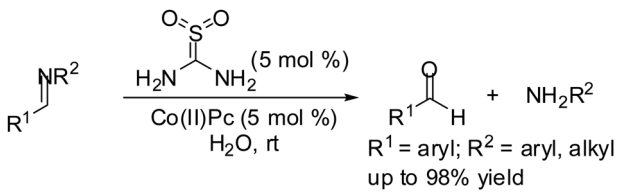
In addition to asymmetric reactions, the combination of transition metal and hydrogen-bonding catalysis has also been used in a racemic reaction. Metal catalyzed hydrolysis of imines to amines is an important synthetic transformation which is extensively used in the synthesis of bioactive complex molecules.



Scheme 72 Mechanism of sequential double Friedel–Crafts type reaction.



Scheme 73 Asymmetric aldol reaction of methyl α-isocyanoacetate by combining a chiral transition metal catalyst with an achiral thiourea.



Scheme 74 Catalytic hydrolysis of imines by combined catalysis.

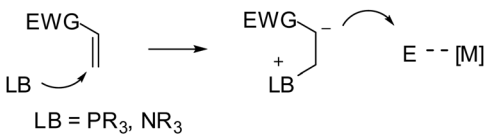


Fig. 4 Lewis base-activated electron-deficient alkenes as nucleophiles.

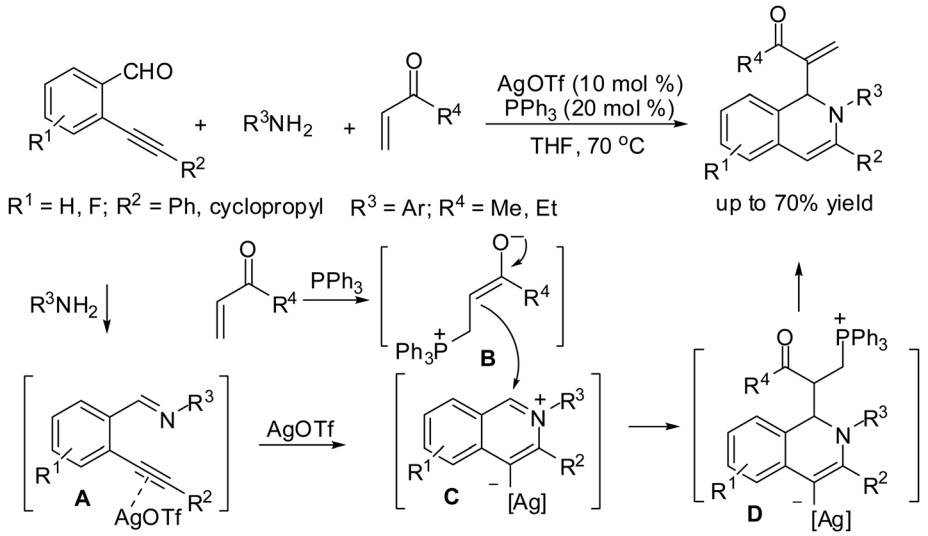
However, this reaction mainly requires strong acidic or basic conditions. Recently, Jain and Sain developed a new efficient approach using cobalt(II) phthalocyanine and thiourea dioxide as catalysts for the catalytic hydrolysis of imines to amines without using acidic or basic conditions (Scheme 74).[122] In general, the reaction occurred efficiently with the aromatic aldimine substrates having *N*-alkyl and *N*-aromatic groups and provided the corresponding hydrolyzed products in good yields. The limitation of the current combined catalysis lies in the aldimines derived from the aromatic aldehydes having electron-withdrawing substituents on the aryl rings resulting in low yields.

8. Combining Lewis base (nucleophilic) and transition metal catalysis

As an important class of organocatalysts, Lewis bases are generally used to activate electron-deficient alkenes, producing nucleophiles *in situ* (Fig. 4). In this regard, Lewis base catalysts based on tertiary phosphanes and tertiary amines have been extensively studied.[12]

The first example of combining transition metal and Lewis base catalysis was reported by Krische and co-workers in 2003 when an effective dual catalytic process was achieved with a starting enone-tethered terminal allyl carbonate, through both the use of tributylphosphane as the Lewis base and of palladium-activated Tsuji–Trost π-allyl as the electrophile.[123] The allylated cyclic enone products were obtained in excellent yields. This work also initiates the field of combining transition metal and Lewis base catalysis. Most importantly, the concept of combining organocatalysis and transition metal catalysis was mentioned for the first time.

Recently, Wu and co-workers reported a new example of transformations of this type, in which AgOTf was employed as the π-acid in combination with PPh_3 Lewis base.[124] Three-component reaction between 2-alkynylbenzaldehydes, amines and α,β-unsaturated ketones was developed, and functionalized



Scheme 75 Three-component reaction between 2-alkynylbenzaldehydes, amines and α,β-unsaturated ketones.

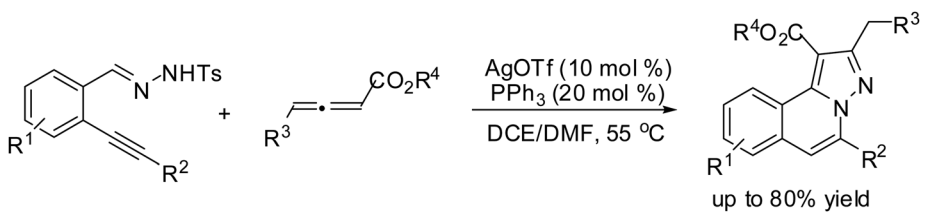
1,2-dihydroisoquinolines were synthesized in good yields (Scheme 75). The authors proposed that alkynylbenzaldehyde condensed with amine to form the imine **A** while α,β-unsaturated ketone reacted with PPh_3 to form the enolate **B**. The imine **A** coordinated AgOTf, which triggered a cyclization reaction to afford the isoquinolinium intermediate **C**. The enolate **B** attacked the isoquinolinium intermediate **C** to generate phosphinium **D**. Elimination of phosphine gave rise to the 1,2-dihydroisoquinoline product.

Using the same catalyst combination (AgOTf and PPh_3), Wu, Chen and co-workers developed a new two-component reaction of this type.[125] In this protocol, *N*′-(2-alkynylbenzylidene)hydrazides were utilized together with allenoates. Diverse *H*-pyrazolo[5,1-α]isoquinolines were obtained in good yields (Scheme 76).

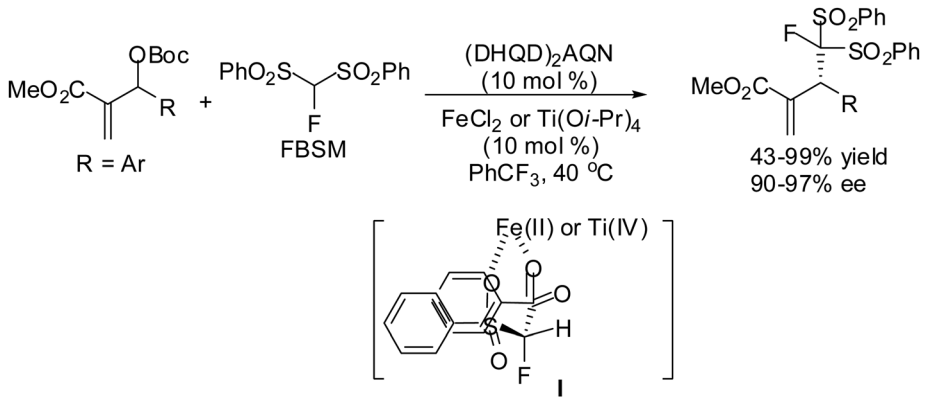
In addition to tertiary phosphane Lewis bases, tertiary amines have also been combined with transition metal catalysts for the development of new reactions. In this regard, the catalyst combinations with cinchona alkaloid derivatives have been extensively studied.[126]

Using a bis(cinchona alkaloid), $(DHQD)_2AQN$, in combination with a transition metal Lewis acid ($FeCl_2$ or $Ti(Oi\text{-}Pr)_4$), Shibata and co-workers developed a highly enantioselective allylic monofluoromethylation of Morita–Baylis–Hillman carbonates with FBSM (Scheme 77).[127] While this enantioselective allylic monofluoromethylation can also be achieved using $(DHQD)_2AQN$ as the only catalyst without any transition metal Lewis acid catalyst, the dual catalysis provides the corresponding products with the improvement of enantioselectivity by up to 10% ee. The improvement of enantioselectivity could be explained by bidentate chelation of FBSM with the Lewis acid, thus locking the FBSM conformation so as to favor a more closed conformation **I**. This study demonstrates further the utility of the organo-/transition metal dual catalysis in known and new reactions.

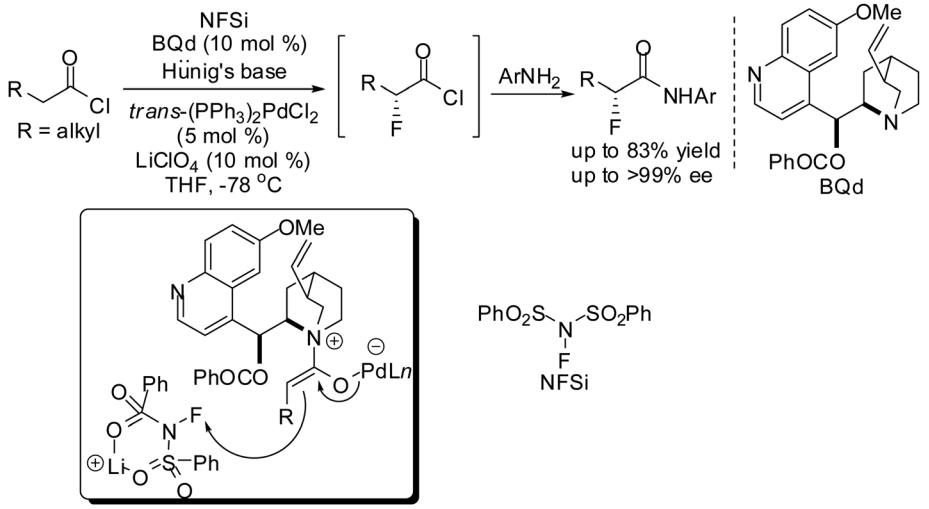
Other recent examples of combinations of cinchona alkaloid Lewis bases and transition metal Lewis acids were reported by Lectka and co-workers. With the application of cinchona alkaloid-derived Lewis base and palladium catalysts, they developed a highly enantioselective α-fluorination of acid chlorides. A variety of optically active α-fluorinated carboxylic acid derivatives[128] including biologically relevant α-fluorinated carbonyl derivatives[129] were obtained in good yields with high enantioselectivity. While this protocol worked well with a variety of aromatic acid chlorides (R = aryl), for most aliphatic substrates (R = alkyl) the yields were quite low.[128] To address this, they envisaged that a second Lewis acid could specifically coordinate with the NFSi, thereby increasing its electrophilicity. Finally, they found that adding of a Lewis acidic lithium salt to the dually activated system led to an increase in product yields while maintaining excellent enantioselectivity (Scheme 78).[130]



Scheme 76 AgOTf/PPh_3 catalyzed reaction of *N*′-(2-alkynylbenzylidene)hydrazides with allenoates.



Scheme 77 Asymmetric allylic monofluoromethylation of Morita–Baylis–Hillman carbonates by cinchona alkaloid/metal Lewis acid catalysis.

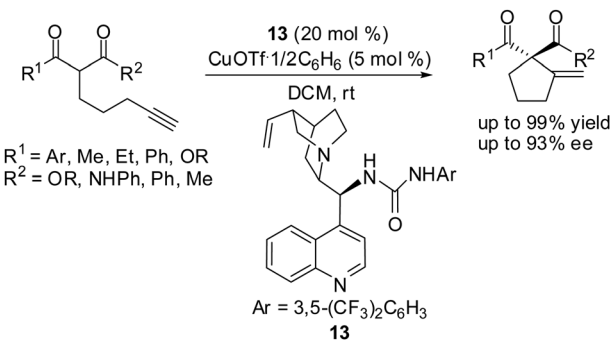


Scheme 78 Enantioselective α-fluorination of aliphatic acid chlorides by tricomponent catalysis.

9. Combining Brønsted base and transition metal catalysis

The prospect of combining Brønsted base catalysis[9] and transition metal catalysis (Fig. 5) was first touched upon by Jørgensen and co-workers in 2005 by a combined utilization of quinine as the chiral Brønsted base and (*R*)-Ph-BOX-Cu(OTf)$_2$ as the chiral Lewis acid in the asymmetric aza-Henry reaction.[131] Since then, several groups have made some advances in this field.

In 2009, using a combination of CuOTf·1/2C$_6$H$_6$ and a chiral cinchona-derived urea catalyst, Dixon and co-workers developed an enantioselective Conia-ene reaction (Scheme 79).[132]



Scheme 79 Cu(I)/Brønsted base catalyzed enantioselective Conia-ene reaction.

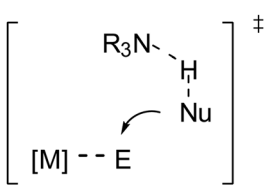
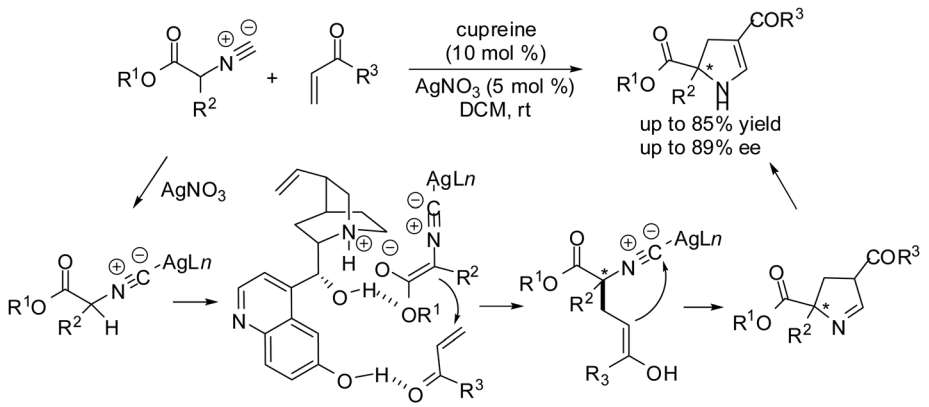


Fig. 5 The concept of Brønsted base/transition metal dual catalysis.

In this protocol, the cinchona-derived urea was proposed to deprotonate the β-keto ester *via* Brønsted base catalysis and generate the enolate nucleophile, whereas CuOTf·1/2C$_6$H$_6$ would function as Lewis acid for alkyne activation. As mentioned by the authors, the urea functional group and the tertiary amine, which might provide Brønsted/Lewis base and hydrogen-bonding donor functionalities, were crucial for this



Scheme 80 Formal [3+2] cycloaddition of isocyanoacetates to α,β-unsaturated ketones by metal/Brønsted base catalysis.

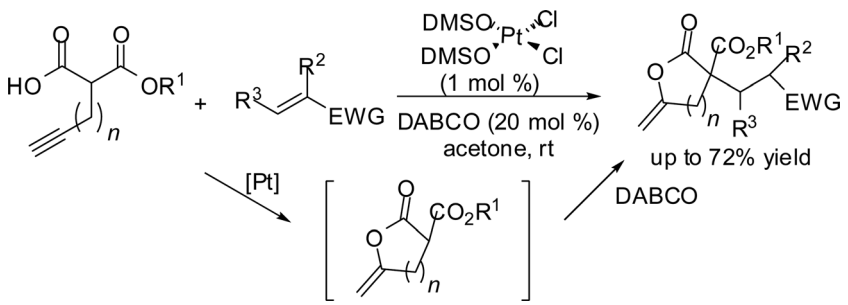
enantioselective transformation. Under the dual catalysis, the cyclic products were obtained in good yields and with high enantioselectivities.

Recently, a new example of combined use of a chiral Brønsted base and a transition metal Lewis acid catalyst was reported by Escolano and co-workers. With the application of cupreine and $AgNO_3$ catalysts, they developed a formal enantioselective [3+2] cycloaddition reaction of isocyanoacetates to α,β-unsaturated ketones, providing 2,3-dihydropyrroles in up to 89% ee (Scheme 80).[133] In the proposed mechanism, silver coordinates to the terminal carbon of isocyano group, resulting in the increase of the acidity of the α-proton so that the quinuclidine nitrogen of cupreine α-deprotonates isocyanoacetate. After the α-deprotonation, a rigid chiral ion pair is formed by the hydrogen-bonding interaction between the C9-hydroxy group and the substrate. Then vinyl ketone undergoes 1,4-addition by the nucleophile, generating the stereogenic center of the product. Finally, a 5-*endo-dig* cyclization takes place to afford the final product under the electrophilic silver isocyanide activation.

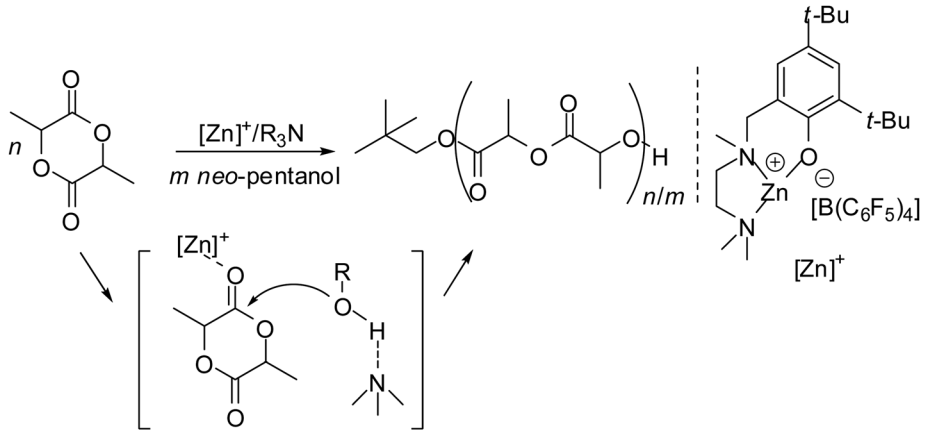
In addition to chiral Brønsted bases, achiral Brønsted base catalysts have been combined with transition metal catalysts for the development of new racemic reactions. By applying the combination of Brønsted base, DABCO, and platinum catalysis, Alemán and co-workers developed a tandem cyclization/Michael reaction (Scheme 81).[134] This protocol allows the synthesis of lactones with a quaternary center at C-3 and substitution at C-5 in a facile manner.

Another recent example of transition metal/achiral Brønsted base dual catalysis is demonstrated by Guillaume and Bourissou in the ring-opening polymerization (ROP) of lactide (Scheme 82).[135] In this instance, the electrophilic zinc cation activates the monomer by coordination to the carbonyl moiety while the amine activates the initiating/propagating alcohol through hydrogen bonding. Importantly, this work demonstrates the utility and potential of organo-/transition metal dual catalysis in polymer chemistry.

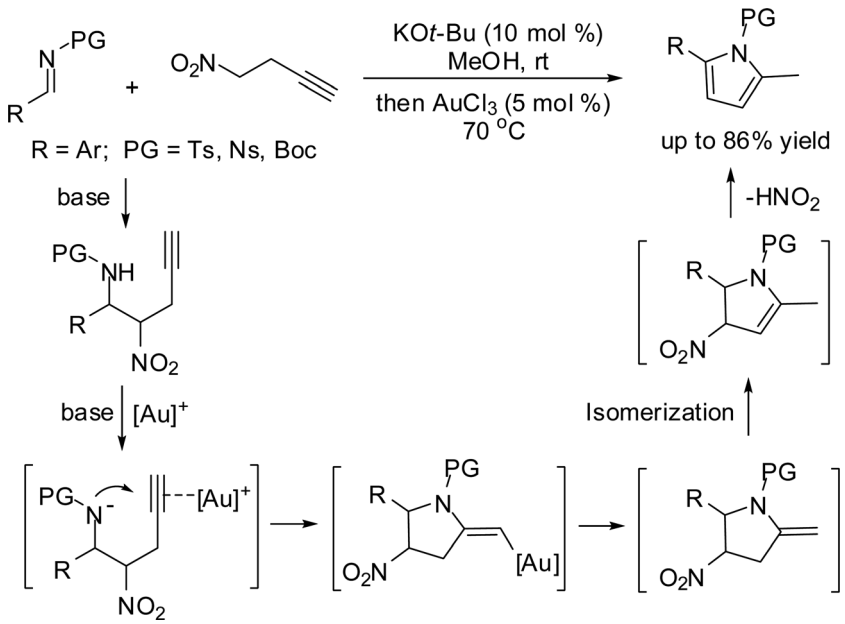
In addition to achiral organic Brønsted bases, achiral inorganic Brønsted bases have been reported to combine successfully with transition metal catalysis for new reactions. Recently, using the combination of $AuCl_3$ and an achiral inorganic Brønsted base, KO*t*-Bu, Dixon and co-workers developed a sequential nitro-Mannich/hydroamination reaction, which afforded 2,5-disubstituted pyrroles in good yields (Scheme 83).[136] This protocol was applicable to a range of aromatic imines. Both electron-rich and electron-poor aromatic imines reacted effectively with 4-nitrobut-1-yne to afford the desired 2,5-disubstituted pyrroles in moderate to good yields. The substituted nitro alkyne such as 5-nitropent-2-yne was not a suitable substrate for this sequential reaction. However, using $Au(PPh_3)Cl$ (5 mol%) with AgOTf (5 mol%) was found to facilitate the desired sequential reaction, affording the desired pyrrole product in an unoptimized 21% yield after heating in methanol at 70 °C for 72 hours.



Scheme 81 Tandem cyclization/Michael reaction by combining Brønsted base and platinum catalysis.



Scheme 82 ROP of lactide catalyzed by the combination of cationic zinc complex with a tertiary amine.

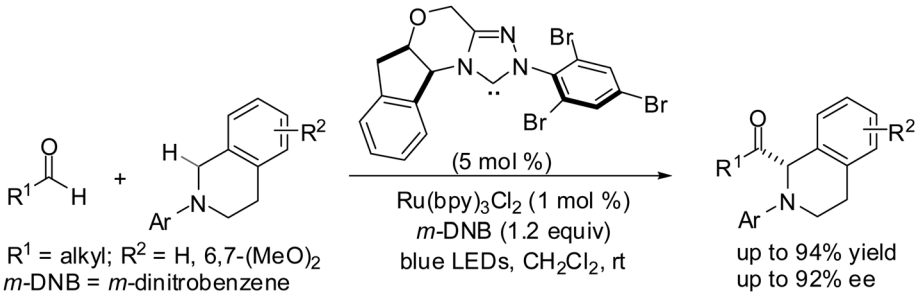


Scheme 83 Nitro-Mannich/hydroamination cascade using Brønsted base and gold catalysis.

10. Combining *N*-heterocyclic carbene and transition metal catalysis

N-Heterocyclic carbenes (NHCs) are the subject of rapidly growing interest in the synthetic community.[10] These compounds are also well-known ligands for transition metals.[137] While the first successful example of a combination of transition metal and NHC catalysis was reported by Hamada and co-workers in 2006 in an efficient synthesis of 3-substituted 2,3-dihydroquinolin-4-ones,[138] only recently have impressive developments in this field been made.[139a] The compatibility between NHCs as organocatalysts and transition metal cations was an appreciable challenge because of potential self-quenching of these two catalysts. Because significant advances in combined transition metal and NHC catalysis have been summarized in a very recent minireview by Scheidt *et al.* published in 2012,[139b] herein we would like to present a very recent elegant example published after Scheidt's review to demonstrate the power of this dual catalysis strategy.

The generation of acyl anion or homoenolate equivalents from aldehydes represents a powerful strategy in NHC catalysis, wherein an aldehyde is converted to a nucleophilic species under mild conditions.[140] On the other hand, the generation of reactive iminium ions from tertiary amines in the presence of transition metal complexes *via* the activation of the α-C(sp^3)–H bond represents another effective tool for the development of novel chemical transformations.[48] Visible-light photoredox catalysis[141] has recently been used to generate these reactive species as the reaction conditions are mild, thereby allowing for potential compatibility between multiple catalytic pathways. Through the powerful combination of NHC catalysis and visible-light photoredox catalysis, very recently these two chemically distinct activation events have been successfully unified by Rovis and DiRocco, and an elegant catalytic

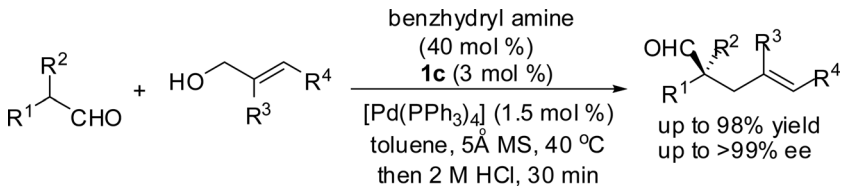


Scheme 84 Catalytic asymmetric α-acylation of tertiary amines by the merger of NHC catalysis and photoredox catalysis.

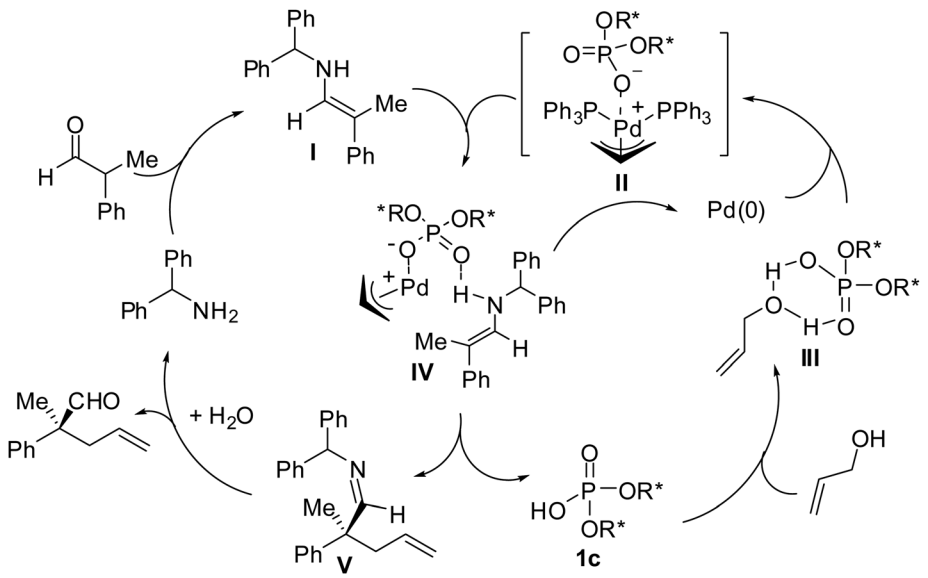
asymmetric α-acylation of tertiary amines with aldehydes has been developed (Scheme 84).[142] Notably, H_2 is the only byproduct in this protocol. This productive dual-catalysis allows access to α-amino ketones in good yield and high enantioselectivity.

11. Miscellaneous combinations

While we have categorized the main combinations of organo- and transition metal catalysis in the sections above, in a separate section we would like to highlight a recent elegant combination of organocatalysis and transition metal catalysis by List and co-workers,[143a] in which three different catalysts, transition metal, Brønsted acid and amine catalysts, were effectively used to mediate the enantioselective direct α-allylation of α-branched aldehydes (Scheme 85).[143b] The allylated aldehydes bearing an all-carbon quaternary stereogenic center were obtained in excellent yields with high enantioselectivities. Unlike in their previous work,[143c] allylic alcohols rather than benzhydryl allyl amines were used directly as the allylating reagents in this instance, thus simplifying previous α-allylation protocol as benzhydryl allyl amines have to be synthesized individually in a separate step. The process is quite general and tolerates α-methyl-branched aromatic aldehydes bearing electron-donating and electron-withdrawing groups at different positions. For the α-ethyl-substituted substrate such as 2-phenylbutanal, slightly higher catalyst loading was required to achieve the



Scheme 85 Direct asymmetric α-allylation of α-branched aldehydes with allylic alcohols.



Scheme 86 Mechanism for the direct asymmetric α-allylation of α-branched aldehydes with allylic alcohols.

corresponding product in 77% yield and 62% ee. The aliphatic aldehydes were not good substrates for this protocol. However, it was found that when the aliphatic aldehyde 2-cyclohexylpropanal was treated with [$Pd(PPh_3)_4$], (*S*)-TRIP **1c**, and 80 mol% of (*S*)-1-phenylethylamine instead of benzhydryl amine at higher temperature (110 °C), the corresponding allylated product could be obtained in high yield with promising enantioselectivity. Moreover, this protocol can also be easily extended to a range of substituted allylic alcohols.

The mechanism of this remarkable transformation is outlined in Scheme 86. Firstly, the aldehyde reacts with the primary amine catalyst to generate configurationally defined (*E*)-enamine **I**, which is crucial for high enantioselection. Then the catalytic enamine intermediate **I** is allylated by the π-allyl-Pd-phosphate **II** which is generated by the oxidative addition of Pd(0) into the allylic alcohol activated by Brønsted acid (*S*)-TRIP **1c**, leading to the imine **V** and regenerating Pd(0) and (*S*)-TRIP **1c**. Subsequently, the hydrolysis of the imine **V** affords the final product.

12. Conclusion

Even within the short time covered by this update review and our summary on this topic three years ago, a tremendous increase in combined transition metal catalysis and organocatalysis took place. Besides many new types of catalyst combinations, various reaction types and unprecedented transformations have increased immensely. This demonstrates that the combination of transition metal catalysis and organocatalysis has become a new and exciting research area in current chemistry. Despite these remarkable developments, when compared to transition metal catalysis or organocatalysis, the concept of combined transition metal catalysis and organocatalysis so far is still limited in number. In our opinion, the development of novel types of transformations, in particular based on new strategies, will still be one main area for researchers to look into. On the other hand, the development of new catalyst combinations represents another future research direction. Additionally, the exploration of the applications of this dual catalysis concept in the total synthesis of natural products is worthy of further investigation. In summary, the examples described in this review have highlighted the remarkable utilities and potential of this concept. As the concept of combined catalysis expands, the number of novel transformations, new catalyst combinations and new applications will continue to increase.

Acknowledgements

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