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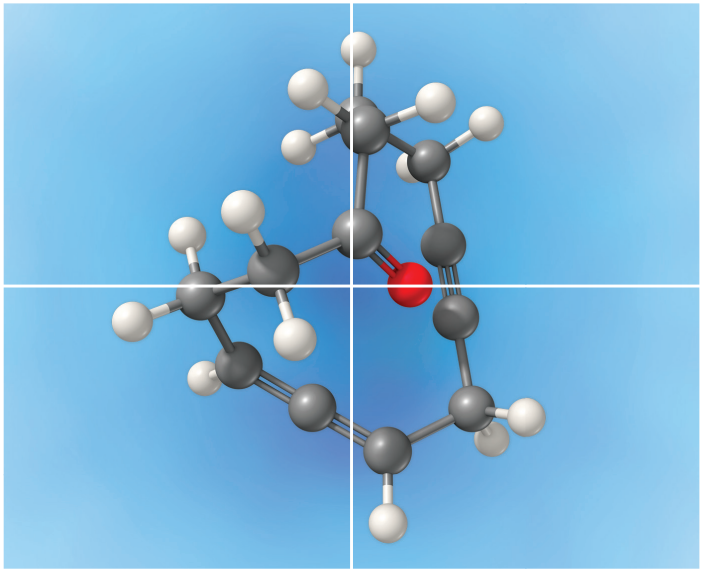

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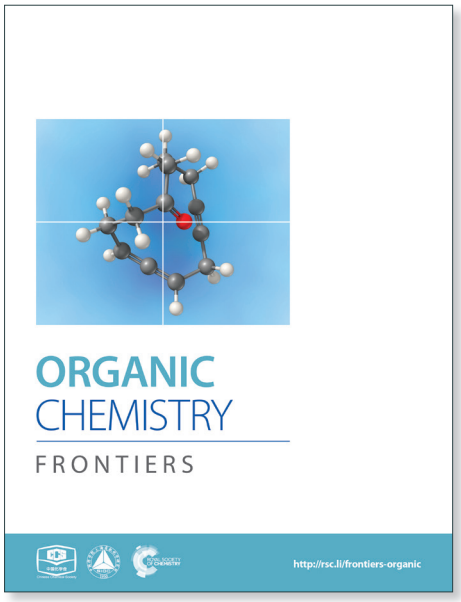

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ARTICLE

Metal-organo Catalysis: Cooperating Transition-metal Catalysis and Organocatalysis Through a Covalent Bond

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Asymmetric catalysis has grown rapidly and made considerable progress in last decades, but there still remain significantly unachievable reactions through either organocatalysis or transition-metal catalysis alone. The concept of combination transition-metal catalysis with organocatalysis was emerged as a powerful strategy for developing asymmetric catalysis, and has attracted great attention. In order to avoid the incompatibility existing in catalysts, substrates, intermediates and solvents through combining transition-metal catalysis and organocatalysis, it is urgently necessary to develop a new catalytic strategy to resolve these problems. Therefore, we are devoted to design a series of novel bifunctional catalysts based upon the synergistic activation strategy via cooperating transition metal-catalysis and organocatalysis through a covalent bond forming a bifunctional molecule. In this critical review, this momentous strategy is illustrated with several recent outstanding examples and prospectively promising application, with the aim of elaborating the synthetic utilities and potentialities of this concept as a powerful tool in organic synthesis.

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1. Introduction

Asymmetric catalysis has been regarded as one of the most fascinating approaches for construction of functionalized optically active compounds and played an important role in organic synthetic chemistry.[1] Asymmetric catalysis including enzyme catalysis, transition-metal catalysis and organocatalysis had obvious advantages over chiral pool synthesis and chiral auxiliary approaches (Scheme 1). Transition-metal catalysis and organocatalysis have been well established to allow lots of different organic reactions

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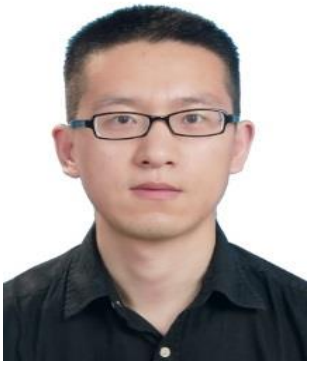
Xiu-Qin Dong was born in 1985. She received her B.S. degree from Huanggang Normal College in 2007, and a Ph.D. degree from the Wuhan University under the guidance of Professor Chun-Jiang Wang in 2012. After postdoctoral research (2012-2014) at Hong Kong University of Science and Technology in Prof. Jianwei Sun's group, she joined Wuhan University as an Associate Professor in 2015. Her research interests mainly focused on asymmetric metal-organo catalysis, hydroformylation, hydrogenation and the development of new synthetic methods for biologically active compounds.



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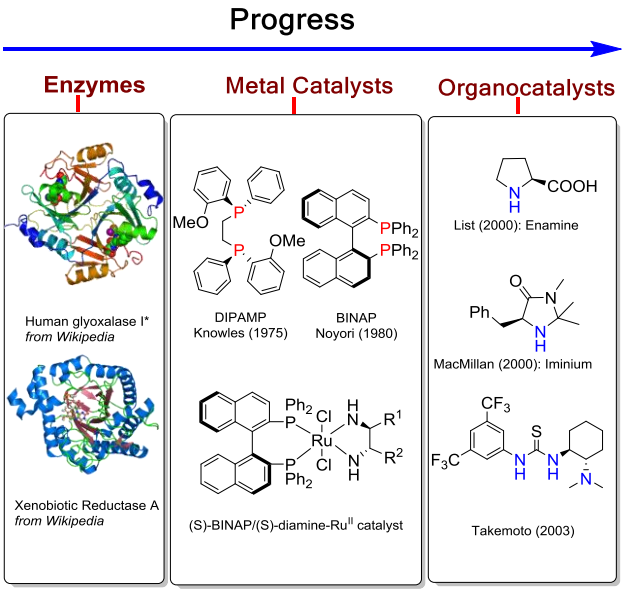
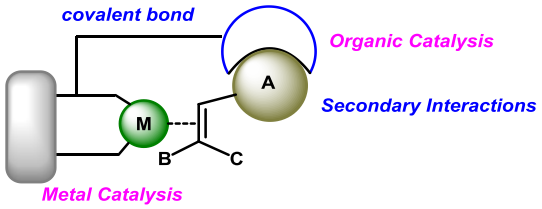


Scheme 1 Progress of asymmetric catalysis

serving as powerful tools in modern organic synthesis.[1] Since the initiative works in the 1960s,[2] asymmetric transition-metal catalysis has dominated the center of asymmetric synthesis for a long period and has received great success, mainly owing to development of privileged chiral ligands.[1] Asymmetric transition-metal catalysis has allowed the reactions through coordination between metal-ligand complex and substrates. On the other hand, organocatalysis has grown explosively to be recognized as one of the most promising research areas in current organic chemistry by the breaking work in the 1990s and early 2000s.[3] It can promote various organic transformations through distinct activation modes between catalysts and substrates, [4-12] such as, by forming enamine intermediates,[6] imine intermediates,[7] hydrogen-bond[11] and ion-pair complexes.[13] In general, transition-metal catalysis and organocatalysis owned their unique advantages. Transition-metal catalysis has enabled a broader scope of chemical transformations to participate in organic synthesis, while organocatalysis has permited a diverse range of functional groups to perform asymmetric reactions. However, there are still a lot of challenging transformations which can't be realized by either of these catalytic systems alone.

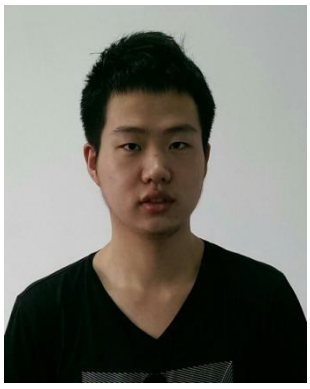


Scheme 2 Proposed activation modes of metal-organo catalysis

In recent years, the combination of transition-metal catalysis and organocatalysis as a promising strategy has been introduced to develop challenging and unprecedented transformations.[14] Some effective strategies such as cooperative catalysis,[15] synergistic catalysis,[16] sequential/relay catalysis[17] and supramolecular catalysis,[18] have been established. However, these strategies were hindered by the incompatibility of catalysts, substrates, intermediates and solvents. For example, the potential self-quenching of a Lewis basic amine and a Lewis acidic transition-metal may lead to catalyst inactivation.[19] Therefore, it is urgent to develop new resolution. A different and special strategy, wherein both activation modes of transition-metal catalysis and organocatalysis were incorporated into one single bifunctional molecule, could avoid these tough problems and catalyze the reactions smoothly through multiple activation modes (Scheme 2). In this review, we summarize recent some remarkable research results and illustrate its future promising wide applications in organic synthesis as a novel methodology.

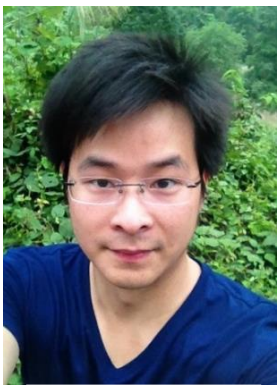
2. Recent advances

To the best of our knowledge, there are only a few reported examples of this powerful strategy of combining transition-metal catalysis with organocatalysis through a covalent bond.[20-26] Most of them were applied in asymmetric carbon-carbon bond-forming reactions, such as Aldol reaction, hydrocyanation of aldehydes reaction, inverse-electron-demand hetero-Diels-Alder reaction, nitro-Aldol reaction, hydrogenation reactions with high activities and selectivities. Early in 1986, Hayashi and co-workers have reported asymmetric Aldol reaction of isocyanoacetate with aldehydes



Pan Li

Pan Li was born in 1990. He obtained his B.S. degree (2012) at Zhejiang University of Technology. He started his Ph.D. under the guidance of Professor Xinquan Hu at the same university. As a visiting student of Xumu Zhang's group, his research work mainly focused on metal-organo catalysis and asymmetric hydrogenation.



Caiyou Chen

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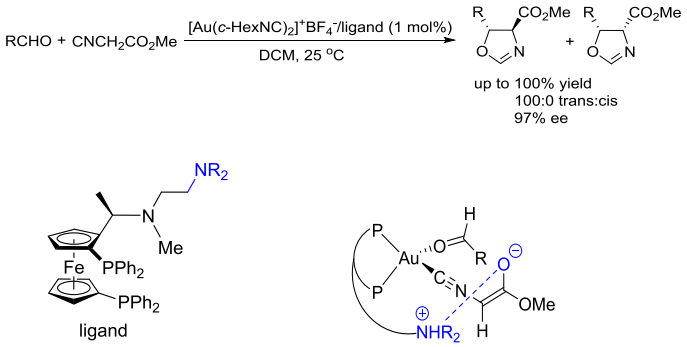
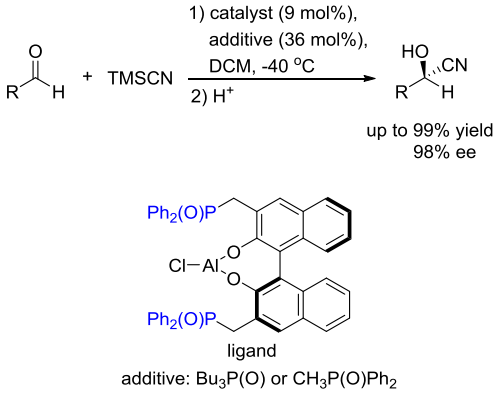


Scheme 3 Asymmetric Aldol reaction of isocyanoacetate with aldehyde



Scheme 4 Asymmetric hydrocyanation of aldehydes

catalyzed by chiral bifunctional ferrocenylphosphine-gold (I) complex, producing optically active 5-alkyl-2-oxazoline-4-carboxylates with excellent selectivities (Scheme 3).[20] The corresponding products are useful synthetic intermediates to access optically active 8-hydroxyamino acids and their derivatives. They proposed that the high efficiency of the bifunctional ferrocenylphosphine ligand was mainly ascribed to the dialkylamino group, which was at the end of the side chain. This secondary interaction participated in the formation of enolate of isocyanoacetate coordinated with gold.

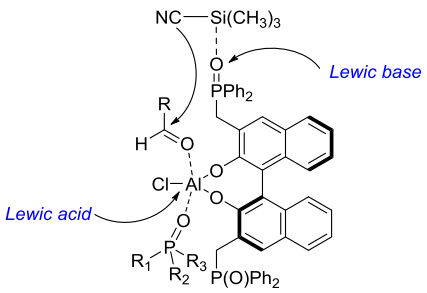
Unfortunately, this new catalytic strategy didn't attract people's attention for a long time. Until 1999, this concept was proceeded by Shibasaki's group through a new type of chiral monometallic and bifunctional phosphinoyl-containing catalysts.[21] It was successfully applied into the asymmetric hydrocyanation of aldehydes, which was able to coordinate both nucleophilic and electrophilic substrates through dual Lewis acid/Lewis base activation (Scheme 4). It was helpful to drastically improve the efficiency of asymmetric reactions with respect to the enantioselectivity and conversion rate. In this reaction system, the external additive phosphine oxide should coordinate with aluminum, thus converting the tetragonal Al (III) into a pentavalent center metal. As shown in Scheme 5, this geometry would allow the aldehyde to position itself at the apical side and close to the phosphine oxide of the ligand, and the trimethylsilylcyanide interacts with the Lewis base part of the chiral ligand. Both the aldehyde and trimethylsilylcyanide are coordinated to the bifunctional catalytic complex through dual Lewis acid/Lewis base activation. Subsequently, the attack of the cyanide to the aldehyde results in excellent enantioselectivities.

Ten years later, Wang and co-workers developed a novel class of primary amine-based enamine-metal Lewis acid cooperative bifunctional catalysts, and successfully applied them into asymmetric direct Aldol reactions with good to excellent stereoselectivities (Scheme 6).[22] It was worth noting that the coexistence of the secondary amine and metal Lewis acid is critical for the reaction. They speculated that the metal coordinated with chelating ligand to form a rigid chiral structure and acted as a Lewis acid to activate the aldehyde, and the secondary amine reacted with ketone to form an enamine. Then the enamine attacked the activated aldehyde from the *Re*-face to produce the desired products (Scheme 7).

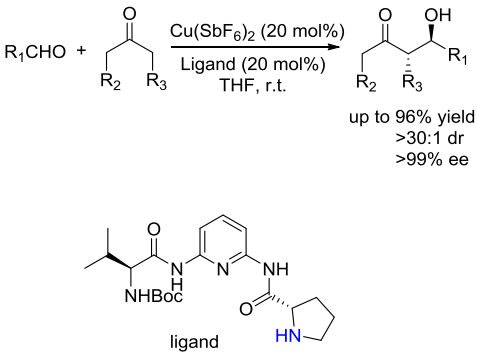
Subsequently, Wang's group successfully introduced the novel

Xumu Zhang

Xumu Zhang received his Ph.D. degree from Stanford University under the guidance of Professor James P. Collman in 1992. After two-year postdoctoral work at Stanford University, he joined the department of chemistry at The Penn State University as an Assistant Professor. In 1999, he was promoted to an Associate Professor. 2003-2007, he was appointed as a full professor. In 2007, he moved to The State University of New Jersey as a distinguished Professor. 2011-present, he was appointed as Professor (Thousand Talent Program) in Wuhan University. His research interests include the development of chiral phosphine ligands for asymmetric reactions and ligands for hydroformylation, hydrogenation of esters, copolymerization reactions.



Scheme 5 Mechanism of Lewis acid/Lewis base catalysis



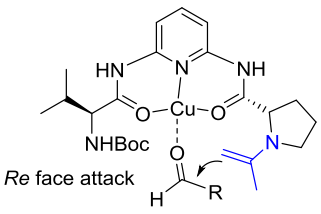
Scheme 6 Asymmetric direct Aldol reaction

concept of enamine/metal Lewis acid bifunctional catalysis into challenging asymmetric inverse-electron-demand hetero-Diels–Alder reaction, providing chiral dihydropyran derivatives bearing stereochemically well-controlled quaternary carbon center products with highly chemo- and enantioselectivities (Scheme 8).[23]

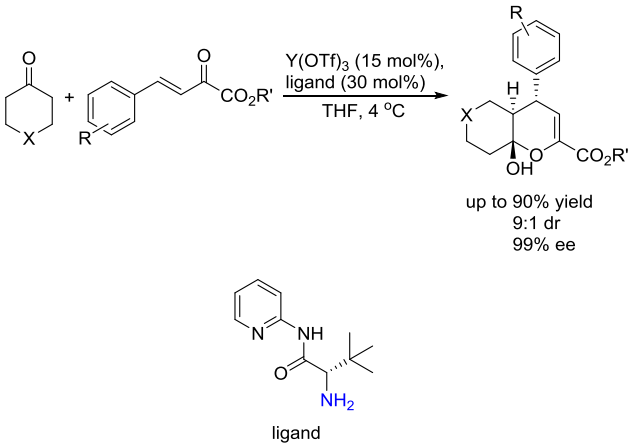
The strong activation of the activated enone through chelation with the metal and intramolecular nature of the bifunctional catalyst was helpful to obtain high activities and stereoselectivities. As shown in Scheme 9, the proposed transition state matched well with the relative stereochemistry bearing an *endo*-selective mode of the reaction. In addition, the sterically hindered R (tert-butyl) group shielded the *Re* face of the enamine, thus the activated enone tended to attack from the *Si* face, contributing for the absolute configuration of the final products.

And then a new type of cooperative catalyst featuring urea H-bonds and a cobalt center has been developed for *anti*-selective asymmetric nitro-Aldol reactions. In 2012, Hong's group has developed high *anti*-selective asymmetric nitro-Aldol reactions catalyzed by a cooperative catalyst bearing bisurea H-bonding and salen-Co (III) (Scheme 10).[24] The urea-cobalt bifunctional catalytic system successfully extended the substrate scope of *anti*-selective nitro-Aldol reactions to previously unexplored aldehydes, and the synthetic utility is demonstrated by the concise asymmetric synthesis of (*1R, 2S*)-methoxamine hydrochloride. The urea H-bonds played an important role in the impressive improvement of reaction activities and selectivities.

In 2013, our group developed a series of novel chiral bisphosphine-thiourea ligand based on the concept of combining transition-metal catalysis with organocatalysis into a bifunctional molecule. We have successfully applied them into Rh-catalyzed



Scheme 7 Proposed reaction transition state

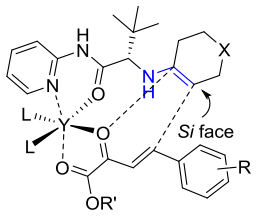


Scheme 8 Asymmetric inverse-electron-demand hetero-Diels–Alder reaction

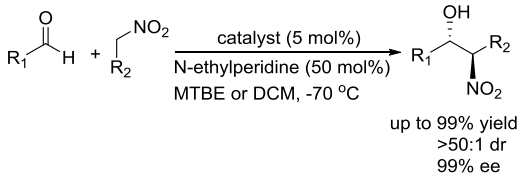
asymmetric hydrogenation of challenging various β,β-disubstituted nitroalkenes with excellent enantioselectivities (Scheme 11).[25] The thiourea backbond played a remarkable role in this catalytic system through forming hydrogen bonding with nitro group to activate substrate. As a result, the sensitive nitro group was reserved without hydrogenation.

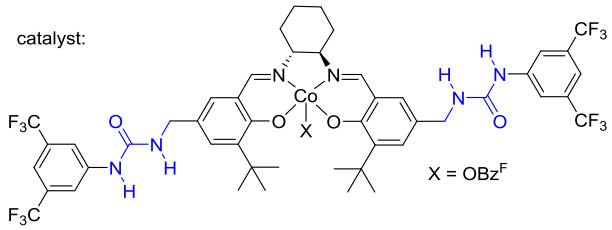
It is generally known that thiourea unit was widely used as a hydrogen bonding donor in organocatalysis.[26] In addition, some research work took advantage of its anion binding of ion-pairing intermediates.[27] Inspired by the strategies developed in organocatalysis[28-30] and our previous research work about Rh-bisphosphine-thiourea catalytic system for asymmetric hydrogenation of β,β-disubstituted nitroalkenes,[25] our group made efforts to broaden anion-binding interaction into the transition-metal-catalyzed asymmetric hydrogenation. We envisioned that thiourea block could interact with a counterion in the catalytic system (Scheme 12).

Then we successfully developed asymmetric hydrogenation of unprotected NH imines catalyzed by Rhodium/bis(phosphine)-thiourea for the first time (Scheme 13).[31] The corresponding chiral amines products were obtained in high yields and enantioselectivities. We proposed that the anion-binding interaction between the thiourea and chloride counterion played a crucial role in the catalytic system based on the control experiments and ^{1}H NMR studies.



Scheme 9 Proposed reaction transition state



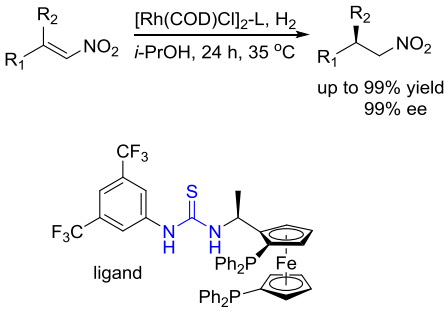


Scheme 10 Asymmetric nitro-Aldol reaction

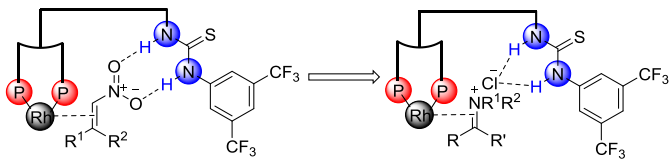
3. Catalyst Design and Applications

Catalyst is the core of chemical transformations, so it is greatly important to design appropriate catalysts. Inspired by the previous excellent research results, it is extremely critical to develop novel bifunctional catalysts through synergistic activation strategy via cooperating transition-metal catalysis and organocatalysis with a covalent bond. The metal unit and organic unit works cooperatively to promote many types of unprecedented transformations. Generally, metal catalysts can offer high activities in hydrogenation and other carbon-carbon bond forming reactions, the organic motif can achieve excellent selectivities through secondary interactions providing an excellent directing induction.

Chiral metal catalysts bearing monophosphine, biphosphine, amino alcohol, oxazoline, or salen ligands et.al are powerful for a variety of asymmetric reactions. The great catalytic potential of these catalysts can be enhanced by introducing organic motif to provide secondary interactions between substrates and organic motif. Until now many types of organocatalysts have been developed, such as chiral amines, thioureas, squaramides, phosphoric acids. Combining these kinds of organic motif with transition-metal catalysts will produce a tremendous amount of metal-organo catalysts forming a catalytic library (Scheme 14).



Scheme 11 Asymmetric hydrogenation of challenging β, β-disubstituted nitroalkenes

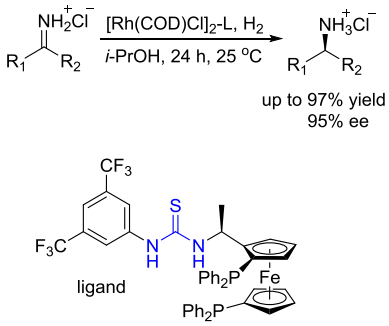


Scheme 12 Activation model of thiourea block

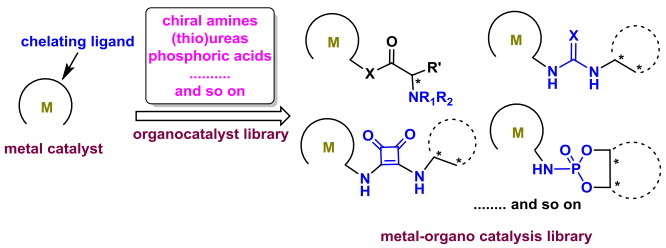
We believe this new catalytic concept will enable unprecedented transformations with excellent activities and selectivies, and be efficient to resolve some challenging problems. These new catalytic systems will be applied to develop highly enantioselective asymmetric reactions, such as hydrogenation reaction, asymmetric allylic alkylation (AAA), Michael addition, Aldol reaction, Mannich reaction and Henry reaction et.al. In the future, the novel bifunctional catalysts through synergistic activation strategy via cooperating transition-metal catalysis and organocatalysis with a covalent bond will occupy a special place in organic chemistry and it is extremely necessary to be explored.

4. Conclusion

The new research direction of combining metal catalysis with organocatalysis has emerged as a powerful tool for challenging and unprecedented transformations. Up to now, some effective strategies have been developed, such as cooperative catalysis,[15] synergistic catalysis,[16] sequential/relay catalysis[17] and supramolecular catalysis.[18] However, there are always existing incompatibility of catalysts, substrates, intermediates and solvents. A different strategy is needed to avoid these problems and promote the transformations through multiple activation modes. Several groups made use of single bifunctional molecule combining activation modes of metal catalysis and organocatalysis to efficiently resolve these problems. In this critical review, we summarize some recent remarkable examples and propose a library of bifunctional catalysts backbone combining activation modes of transition-metal catalysis and organocatalysis through a covalent bond. In the near future, they will be widely applied into asymmetric reactions, such as asymmetric allylic alkylation (AAA), Michael addition, Aldol reaction, Mannich reaction and Henry reaction. We believe this momentous strategy will become a powerful tool in organic synthetic chemistry.



Scheme 13 Asymmetric hydrogenation of unprotected NH imines



Scheme 14 Proposed metal-organo catalysis library

Acknowledgements

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