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When Organocatalysis Meets Transition-Metal Catalysis

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In the past several years, applications of transition metal complexes in tuning the reactivity of organocatalyst-promoted transformations have attracted increasing attention in the synthetic community. Efforts in this direction have led to the discovery of unprecedented reactivities, which are not accessible through the use of either of these two catalytic systems separately. The concept continues to develop and offers huge potential. This microreview describes and summarizes recent progress in this field, focusing on discussion of the enhancement and diversification of reactivity patterns in organocatalysis through the deployment of transition metal complexes.

1. Introduction

The last decade has witnessed explosive advances in organocatalysis, in which small organic molecules are used as catalysts to facilitate chemical transformations.[1] A highly robust methodology, organocatalysis has become one of the most popular and fundamental tools used to target enantiomerically enriched compounds.[2] Along with their newly discovered patterns of reactivity, organocatalysts also have advantages that are appealing from a practical point of view, which have resulted in large numbers of scientific documents having been contributed from both academic and industrial researchers over the last 10 years.[3] On the other hand, organic synthesis has historically been dominated by transition metal catalysis.[4] Through extensive efforts, chemists have continued to make remarkable achievements in relation to understanding of metal properties and the applications of their versatile reactivity patterns in various transformations, more of which are undoubtedly yet to be discovered.[5]

During recent years, the hypothetical goal of combining pairs of distinct catalytic systems in different permutations has been examined in organic synthesis. Examples include combining different transition metals in one catalysis,[6] combining biocatalysis or enzyme catalysis with metal catalysis[7] and combining organocatalysis with transition metal catalysis.[8] The driving force behind these efforts is to discover more efficient approaches for complex molecule synthesis with good chemo- and stereoselectivity inaccess-

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Xiaodong Michael Shi was born in Tianjing, China. He went to Nankai University in 1990 and received his BS and MS degrees in 1994 and 1997, respectively. He then went to the United States and earned his Ph.D. degree in 2002 from the University of Maryland College Park, under the guidance of Professor Jeffery T. Davis, with research focused on self-assembled nucleosides. After finishing graduate school, Dr. Shi moved to the Chemistry Department at the University of California, Berkeley and joined Professor Paul A. Bartlett's group as a postdoctoral research associate. In July 2003, he joined Professor F. Dean Toste's group and studied transition metal catalysis. Professor Shi started his independent research in the autumn of 2005 at the Chemistry Department of West Virginia University. His research is currently focused on the development of new synthetic methodologies and new material constructions.

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ible through the use of single specific catalytic systems. The development of organocatalysis has seen it increasing applied in combination with transition metal complexes in the search for more valuable chemical transformations, taking advantages of both forms of catalysis while maximizing their compatibility. This concept, first introduced in 2003,[9] has demonstrated its vitality in chemists' growing interests in new catalytic systems. With increasing attention being given to this new area, momentous chemical transformations, many of them cascade reactions, are being discovered. This microreview summarizes recent advancements in this field, focusing on how transition metal complexes can assist in and adjust the reactivities of organocatalysts, demonstrating the advantages of combinations of these two catalytic systems.

2. Amine-Activated Carbonyl Compounds React with Transition-Metal-Activated Substrates

Amine activations of carbonyl compounds are by far the most intensely studied organocatalytic systems.[10] These processes involve two common reaction modes: the formation either of enamine nucleophiles or of iminium electrophiles (Figure 1).

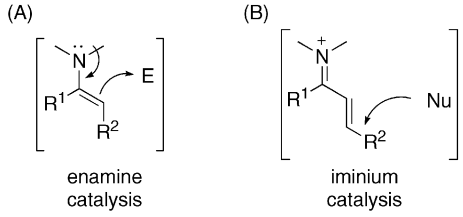


Figure 1. Two general activation modes of amine-activated carbonyl compounds.

The mechanism of enamine catalysis having been well investigated,[11] studies directed towards combining enamine nucleophiles and transition-metal-activated substrates have been carried out by several groups. These efforts have led to significant successes, and known literature reports can be categorized into three major themes as shown below:

1. Addition of enamine nucleophiles to transition-metal-activated electrophiles;
2. Enamine SOMO photoredox processes;
3. Multi-component cascade process involving enamine and transition-metal-activated substrates.

Equally significantly, iminium catalysis offers the potential for LUMO-lowering activation of α,β-unsaturated aldehydes and ketones as improved electrophiles, allowing 1,4-conjugate additions to be carried out with excellent enantioselectivities.[12] No examples of direct combinations of iminium catalysis and transition metal catalysis have so far been reported, however, which might be due to the challenges involved in finding suitable metal-activated nucleophiles as partners.

2.1 Enamine Addition to Transition-Metal-Activated Electrophiles

Enamine-promoted intramolecular aldol reactions can be traced back to the early 1970s,[13] but the potential of the underlying HOMO-raising activation mode for much more versatile applicability was ignored until the new millennium. Pioneered by Barbas,[14] List,[15] MacMillan[16] and many others,[17] enamine catalysis in organic synthesis has been re-evaluated, particularly because it can allow excellent control of stereochemistry with chiral amines as catalysts. Aliphatic aldehydes/ketones can readily be activated in situ as nucleophiles to react with transition-metal-activated electrophiles. Combinations of such enamine nucleophiles and transition-metal-activated electrophiles represent one of the most popular strategies involving both organocatalysts and transition metals in current catalysis research (Figure 2).

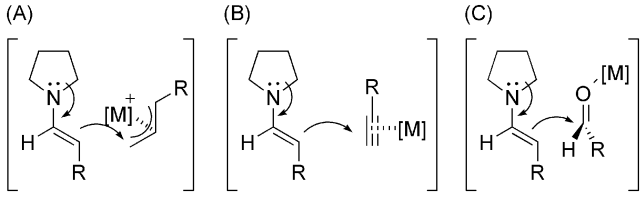
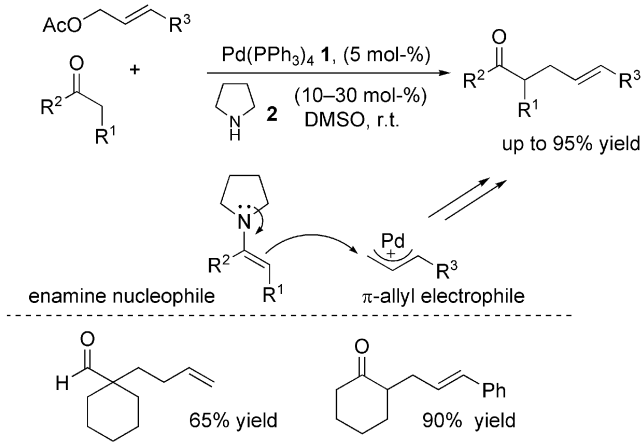


Figure 2. Combinations of enamine nucleophiles and transition metal electrophiles.

2.1.1 Enamine Nucleophilic Addition to Palladium π-Allyl Electrophiles

α-Alkylation of carbonyl compounds, as a fundamental C–C bond formation reaction, had overwhelmingly been carried out by pregeneration of enolates through metal activation.[18] The direct α-alkylation of aldehydes and ketones suffered from unavoidable side reactions.[19]

In early 2006, Cordova's group[20] addressed this problem and designed a new catalytic system that combined enamine nucleophiles derived from aldehydes/ketones with Tsuji–Trost palladium π-allyl electrophiles[21] (Scheme 1). In the



Scheme 1. α-Allylation of aldehydes and ketones.

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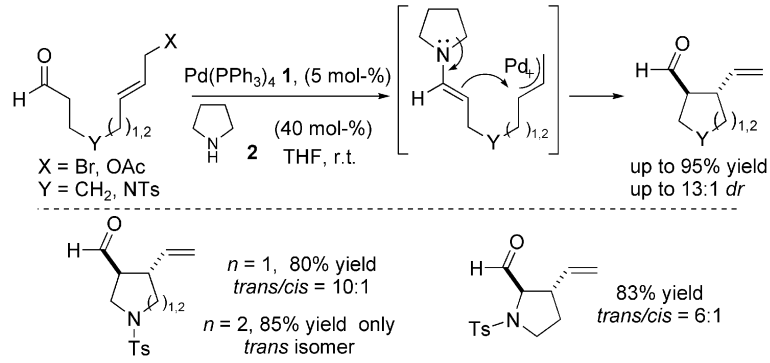
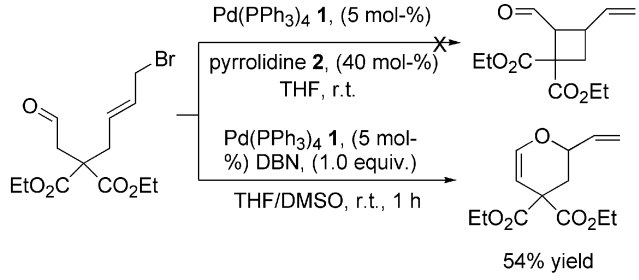


Scheme 2. Intramolecular additions of enamines to palladium π-allyl electrophiles.

presence of pyrrolidine (10–30%) and $Pd(PPh_3)_4$ (5%), the allylation of aldehydes/ketones in one-pot fashion was achieved, giving α-allylated carbonyl products in good to excellent yields (up to 95%). This reaction was suitable for both primary and secondary aldehydes. In addition, a cyclic ketone, though lower in reactivity, was also subjected to this transformation, giving a moderate yield with a slightly higher catalyst loading (30 mol-% of pyrrolidine). Notably, this is the first direct intermolecular α-allylation of aldehydes involving catalytic enamine catalysis. Further efforts were also put into asymmetric transformations in this report, but no good enantioselectivity was obtained with decent yields.

The intramolecular version of α-allylation was later reported by Saicic and co-workers (Scheme 2).[22] Through the use of similar combinations of enamine nucleophiles and palladium π-allyl electrophiles, five- or six-membered ring cyclic products were prepared. As a control, enolates pregenerated with LDA or KHDMS were also tested, but did not give the desired products in good yields. Addition of enamines, as milder nucleophiles, to the palladium π-allyl electrophiles gave much higher efficiency, resulting in good yields and good diastereoselectivities. The reactions were fast and smooth in THF, going to completion in less than an hour, although 40 mol-% of pyrrolidine was required as catalyst for optimal performance.

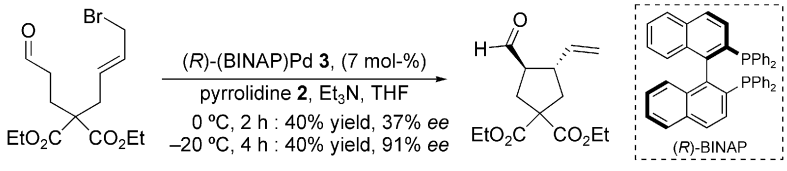
Various starting materials were prepared with the goal of targeting products with different ring sizes (three-, four- and seven-membered rings), but these reactions failed to proceed through enamine addition. The attempt to produce the four-membered ring, interestingly, instead gave the alternative oxygen addition product in modest yield (Scheme 3).



Scheme 3. Attempts to produce a four-membered ring gave the alternative *O*-allylation product.

Asymmetric catalysis was also investigated. Various chiral secondary amines including (*S*)-proline, (*S*)-2-diphenylprolinol, (*S*)-2-methoxymethylpyrrolidine and MacMillan's catalyst were examined. Unfortunately, all of these tested chiral amine catalysts failed to provide good stereoselectivity. On the other hand, when chiral phosphorus ligands such as that shown in Scheme 4 was applied to adjust the spatial environments of the metal-activated electrophiles, moderate to excellent enantioselectivities (37–91% *ee*) were obtained with moderate yields (40%).

Later on, the same group further studied the asymmetric synthesis of five- or six-membered rings through combinations of enamine catalysis and transition metal catalysis.[23,24] The application of an allyl phosphate substrate and (*R*)-(Ph-MeOBIPHOS) ligands (Scheme 5, a) greatly improved the yield (76%) and the enantioselectivity (98%). In addition, allylation catalysed by an iridium complex[25] (Scheme 5, b) was also tested, though poor diastereoselectivity and enantioselectivity were observed even with application of large amounts of phosphoramidite ligand. However, a quantitative yield was obtained.



Scheme 4. Asymmetric cyclization in the presence of chiral phosphorus ligands.

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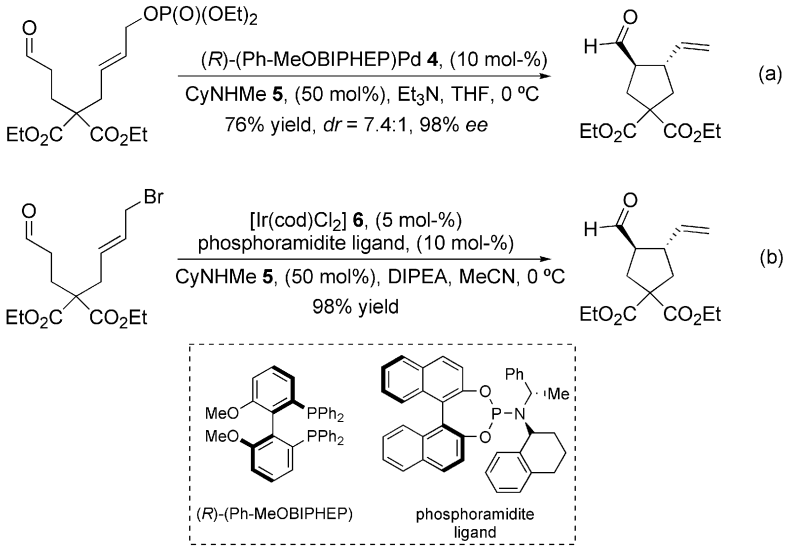
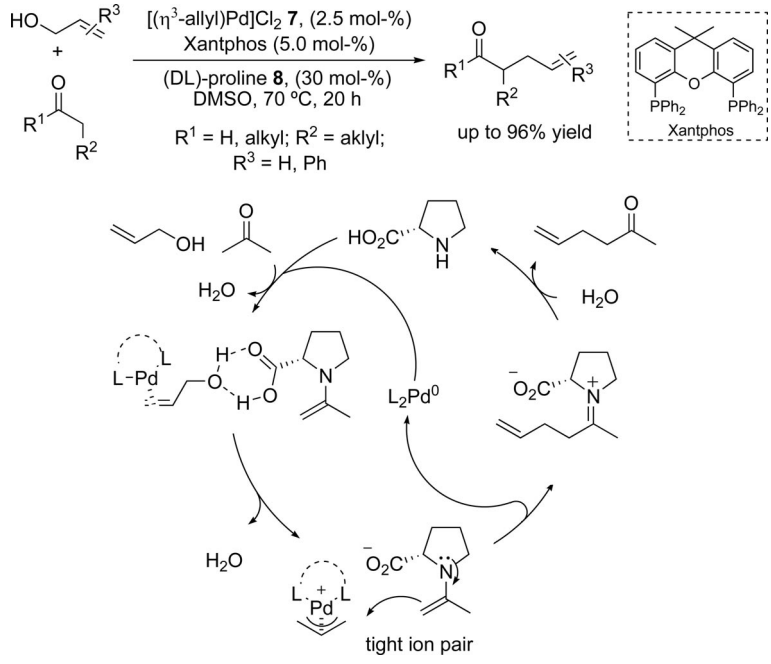


Scheme 5. Extended investigation of asymmetric cyclization through combined catalysis systems.

In early 2009, Breit's group reported another intermolecular enamine addition to a palladium π-allyl complex (Scheme 6).[26] Instead of allyl bromide, allyl acetate or allyl phosphate, the authors found that allyl alcohol could be applied directly as an effective π-allyl precursor. A proline/palladium/xantphos combination was identified as the best catalytic system for this transformation. Although the reaction mixture needed to be heated in DMSO for 20 h, the chemical yields were good to excellent (up to 96%). It was believed that the xantphos ligand provided the biggest bite angle, tuning the geometry of the palladium π-allyl complex for better reactivity.[27] This strategy was subjected to a wide range of substrates, including α-branched aldehydes, which resulted in attractive quaternary carbon formation.

In the proposed mechanism, the proline carboxylic acid group helped the ionization of the palladium olefin complex formed from the allylic alcohol through H-bonding and protonation of the hydroxy leaving group. The interpretation was that the dual functionalities of proline might help the formation of a tight ion pair between enamine nucleophile and palladium π-allyl electrophile, which would lead to rapid allylation. No significant enantioselectivity was observed when a chiral amine catalyst was used in the reaction. However, this strategy provided an interesting example of dual action of organocatalyst and metal catalyst, indicating the bifunctional property of the organocatalyst, which is also discussed in later sections.



Scheme 6. Proline-assisted palladium π-allyl formation.

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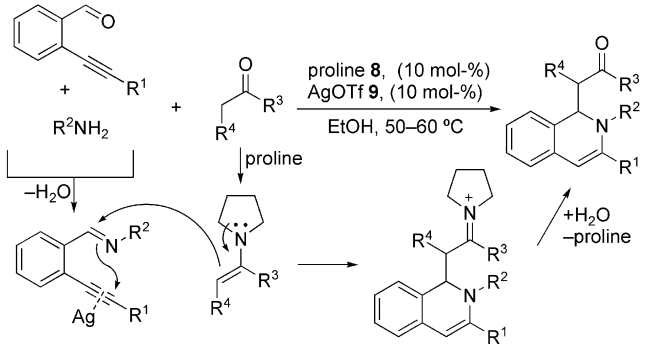
2.1.2 Enamine Addition to π-Acid-Activated Alkynes

In recent years, cations of group IIB metals (Cu, Ag, Au)[28] have been discovered to act as powerful π-acids for electrophilic activation of sp^2- and sp-hybridized carbon–carbon multiple bonds. These metal cations, Ag and Au in particular, undergo dynamic binding with amines,[29] which has allowed them to serve as orthogonal catalysts with amine-based organocatalysis.

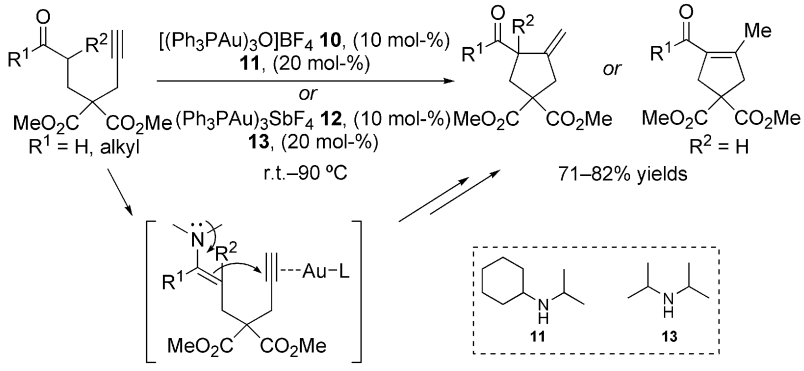
In 2007, Wu and co-workers reported combinations of enamine catalysts and π acid catalysts through the use of proline and AgOTf in one catalytic reaction system (Scheme 7).[30] In these cascade reactions, 1,2-dihydroisoquinoline derivatives were successfully synthesized through condensations of 2-alkynalaldehydes, amines and ketones. As the authors proposed, upon formation of the Schiff bases from the aldehydes and the amines, intermolecular Mannich reactions occurred with the enamines as the nucleophiles. Sequential intramolecular hydroamination of the Ag(I)-cation-activated alkynes gave the desired dihydroisoquinoline products in one-pot fashion. Notably, this was the first example of the combining of enamine catalysts and π acidic transition metal catalysts and was to trigger the expansion of effective incorporation of group IIB metal cations in suitable organocatalysis.



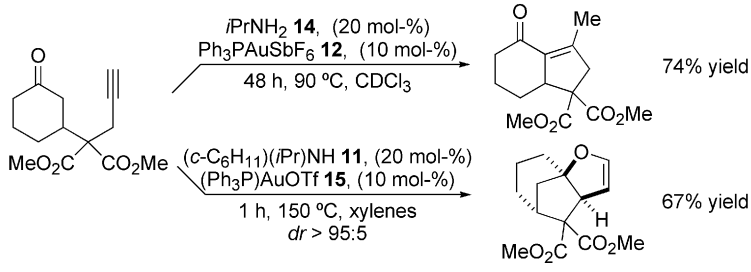
Scheme 7. Multi-component reactions of 2-alkynylbenzaldehydes, amines and ketones through proline/AgOTf combined catalysis.

During recent decades, cationic gold complexes have been extensively studied as effective catalysts for alkyne electrophilic activation.[31] Whether enamine nucleophiles could be suitable for gold-activated alkyne electrophiles has attracted considerable attention. In early 2008, Kirsch and co-workers demonstrated effective combinations of enamine catalysis and cationic gold(I) catalysis through successful intramolecular cyclizations with terminal alkynes (Scheme 8).[32] The reactions resulted in 5-*exo*-*dig* cyclizations. In cases of unbranched aldehydes, the cyclizations were followed by double bond migrations, whereas in those of α-substituted aldehydes no migration was observed. Ketones were also subjected to this transformation, giving decent yields. From the observed data, the authors proposed a mechanism involving direct carbocyclization between enamine nucleophiles and cationic-gold-activated alkyne electrophiles. Interestingly, application of slightly different reaction conditions gave formal [3+2] reactions with moderate yields and excellent diastereoselectivities (Scheme 9).

Later, Dixon's group further extended this strategy and reported cascade reactions in which alkyne-modified nucleophiles attacked amine-activated enones/enals to form enamine-alkyne intermediates in situ (Scheme 10). Without release of the organocatalysts, the intramolecular enamine



Scheme 8. Intramolecular carbocyclizations of aldehydes with alkynes.



Scheme 9. Unexpected formal [3+2] cyclizations.

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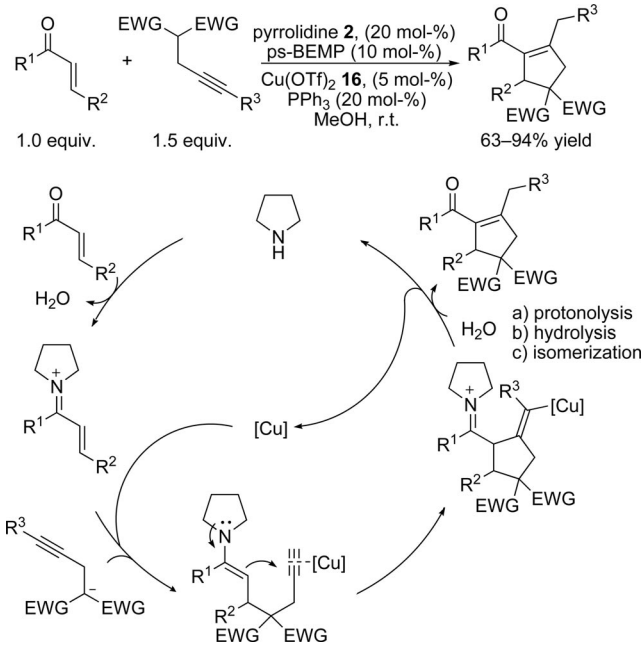
nucleophiles attacked the Cu^I-activated alkynes and gave the desired carboannulation products in good to excellent yields.[33]



Scheme 10. Combination of enamine catalysis and Cu^I catalysis.

Although enantioselective chiral enamine additions to various electrophiles have been extensively reported in the literature, poor performances with regard to enantioselectivity have so far generally been observed with chiral enamines and achiral metal-complex-activated electrophiles. Chiral metal ligands have therefore usually been considered more practical solutions for asymmetric transformations in reactions of this type.

2.1.3 Enamine-Metal Lewis Acid Bifunctional Catalysis for Asymmetric Direct Aldol Reactions

Asymmetric direct aldol condensations were believed to be one of the first milestones in enamine catalysis.[34] Mechanisms of proline-catalysed aldol reactions have been thoroughly studied and this has suggested a bifunctional role for proline in the catalytic cycles.[35] The secondary amine is believed to attack the carbonyl group to form the corresponding enamine nucleophile, while the carboxylic acid interacts with the second electrophilic carbonyl groups through hydrogen bonding, indicating a combination of enamine and Brønsted acid functions.

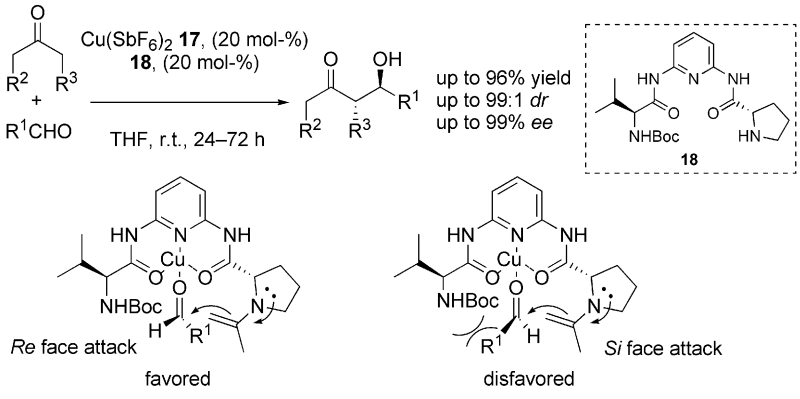
On the other hand, the combination of a enamine and a metal Lewis acid for the asymmetric direct aldol reaction was not reported until 2009, when Wang and co-workers[36] successfully developed a tridentate-ligand-tethered secondary amine as a bifunctional catalyst to maximize the compatibility of a Lewis basic secondary amine and a Lewis acidic transition metal for the direct aldol reaction (Scheme 11). $Cu(SbF_6)_2$ was found to be the optimal metal choice for the best reactivity and stereoselectivity. Its wide substrate scope and excellent yields and enantioselectivities indicated a promising future for this bifunctional system for similar catalytic transformation.

2.2 Enamine Catalysis with SOMO Photoredox Catalysis

As a landmark in organocatalysis, enamine chemistry has been extensively studied and has given rise to many new transformations and unique catalytic systems.[37] One particularly inspiring new direction has been the recently developed enamine SOMO (single-electron occupied molecular orbital) catalysis pioneered by MacMillan's group (Scheme 12).[38]

In this SOMO activation strategy, single-electron oxidation of a transient chiral enamine intermediate was achieved on treatment of enamines with suitable metal oxidants (such as CAN), resulting in the formation of three-π-electron radical species. Conceptually, the enamine nucleophiles were transformed into radical cationic electrophiles. With addition by suitable nucleophiles, new covalent bonds would be formed, giving the α-functionalized carbonyl-containing products in an enantioselective fashion. Different nucleophiles (including allylic silanes, enolsilanes, vinyl trifluoroborates, styrenes, silyl nitronates, electron-rich aromatic rings and even chlorides) have been used with good to excellent yields and excellent enantioselectivities.[39]

The authors then made an impressive move to combine this concept further with a photoredox process by generating the cationic radicals with the aid of photoactive cata-



Scheme 11. Enamine-metal Lewis acid bifunctional catalysis for asymmetric direct aldol reactions between ketones and aldehydes.

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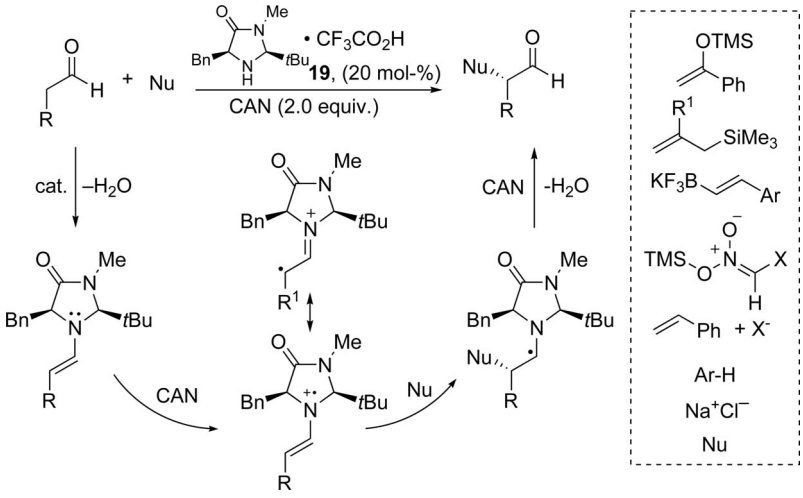
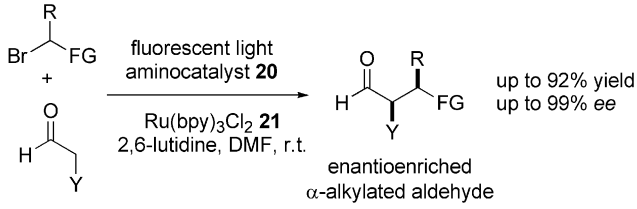


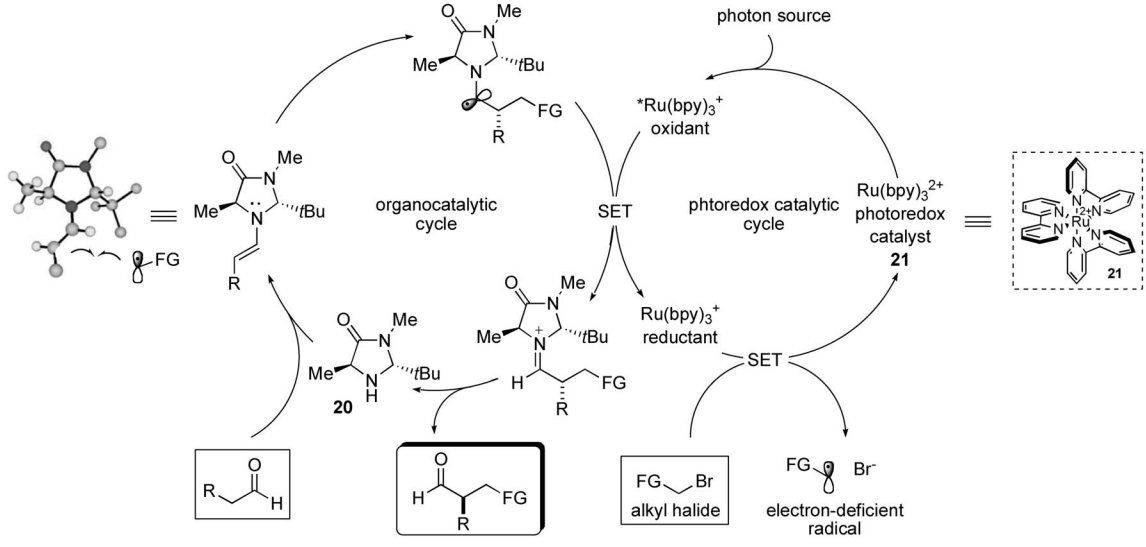
Scheme 12. Enantioselective enamine SOMO catalysis.

lysts. However, when $Ru(bpy)_3Cl_2$ (bpy stands for 2,2′-bypyridine) was applied, the reaction reverted to the category of chiral enamine nucleophilic additions to the electron-deficient radical electrophiles (Scheme 13).[40] In other efforts, in 2008 MacMillan and co-workers successfully developed asymmetric α-alkylations of aldehydes through combining enamine catalysis and transition-metal-initiated photoredox catalysis (Scheme 14).[41]



Scheme 13. α-Alkylation of aldehydes: combination of organocatalysis and photoredox catalysis.

It was proposed that the $Ru(bpy)_3^{2+}$ complex could readily absorb a visible light photon to generate the $*Ru(bpy)_3^{2+}$ species, through metal-to-ligand charge transfer (MLCT) excitation. An electron was then removed through a single-electron transfer (SET) process from a sacrificial quantity of enamine intermediate to produce the relatively electron-rich $Ru(bpy)_3^+$, which then went through another SET to populate the electron-deficient alkyl radical with reversion of the ruthenium complex to the ground state for another catalytic cycle. Concurrently, in the organocatalysis cycle, the "SOMOphilic" enamine was prepared and was ready to attack the electron-withdrawing alkyl radical to generate the relatively electron-rich α-amino radical species. At this point the organocatalysis cycle and the photoredox cycle intersected with each other and guaranteed a SET to form the iminium species, which then released the products and the electron-rich $Ru(bpy)_3^+$ species to generate the alkyl radical (Scheme 14).



Scheme 14. Mechanism of combined organocatalysis and photoredox catalysis cycles.

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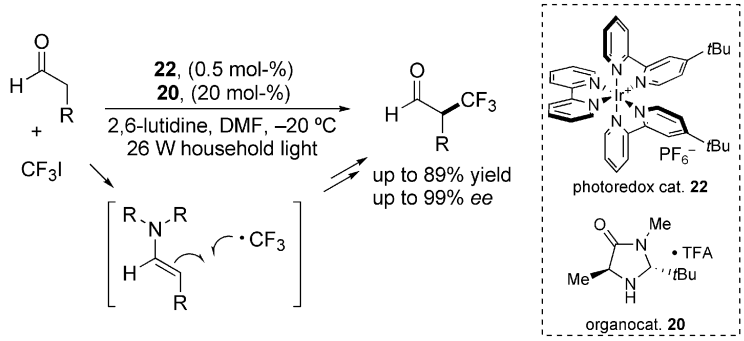


Scheme 15. α-Trifluoromethylation of aldehydes through a combination of organocatalysis and photoredox catalysis.

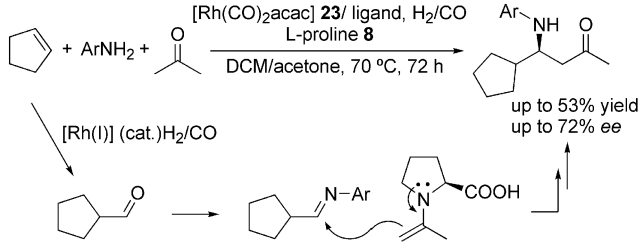
Later, the same group reported a further example of combined enamine and photoredox catalysis in an investigation of α-trifluoromethylation of aldehydes.[42] This time, the $Ir(ppy)_2(dtb\text{-}bpy)PF_6$ complex was used as the photon radical initiator and only visible household light was needed as the photon source for the photoredox transformation (Scheme 15). A large variety of α-trifluoromethylated aldehydes were prepared with good yields and excellent enantioselectivities and were then readily converted into several valuable organofluorine synthons.

2.3 Cascade Metal- and Enamine-Catalysis – Rhodium-Catalysed Hydroformylation

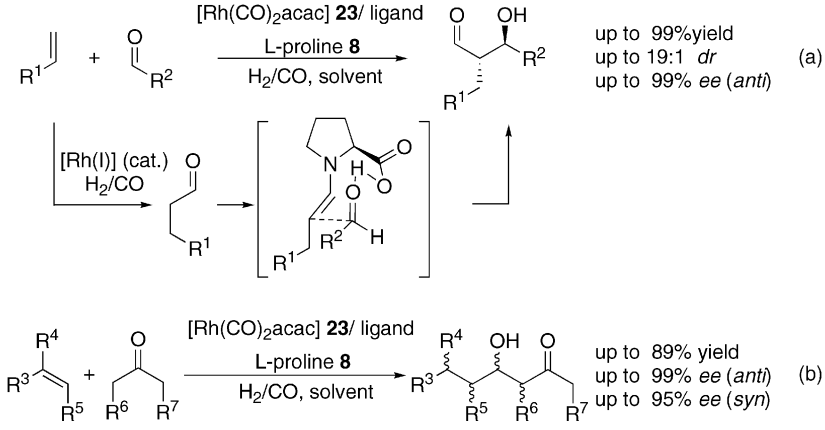
As an important means for furnishing olefins, hydroformylation has been extensively studied, especially in tandem reactions.[43] Interest in this unique transformation, generally catalysed by rhodium complexes, is strong both in academic and in industrial research. This clean and economical catalysis has also been widely applied in cascade reaction strategies.

In 2007, Breit's group[44] and Eilbracht's group[45] independently reported two tandem hydroformylation/enantioselective aldol reactions. In both reports hydroformylation proceeded in situ to produce the aldehydes for the following cross-aldol reaction. In Breit's report aldehydes were used as the aldol reaction acceptors (Scheme 16, a). Extensive discussion focused on the influence of the organocatalyst (proline) on the hydroformylation step. In addition, the effects of different pressures, combinations of CO and H_2 gases and different rhodium ligands were also investigated. In Eilbracht's report, ketones, which were considered to be more challenging substrates, were applied as the aldol acceptors (Scheme 16, b). Different organocatalysts were studied and good to excellent yields and stereoselectivities were obtained.

Eilbracht and co-workers have recently extended this strategy, reporting sequential hyroformylation and enantioselective multi-component Mannich reactions (Scheme 17).[46] Only moderate yields and enantioselectivities were observed, even when high CO/H_2 pressures were applied.



Scheme 17. Combinations of rhodium catalysis and enamine catalysis for cascade hydroformylation/enantioselective Mannich reactions.



Scheme 16. Combinations of rhodium catalysis and enamine catalysis for tandem hydroformylation/enantioselective aldol reactions.

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3. Chiral Organic Brønsted-Acid/Base-Controlled Stereoselective Reactions with Metal-Activated Substrates

Chiral organic Brønsted acids and their conjugated bases (counter anions) have been demonstrated to represent a powerful strategy in facilitating stereoselectivity in organocatalysis.[47] This field was initiated by the introduction of chiral BINOL-derived phosphoric acids in 2004 by Akiyama[48] and Terada.[49] Shortly after, it had became one of the most active research areas in enantioselective organocatalysis. During the last five years, List,[50] Rueping[51] and Antilla[52] have presented significant contributions with the discoveries of various well-designed transformations. In combination with transition metal catalysis, the chiral Brønsted acid/base catalysts have usually involved three approaches: H-bonded counter anion, chiral acid and chiral base (Figure 3). The general rationale is the production of H-bond activation in the transition state, while specific Brønsted acid catalysis (also referred to as proton catalysis) effects a more or less complete proton transfer from the catalyst to the substrate. This then further branched out a new concept: asymmetric counter-anion-directed catalysis (ACDC).[53,54]

3.1 Metal Catalysis Directed by Chiral Brønsted Acid Counter Anions

Pioneered by Toste,[55] Hashmi,[56] Nolan[57] and Zhang,[58] homogeneous gold catalysis has in recent years emerged as a hot area in transition metal catalysis. Although the Au cation displayed superior reactivity with regard to electrophilic activation of alkynes and allenes, stereoinduction based on gold catalysis has been considered an extremely challenging task. The linear coordination geometry of Au(I) represented an unconventional obstacle to delivery of the chiral environment from the remote ligands to the reaction site, which resulted in only limited asymmetric gold catalysis based on chiral phosphorus ligands.[59]

On the other hand, however, because the Au(I) cation always requires a counter anion, the possibility of ensuring enantioselectivity with the aid of a suitable chiral counter anion during the catalysis has received considerable interest. Toste and co-workers reported the first example of an asymmetric counter anion for enantioselective gold catalysis (Scheme 18).[60]

Taking advantage of asymmetric counter-anion-directed catalysis (ACDC), $PhMe_2PAuCl$ and $dppm(AuCl)_2$ were used for the hydroamination and hydroalkoxylation, respectively, of allenes in the presence of (*R*)-TIRP [3,3′-bis-(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate] as the counter anion. Excellent yields and enantioselectivities were observed as the consequence of the combination of the cationic Au-allene intermediate and the (*R*)-TRIP anion.

Another good example of the use of the ACDC strategy to control the stereochemistry in metal-mediated catalysis is the chiral Brønsted-acid-mediated asymmetric counter-anion-directed Tsuji–Trost allylation of branched aldehydes, reported by List and co-workers (Scheme 19).[61] With a

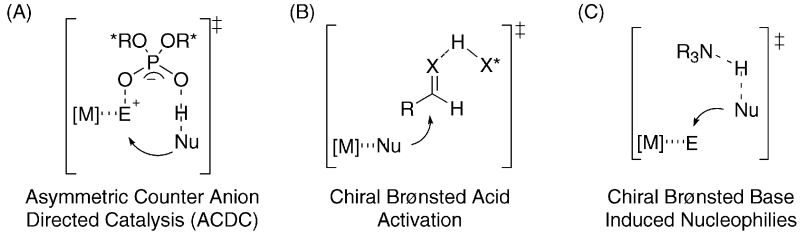
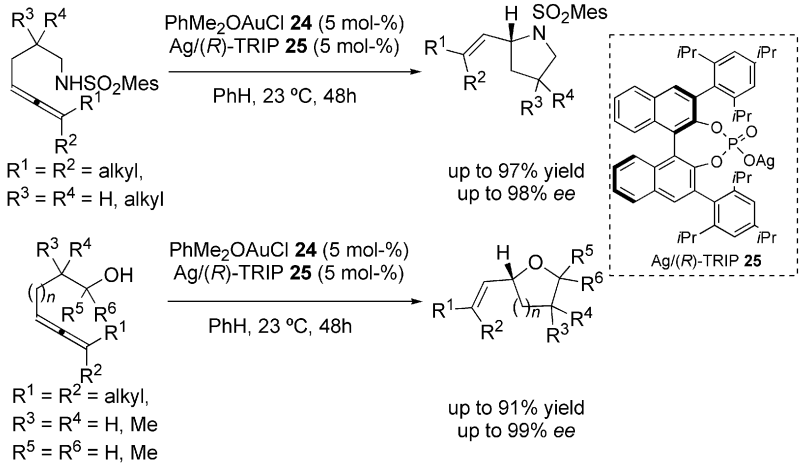


Figure 3. Chiral Brønsted acid/base catalysis.



Scheme 18. Asymmetric Au(I)-catalysed heteroatom cyclization reactions directed by organic counter anions.

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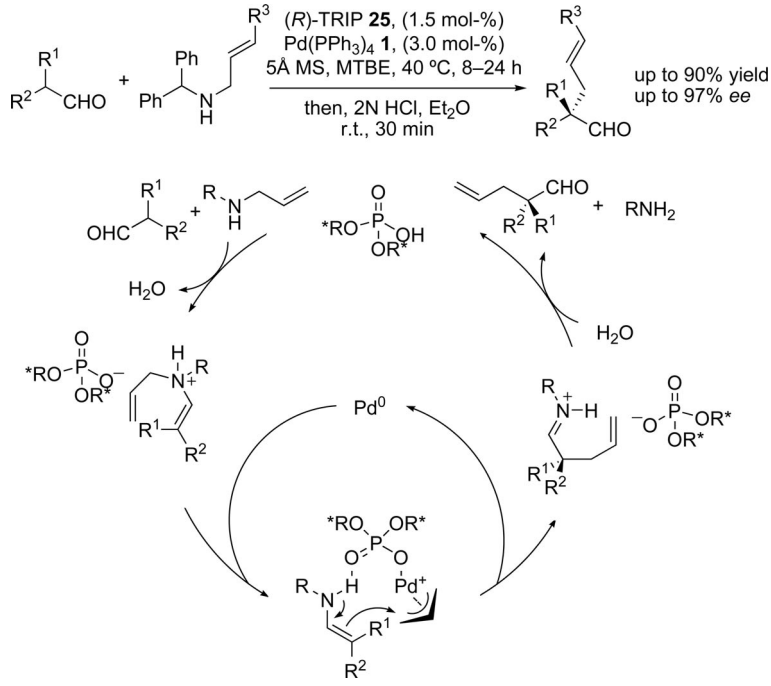
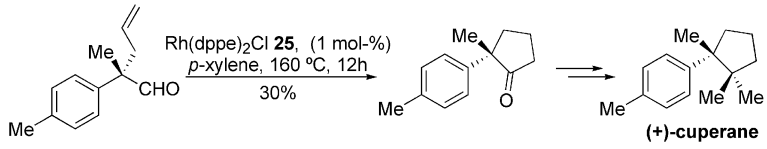


Scheme 19. Asymmetric Tsuji–Trost allylation of branched aldehydes through ACDC.

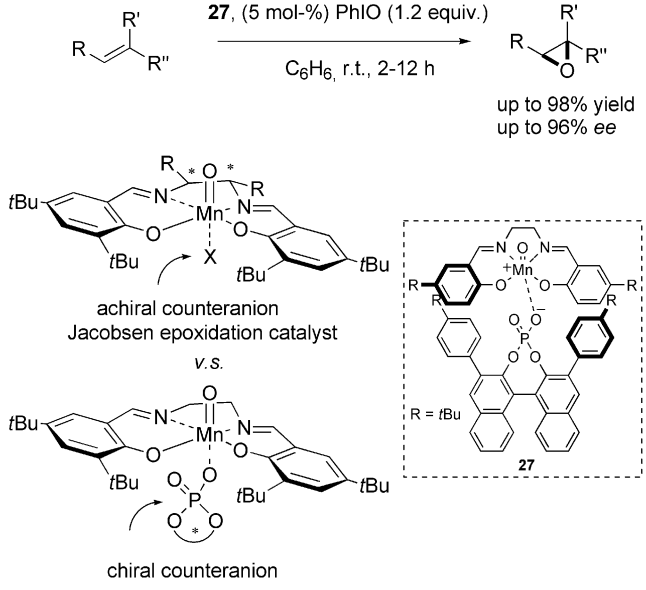


Scheme 20. Application in a synthesis of (+)-cuperane.

combination of the chiral phosphoric acid and palladium catalysis, challenging all-carbon quaternary stereogenic centres were obtained. A short synthesis of (+)-cuperane through Rh-catalysed intramolecular hydroacylation of a tertiary aldehyde substrate was also described (Scheme 20).

As described by the authors, the mechanism started with enamine formation from the aldehyde and the allylic amine. Sequential protonation led to the enammonium phosphate salt, which was attacked by palladium to give the corresponding Pd π-allyl complex. A complex of cationic palladium tethered with the chiral phosphate anion, leading to the stereoselective enamine addition, was proposed. The α-allylated iminium salt was then hydrolysed to yield the aldehyde product. The authors were not completely certain of an exclusively chiral counter anion strategy, because the mechanism suggested that the phosphoric acid might also serve as an anionic ligand for palladium to provide the critical spatial arrangement in the nucleophilic π-allyl addition.

Most recently, List's group reported enantioselective epoxidations of alkenes by application of manganese(III) salen and phosphate complexes as a further attractive extension of the ACDC strategy in transition-metal catalysis (Scheme 21).[62]



Scheme 21. ACDC-mediated Mn^{III}-salen epoxidation.

Initiated by Kochi,[63] Jacobsen[64] and Katsuki[65] have extensively studied catalytic asymmetric epoxidations of unfunctionalized alkenes in the presence of chiral Mn^{III}-salen catalysts. Enantioselectivity was delivered with aid of chiral salens of different sizes and with different substituents, together with the appropriate counter anions.[66]

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List and co-workers postulated the possibility of introducing stereoselectivity from chiral counter anions. Ion-pair catalysts were simply prepared by treating mixtures of the appropriate phosphoric acid and Mn-salen chloride complex with aqueous NaOH. A large variety of alkenes were subjected to the reported chiral counter-anion-mediated Mn-salen epoxidation with PhIO as the oxidant, resulting in good to excellent yields and enantioselectivities. Extensive screening of chiral phosphoric acid and Mn-salen complexes produced the optimized combination. The unique properties of the chiral counter anion in stabilizing the cationic catalyst promises exciting contributions in transition-metal catalysis, expected in the near future.

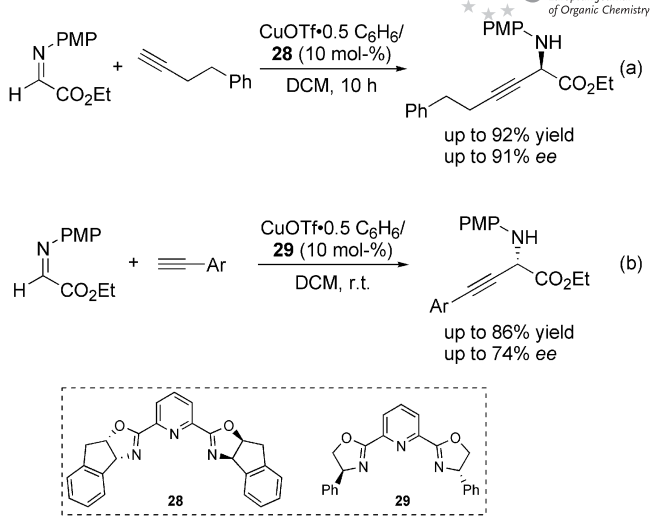
3.2 Reactions between Metal-Mediated Nucleophiles and Organic Brønsted-Acid-Activated Electrophiles

Unlike the amine-carbonyl activation strategy, effective metal-activated nucleophile additions to Brønsted-acid-mediated electrophiles have been successfully achieved. Transition-metal-mediated nucleophiles, including *sp*-hybridized carbon nucleophiles,[67] carbene-type nucleophiles[68] and enolate nucleophiles,[69] have demonstrated their versatility towards various electrophiles (Figure 4). Combinations of these modes of reaction of metals with organocatalyst-mediated electrophiles have attracted increasing attention in the synthetic community recently.

3.2.1 Transition-Metal-Mediated sp-Carbon Nucleophiles and Chiral Brønsted-Acid-Directed Electrophiles

In 2005, Chan and co-workers reported the first asymmetric synthesis of β,γ-aliphatic alkynyl α-amino acid derivatives, with *ee* values of up to 91%, by direct addition of terminal aliphatic alkynes to α-imino esters in the presence of chiral copper(I) complexes (Scheme 22, a). When a similar strategy was applied to aromatic alkynes, however, the reactivities and enantioselectivities were slightly diminished (Scheme 22, b).[70]

In 2007, Rueping and co-workers[71] reported the utility of the combinations of catalysts obtained by joint use of chiral Brønsted acids and transition metals in the synthesis of α-alkynylated amino esters (Scheme 23). A chiral binaphthol-derived phosphoric acid and a silver salt were used in this combined catalytic reaction. The optimized reaction conditions offered a greater scope of substrates with better yields and improved enantioselectivities than the previous work done by Chan and co-workers.



Scheme 22. Asymmetric alkynylation of α-imino esters catalysed by copper(I) PyBOX complexes.

The authors first postulated a pathway in which the chiral Brønsted acid activated the α-imino ester through the formation of the intermediate ion pair to lock the stereoarrangement of the imine, followed by the enantioselective nucleophilic attack of the silver-activated terminal alkyne, giving the desired products. On second thoughts, though, one cannot exclude the possibility of exchange of the metal counter anion leading to the formation of a chiral silver complex.

More recently, Arndtsen and co-workers[72] have reported another interesting example, involving the use of the *N*-protected amino acid as the Brønsted acid catalyst in combination with a copper(I) catalyst, in their investigation of asymmetric propargylamine synthesis (Scheme 24). Simple and inexpensive chiral amino acid derivatives were tested for enantioselectivity, which revealed *N*-Boc proline to be the optimal choice of catalyst. Cu^{I} ligand effects were also discussed. A wide substrate scope with good to excellent yields and enantioselectivities was achieved.

As the authors reported, hydrogen bonding involving both the chiral amino acid catalyst and the iminium contributes to the formation of the chiral environment, followed by the Cu^{I}-activated terminal alkyne nucleophilic addition. Because proline derivatives have been found to be suitable to coordinate with transition metals, especially copper,[73] the authors carried out a series of NMR studies to support this proposed mechanism.

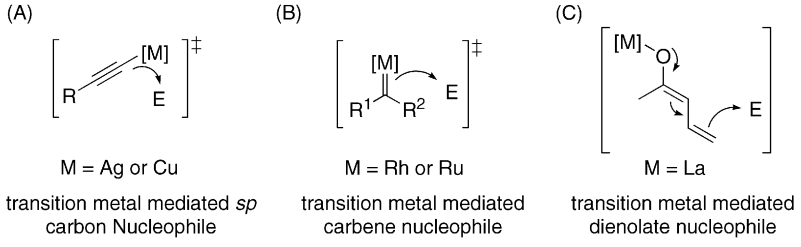


Figure 4. Transition-metal-mediated nucleophiles.

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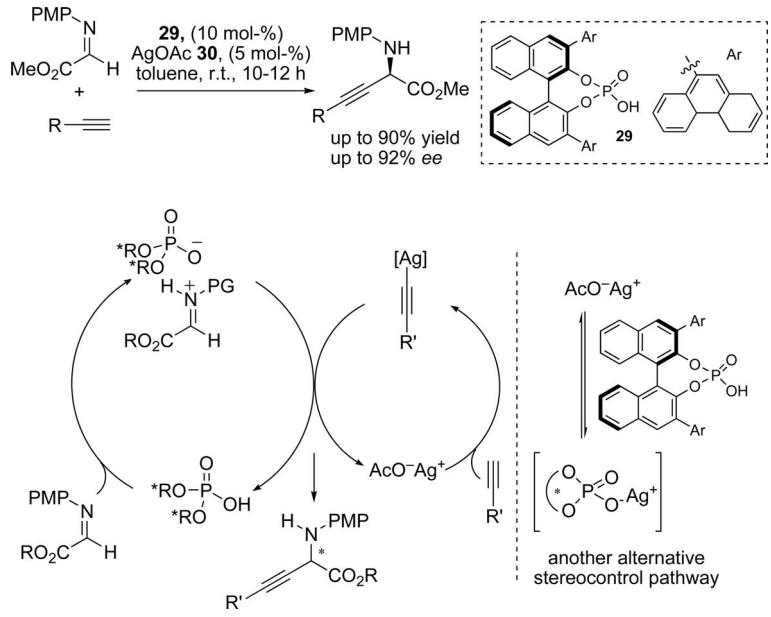
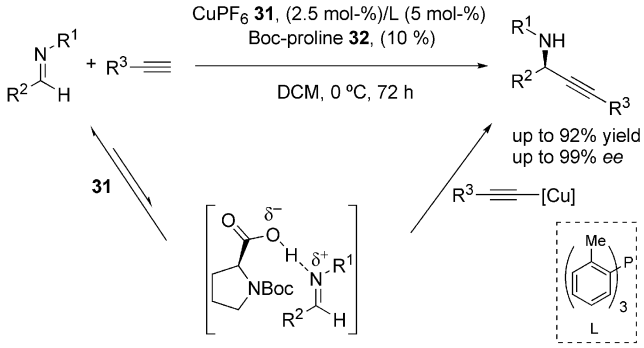


Scheme 23. Asymmetric alkynylation of an α-imino ester through Brønsted acid and silver catalysis.



Scheme 24. Asymmetric propargylamine synthesis through a combination of *N*-protected amino acid and copper catalysis.

3.2.2 Rhodium-Mediated Carbene Nucleophiles with Brønsted-Acid-Mediated Electrophiles

Hydrogenation-mediated carbon–carbon bond formation, in which a sp^2- or sp-hybridized carbon–carbon multiple bond is activated by a rhodium hydride complex to allow nucleophilic addition to a suitable electrophile (Figure 5), has been cited as a unique strategy in organic synthesis.[74]

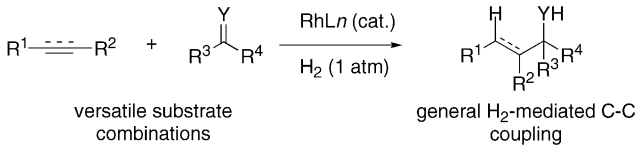


Figure 5. Rhodium-catalysed hydrogenative C–C coupling.

In 2005, Krische and co-workers[75] reported rhodium-catalysed enantioselective hydrogenative C–C couplings between enynes and pyruvate esters (Scheme 25). Interestingly, the addition of a Brønsted acid was found to be crucial for optimal performance. As a result, ketone electrophiles – usually considered challenging substrates, due to their poor reactivities – could also give excellent yields and enantioselectivities with a variety of substrates. A deuteron exchange study was performed and indicated selective deuteration at the vinylic position shown, which strongly supported the proposed mechanism.

Heteroaromatic aldehydes/ketones with structures isoelectronic to pyruvate esters were also examined, giving good to excellent enantioselectivities (Scheme 26).[76] Notably, no chiral ligands to coordinate with Rh cations were applied in this transformation; the resulting enantioselectivity came only from the chiral Brønsted acid. This strongly suggested that the Brønsted acid co-catalyst protonated and/or provided considerable hydrogen bonding to the heteroatom aromatic aldehyde when the stereogenic C–C was formed. The LUMO lowering effect could also be invoked to account for the observed good enantioselectivity.

As well as hydrogenative C–C coupling and the ubiquitous hydroformylation, another well known property of rhodium complexes is their unique reactivity towards diazo compounds, introducing carbenoid nucleophiles.[77] In 2008, Gong, Hu and co-workers[78] reported enantioselective three-component reactions of diazo compounds, alcohols and imines, in the presence both of chiral Brønsted acids and of $Rh_2(OAc)_4$ as catalysts (Scheme 27). These reactions provided efficient access to enantiomerically enriched β-amino-α-hydroxy acid derivatives containing quaternary carbon stereogenic centres.

In the proposed mechanism (Scheme 27), addition of the alcohol to the Rh carbene gives an oxonium ylide as the effective nucleophile. Concurrently, the chiral phosphoric acid protonates the imine (or a counter ion strategy may be used) to provide the needed spatial arrangement around the

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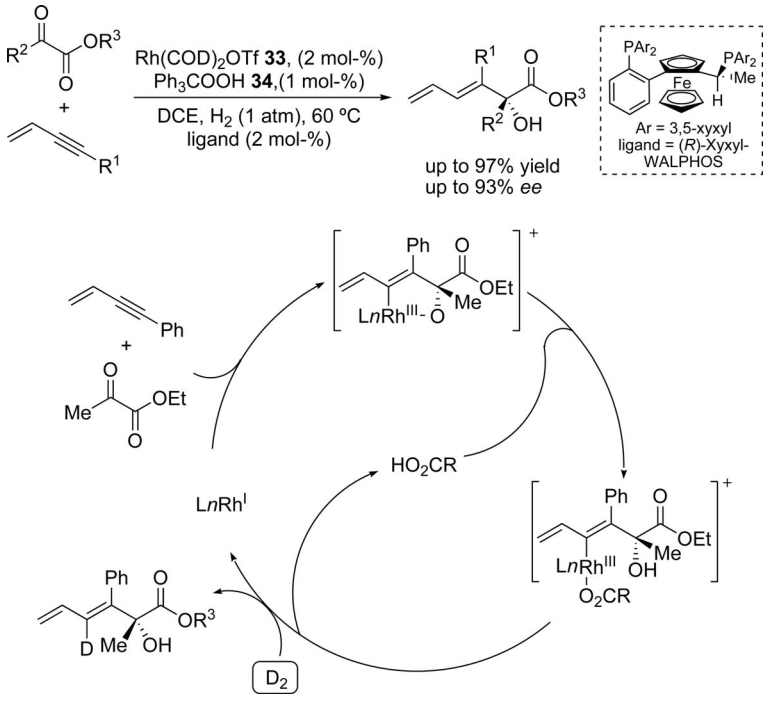
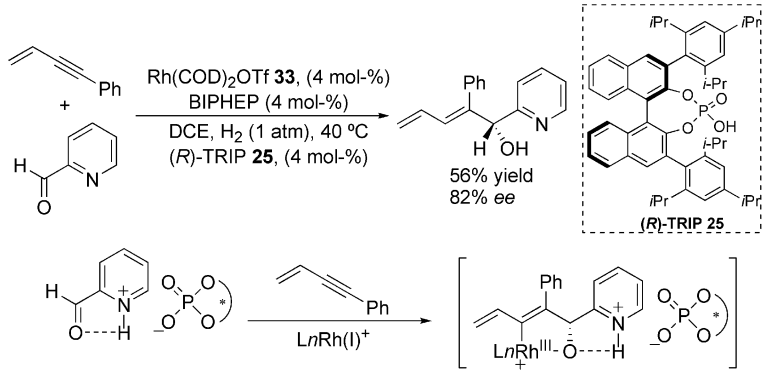


Scheme 25. Enantioselective hydrogenative C–C couplings of enynes and pyruvate esters.



Scheme 26. Possible mechanisms in combined chiral Brønsted acid/achiral Rh^{I} complex catalysis.

electrophile. A Mannich-type condensation to yield the optically active products thus occurs. The optimized conditions were suitable for various substrates with good to excellent yields and stereoselectivities.

Hu and co-workers[79] later reported similar four-component reactions with aryl diazoacetates, alcohols, aldehydes and amines, in which imines were generated in situ. Good yields and excellent enantioselectivities were obtained (Scheme 28).

3.2.3 Dienolate Nucleophiles Mediated by Transition Metal Lewis Acids and Tuned by Brønsted Acids

The lanthanides, or other rare earth metal cations, are well known as oxophilic catalysts for activation of ketones or conjugated ketones and formation of the corresponding enolate nucleophiles.[80] In 2008, Matsunage, Shibasaki and co-workers[81] reported asymmetric Mannich-type reactions between γ-butenolides and *N*-diphenylphosphinoyl imines, through Brønsted-acid-assisted La^{III}-imine activation (Scheme 29). In the presence of catalytic amounts of TfOH and La^{III}-Py-Box complex, enantioselective additions of imines were achieved. From NMR studies of the reactions, the authors concluded that the catalytic amounts of TfOH (in addition to activating the imine) helped the coordination of the metal cation with the chiral Py-Box ligand, which not only improved the yields (up to >99%), but also increased the stereoselectivities (up to >97:3 *dr*, *anti*/*syn* and 84% *ee*).

3.3 Brønsted Base and Transition Metal Lewis Acid Catalysis

Transition metal cations are commonly used for activation of electrophiles. The equally well studied chiral Brønsted-base-mediated nucleophiles also represent an at-

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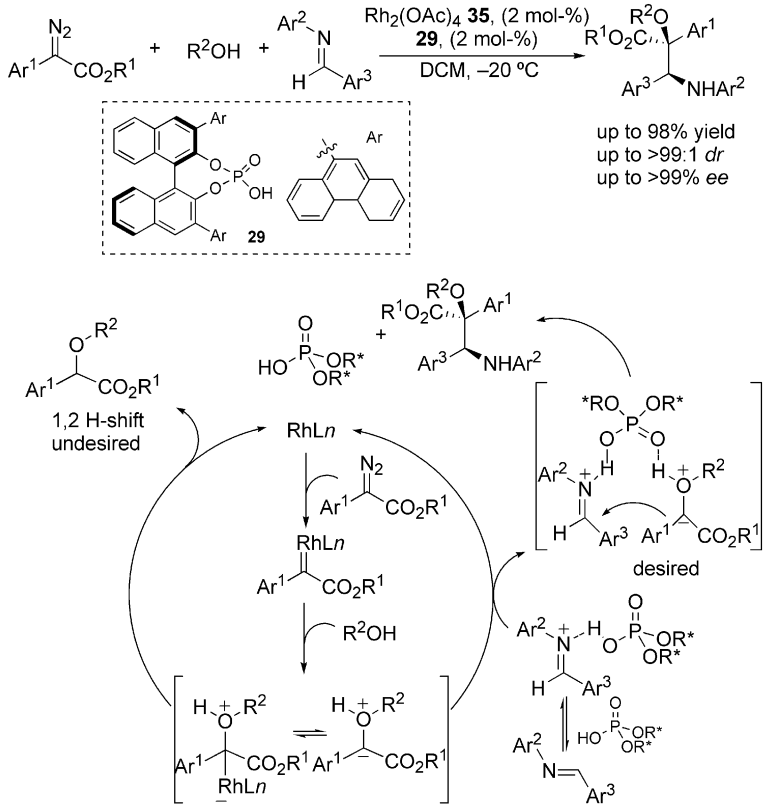
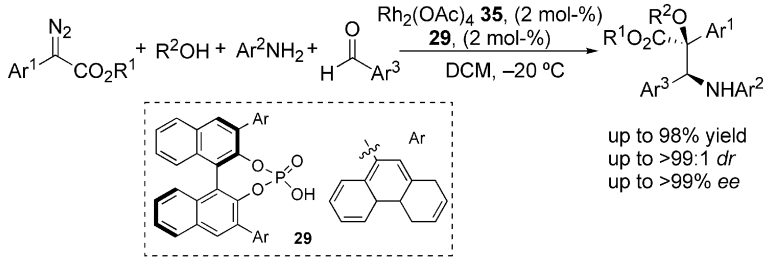
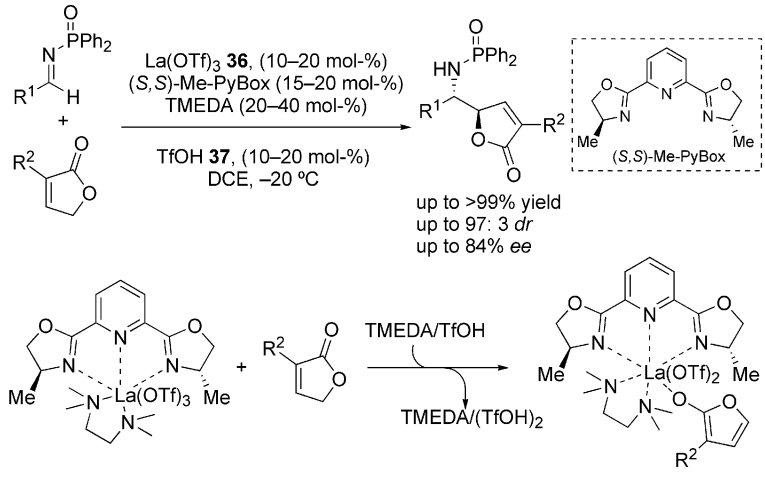


Scheme 27. Asymmetric three-component reactions of diazo compounds, alcohols and imines.



Scheme 28. Asymmetric four-component reactions of diazo compounds, alcohols, aldehydes and amines.



Scheme 29. TfOH-tuned Mannich-type reaction catalysed by La^{III}-Py-Box complex and the formation of the La-dienolate nucleophile.

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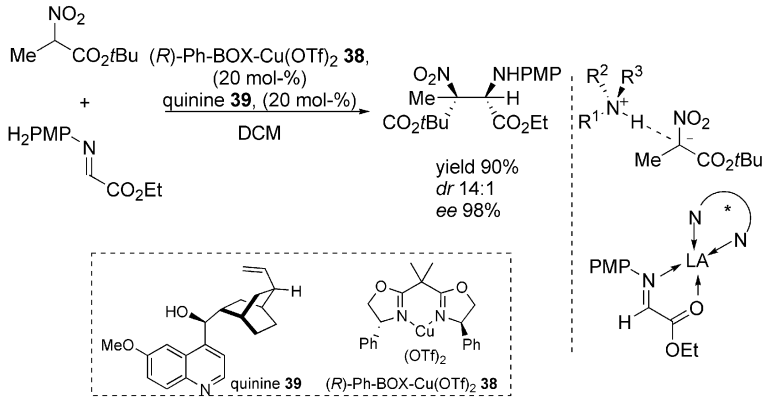
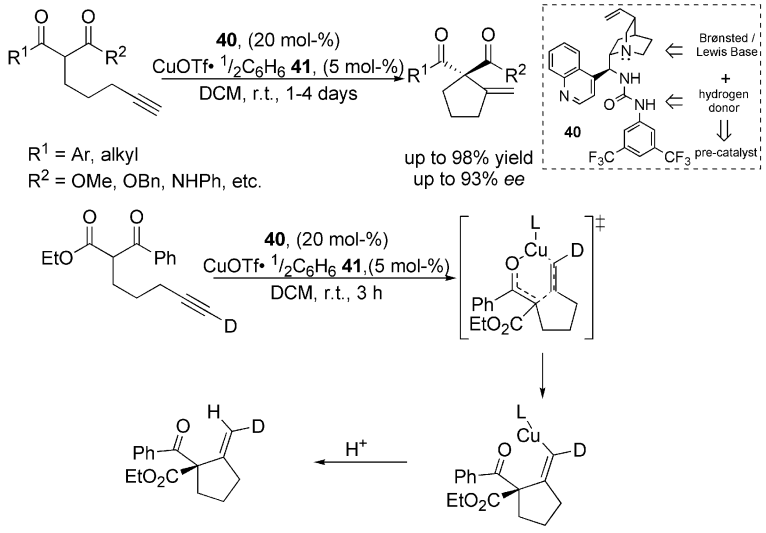
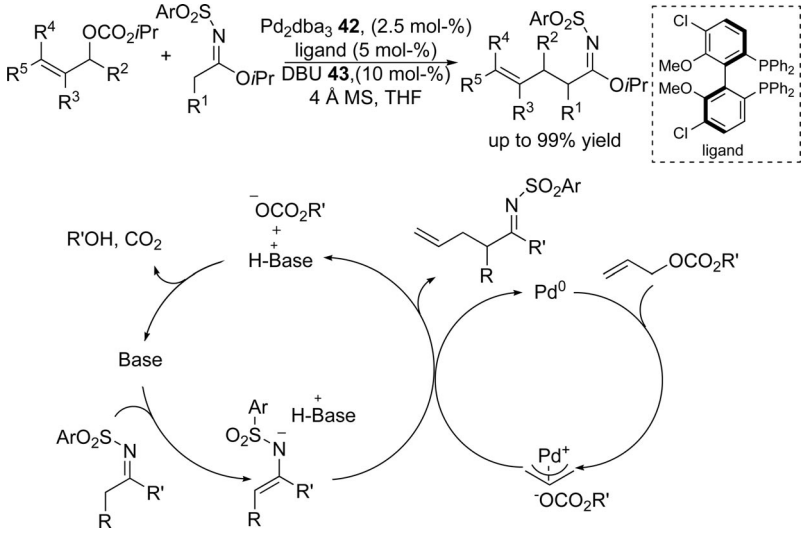


Scheme 30. Aza-Henry reaction based on a combination of chiral base and chiral Lewis acid dual catalysis.



Scheme 31. Brønsted base/Lewis acid cooperative catalysis of Conia-ene reactions and related mechanistic studies.

tractive strategy for enantioselective synthesis. In 2005, Jørgensen and co-workers successfully applied the concept of Brønsted base and metal complex Lewis acid dual catalysis in the asymmetric aza-Henry reaction (Scheme 30).[82] Detailed investigations were performed to elucidate the best match of catalyst pairs. A combination of quinine as the



Scheme 32. Pd-DBU combined catalysis of decarboxylative allylation of sulfonylimidates.

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chiral Brønsted base and (*R*)-Ph-BOX-Cu(OTf)$_2$ as chiral Lewis acid gave good to excellent yields and excellent stereoselectivities.

In 2009, other examples of combinations of organic bases and metal Lewis acids were reported by Dixon and co-workers (Scheme 31).[83] With the application of cinchona-derived urea and CuOTf catalysts, enantioselective Conia-ene reactions were developed with excellent yields and enantioselectivities.

In the proposed mechanism, the cinchona-derived urea catalyst deprotonates the β-keto ester and generates the enolate nucleophile. After 5-*exo*-*dig* cyclization, the products were obtained with excellent yields and enantioselectivities. Different metal complexes were also investigated and CuOTf·1/2 C_6H_6 was identified as the optimal choice of metal Lewis acid for alkyne activation. As mentioned by the authors, the urea functional groups and the tertiary amine, which might provide Brønsted/Lewis base and hydrogen-bonding donor functionalities, were crucial for this transformation. A deuterated alkyne was also used to help understanding of the mechanism and gave the corresponding isotope-labelled product.

Other examples of Brønsted base and metal Lewis acid dual catalysis were recently reported by Kobayashi and co-workers (Scheme 32).[84] A simple tertiary amine (DBU) was used as the Brønsted base to mediate the nucleophile and the Tsuji–Trost palladium π-allyl was applied as the electrophile for the allylation of the imines. Excellent yields with a wide substrate scope were observed. No enantioselectivity was observed in this transformation, but further enantioselective investigation was promised by the authors.

4. Organic Lewis-Base-Initiated Nucleophiles and Transition-Metal-Mediated Electrophiles

In an important class of synthetic reactions, Lewis bases are used to activate electron-deficient alkenes, producing nucleophiles in situ. Lewis base catalysts based on tertiary phosphanes and tertiary amines have been extensively studied.[85] Most recently, secondary amines such as proline analogues have also been used as Lewis bases to activate nitroalkenes as nucleophiles through neutral adducts (Figure 6).[86] From the point of view of combinations with transition metal catalysis, however, the compatibilities of Lewis base and metal cation are causes for considerable concern, due to the potential for interactions between these two catalyst types.

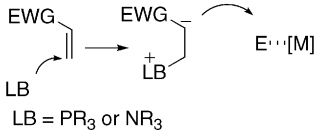
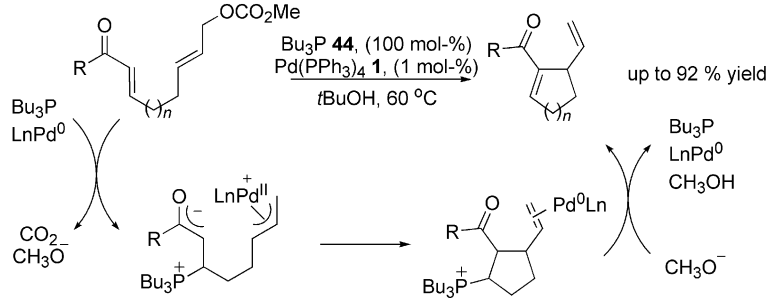
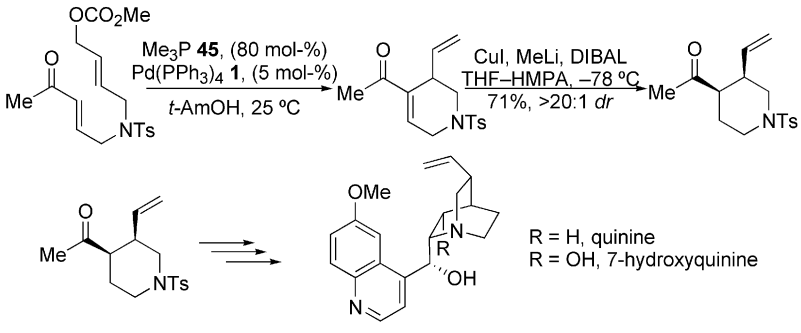


Figure 6. Lewis-base-activated electron-deficient alkenes as nucleophiles.

The first representative combination of Lewis base catalysis and transition metal catalysis was developed by Krische and co-workers in 2003,[9] when the concept of combining organocatalysis and transition metal catalysis was mentioned for the first time. An effective dual catalytic process was achieved with a starting enone-tethered terminal allyl carbonate, through the use both of tributylphosphane as the Lewis base and of the palladium-activated Tsuji–Trost



Scheme 33. Combinations of Lewis-base-activated nucleophiles and transition-metal-activated electrophiles.



Scheme 34. Synthesis of quinine and 7-hydroxyquinine through a combination of the Morita–Baylis–Hillman reaction and Tsuji–Trost cyclization.

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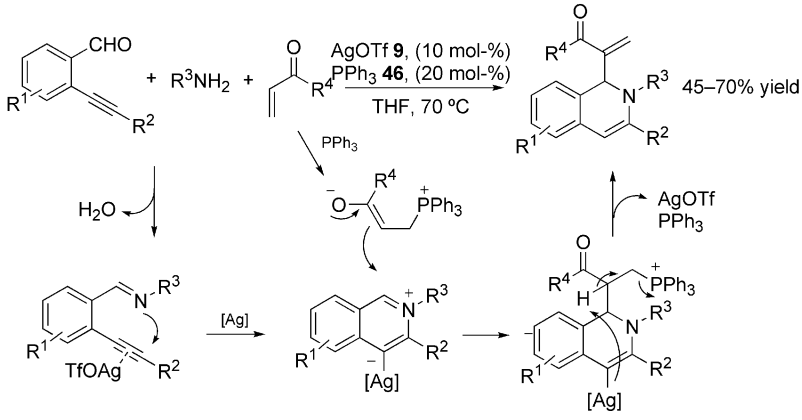


Scheme 35. Combination of Lewis base catalysis and AgOTf catalysis.

π-allyl as the electrophile (Scheme 33). The desired allylated cyclic enone products were obtained in excellent yields. No investigation of enantioselectivity was performed in this work.

This strategy was later further extended to the total synthesis of quinine and its derivatives (Scheme 34).[87]

Most recently, Wu and co-workers reported other examples of transformations of this type as an extension of their previously reported works.[88] Three-component reactions of 2-alkynylbenzaldehydes, amines and α,β-unsaturated ketones were developed and functionalized 1,2-dihydroisoquinolines were synthesized in good yields (Scheme 35).

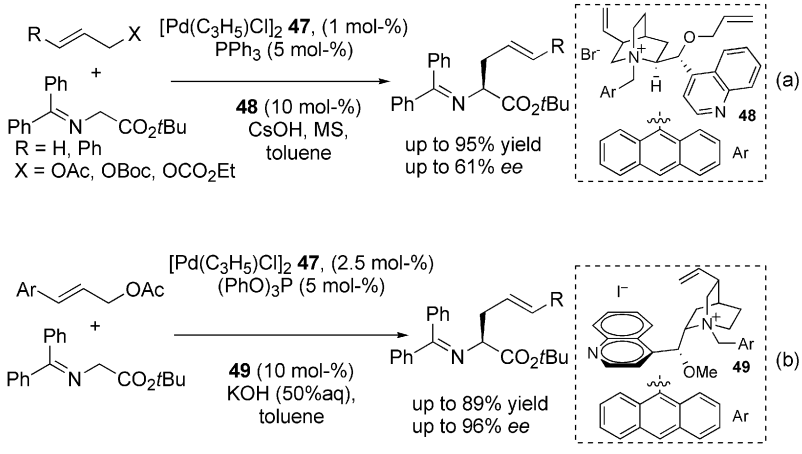
In the investigation, AgOTf was found to be the most effective catalyst for triple bond activation and PPh_3 was employed as the Lewis base to provide the Morita–Baylis–Hillman nucleophile. The imines were formed in situ, followed by 6-*endo*-*dig* cyclization. After consecutive protonolysis and elimination of phosphane catalyst, the products were then obtained in good yields.

5. Nucleophiles Mediated by Phase-Transfer Catalysts and Electrophiles Mediated by Transition Metals

Phase-transfer catalysis has been well developed and studied as an important form of asymmetric organocatalysis[89] and has also been combined with transition metal catalysis for further applications. In 2001, Gong, Mi and co-workers[90] reported, for the first time, the allylic alkylation of glycine imino ester, through the use of a combination of phase-transfer catalysis (PTC) in the presence of a chiral iminium salt with palladium π-allyl catalysis (Scheme 36, a). The effects of molecular sieves, chiral phosphane ligands and the substituent groups on the allyl starting materials with regard to enantioselectivity were discussed. Good yields and moderate *ee* values were observed. Soon after, Takemoto and co-workers[91] followed up and greatly improved the enantioselectivity without sacrificing the reactivity by a similar strategy (Scheme 36, b). Notably, no chiral phosphane ligand was applied in this case.

6. Consecutive Reactions with Combinations of Organocatalysis and Transition Metal Catalysis

Stimulated by the tremendous developments in tandem reactions (or domino reactions) both in organocatalysis[92] and in transition metal catalysis,[93] the idea of combining two totally different chemical transformations catalysed by organocatalysts and transition metal catalysts has been tested with growing success.



Scheme 36. Combinations of chiral PTC and transition metal catalysis.

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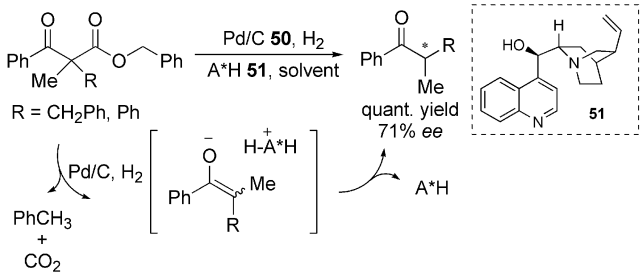
6.1 Palladium-Based Hydrogenative Decarboxylation Followed by Chiral Amino-Alcohol-Mediated Protonation

Hénin and co-workers[94] reported syntheses of asymmetric linear ketones based on heterogeneous palladium-carbon hydrogenative decarboxylation of β-keto esters in the presence of catalytic amounts of chiral protic sources. Excellent yields and moderate enantioselectivities were obtained. The amino alcohol functionalities in the catalysts were found to be effective for kinetic resolution of the decarboxylated enolates (Scheme 37).

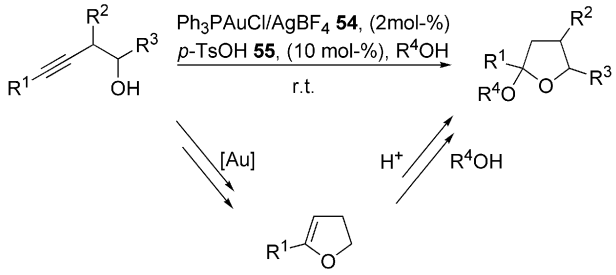


Scheme 37. Palladium hydrogenative decarboxylation in combination with quinine-mediated protonation.

2-Fluoro-1-tetralone[95] and 3-methyl-4-chromanone derivatives[96] were synthesized by this strategy (Scheme 38).[97]

6.2 π-Acidic Metal Catalysis Followed by Brønsted Acid Catalysis

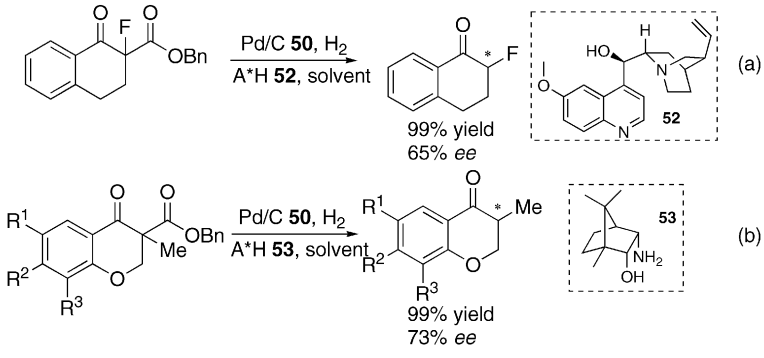
In 2006, Krause and co-workers reported gold-catalysed tandem cycloisomerization/hydroalkoxylations of homopropargylic alcohols (Scheme 39).[98] Different tetrohydrofuran ethers were synthesized in good yields. The Au^I catalyst initiated the reaction by coordinating with the triple bonds, followed by 5-*endo-dig* cyclization to form vinyl-gold intermediates. Upon protonolysis these provided the dihydrofuran intermediates. TsOH, as the protic acid, catalysed subsequent hydroalkoxylation in the alcohols used as solvents.



Scheme 39. Combination of Au^I-catalysed cyclization and acid-catalysed hydroalkoxylation.

Krause, Alexasis and co-workers reported combinations of gold-catalysed tandem acetylization/cyclization and enamine catalysis based on this strategy (Scheme 40).[99] Simple aldehydes and conjugated nitro enynes were used as starting materials, and nitro-substituted tetrahydrofuran ethers were successfully synthesized in good yields and with excellent diastereoselectivities and enantioselectivities. In their report, the enamine conjugate additions and the subsequent gold-catalysed tandem reactions were evaluated independently. The authors believed that Au^I might also serve as an oxophilic Lewis acid to activate the aldehyde directly after the enamine catalysis. Another alcohol could come in and form the hemiacetal gold salt, which could then rapidly undergo cyclization with the Au^I-activated triple bond. After protonolysis the product would be released and the catalyst would go onto the next cycle.

As well as Au cations, it was also known from the literature that platinum(II) could also be applied as a π-acid in the activation of triple bonds.[100] The combination of platinum catalysis and Brønsted acid catalysis had also been successfully developed by Barluenga and co-workers.[101] In their report, syntheses of spiroquinoline derivatives in good yields were accomplished through three-component reactions between alkynols, aldehydes and aromatic amines (Scheme 41). However, when an unsubstituted alkynol (pent-4-yn-1-ol) was applied with benzaldehyde and aniline,



Scheme 38. Syntheses of 2-fluoro-1-tetralone and 3-methyl-4-chromanone.

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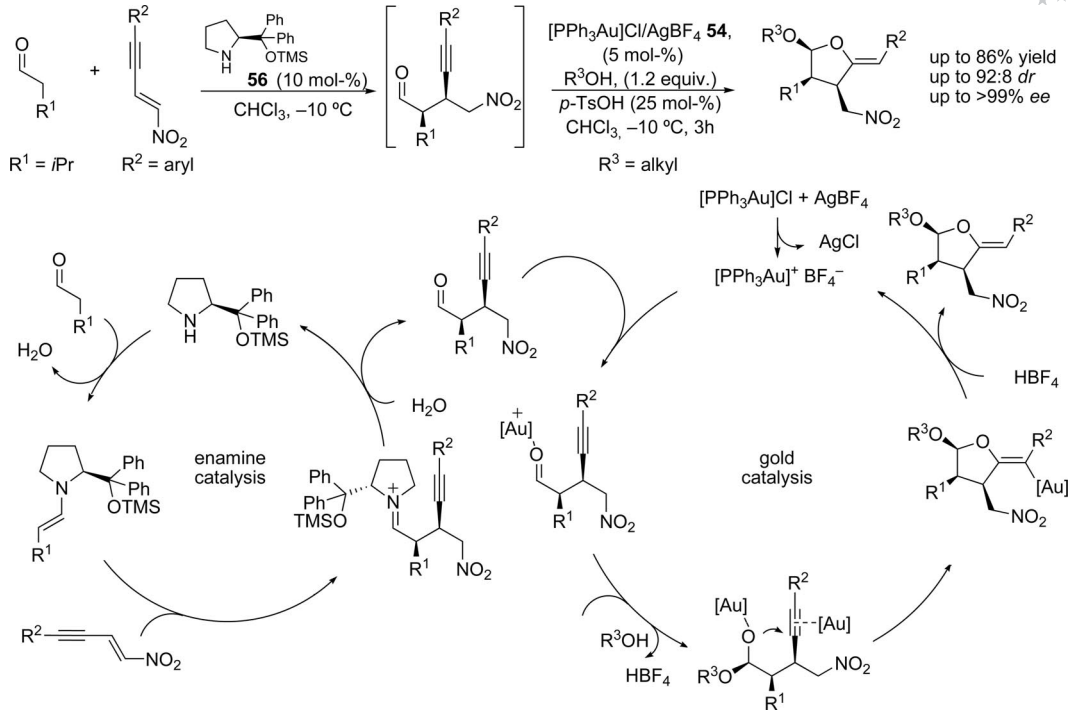
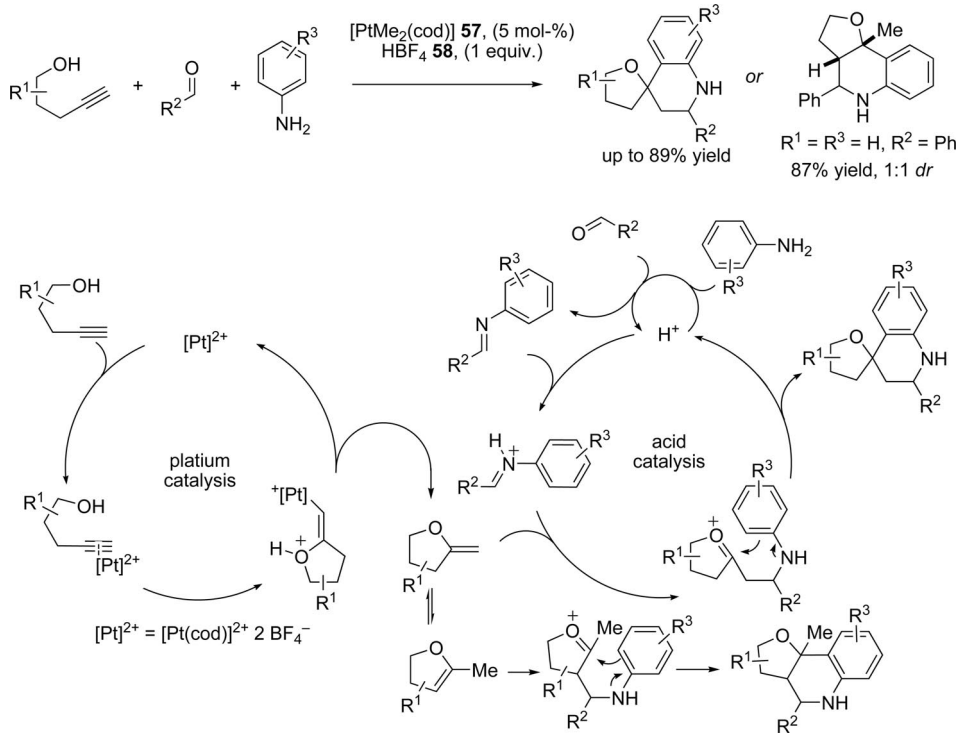


Scheme 40. Combinations of enamine catalysis with gold-catalysed tandem acetylization/cyclization.



Scheme 41. Three-component syntheses of spiroquinolines with combined Pt/Brønsted acid catalysis.

an interesting alternative product, a furo[3,2-*c*]quinoline, was obtained in good yield.

The authors postulated that the reaction began with the Pt^{II}-catalysed 5-*endo*-*dig* cyclization of the alkynol, giving an enol ether intermediate. In the presence of preformed acid-activated iminium cations, Mannich-type reactions would occur to give the highly reactive oxonium intermediates, which would undergo intramolecular nucleophilic additions from the adjacent aromatic ring to yield the products. The unexpected furo[3,2-*c*]quinoline product might be expected from isomerization of the enol ether intermediate and its subsequent transformation.

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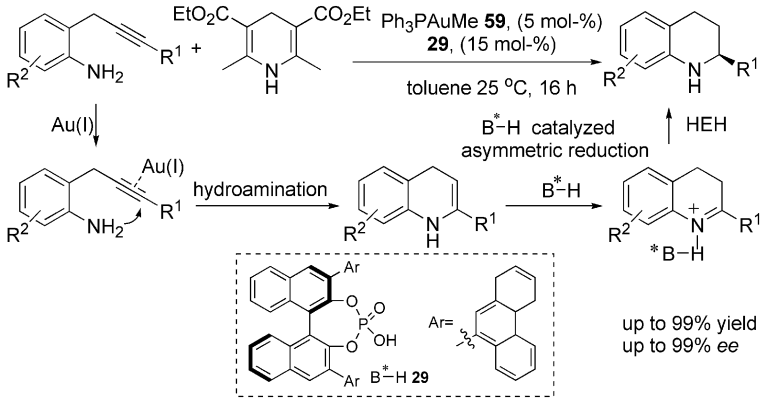
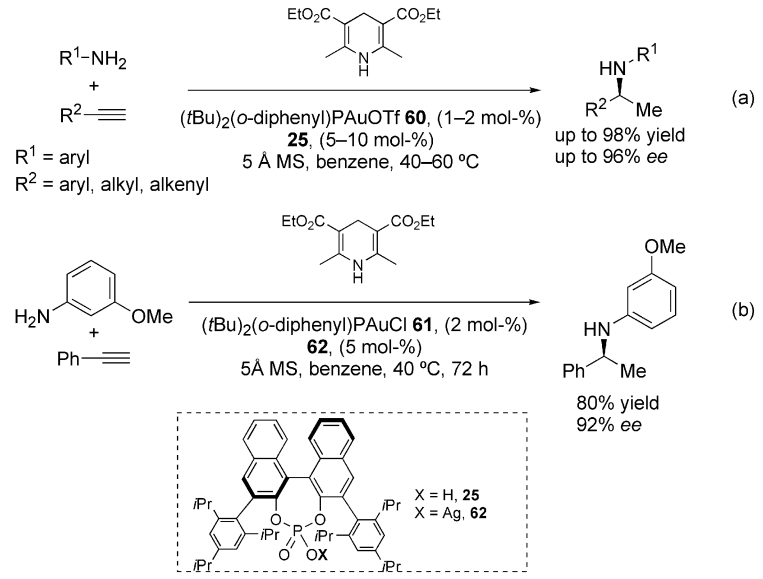


Scheme 42. Combination of intramolecular hydroamination (Au^I) and stereocontrolled HEH (Brønsted acid catalyst).



Scheme 43. Combinations of Au^I-catalysed intermolecular hydroamination and transfer hydrogenation stereocontrolled by Brønsted acid catalysts.

Other recent examples of cascade processes of this type were reported by Gong and co-workers,[102] who combined Au^I-catalysed intramolecular hydroamination and Hantzsch ester transfer hydrogenation catalysed by a chiral Brønsted acid (Scheme 42). Tetrahydroquinoline derivatives were successfully synthesized with excellent yields and enantioselectivities. The silver salt of the Brønsted acid was also prepared and tested, but gave poor reactivity (35% yield, 90% *ee*, 80 h). The authors therefore concluded that the stereoselectivity was predominantly controlled by the phosphoric acid, rather than by the counter ion pair mechanism.

In the same year an intermolecular tandem reaction, providing chiral secondary amine products with excellent yields and enantioselectivities (Scheme 43, a), had also been studied by Che and co-workers.[103] For better understanding of the mechanism a control experiment was also carried out (Scheme 43, b). Upon treatment of the gold catalyst with the chiral silver phosphate, similar reactivity and enantiomeric control were observed. This, according to the authors, indicated the possibility of exchange of the metal counter anion, leading to the formation of a gold^I complex cation/chiral counter anion ion pair to carry out the subsequent reaction.

6.3 Combinations of Brønsted Acid/Iridium(III) Catalysis in Reductive Amination

As well as Hantzsch ester hydrogenation (HEH), Cp*M^{III}-diamine-catalysed hydrogenation (M = Rh, Ir) had been demonstrated to be a powerful approach for reduction of imines, with elemental hydrogen as a clean and economic source.[104]

Xiao and co-workers[105] recently reported a metal-Brønsted acid cooperative catalysis process for direct asymmetric reductive amination (DARD) of ketones and amines, based on their previous study of asymmetric iridium hydrogenation of acyclic imines (Scheme 44).[106] Different Cp*-diamine ligands for iridium(III) were screened and the (*S*,*S*)-Cp*Ir-H-diamine was found to offer the best match

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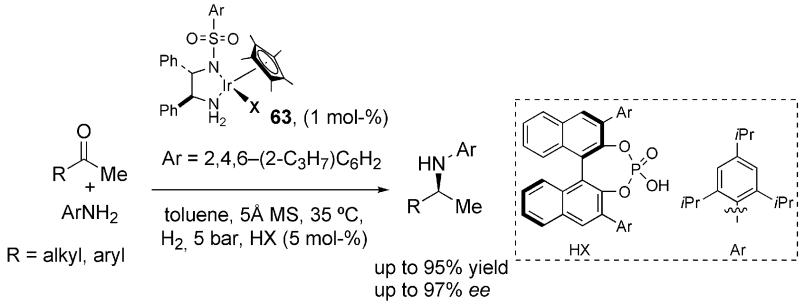


Scheme 44. Combinations of hydroamination catalysed by Ir^{III} and transfer hydrogenation stereocontrolled by a Brønsted acid catalyst.

for the *R*-configured phosphoric acid. Notably, a low yield (45% conversion) and low enantioselectivity (15% *ee*) were observed when an achiral Brønsted acid (HBF_4) was applied, which suggested a possible transition state resembling a counter ion pair in the hydride transfer step.

The influence of the Brønsted acid in terms of reactivity and enantioselectivity was also studied, and indicated acceleration of imine formation by the acid. Use of a slight excess of Brønsted acid greatly improved the yields and enantioselectivities of the aromatic ketones, but for aliphatic ketones the reactivity was totally abolished. Lowering the loading of the Brønsted acid gave the best results.

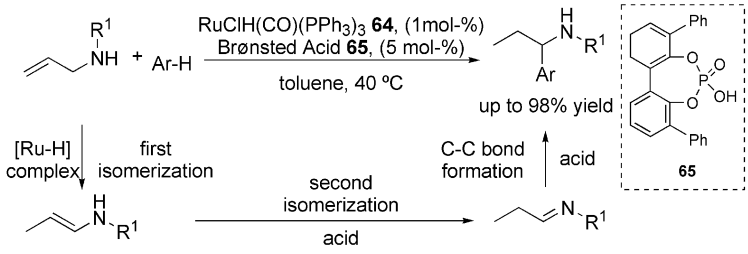
6.4 Ru/Brønsted-Acid-Catalysed Isomerization/Carbon–Carbon Bond-Forming Tandem Reactions

Ruthenium hydride complexes are good catalysts for inducing allylamide isomerization. In 2008, Terada and coworkers[107] successfully developed tandem isomerization/Friedel–Crafts transformations using a combination of a ruthenium hydride complex and a Brønsted acid (Scheme 45). The tandem reactions were executed in the presence of $RuClH(CO)(PPh_3)_3$ (1%) and phosphoric acid (5%).

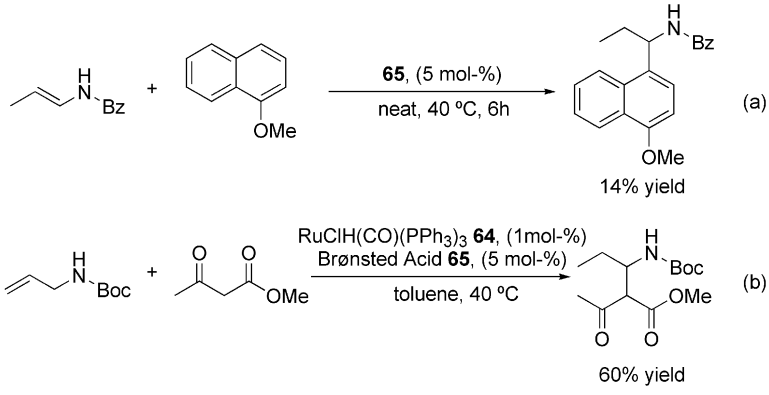
The authors proposed that the ruthenium hydride complex initiated the isomerization of the allylamide to an enamide, which was followed by the Brønsted-acid-catalysed second isomerization, giving the imine intermediate. The Friedel–Crafts reaction took place in the presence of the Brønsted acid and a new C–C bond was formed. This strategy produced an imine, generated in situ, as electrophile, indicating strong potential for future development.

Notably, the Friedel–Crafts reaction did not proceed well when an enamide, rather than an allylamide, was treated directly with a Brønsted acid catalyst (Scheme 46, a).

Moreover, 1,3-dicarbonyl compounds could also serve as nucleophiles under the standard reaction conditions (Scheme 46, b).



Scheme 45. Isomerization/carbon–carbon bond-forming tandem reactions.



Scheme 46. Extended study of the Ru/Brønsted-acid-catalysed tandem reaction.

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6.5 Combinations of Ruthenium-Catalysed Olefin Metathesis and Chiral Brønsted-Acid-Catalysed Friedel–Crafts Alkylation

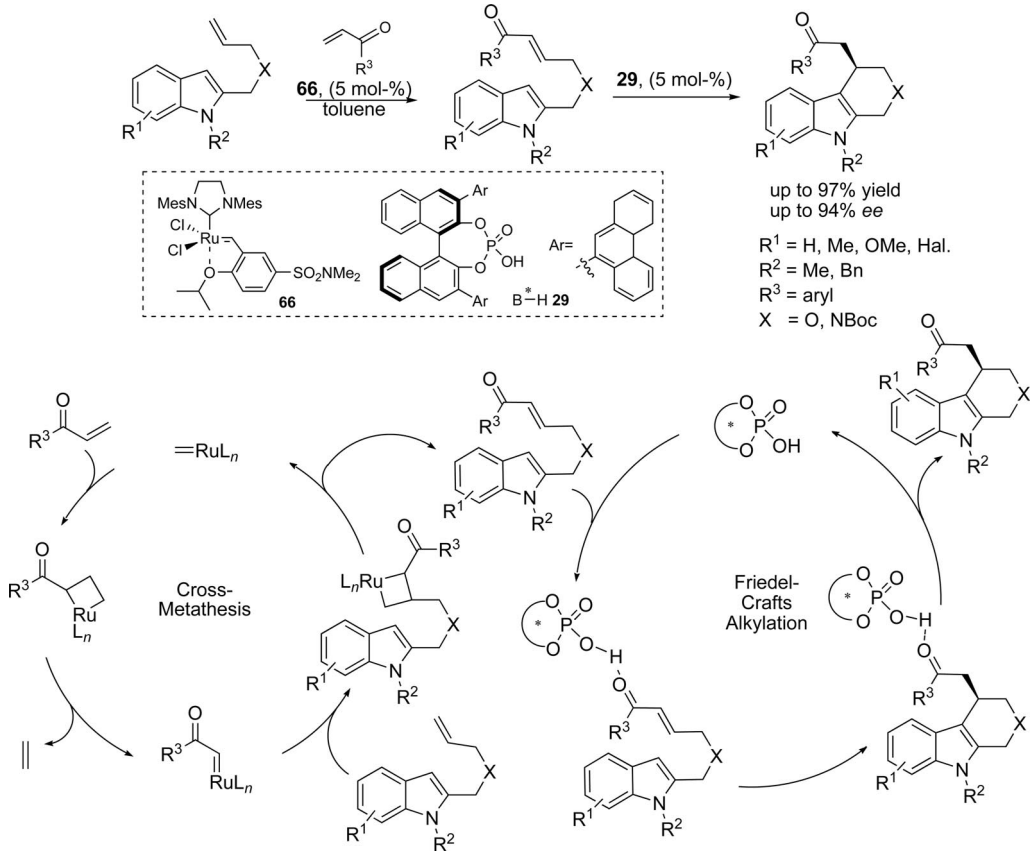
As the most powerful olefin cross-metathesis catalysts, ruthenium complexes have also been combined with organocatalysis for exploration of new types of carbon–carbon bond formation.[108] One recent example was the synthesis of polycyclic indoles through a combination of Ru-catalysed olefin cross-metathesis and Brønsted-acid-catalysed Friedel–Crafts alkylation, reported by You and co-workers (Scheme 47).[109]

The mechanism of this tandem reaction involved two distinct catalysis cycles. The reactions began with the olefin cross-metathesis of the enones and alkenes, catalysed by the Hoveyda–Grubbs catalyst, to produce the intermediate indolyl enones. The Friedel–Crafts reactions were then catalysed by the chiral phosphoric acid to afford the polycyclic indole products with excellent enantioselectivities. The *ee* values were slightly decreased, however, when the two catalytic transformations were performed in a one-pot fashion; according to the authors this might be due to background Ru-catalysed Friedel–Crafts alkylation.

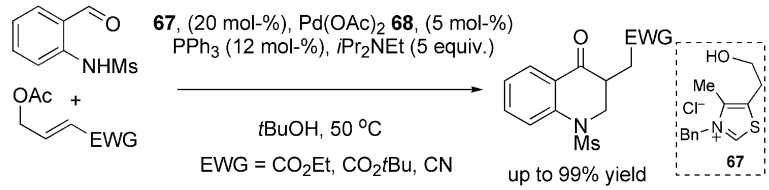
6.6 Combinations of NHC Catalysis and Palladium π-Allyl Catalysis

N-Heterocyclic carbene (NHCs) are the subject of rapidly growing interest in the synthetic community.[110] These compounds are also well-known ligands for transition metals.[111] The compatibility between NHCs as organocatalysts and transition metal cations was an appreciable challenge because of potential self-quenching of these two catalysts.

The first successful example of a combination of NHC carbene catalysis and transition metal catalysis was reported by Hamada and co-workers in their synthesis of 3-



Scheme 47. Combination of Ru-catalysed olefin cross-metathesis and Brønsted-acid-mediated Friedel–Crafts alkylation.



Scheme 48. Pd-catalysed *N*-allylation in combination with NHC-catalysed intramolecular Stetter reactions.

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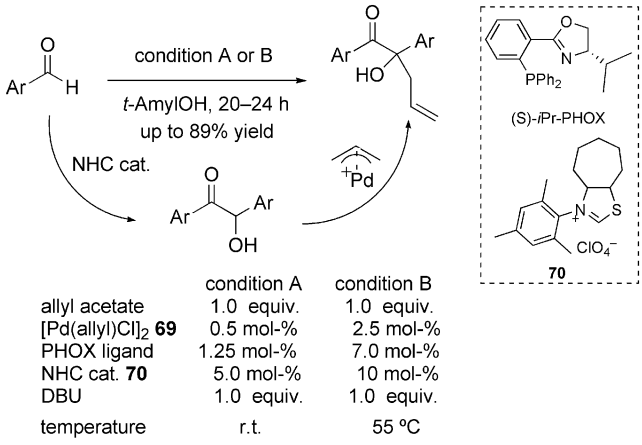
substituted 2,3-dihydroquinolin-4-ones (Scheme 48).[112] *N*-Allylation occurred in the presence of a Pd catalyst and a NHC catalyst, followed by NHC-catalysed intramolecular Stetter reactions. Through kinetic studies the authors found that the presence of the $Pd(OAc)_2$ and AcOH/*i*Pr_2NEt greatly helped NHC catalysis.

Glorius and co-workers[113] recently reported three-component reactions based on a combination of NHC-catalysed benzoin synthesis and palladium-catalysed allylation (Scheme 49). This reactions gave good regio- and chemoselectivities.



	condition A	condition B
allyl acetate	1.0 equiv.	1.0 equiv.
$[Pd(allyl)Cl]_2$ **69**	0.5 mol-%	2.5 mol-%
PHOX ligand	1.25 mol-%	7.0 mol-%
NHC cat. **70**	5.0 mol-%	10 mol-%
DBU	1.0 equiv.	1.0 equiv.
temperature	r.t.	55 °C

Scheme 49. NHC-catalysed benzoin reactions in combination with Pd-catalysed allylations.

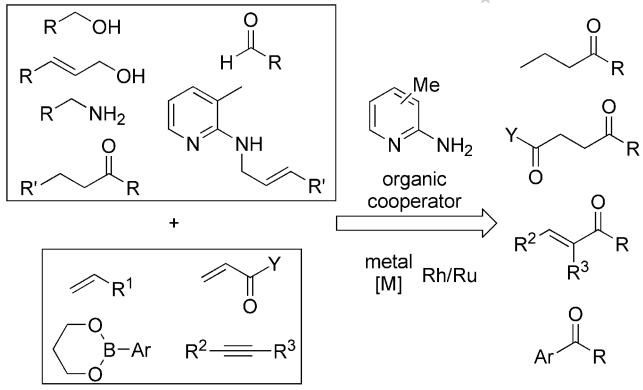
Enantioselective synthesis was briefly discussed, with the focus on the chiral ligands of the palladium complexes. Low enantioselectivities (26%) were observed with *i*Pr-PHOX ligand, BINAP, bisoxazolines and Trost's ligand.

7. Bifunctional Organocatalysts in Cooperation with Transition Metals

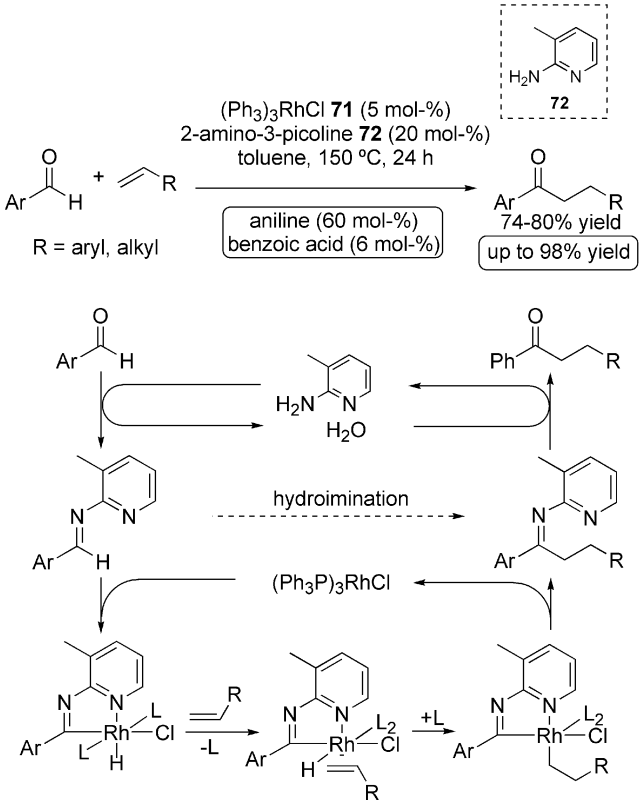
In the broad concept of combinations of organocatalysis and transition metal catalysis, another reaction path was the application of catalytically active organic molecules as ligands (Scheme 50). Some representative works were accomplished by Jun and co-workers.[114] 2-Aminopyridine derivatives were applied as effective dual function species to interact both with organic substrates and with transition metal catalysts.

As one typical example, in the presence of a rhodium complex and 2-amino-3-picoline, hydroacylation of alkenes with arylaldehydes proceeded smoothly and provided ketones as products in good to excellent yields (Scheme 51).

In the proposed mechanism, the arylaldehyde first underwent reversible condensation with the organic catalyst 2-amino-3-picoline, and the pyridine then coordinated with the Rh^I complex, which induced C–H cleavage and hydrometallation to form the Rh^{III} hydride complex. The alkene then came in to substitute one of the ligands, followed by reductive elimination to yield the ketimine, which was then



Scheme 50. Transition metal catalysis in cooperation with organocatalyst.



Scheme 51. Metal-organic cooperative hydroacylation of aldehydes.

hydrolysed to give the final product. Interestingly, addition of benzoic acid and aniline improved the yields to almost quantitative, which were interpreted in terms of imine ketone transformation acceleration.[115]

Some other related reactions, in which the role of the organic catalyst was believed to be essential, have also been well developed. Various transformations, including hydroacylation of alkenes[116] or alkynes[117] with aldehydes, hydroacylation of alkenes with alcohol[118] or amines,[119] and ketone exchange reactions,[120] have been intensely studied (Scheme 52).

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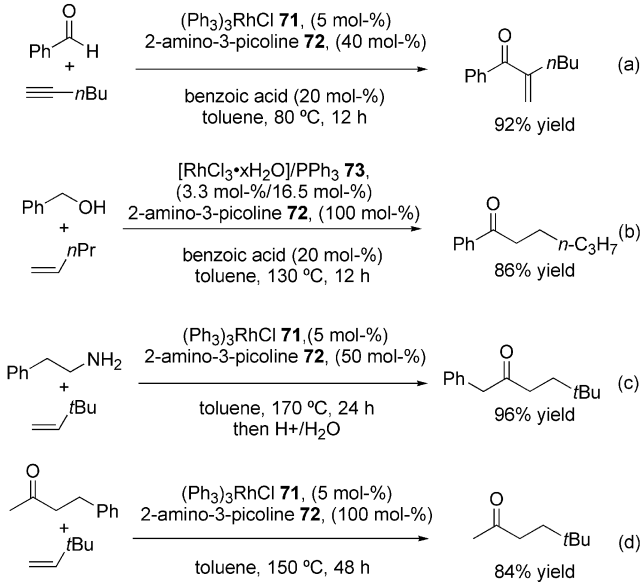

Scheme 52. Other representative reactions.

The previously discussed direct aldol reaction reported by Wang and co-workers[36] can also be considered within this category with application of a tridentate-ligand-tethered secondary amine as bifunctional catalyst.

Summary and Outlook

As illustrated and summarized in this microreview, the combination of organocatalysis and transition metal catalysis has successfully grown from its infancy into adolescence. With more and more unprecedented and valuable chemical transformations being found both in organocatalysis and in transition-metal catalysis, different combinations of these two are being examined. Interest is less in "newer" reactivities, but rather in upgraded understanding of the compatibility and complexity of the fused catalytic systems as one. More revolutionary discoveries combining organocatalysis and transition metal catalysis may be expected to amaze and further enlighten the organic synthesis community.

In nature, chemical catalysis represents a fascinating and complex set of systems in which different factors all precisely perform distinct but essential functions. With the astonishing advances in the combination of organocatalysis and transition metal catalysis, the boundaries delineating the emergent new horizon of catalytic chemical reactions are getting vague.

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