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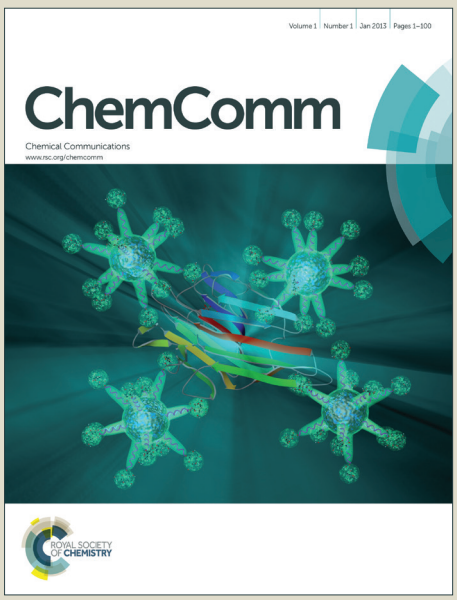

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Synergistic/Cooperative Combination of Enamine Catalysis with Transition Metal Catalysis

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Synergistic/cooperative combination of enamine catalysis with transition metal catalysis is an emerging and exciting field aiming to achieve organic transformations that cannot be accomplished by individual catalysis. The biggest obstacle in this field lies in the catalysts incompatibility arising from Lewis acid-Lewis base interactions. Several strategies including soft/hard combination of a Lewis acid and a Lewis base, the utilization of a chelating ligand, and mixing an amine salt with an Lewis acid have been developed to solve the incompatibility problem. A number of new reactions and new reaction modes have been discovered using these strategies. In this review article, we aim to highlight these new discoveries found in literature.

Introduction

The rapid growth in organocatalysis, in which a small organic molecule serves as the catalyst, over the last decade has dramatically changed the profile of asymmetric catalysis.[1-9] Transition metal catalysis, on the other hand, has long been established as one of the most powerful tools in organic synthesis.[10] In recent years, a new research area: the combination of organocatalysis with metal catalysis, has emerged, aiming to achieve organic transformations that cannot be accessed by organocatalysis or metal catalysis independently.[11-15] Given the rich chemistry established in both fields, this new concept offers tremendous possibilities. Enamine catalysis is one of the most investigated areas in organocatalysis. A large number of new reactions have been developed based on enamine catalysis over the past decade. Although the merging of enamine catalysis with transition metal catalysis promises huge potential, this research area has grown relatively slowly. The major challenge lies in the incompatibility of the catalysts;[16, 17] in particular, the combination of an amine catalyst with a hard metal Lewis acid is very difficult. The combination of an amine catalyst with a transition metal catalyst was first achieved by the Córdova group in 2006.[18] Since then, considerable progress, particularly in recent several years, has been made in the combination of enamine catalysis with metal Lewis acid catalysis leading to a series of exciting discoveries. Enamine catalysis has been combined with metal catalysis in several different ways: cooperative catalysis, synergistic catalysis and sequential/relay catalysis.[14, 15] In cooperative catalysis, the organocatalyst and the transition metal catalyst activate the substrates independently but in the same catalytic cycle, working cooperatively to form a new bond. Synergistic catalysis is defined as concurrent activations of both the nucleophile and the electrophile distinctively by the organocatalyst and the transition metal catalyst in two directly coupled catalytic cycles to create a new single bond. In sequential or relay catalysis, one catalyst (organocatalyst or transition metal catalyst) activates one substrate producing an intermediate, which is sequentially activated by the other catalyst. In this review article, we focus on the synergistic and cooperative enamine/transition metal catalysis in which the metals possess Lewis acidity. We aim to provide our own opinions about the current development of this exciting field, foreseeable problems and future outlook of this field. The summary of sequential/or relay enamine/metal catalysis as well as other mergers of organocatalysis/metal catalysis can be found in four other excellent reviews.[11-15]

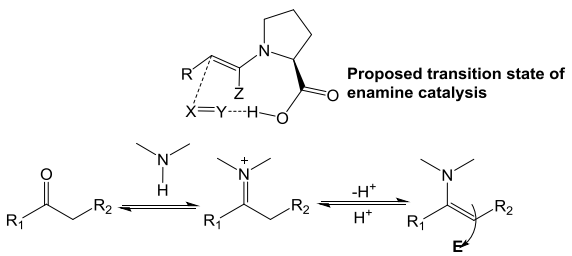


Fig.1 Enamine catalysis

Enamine catalysis is defined as catalysis by primary or secondary amines of electrophilic substitution reactions at the α-position of carbonyl compounds and related reactions via enamine intermediates (Fig. 1). In organo-enamine catalysis, a chiral aliphatic primary or secondary amine, for example proline, acts as the catalyst. These chiral amine catalysts can be treated as bifunctional catalysts, because the carboxylic acid group which is often modified in other chiral amine catalysts also interacts with an electrophilic reaction partner through either hydrogen bonding or electrostatic attraction simultaneously. Aliphatic amines are hard Lewis bases; they are good ligands to a variety of metals, in particular to hard metals. When an amine catalyst is mixed with a metal Lewis acid, acid-base quenching reaction will occur thus causing catalyst inactivation. Several valuable strategies have been developed to alleviate the incompatibility problems: (1) Soft/hard approach in which a hard base is employed with a soft acid or vice versa. (2) The utilization of a chelating ligand to avoid acid-base interaction. (3) The utilization of an amine salt along with a metal Lewis acid. Based on the work in the literature, synergistic and cooperative enamine/transition metal catalysis can be classified into five types of

activation mode (Fig. 2):[11-15] Type I, enamine addition to transition metal-π-allyl complexes. Type II, cooperative enamine addition to a substrate activated by a σ-electrophilic metal Lewis acid. Type III, enamine addition to a cationic species the formation of which is facilitated by a σ-electrophilic metal Lewis acid. Type IV, enamine addition to a reactive Cu(III)-C(sp^2) species. Type V, enamine addition to alkynes activated by π-electrophilic metal Lewis acids (**A** and **B**).

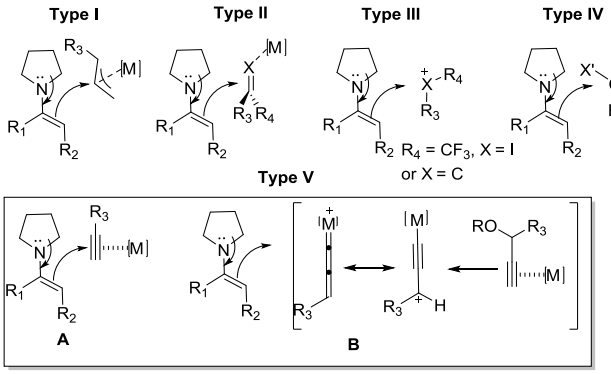


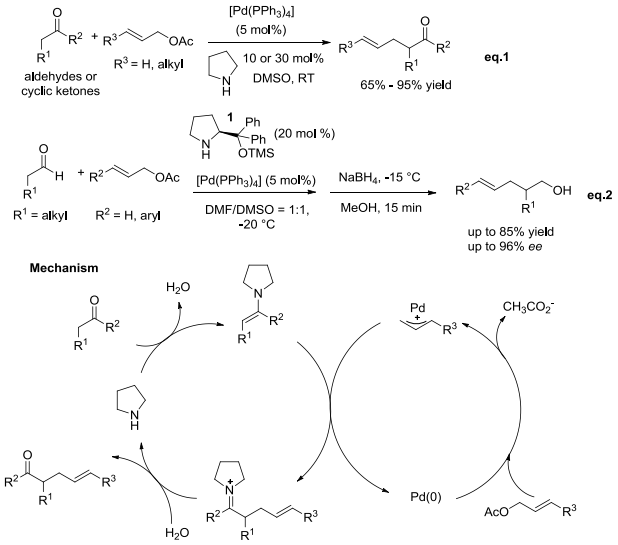
Fig. 2 Reaction modes of synergistic/cooperative enamine/transition metal catalysis

1. Combination of an aliphatic amine with a soft metal: soft/hard approach

The soft/hard approach is a general and effective strategy in combining enamine catalysis with transition metal catalysis. Using this strategy, an aliphatic amine catalyst has been successfully combined with a soft metal catalyst, such as Ag(I), Au(I), Ir(I), Cu(I) and Pd(0 or II). The most investigated and developed reactions in this class are the enamine addition to Tsuji–Trost palladium π-allyl complexes, and to alkynes activated by π-electrophilic Lewis acids.

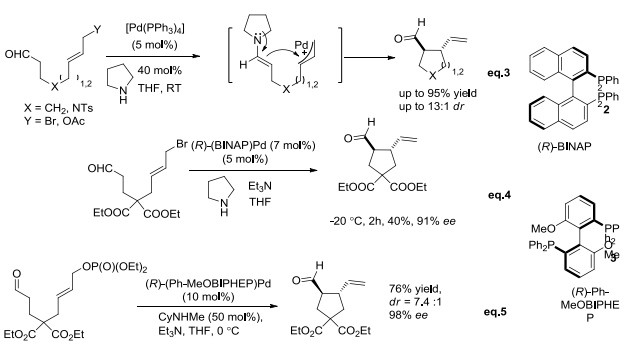
1.1 Enamine addition to metal-π-allyl complexes: allylation of aldehydes and ketones

α-Alkylation of carbonyl compounds was once dominated by addition of stoichiometric amounts of preactivated metal enolates to alkyl halides. Direct α-alkylation of nonstabilized aldehydes and ketones was difficult owing to competing side reactions, such as aldol condensations, Cannizzaro and Tishchenko reactions, and N- or O-alkylations.[19, 20] The direct intermolecular α-alkylation of aldehydes and cyclic ketones was not achieved until 2006 by the Córdova group through combining enamine catalysis with Pd(0) catalysis (Scheme 1, eq.1).[18] The success of this reaction demonstrated the great potential of combining enamine catalysis with transition metal catalysis. The authors proposed that two powerful catalytic cycles were merged in this transformation, enabling both electrophilic and nucleophilic activation (Scheme 1): 1) Activated enamine intermediates were *in situ* formed from aldehydes or ketones with pyrrolidine; 2) Electrophilic Tsuji–Trost palladium π-allyl complexes[21, 22] were catalytically generated in the other catalytic cycle; 3) Nucleophilic attack of enamine intermediates to palladium π-allyl electrophiles followed by reductive elimination leading to iminium intermediate and Pd^0; 4) Subsequent hydrolysis of the iminium intermediate afforded α-allylic alkylated aldehydes or ketones and regenerated the secondary amine catalyst. Both aldehydes and cyclic ketones (30 mol% pyrrolidine was needed) were suitable for this reaction. An asymmetric version of this reaction was also investigated using chiral pyrrolidine derivatives in this report. Good enantioselectivity (up to 88% *ee*) was obtained but only with moderate yields (up to 25%). High enantioselectivity and regiospecificity of this reaction was achieved by the same group in 2012 by more careful condition screening using Jørgensen-Hayashi chiral secondary amine catalyst (**1**) along with $[Pd(PPh_3)_4]$.[23] α-Allylation of aldehydes with allylic acetates was achieved with high enantiomeric excess (up to 96% *ee*) and high yield (up to 85%) in DMSO/DMF (1:1) at -20 °C (eq.2).



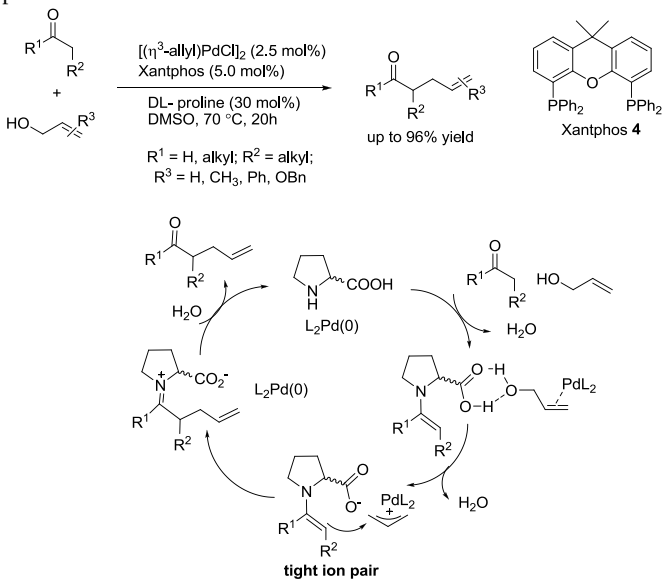
Scheme 1 Córdova's direct α-allylation of aldehydes and cyclic ketones with allyl acetates catalyzed by combined palladium and amine catalyst

Using a similar approach, Saicic and co-workers reported the construction of five and six-membered rings through direct intramolecular α-allylation of aldehydes (Scheme 2, eq.3) in 2007.[24] This intramolecular allylation was highly diastereoselective (up to 13:1 *dr*). The authors also attempted asymmetric transformation. However, the incorporation of a chiral amine either resulted in inactivation (MacMillan's catalyst, (*S*)-proline, and (*S*)-2-diphenylprolinol) or no enantioselectivity of this reaction ((*S*)-2-methoxymethyl pyrrolidine). Good enantioselectivity (91% *ee*) was obtained when using a chiral phosphorus ligand ((*R*)-(BINAP), **2**) for Pd(0) as the asymmetric inductor at low temperature (Scheme2, eq.4), but the activity of the reaction significantly decreased (yield, 40%). Further optimization of this asymmetric α-allylation reaction was performed by the same group (Scheme 2, eq.5).[25] In this reaction, (*R*)-(Ph-MeOBIPHEP, **3**) was used as the chiral ligand for Pd(0), methyl cyclohexylamine was used as the amine catalyst, the bromide leaving group in the previous transformation was also replaced with a phosphate leaving group. This intramolecular α-allylic alkylation proceeded in high enantioselectivity (98% *ee*), good yield (76%) and satisfactory diastereoselectivity (*trans:cis*= 7.4:1).

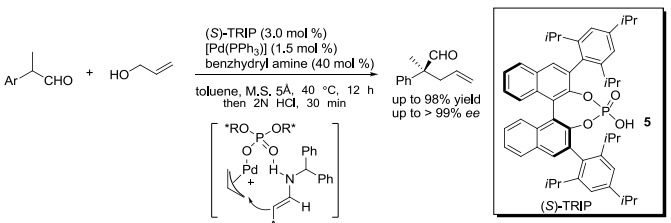


Scheme 2 Direct intramolecular α-allylation of aldehydes

All of the α-allylic alkylation reactions mentioned above involve a good leaving group, such as bromide, acetate and phosphate, to form the active Tsuji–Trost palladium π-allyl electrophiles. Direct α-allylic alkylation using allylic alcohol is an attractive protocol, because it would avoid the necessary conversion of the hydroxyl group into these leaving groups. However, hydroxyl group is a bad leaving group causing this reaction to be much more difficult. In 2009, Breit and co-workers reported a dual Pd/proline-catalyzed α-allylation reaction of aldehydes and ketones using allylic alcohols directly (Scheme 3).[26] Under optimized conditions, up to 96 % yield of direct intermolecular allylation products were obtained. It was believed that the high activity of the catalyst is related to the large bite angle of diphosphine Xantphos ligand (**4**). The presence of a carboxylic acid group in the secondary amine catalyst is also necessary to facilitate the formation of a tight ion pair intermediate proposed by the authors through hydrogen bonding and protonation of the hydroxyl group. Unfortunately, the extension to asymmetric α-allylic alkylation of allylic alcohol using optically pure organocatalysts as the amine catalyst either failed to give any desired product or resulted in a racemic mixture.



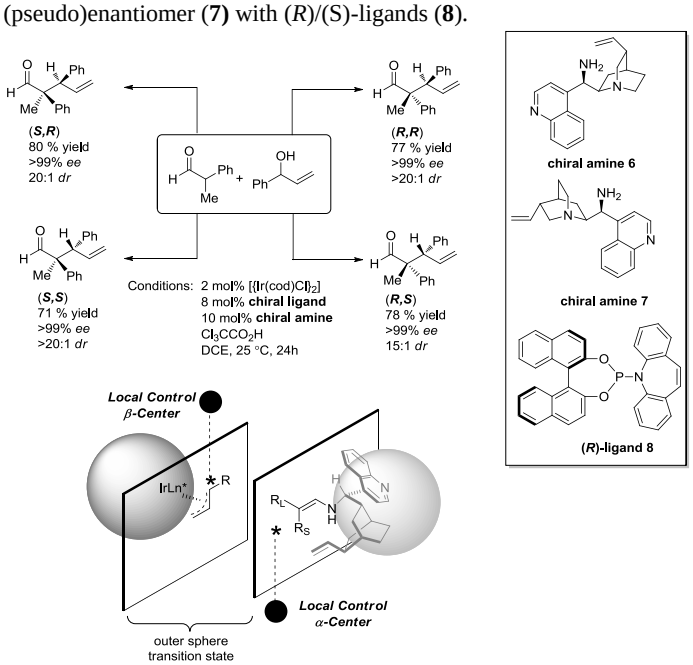
Scheme 3 Pd/proline-catalyzed α-allylation reaction with allylic alcohols



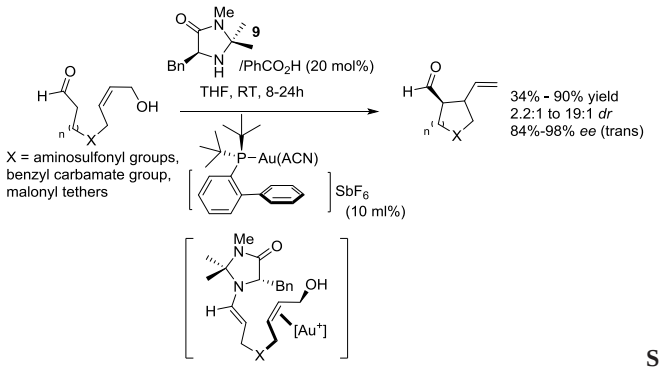
Scheme 4 Asymmetric α-allylation of different aldehydes with allylic alcohols

The first examples of asymmetric Tsuji–Trost-type α-allylation of carbonyl compounds with an allylic alcohol was achieved by the List group in 2011 through the concerted action of three different species, [$Pd(PPh_3)_4$], benzhydrylamine, and TRIP (**5**), generating all-carbon quaternary stereogenic centers in high yields (up to 98%) and enantioselectivity (up to >99% *ee*) (Scheme 4).[27] The high enantioselectivity of this reaction was enabled by asymmetric counteranion-directed catalysis (ACDC).[28, 29] The critical ACDC complex involves all three catalysts: the amine, which ensures the formation of a configurationally defined ***E*** enamine, the Pd(II), and the chiral counteranion.

Another asymmetric α-allylation of branched aldehydes with allylic alcohols was accomplished very recently by the Carreira group (Scheme 5).[30] In this reaction, an allyliridium intermediate similar to Tsuji–Trost palladium π-allyl electrophiles was formed acting as the electrophile. It is notable that γ,δ-unsaturated aldehydes bearing vicinal quaternary/tertiary stereogenic centers were generated in this reaction in good yields and excellent selectivities with wide substrate scope. This difficult asymmetric organic transformation was achieved through a novel stereodivergent dual catalysis engaging both a chiral iridium catalyst and a chiral amine catalyst, which activate the allylic alcohol and aldehyde substrates, respectively. In this stereodivergent dual catalysis, each catalyst exerts high local stereocontrol irrespective of the other's inherent preference, making it possible to access all possible stereoisomers of a target compound in enantiomerically pure form by simple catalyst permutations of a chiral amino catalyst (**6)** and its (pseudo)enantiomer (**7)** with (*R*)/(S)-ligands (**8**).

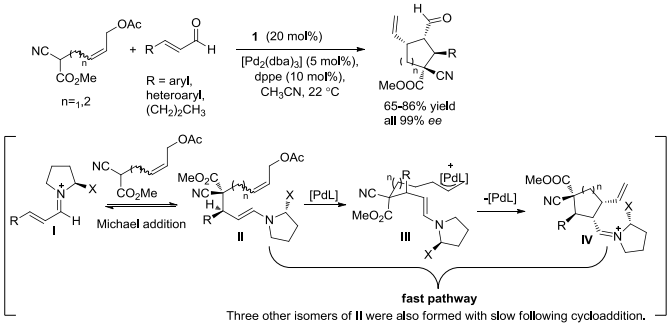


Scheme 5 Carreira's asymmetric α-allylation of branched aldehydes with allylic alcohols using stereodivergent dual catalysis



Scheme 6 Bandini's α-allylation of aldehydes with alcohols by Au(I)/amine catalyst

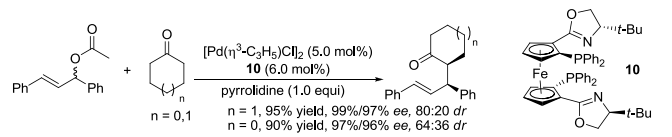
Recently, Bandini demonstrated the feasibility of the addition of enamines to gold(I) activated π-allyl electrophiles for an intramolecular α-allylation of aldehydes with alcohols (Scheme 6).[31] Substrates bearing aminosulfonyl groups, benzyl carbamate groups, and malonyl ethers were all tolerated in this catalysis system leading to desired products with moderate to high yield and high enantioselectivity.



Scheme 7 Córdova's Michael/α-allylic alkylation cascade reaction by of palladium/chiral amine combined catalyst

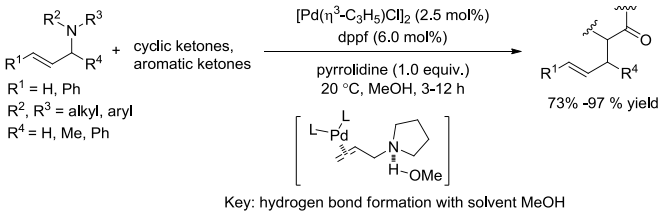
Reaction cascade is an efficient approach to constructing complex molecules from simple starting materials through enabling several bond-forming events to occur in the same reaction vessel. Taking advantage of the powerful combination of palladium and enamine catalysis, the Córdova group designed a Michael/α-allylic alkylation cascade reaction for the synthesis of polysubstituted cyclopentane and cyclohexane bearing an all-carbon stereocenter (Scheme 7).[32] This asymmetric dynamic kinetic transformation[33] is highly chemo- and enantioselective, involving iminium activation to allow Michael addition followed by fast and stereospecific formation of **IV** through cooperative enamine/Pd catalysis to close the ring.

Since the Córdova group introduced the direct allylation of carbonyl compounds in 2006, considerable advances have been achieved in the asymmetric α-alkylation of aldehydes. In contrast, little progress has been made on the enantioselective direct α-alkylation of ketones. In 2011, the Zhang group reported a highly enantioselective palladium-catalyzed allylation of ketones with allyl acetates (Scheme 8).[34] This reaction was proposed to go through the addition of an enamine, formed *in situ* from the ketone and pyrrolidine, to Pd-π-allyl intermediate. The enantioselectivity of this reaction was induced by a chiral phosphorus ligand (**10**) coordinated to palladium. However, a stoichiometric amount of pyrrolidine was required to ensure efficient conversion in the reaction.



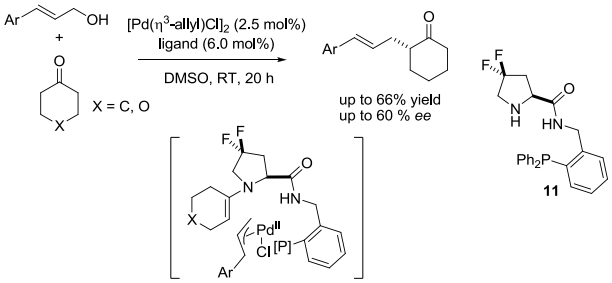
Scheme 8 Zhang's enantioselective allylation of cyclic ketones with allyl acetates

Later on, the same group developed another method for the allylation of ketones in which the *in situ* formed enamine was added to the Tsuji–Trost palladium π-allyl electrophiles, which were formed from allylic amines (Scheme 9).[35] The authors proposed that the difficult C-N bond cleavage of allylic amines was facilitated by hydrogen bond activation with the alcohol solvent. The acidity of the alcohol solvents was proved to play a key role on the effectiveness of the reaction. Both cyclic ketones and aromatic ketones afforded high yields in this transformation. Similar to their earlier report,[34] a stoichiometric amount of pyrrolidine was required to achieve high yields in the reaction. In this report, asymmetric allylation of acetone and 1,3-diphenylpropane-1,3-dione was also attempted with N-(1,3-diphenyl-2-propenyl) pyrrolidine using a chiral ferrocene-based phosphinooxazoline ligand, giving high yields and excellent enantioselectivities (up to 96% yield and up to 98% *ee*).



Scheme 9 Zhang's Pd-catalyzed allylation of ketones with allylic amines

Very recently, Shibasaki's group reported a direct asymmetric α-allylation of ketones with allylic alcohols through cooperative π-allyl-Pd activation and enamine activation (Scheme 10).[36] In order to realize dual activation of ketone and allylic alcohol, a chiral bifunctional ligand (**11**) bearing a proline unit and a phosphine unit was designed and synthesized. In this transformation, the π-allyl-Pd electrophile and the enamine nucleophile were brought in close vicinity by the bifunctional ligand to make the difficult allylation of ketones occur. However, only moderate yields and enantioselectivity were obtained using this cooperative bifunctional catalyst.



Scheme 10 Shibasaki's asymmetric allylation of ketones through bifunctional cooperative enamine/Pd catalysis

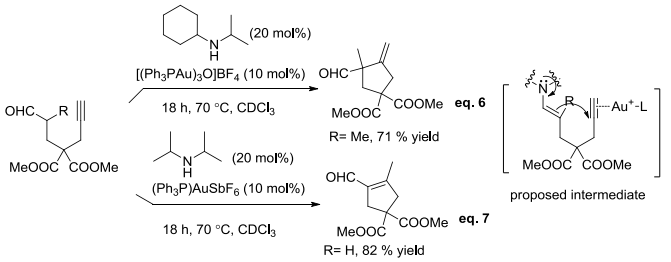
1.2 Enamine addition to alkynes activated by π-electrophilic metal Lewis acids

Enamine addition to metal π-acid activated carbon-carbon triple bond

Homogeneous gold (I) complexes have shown to be efficient carbophilic Lewis acid catalysts for the construction of complex carbocycles.[37-39] In 2008, the Kirsch group demonstrated for the first time the direct carbocyclization of aldehydes with alkynes through cooperative enamine catalysis/Au (I) catalysis (Scheme 11), thus opening a new entry into the direct α-functionalization of aldehydes with unactivated alkynes.[40] The cyclization of secondary formyl alkyne gave the desired 5-*exo-dig* cyclization product (Scheme 11, eq.6) bearing an all-carbon quaternary stereocenter in good yields. Reaction of α-unbranched aldehydes resulted in 5-*exo-dig* cyclization products followed by immediate double bond migration (Scheme 11, eq.7). Other soft metals such as silver(I) and platinum(II) salts also catalyzed the cyclization reaction, albeit in significantly reduced yields.

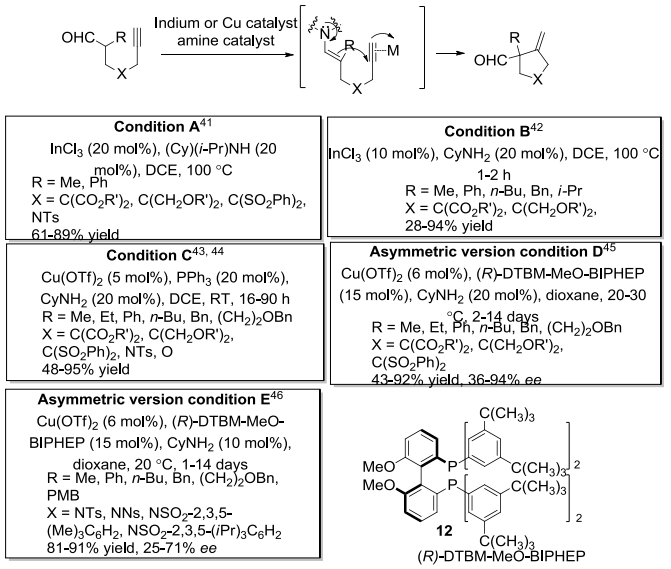
With the intention of extending the substrate scope of Kirsch's work, Michelet and Ratovelomanana-Vidal investigated the combination of an amine catalyst with other transition metal catalysts (Scheme 12).[41-46] Michelet and Ratovelomanana-Vidal disclosed the application of an $InCl_3$/amine dual catalytic system for

the carbocyclization of formyl alkynes with extended substrate scope, however, at elevated temperature (70 °C or 100 °C).[41, 42] In the presence of $InCl_3$/(Cy)(*i*-Pr)NH, cyclization of α-methyl and α-phenyl substituted aldehydes proceeded efficiently (Condition A, Scheme 12).[41] For sterically more bulky aldehydes with *n*-butyl, benzyl, or *i*-propyl substitution at the α-position, a less bulky primary amine, e.g. $CyNH_2$, was used with $InCl_3$ to ensue efficient transformations (Condition B, Scheme 12).[42] Kinetic studies revealed an enamine/*anti*-carbometalation mechanism for the $CyNH_2/InCl_3$ system, while an enolate/*cis*-carbometalation mechanism was favoured in competition with the enamine/*anti*-carbometalation process for the $InCl_3$/(Cy)(*i*-Pr)NH system.[13] Later on, Michelet and Ratovelomanana-Vidal further optimized the reaction conditions of the cyclization and brought down the reaction temperature to room temperature using $Cu(OTf)_2$-PPh_3/$CyNH_2$ as the catalyst (Condition C, Scheme 12).[43, 44] Given that $InCl_3$ is a hard Lewis acid and $Cu(OTf)_2$ is a moderate hard Lewis acid,[47] it is interesting to note that acid-base quenching problem was not observed/mentioned in these reactions.

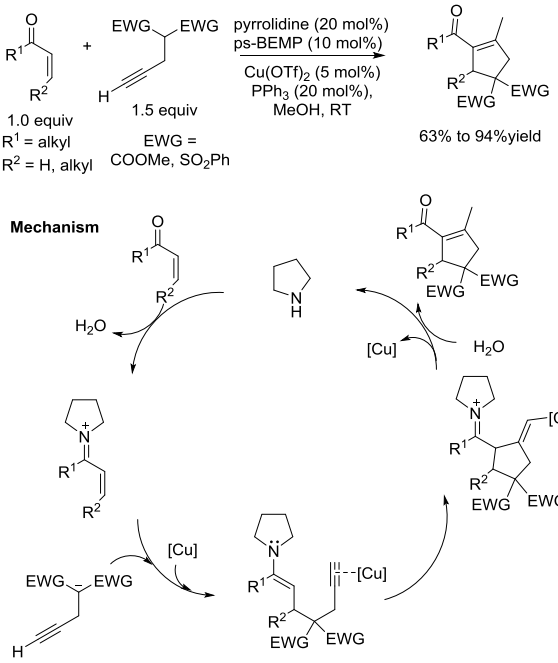


Scheme 11 Kirsh's 5-*exo*-*dig* cyclization of formyl alkyne catalyzed by combined gold(I)/amine catalysts

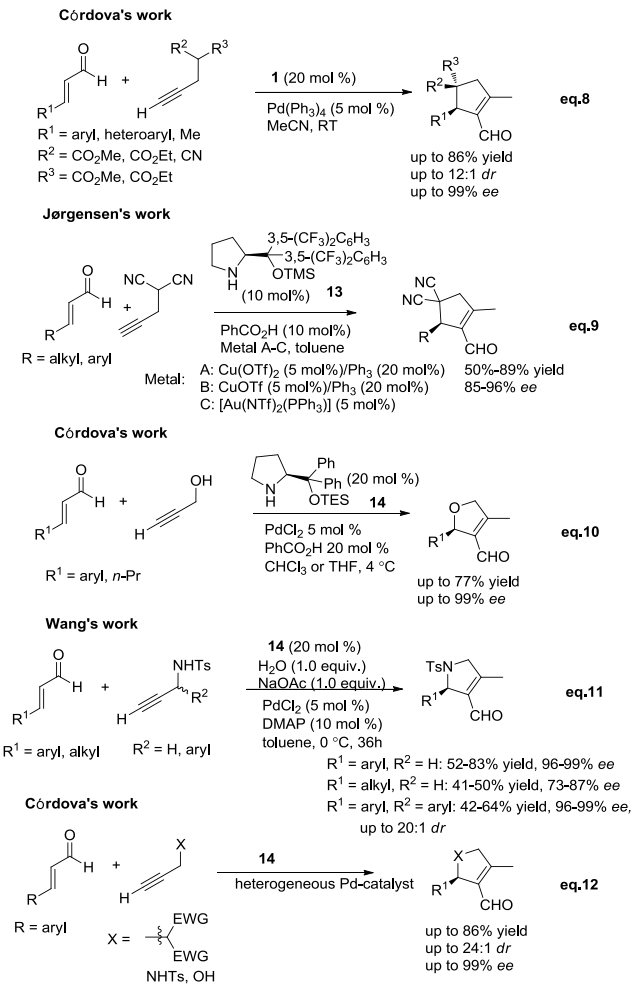
Very recently, asymmetric carbocyclization was finally achieved by the same group using a chiral phosphorus ligand for $Cu(OTf)_2$ in these reactions (Conditions D and E, Scheme 12).[45, 46] Both cyclopentanes and pyrrolidines were produced with moderate to excellent enantioselectivities.



Scheme 12 Michelet and Ratovelomanana-Vidal's carbocyclizationof α-substituted formyl alkynes



Scheme 13 Dixon's Michael/carbocyclization of α,β-unsaturated ketones and propargylated carbon acids

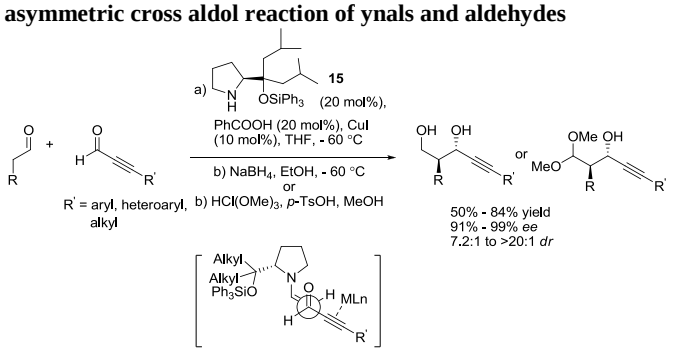


Scheme 14 Asymmetric cascade annulation reactions based on sequential combination of iminium catalysis with cooperative enamine/π-acid metal catalysis

Through one-pot combination of catalytic iminium activation of α,β-unsaturated ketones, enamine activation of ketones and simultaneous metal ion activation of alkynes, the Dixon group developed a cascade reaction of α,β-unsaturated ketones and propargylated carbon acids to generate cyclopentenes in moderate to good yields under mild conditions (Scheme 13).[48] This cascade reaction was catalyzed by a mutually compatible combined pyrrolidine/$Cu(OTf)_2$-PPh_3 catalyst. A Cu(I) species generated from the reduction of the Cu(II) complex by PPh_3 was postulated to be responsible for the alkyne activation. The reaction was initiated by Michael addition to the iminium ion activated enone, generating the enamine intermediate, subsequent nucleophilic attack of the enamine species to the metal ion activated alkynes followed by protonolysis, hydrolysis and isomerization provided the desired cyclopentenes.

Inspired by Dixon's seminal work, several asymmetric cascade annulation reactions have been developed based on the sequential combination of iminium catalysis with cooperative enamine/π-acid metal catalysis, including Michael/carbocyclization of α,β-unsaturated aldehydes and propargylated carbon acids to generate functionalized cyclopentenes (Scheme 14, Córdova's work, eq.8; Jørgensen's work, eq.9),[49, 50] oxa-Michael/carbocyclization of enals and propargyl alcohols to produce dihydrofurans (Córdova's work, eq.10),[51] aza-Michael/carbocyclization of enals and N-tosylpropargylamines to yield dihydropyrroles (Wang's work, eq. 11).[52] The asymmetry of the reactions was induced by a chiral secondary amine in conjunction with a soft metal Lewis acid (Pd(0), Pd(II) or Cu(I)) giving the desired cyclization products in good to excellent enantioselectivities. Heterogeneous Pd catalyst also effectively catalyzed the annulation reaction (eq.12).[53]

Enamine addition to ynals activated by metal π-acids: Direct asymmetric cross aldol reaction of ynals and aldehydes

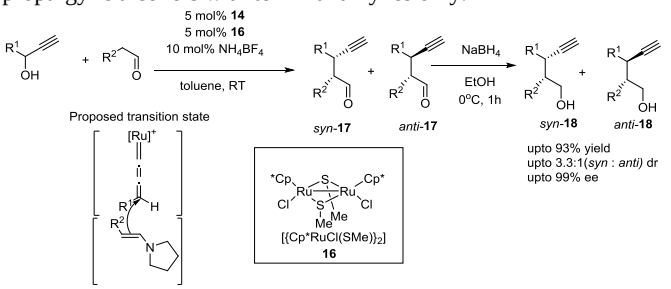


Scheme 15 Direct asymmetric cross aldol reaction of ynal and aldehyde by cooperative prolinol ether-transition metal-Brønsted acid catalysis

In 2013, the Palomo group reported a highly stereocontrolled synthesis of functionalized propargylic alcohols via asymmetric direct aldol reaction of aldehydes and ynals catalyzed by a ternary catalyst system comprised of a chiral prolinol ether, CuI, and benzoic acid (Scheme 15).[54] The authors proposed that this asymmetric cross aldol reaction was achieved through the nucleophilic attack of the *in situ* generated enamine to the aldehyde group of the ynals activated by the formation of ynal–metal complex. While $Zn(OTf)_2$, $FeCl_3$, $AuCl_3$, $YbCl_3$, $Cu(OTf)_2$, CuOTf turned out to be ineffective for this reaction, other carbophilic metal salts, such as Ph_3PAuCl, $Rh_2(OAc)_4$, and AgOAc, were also suitable to promote the aldol reaction affording propargylic alcohol in good yield, excellent diastereoselectivity (over 20/1 *dr* (*anti*/*syn*)), and enantioselectivity (up to 99% *ee*). It was suggested that the high diastereoselectivities might arise from the steric inflation of the alkyne moiety as a consequence of metal–alkyne association. This ternary catalyst system was compatible with a broad substrate scope of ynals and aldehydes bearing both linear and branched alkyl chains with various functional groups including alkene, carbamate, ester, ether, and acetal.

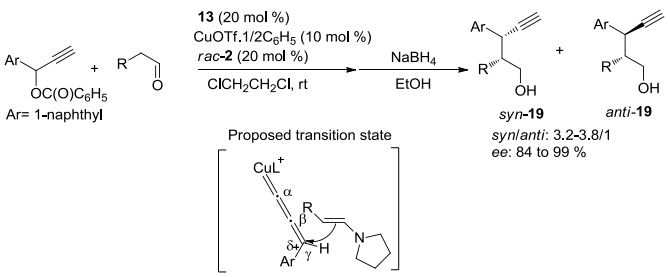
Enamine addition to metal-allenylidene complexes: Propargylation of aldehydes

In 2010, Nishibayashi and co-workers reported the first enamine-based enantioselective propargylation of aldehydes with propargylic alcohols through cooperative enamine/transition metal catalysis using a chiral pyrrolidine derivative (**14**) and a ruthenium complex (**16**) (Scheme 16).[55] The ruthenium catalyst activates the propargyl alcohol by forming an allenylidene complex and the pyrrolidine activates the aldehyde by forming an enamine. The enamine attacks the allenylidene complex from the *si* face of the *anti-(E)*-enamine favouring a *syn* configuration (2R, 3S), affording alkylated products in excellent yields, moderate diastereoselectivities and high enantioselectivities. This reaction was effective for a wide variety of aldehydes; however, the alcohols were limited to aromatic propargylic alcohols with terminal alkynes only.



Scheme 16 Nishibayashi's cooperative enamine/Ru catalysis for asymmetric propargylation of aldehydes with propargylic alcohols

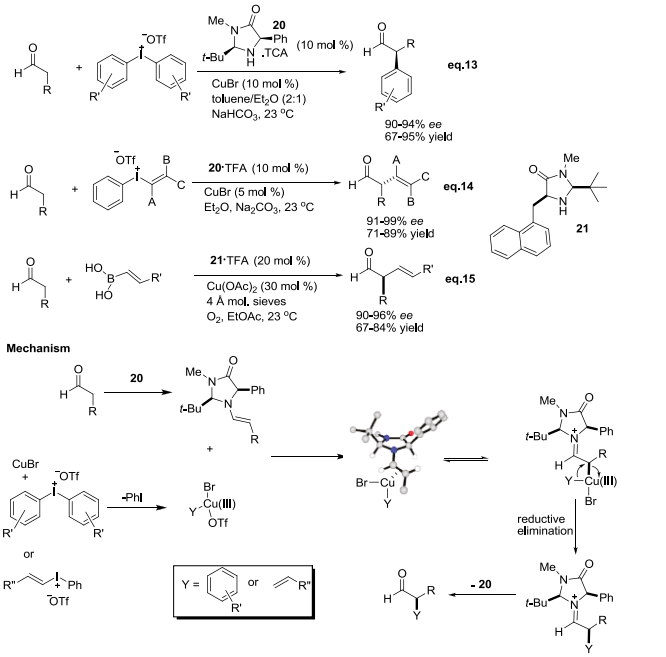
Later on, the same group developed a new catalytic system for the asymmetric propargylic alkylation of aldehydes using much cheaper CuOTf and a chiral pyrrolidine (Scheme 17).[56] It was suggested that the reaction occurred through the nucleophilic addition of the enamine generated *in situ* from the aldehydes and pyrrolidine to the Cu(I)-allenylidene complex formed from propargyl alcohol and Cu(I). The presence of excess BINAP(**2**) ligand to stabilize the active Cu(I) complex was necessary for the effectiveness of this reaction, although the chirality of the BINAP ligand did not play a role in determining the absolute configuration of the products. Compared with the ruthenium version of this reaction, high loading of both the amine and the metal catalysts were required to obtain good yields with much narrower substrate scope, but with higher stereoselectivities; in addition, propargylic esters were used instead of propargylic alcohols.



Scheme 17 Nishibayashi's cooperative enamine/Cu(I) catalysis for asymmetric propargylation of aldehydes with propargylic esters

1.3 Enamine addition to highly electrophilic Cu(III)−C(sp^2) species: α-Arylation and α-alkenylation of aldehydes

Through synergistic combination of copper catalysis, organocatalysis, and iodonium salts, the MacMillan group has developed two protocols for the challenging asymmetric α-arylation and α-vinylation of aldehydes, respectively (Scheme 18, eq.13 & 14).[57, 58] In both protocols, CuBr was used to activate the iodonium salts by forming a highly electrophilic Cu(III)−C(sp^2) species arising from oxidative addition of Cu(I) into the C-I bond of iodonium compounds; the aldehydes were activated by the salt of MacMillan catalyst (**20**) as an enamine intermediate; the Cu(III)−C(sp^2) species rapidly coordinates to the enamine from the *Re* face of the enamine to form a π-Cu complex followed by bond isomerization leading to the η^1–iminium organocopper; subsequent reductive elimination enables a carbon−carbon bond formation and reconstitutes the active Cu(I) catalyst to complete the metal cycle. Both reactions produced α-arylated and α-alkenylated aldehydes in high yields (up to 95%) and high enantioselectivities (up to 99% *ee*). Very recently, the MacMillan group extended this strategy to using boronic acids (eq.15), one of the most pervasive building blocks in organic chemistry, to replace iodonium compounds as alkenylating reagents;[59] furthermore, readily available and bench stable Cu(II) salts, e.g. $Cu(OAc)_2$, were employed in conjunction with the salt of MacMillan catalyst. The α-alkenylation products were generated in high yields and enantioselectivities with broad scope of both boronic acids and aldehydes. This new concise and convenient strategy for merging enamine catalysis with transition metal catalysis provides a new entry to functionalize the α-position of aldehydes.

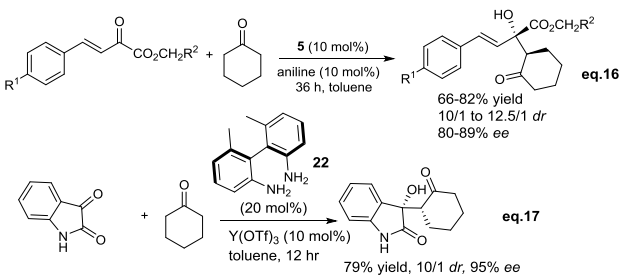


Scheme 18 MacMillan's asymmetric α-arylation and α-alkenylation of aldehydes

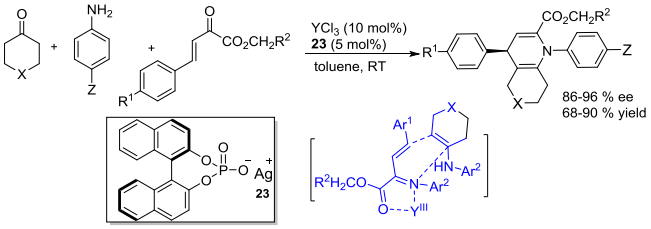
2. Combination of an arylamine with a hard metal: soft/hard inversed

In organo-enamine catalysis, a (chiral) secondary or a primary aliphatic amine is often used as the amine catalyst. Despite their longevity in organic chemistry, arylamines have been very rarely used in enamine catalysis. In 2013, our group reported the first application of arylamines in enamine catalysis.[60] Arylamines are much softer than aliphatic amines (pKa, 9-11) due to the delocalization of the lone pair into the aromatic π-system with much lower pKa (4-6). Hence, it is possible to combine an arylamine with a hard metal Lewis acid in a cooperative manner. The lower nucleophilicity of the enamines formed from arylamines can be compensated by higher activation of the electrophiles by a stronger metal Lewis acid. Through combination with either a metal Lewis acid or a phosphoric acid, arylamines successfully catalyzed the aldol reaction of cyclohexanone with both isatin and enones (Scheme 19). The enantioselectivity of the aldol reaction of the enones was introduced by a chiral phosphoric acid (**5**), and the enantioselectivity of the aldol reaction of isatin was introduced by a chiral arylamine (**22**).

Using this concept, a challenging three-component inverse-electron-demand aza-Diels-Alder reaction was developed using an arylamine and $Y(OTf)_3$ (Scheme 20).[60] In this reaction, the arylamine acted as a substrate to *in situ* form a 1-azadiene with the enone reversibly; at the same time, the arylamine also served as the amine catalyst to form an enamine intermediate with the cyclic ketone; the 1-azadiene which was activated by the metal Lewis acid reacted with the enamine dienophile to give the Diels-Alder products after hydrolysis followed by dehydroxylation. A variety of cyclic ketones including 5-, 6- and 7-membered ketones, arylamines with both electron-donating and -withdrawing groups at the *para*-position, and β,γ-unsaturated-α-ketoesters with various aryl substituents at the γ-position were appropriate substrates in this reaction, affording the desired Diels-Alder products in high yields and excellent chemoselectivities. The asymmetric version of this reaction was also investigated. The incorporation of a chiral ligand for the metal including BOX, PyBOX, naphthol and Salen ligands either led to low enantioselectivities and decreased activities or increased by-products. High enantioselectivities of the reaction for 6-membered cyclic ketones were achieved (up to 96% *ee*) when a chiral anion approach was employed through treatment of YCl_3 with a simple chiral silver phosphate (**23**). However, the chiral anion approach failed to induce high enantioselectivities for 5- and 7-membered cyclic ketones. Very recently, the authors have developed a novel class of chiral metal Lewis acid-assisted metal Lewis acid (LLA) catalysts.[61] These highly active LLA catalysts successfully catalyzed the three-component hetero-Diels-Alder reaction of cyclic ketones including 5-, 6- and 7-membered ketones, arylamines and enones in high yields, excellent chemoselectivities and enantioselectivities.



Scheme 19 Cooperative arylamine/metal Lewis acid (Brønsted acid) catalyzed asymmetric aldol reaction of cyclohexanone and isatin/enone

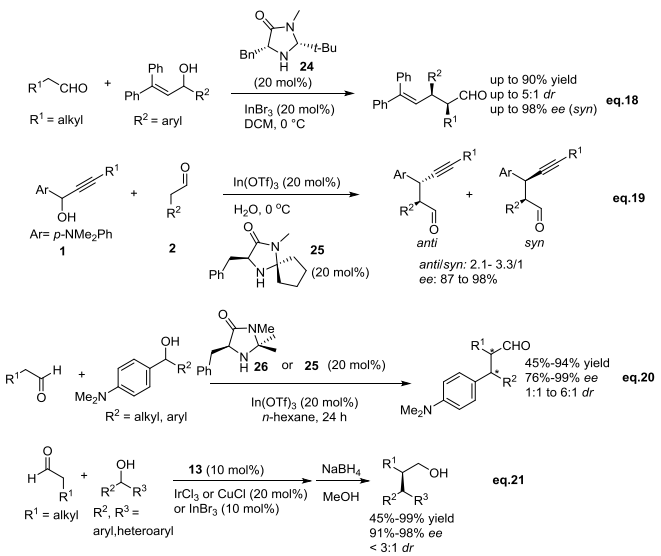


Scheme 20 Wang's asymmetric three-component inverse-electron-demand aza-Diels-Alder reaction of cyclic ketones through cooperative enamine/metal Lewis acid catalysis

Use of arylamines as the amine catalyst in enamine catalysis is a new concept. The nucleophilicity of arylamines can be easily tuned through the introduction of different electronic groups at the aromatic ring(s). Given the large variety of substrates that can be activated by harder metal Lewis acids, the combination of an arylamine with a metal Lewis acid for cooperative enamine/metal catalysis may provide a new powerful tool to access some untackled reaction space.

3. Combination of an aliphatic amine catalyst with a σ-electrophilic metal Lewis acid catalyst: enamine addition to a carbocation intermediate

All the α-alkylation reactions discussed in section 1 engage a soft carbophilic acid such as Pd(0/II), Ag(I), Au (I), etc., activating the substrates through the formation of metal-double/triple bond complexes. In order to extend the scope, and to improve the stereoselectivities of α-alkylation reactions of aldehydes, the Cozzi group has developed several new methods to combine an indium(III) salt with an MacMillan's chiral amine catalyst for stereoselective α-alkylation of aldehydes with alcohols.[62-65] The indium(III) salts, which are hard metal Lewis acids,[47] were believed to promote the formation of a stable carbocation from the alcohol. The α-alkylation reactions occurred through the reaction of an enamine intermediate formed from an aldehyde and the chiral amine catalyst with the carbocation intermediate (Fig. 2, Type III). The stability of the carbocation involved in the process was proved to be the primary driving force for these S_N1-type reactions. The steric hindrance of the carbenium ion was one of the major factors determining the outcomes of the stereoselectivity of the reaction.

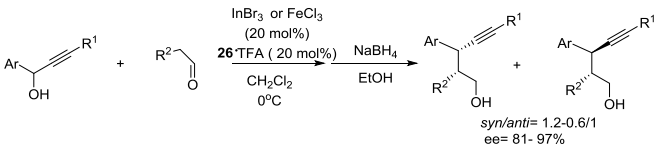


Scheme 21 Stereoselective α-alkylation of aldehydes with allylic alcohols by combination of enamine catalysis and metal Lewis acid catalysis through a carbocation intermediate

Using this approach, allylic (Scheme 21, eq.18),[65] propargylic (eq.19),[62] benzylic and benzhydrylic (eq.20)[64] alkylation of aldehydes were accomplished in good yields, moderate diastereoselectivities and high enantioselectivities. These new methods largely extended the scope of the alkylation reaction of aldehydes using alcohols. In addition, cheaper indium(III) salts were used in place of much more expensive noble metals such as palladium, ruthenium and gold in these methods. The limitation of these methods lies in that a benzyl alcohol that can form a relative stable carbocation is required to achieve successful alkylation. Alcohols that form carbenium ions located at -1 or above on the Mayr scale were not reactive with the enamine addition. Particularly in propargylic, benzylic and benzhydrylic alkylations, the presence of a strong electron-donating group such as dimethylamino group at the *para*-position of the aryl group is necessary to stabilize the carbenium ion generated in the reaction.

In their initial investigation,[65] a number of metal Lewis acids including $Zn(OTf)_2$, $Cu(OTf)_2$, $AuCl_3$, Ph_3PAuCl, $Bi(OTf)_3$, $Sc(OTf)_3$ and $La(OTf)_3$ were screened with a chiral secondary amine catalyst. These combined metal Lewis acid/amine systems either were inactive for the alkylation reaction or led to a complex mixture; several chiral secondary amines including proline and a prolinol ether were also examined with $InBr_3$, but only the MacMillan catalysts were compatible with $InBr_3$ to give the desired alkylation product. Given the hard Lewis acidic nature of In(III) salts (i.e., $InBr_3$ and $In(OTf)_3$), it is intriguing that acid-base quenching problems were not observed in these reactions although it is notable that in performing the reaction the Lewis acid was added slowly to the reaction after the MacMillan catalyst was added. The authors mentioned that the dynamic exchange between indium and basic nucleophiles allows Lewis acid catalysis in the presence of basic amines;[65] but the work[66] cited by the authors involves the interactions between arylamines and In(III) salts which are expected to be dynamic due to the soft Lewis basic nature of arylamines (refer to section 2). From our point of view, it will be very interesting to further investigate the nature of the interactions between In(III) salts and the aliphatic secondary amines to provide more insight into these systems. Very recently, the Cozzi group developed a chiral ferrocenyl pyrrolidine for enamine catalysis.[63] This amine catalyst displayed activities toward propargylic alkylation of linear aliphatic aldehydes, but the stereoselectivities were moderate (53/47 *dr*, <54% *ee*).

Although in Cozzi's methods, the chiral diphenylprolinolsilyl ether was not effective in combining with a In(III) salt to enforce alkylation reaction of aldehydes, Xiao reported successful combination of diarylprolinolsilyl ether (**13**) with CuCl, $IrCl_3$, or $InBr_3$ to effect intermolecular α-alkylation of aldehydes with alcohols through a S_N1 pathway (Scheme 21, eq.21).[67] A large variety of aldehydes and alcohols were appropriate substrates in this reaction producing the desired highly functionalized aldehydes in good yields (63 to 96%) and excellent enantioselectivities (90-99% *ee*). It is worthy of noting that even the problematic (1*H*-indol-3-yl)(phenyl)methanol and acetaldehyde were also well-tolerated in this reaction.



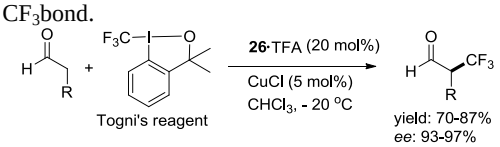
Scheme 22 Nishibayashi's propargylation of aldehydes with propargylic alcohols bearing an internal alkyne through a carbocation intermediate

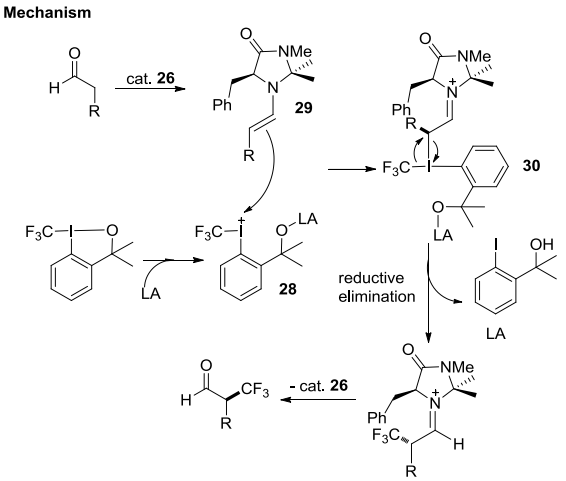
Nishibayashi and co-workers were the first to report asymmetric propargylation of aldehydes with propargylic alcohols bearing an internal alkyne (Scheme 22).[68] Cozzi's work mentioned above (Scheme 21, eq.19)[62] further extended and optimized this method to using a water solution. In Nishibayashi's approach, the trifluoroacetate salt of MacMillan catalyst was combined with $InBr_3$

or $FeCl_3$ to activate the aldehydes and propargylic alcohol respectively, yielding the alkylation products in high enantioselectivities but poor diastereoselectivities. Similar to Cozzi's work, this reaction was proposed to go through an S_N1 pathway, and the presence of a strong electron-donating group is essential to stabilize the carbocation intermediate.

Enamine addition to Togni's reagent activated by a metal Lewis acid: α-Trifluoromethylation of aldehydes

The incorporation of polyfluorinated alkyl substituents in drug candidates has proved to be a powerful strategy to enhance binding selectivity and lipophilicity as well as to resolve metabolism issues relating to in vivo C-H bond oxidation. The MacMillan group achieved the first highly enantioselective α-trifluoromethylation of aldehydes using photoredox organocatalysis.[69] Recently, the MacMillan group successfully accomplished a similar reaction through the merger of Lewis acid and organocatalysis with an electrophilic trifluoromethyl alkylating reagent (Togni's reagent) in high yields (70-87%) and enantioselectivities (93-97% *ee*) (Scheme 23).[70] In this reaction, the metal Lewis acid facilitates the bond cleavage of Togni's reagent to generate a highly electrophilic iodonium salt **28**; enamine **29**, *in situ* formed from the aldehyde and the salt of MacMillan catalyst, reacts with **28** forming a C-I bond via a closed-shell pathway; the resulting λ^3-iodane species **30** undergoes reductive elimination to forge the stereoselective formation of C-CF_3bond.

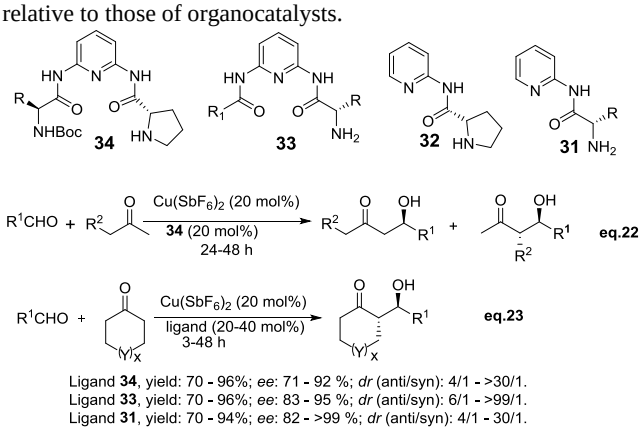




Scheme 23 MacMillan's α-trifluoromethylation of aldehydes using Togni's reagents

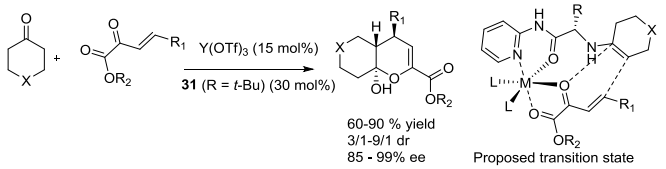
4. Bifunctional amine/metal Lewis acid catalysts

In order to solve the acid-base quenching problem, our group designed and developed a class of bifunctional amine/metal Lewis acid catalysts for cooperatively incorporating enamine catalysis with metal Lewis acid catalysis (Scheme 24). In these bifunctional catalysts, the Lewis base (primary or secondary amine) is tethered to a chelating ligand, which serves as a "trap" for the incoming metal. In this way, the base and the metal Lewis acid are brought into close proximity without interacting with each other. Theoretically, a large variety of metal salts including both soft and hard metal Lewis acids can be incorporated in this bifunctional catalytic system. Two types of bifunctional catalysts were developed (Scheme 24). One is based on a bidentate ligand (**31** and **32**) and the other one is based on a tridentate ligand (**33** and **34**).These bifunctional catalysts were evaluated in asymmetric direct aldol reactions.[71-73] In combining with the ligands, a number of metal salts including Zn(II), Co(II), La(III) were able to catalyze the direct cross aldol reaction of ketones and aldehydes, Cu(II) salts turned out to be most active catalysts affording the aldol products in high yields, high diastereoselectivities and high enantioselectivities. The stereoselectivities of these bifunctional catalytic systems are comparable with those of organocatalysts. It is notable that the activities of these catalysts in aldol reactions are much enhanced relative to those of organocatalysts.



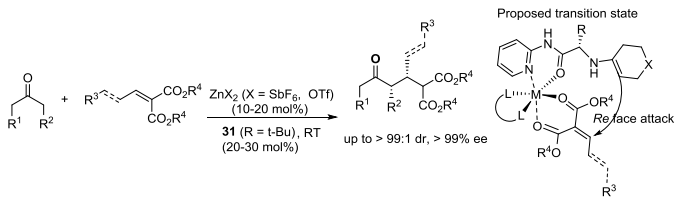
Scheme 24 Asymmetric direct cross aldol reaction of ketones and aldehydes catalyzed by Wang bifunctional amine/metal Lewis acid catalysts

Using these bifunctional amine/metal Lewis acid catalysts, a difficult inverse electron-demand hetero-Diels-Alder (IED-HDA) reaction of cyclic ketones and β,γ-unsaturated-α-ketoesters was developed (Scheme 25).[74] Asymmetric inverse-electron-demand hetero-Diels-Alder reactions of an electron-rich alkene with an electron-deficient α,β-unsaturated ketone (enone) offers a convenient and valuable entry to the synthesis of dihydropyran and tetrahydropyran derivatives, which constitute important structural motifs in natural products and in a variety of biologically important compounds.[75-79] Organoamine catalysts were only able to catalyze IED-HDA of enolizable aldehydes with an enone.[77, 80-82] Ketones are much less reactive due to both electronic and steric reasons. In the bifunctional amine/metal Lewis acid catalyzed IED-HAD reactions, a 6-memberd cyclic ketone reacted readily at 4°C with an β,γ-unsaturated-α-ketoester producing bicyclic dihydropyrans in excellent chemo- (up to >99/1, HDA/aldol), moderate diastereoselectivities and very good to excellent enantioselectivity (up to 99% *ee*). All of the tested metal salts were active in these bifunctional catalytic systems leading either to the direct aldol product ($Cu(SbF_6)_2$, Eu(FOD) and $Sc(OTf)_3$), or HDA product ($Y(OTf)_3$ at 4°C), or both ($La(OTf)_3$, $Y(OTf)_3$ and $Yb(OTf)_3$). While all the bidentate and tridentate ligands examined displayed activity toward the HDA reaction, a bidentate ligand with a *tert*-butyl group at the α-position (**31**, R = *t*-Bu) showed the best stereoselectivities. We proposed that, in this HDA reaction, the ketone formed an enamine with the amine function of the ligand; the diene was activated by the metal Lewis acid coordinated to the ligand; the enamine and diene were brought in close proximity by the bifunctional ligand, enabling a highly stereoselective attack of the enamine onto the diene.



Scheme 25 Asymmetric inverse-electron-demand hetero-Diels-Alder reaction of cyclic ketones catalyzed by Wang bifunctional amine/metal Lewis acid catalysts

Similarly, a difficult asymmetric Michael addition of ketones to akylidene malonates and allylidene malonates was developed via the enamine-metal Lewis acid bifunctional catalysis (Scheme 26).[83] When $Zn(SbF_6)_2$ was combined with ligand **31** (R = *t*-Bu), the Michael addition products of akylidene malonates were generated in high yields (up to 99%) and excellent enantioselectivities (up to >99% *ee*) and diastereoselectivities (up to >99 *dr*). The combination of $Zn(OTf)_2$ with **31** led to the Michael addition products of allylidene malonates in good yields (up to 99%), high enantioselectivities (up to 98% *ee*) and moderate diastereoselectivities (up to 4/1 *dr*).



Scheme 26 Asymmetric Michael addition of ketones to alkylidene malonates and allylidene malonates via enamine-metal Lewis acid bifunctional catalysis

Summary and future outlook

Since the realization of the first combination of enamine catalysis with transition metal catalysis in 2006 by the Córdova group, considerable progress has been made on synergistic and cooperative enamine/transition metal catalysis. In particular, significant advances have been achieved in direct α-allylation and α-propargylation of aldehydes in the past several years. Despite these advances, this research area is still in its infancy, the potential of which is far from fully explored. At the current stage, the development of this research area is still limited in our opinion. For example, asymmetric direct alkylation of aldehydes has been well investigated, even the challenging asymmetric arylation and alkenylation have been achieved with high yields and stereoselectivity; however, activity and stereoselectivity of asymmetric direct alkylations of ketones are still very low. The majority of the reactions developed in this area are based on α-alkylation of aldehydes. Only very few other types of asymmetric organic transformations has been reported.

The foreseeable problems in developing synergistic and cooperative enamine/metal catalysis still lie in catalyst incompatibility arising mainly from acid-base quenching reactions. Although perceivable problems exist, several strategies, including soft/hard combination of a Lewis acid and a Lewis base, the utilization of a chelating ligand, as well as mixing an amine salt with a Lewis acid, have been developed to overcome these problems; in addition, the discovery of the interesting dynamic interaction of σ-electrophilic In(III) salt with a chiral aliphatic amine offers a convenient and flexible tool to explore this field. We hope that we have illustrated these strategies in this review article. In our opinion, the biggest challenge in this field will be combining an amine catalyst with a strong metal Lewis acid to achieve well-known difficult organic transformations such as asymmetric direct cross aldol reaction of ketones, normal electron-demand hetero-Diels-Alder reaction of ketones, inverse electron-demand hetero-Diels-Alder reaction of unactivated enones, etc. Compared to the earlier years, this research area has attracted much more attention, and has grown much more rapidly in recent years. Given the new strategies and new reaction modes developed, the judicious selection of metals and amines, the ease and the flexibility of the combination, and very importantly, that many unknowns are waiting to be explored in this field, we believe that this research area is about to take off and will prosper in the near future.

Acknowledgements

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