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Catalytic Asymmetric Reactions by Metal and Chiral Phosphoric Acid Sequential Catalysis

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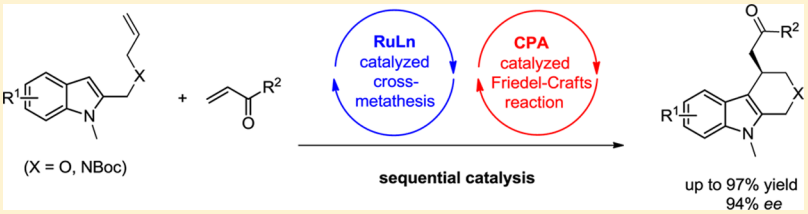


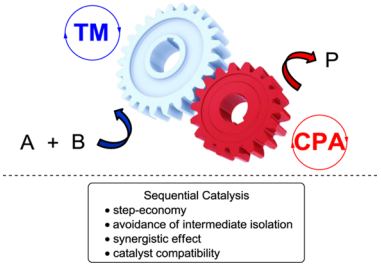
ABSTRACT: Catalytic asymmetric reactions promoted by metal catalysts and chiral phosphoric acids have become useful processes for the preparation of structurally diverse and complex organic compounds. This JOCSynopsis provides an overview of the most recent developments made in studies of these reactions. The paper focuses mainly on sequential catalysis and relay catalysis, which are accomplished by employing a combination of metal complexes and chiral phosphoric acids.

Over the past few decades, asymmetric catalysis has become an extremely important topic in the field of synthetic organic chemistry.[1] Although arguments remain about the superiority of metal catalysis and organocatalysis, increasing efforts have been given to a synergistic combination of these two strategies.[2] In addition to simplifying experimental operations by employing a one-pot tactic, tandem asymmetric processes can be used to promote unprecedented reactions.[3] In this regard, chiral phosphoric acids have shown great promise as organocatalysts that operate synergistically with metal catalysts. Since the initial pioneering reports on their use as organocatalysts by Terada et al. and Akiyama et al.,[4] chiral phosphoric acids have become privileged catalysts in that they promote numerous, exceptionally efficient and stereocontrolled asymmetric reactions.[5] Soon after the initial reports, many new asymmetric reactions, invloving dual catalytic systems consisting of chiral phosphoric acids and metal complexes, have been developed. Owing to rapid progress that has been made of this area, several elegant reviews have been prepared describing processes promoted by a combination of chiral phosphoric acids with metal complexes.[6]

Depending on the role played by the chiral phosphoric acid, the reactions can be classified as relay catalysis, sequential catalysis, cooperative catalysis, and anion catalysis. Sequential and relay catalysis are basically the same concept in which chiral phosphoric acid catalyzed asymmetric process employs a substrate (or an intermediate) generated in situ by a metal-catalyzed transformation. The advantages of sequential catalysis include the utilization of simpler substrates offered by the programmed catalysis, the avoidance of reaction intermediate isolation, and the discovery of unprecedented reactions that are not possible a single catalyst alone is employed. In many cases, synergistic effects can be observed between the two catalytic reactions. This feature results in a much more efficient cascade process compared to one that depends on a simple sum of the outcomes of two individual reactions. At the same time, challenges exist in designing synergistic processes, such as those associated with the compatibility of two catalysts and interference with the step controlling enantioselectivity by the other catalyst.

In this Review, we provide an overview of sequential (relay) catalysis involving a combination of metal complexes and chiral phosphoric acids which act as catalysts for two different reactions in the cascade (Scheme 1). The presentation follows a format that is based on the type of metal present in the metal complex component of the catalytic system.

Scheme 1. Sequential (Relay) Catalysis



SEQUENTIAL CATALYSIS WITH RUTHENIUM AND IRIDIUM COMPLEXES

In 2008, Sorimachi and Terada reported an unprecedented use of relay catalysis to promote Friedel–Crafts alkylation reactions of electron-rich aromatic compounds with iminium ion intermediates derived from readily available allylamides.[7] As shown in Scheme 2 (top), in these processes a three-step sequential

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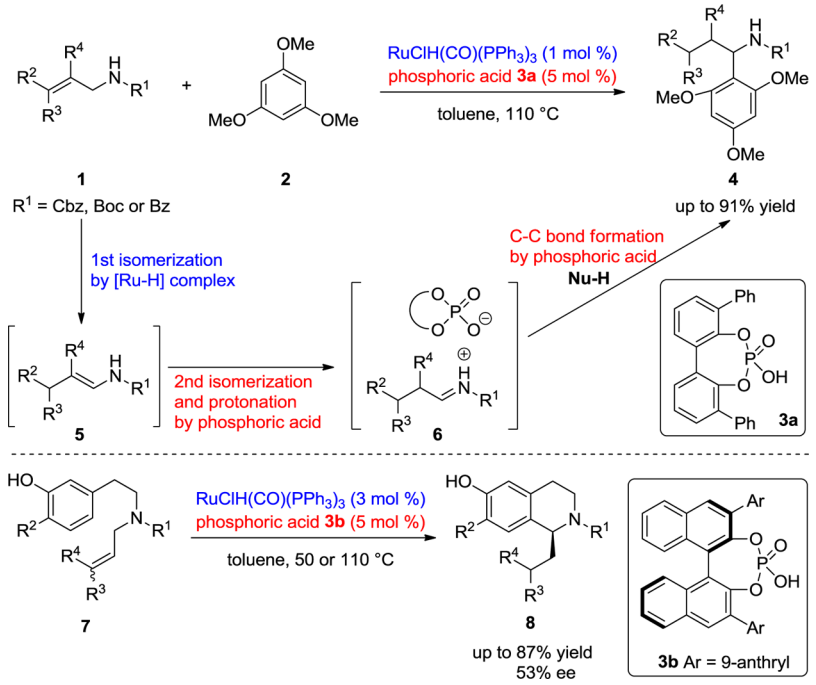
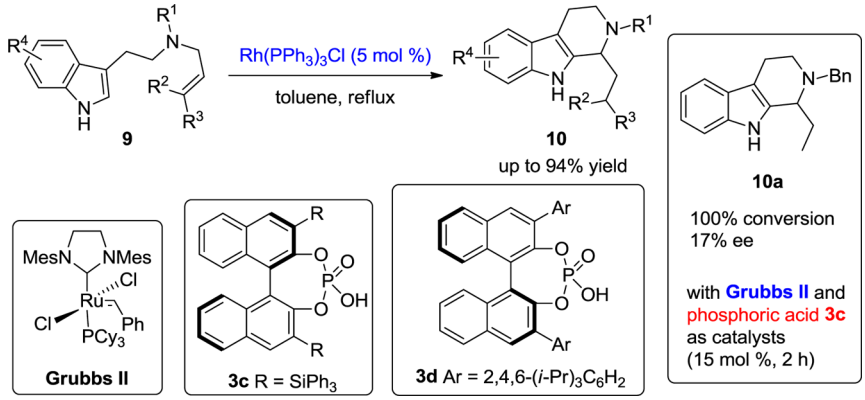
Scheme 2. Ru/Phosphoric Acid Catalyzed Isomerization of Allylamides and Friedel–Crafts Alkylation Reactions



Scheme 3. Ru/Phosphoric Acid Catalyzed Olefin Isomerization and Pictet–Spengler Reactions



transformation takes place involving (1) Ru-catalyzed isomerization of allylamides **1** to form enamides **5**, (2) phosphoric acid catalyzed isomerization of enamides **5** to generate reactive iminium ion intermediates **6**, and (3) phosphoric acid catalyzed Friedel–Crafts alkylation. Although only the racemic version of the process was explored originally, its unique features stimulated numerous follow-up studies probing asymmetric counterparts. Very recently, Toda and Terada reported an enantioselective version of this cascade reaction in which *N*-protected *m*-tyramine derivatives **7** are converted to the chiral tetrahydroisoquinolines **8** using the relay catalysis by $RuClH(CO)(PPh_3)_3$ and chiral phosphoric acid **3b** (bottom, Scheme 2).[8,9]

A protocol that takes advantage of Rh- or Ru-catalyzed isomerization of allylic amines to form enamines and the subsequent isomerization of enamines to generate iminium ions, which undergo subsequent phosphoric acid promoted Pictet–Spengler reactions, has been developed by Nielsen and co-workers.[10,11] This strategy was used to prepare 1,2,3,4-tetrahydro-ß-carbolines **10** from *N*-allyltryptamines **9** in excellent yields (Scheme 3). Moreover, the results of preliminary studies showed that an enantioselective version of this process occurs when chiral phosphoric acids are utilized. As shown in Scheme 3, **10a** was produced in 17% ee when chiral phosphoric acid **3c** was employed. In a later effort, it was observed that the use of the dual catalytic system composed of $RuClH(CO)(PPh_3)_3$ and chiral phosphoric acid **3d** leads to an improved level of enantiocontrol (57% ee).[12]

In 2013, You and co-workers devised an efficient method for enantioselective synthesis of 1,2,3,4-tetrahydro-*β*-carbolines **12** from *N*-allyltryptamines **11** that employs a combination of the Hoveyda–Grubbs II catalyst and chiral phosphoric acid **3e** (Scheme 4).[13] High levels of stereocontrol (up to 90% ee) attend this sequential catalytic reaction.

Recently, Scheidt and co-workers developed a tandem catalytic isomerization/Prins-type cyclization reaction that produces three types of pyran-fused indole derivatives (Scheme 5).[14] By using this method and 5 mol % of chiral phosphoric acid **3f**, pyran-fused indole **15** is generated in 60% ee.

In addition to catalyzing carbon–carbon double-bond isomerizations, Ru complexes also promote cross-metathesis (CM) reactions as part of tandem processes associated with other transformations. However, asymmetric CM reactions are less

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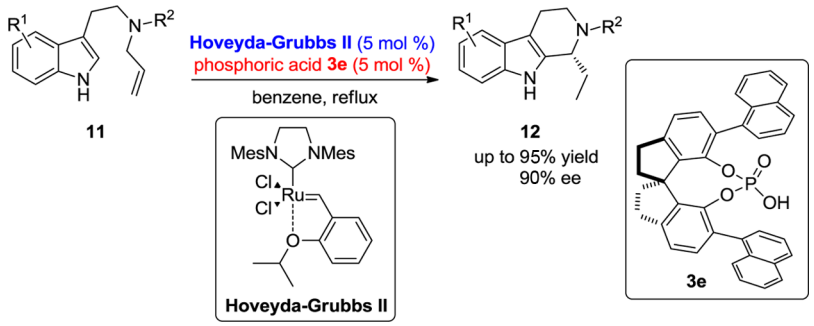
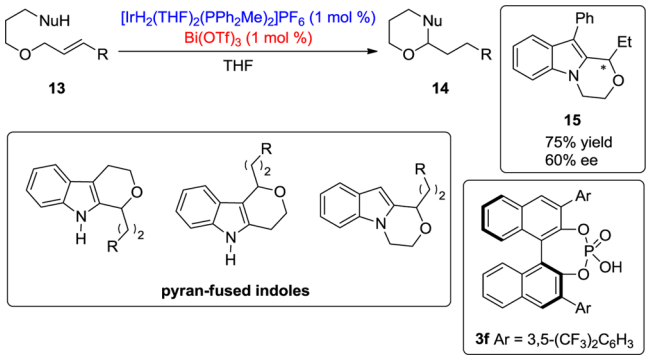
Scheme 4. Ru/Phosphoric Acid Catalyzed Olefin Isomerization and Pictet–Spengler Reactions



Scheme 5. Ir/Phosphoric Acid Catalyzed Olefin Isomerization and Prins-Type Reactions



explored owing to the general absence of chiral Ru catalysts. As a result, asymmetric tandem processes in which CM reactions are used require that one or more of the other steps be promoted by chiral catalysts. An example of this feature is found in the 2009 report by Xiao and co-workers of an elegant Ru-catalyzed tandem cross-metathesis/intramolecular hydroarylation sequence.[15] In addition, in 2009, You and co-workers developed an enantioselective method for construction of polycyclic indoles through sequential catalysis employing a chiral phosphoric acid.[16] This tandem process is composed of a Ru-catalyzed cross-metathesis reaction and a chiral phosphoric acid catalyzed Michael addition reaction. An aza-Michael version of this method has been applied to the synthesis of enantioenriched indole derivatives **21** (bottom, Scheme 6).[17,18]

In 2013, Yu and co-workers described an application of sequential olefin cross-metathesis and aza-Michael addition to the synthesis of 2-substituted pyrrolidines (top, Scheme 7).[19] At almost the same time, You and co-workers reported the use of sequential catalysis involving olefin cross-metathesis and oxa-Michael for the synthesis of benzofurans (**25**, X = CH_2) as well as benzoxazine derivatives [**25**, X = $N(CH_2Ar)CH_2$, bottom, Scheme 7].[20]

A sequential catalytic process, involving cross-metathesis catalyzed by a Ru complex and the isomerization of carbon–carbon double bond isomerization catalyzed by chiral phosphoric acid was described by You in 2012 (top, Scheme 8).[21] Later, the same group described a three-step catalytic sequence consisting of cross-metathesis, phosphoric acid catalyzed double-bond isomerization, and *N*-alkylation for synthesis of indole-substituted pyrrolidones **30** (bottom, Scheme 8).[22,23] This sequence, starting with *N*-allyl-*N*-benzylacrylamide **28** and various indoles and using **Zhan-1B** and chiral phosphoric acid **3i** as catalysts, generates **30** in satisfactory yields and enantioselectivities.

Reduction–oxidation (redox) reactions are among the most common processes employed in synthetic organic chemistry. A subclass of these reactions involves disproportionation, in which the starting material is both reduced and oxidized. In general, this type of process lacks atom economy if the reduction product is the target compound. However, more interesting convergent disproportionation reactions (top, Scheme 9) are ones in which the starting material undergoes disproportionation to give the desired reduction product and the undesired oxidation product reforms the starting material for the next redox cycle in the presence of a reductant. Using this strategy, Zhou and co-workers devised a Ru/phosphoric acid sequential catalytic system for highly efficient and enantioselective hydrogenation reactions of quinoxalines (bottom, Scheme 9).[24] With hydrogen gas as the terminal reductant and Ru as the catalyst, quinoxaline **31** is reduced to form dihydroquinoxaline **33**, which is then transformed to the chiral tetrahydroquinoxaline **32** in a subsequent self-transfer hydrogenation reaction. Good to excellent levels of enantioselectivity accompany this process owing to the fact that the rate of chiral phosphoric acid **3j** catalyzed self-transfer hydrogenation (k_2) is higher than that the one catalyzed by Ru (k_3).

In the past decade, Hantzsch esters have become popular hydrogen donors in transfer hydrogenation reactions. However, the atom economy for these reactions is generally low owing to the requirement of stoichiometric amounts of these esters and the fact that stoichiometric amounts of pyridine type byproducts are generated. In 2011, Zhou and co-workers developed a method which relied on Ru-catalyzed regeneration of Hantzsch ester **36** from Hantzsch pyridine **36′** (Scheme 10).[25] In the new sequential catalysis process, chiral phosphoric acid promotes reduction of benzoxazinones **34** in the presence of catalytic amounts of in situ regenerated Hantzsch ester **36**. The success of this cycle results from the fact that benzoxazinones are not hydrogenated under the Ru catalytic conditions but are readily reduced under chiral phosphoric acid-catalyzed transfer hydrogenation conditions.

In 2012, Zhou and co-workers developed dihydrophenanthridine **43** as a novel and highly efficient hydride donor for the transfer hydrogenation process (top, Scheme 11).[26] Because mild conditions are used to promote reactions involving **43**, the substrate scope of the process is expanded to include benzoxazines **37**, quinoxalines **39**, and quinolines **41**. Interestingly, when the different reductants (Hantzsch ester **36** or dihydrophenanthridine **43**) are employed, products with opposite configuration are generated. This difference is possibly related to the different nature (1,2 for **43** and 1,4 for **36**) of the hydride-transfer processes. Recently, the same group developed other processes that utilize novel, efficient and tunable hydrogen sources and applied them

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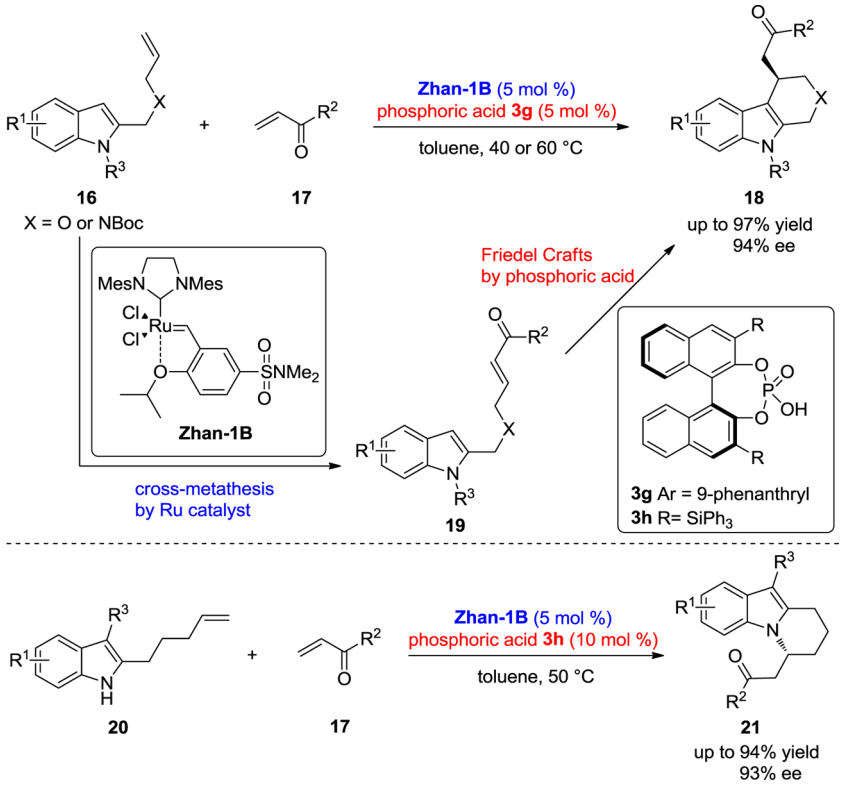
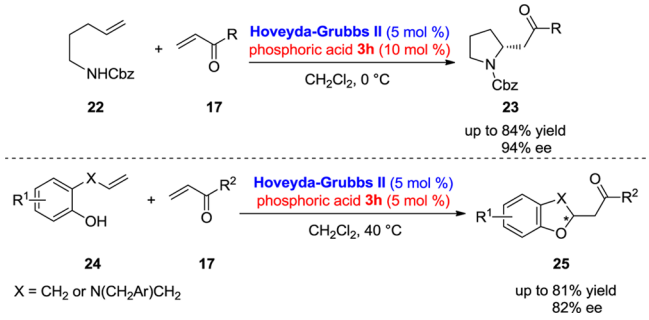
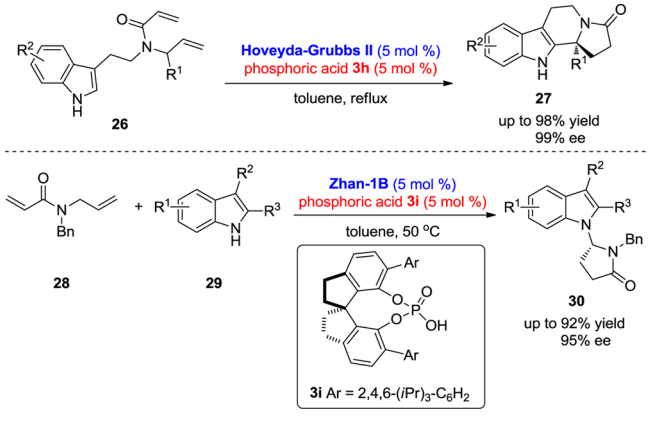
Scheme 6. Ru/Phosphoric Acid Catalyzed Cross-Metathesis and Michael Addition Reactions



Scheme 7. Ru/Phosphoric Acid Catalyzed Cross-Metathesis and Aza(Oxa) Michael Addition Reactions



Scheme 8. Ru/Phosphoric Acid Catalyzed Ring-Closing-Metathesis and Pictet−Spengler (Mannich) Reactions



to new asymmetric transfer hydrogenation reactions (bottom, Scheme 11).[27]

SEQUENTIAL CATALYSIS WITH RHODIUM AND PALLADIUM COMPLEXES

The combination of metal and chiral phosphoric acid catalysis is also applicable to the promotion of multicomponent reactions (MCRS). In 2008, Hu, Gong, and co-workers reported the first asymmetric three-component reaction taking place by cooperative catalysis by $Rh_2(OAc)_4$ and a chiral phosphoric acid (top, Scheme 12).[28] The authors proposed a pathway for formation of β-amino-α-hydroxyl acid derivatives **48** that involves initial reaction of diazoacetates **45** with Rh to form Rh carbene complexes **49**, which then react with alcohols **46** to give the oxonium ylide intermediates **50** or **50′**. The iminium salts **51**, formed by reaction of imines **47** with chiral phosphoric acid **3m**, then undergo Mannich reaction with **50** (or **50′**) through transition states **52** to form **48**. This process forms β-amino-α-hydroxyl acid derivatives **48** in excellent yields and high levels of stereocontrol. By employing this strategy, Hu and co-workers showed that the three-component reaction is general and can be used to generate β-amino-α-hydroxyl acid derivatives[29−31] (bottom, Scheme 12).

In 2008, Hu and co-workers expanded their studies of asymmetric cooperative catalysis in order to develop a new four-component process (top, Scheme 13).[32] In this approach, imines utilized in a previous effort,[28] formed in situ from aldehydes **54** and amines **55**, react to yield **48**, the same product produced previously from less readily available starting materials. Chiral phosphoric acid **3h** plays a dual role in the process by both controlling the stereoselectivity of the final Mannich reaction and catalyzing imine formation. Later, Hu and co-workers developed a new four-component reaction, and recently, the same group

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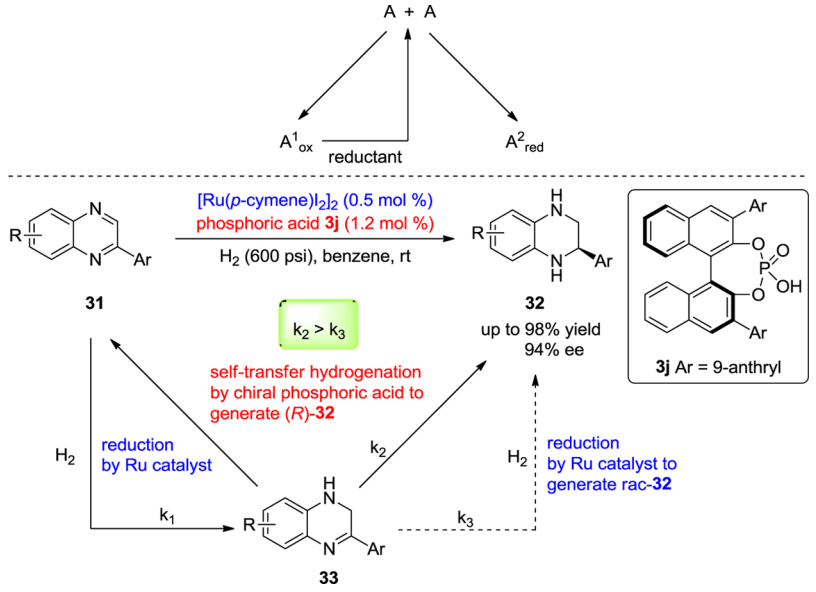
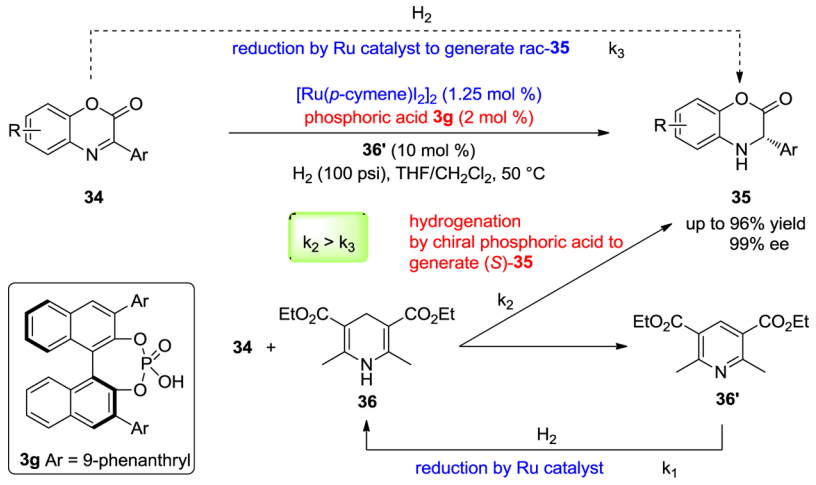
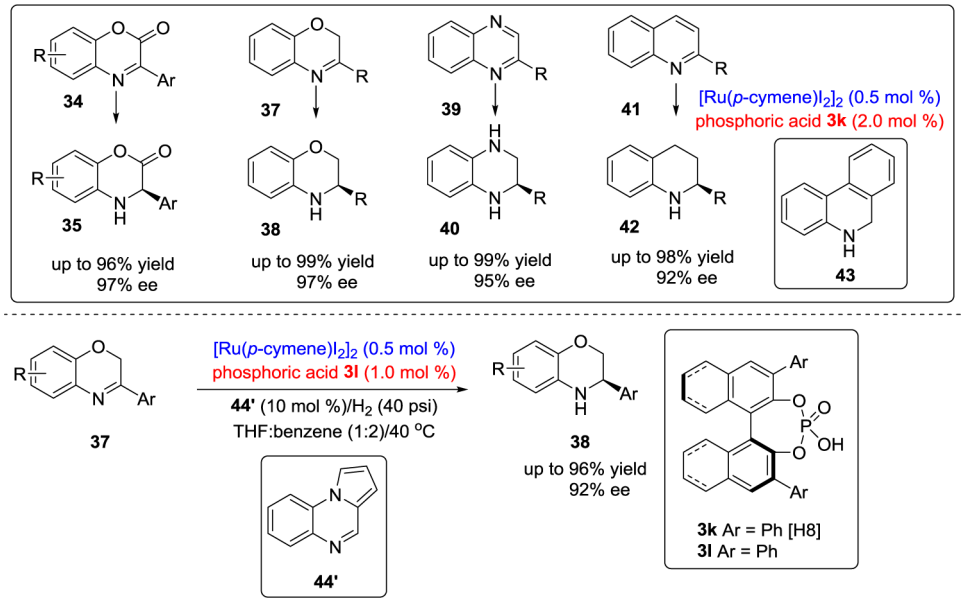
Scheme 9. Ru/Phosphoric Acid Catalyzed Hydrogenation and Self-Transfer Hydrogenation Reactions



Scheme 10. Ru/Phosphoric Acid Catalyzed Hydrogenation and Transfer Hydrogenation Reactions with Hantzsch Ester



Scheme 11. Ru/Phosphoric Acid Catalyzed Hydrogenation and Transfer Hydrogenation Reactions with Novel Hydride Sources



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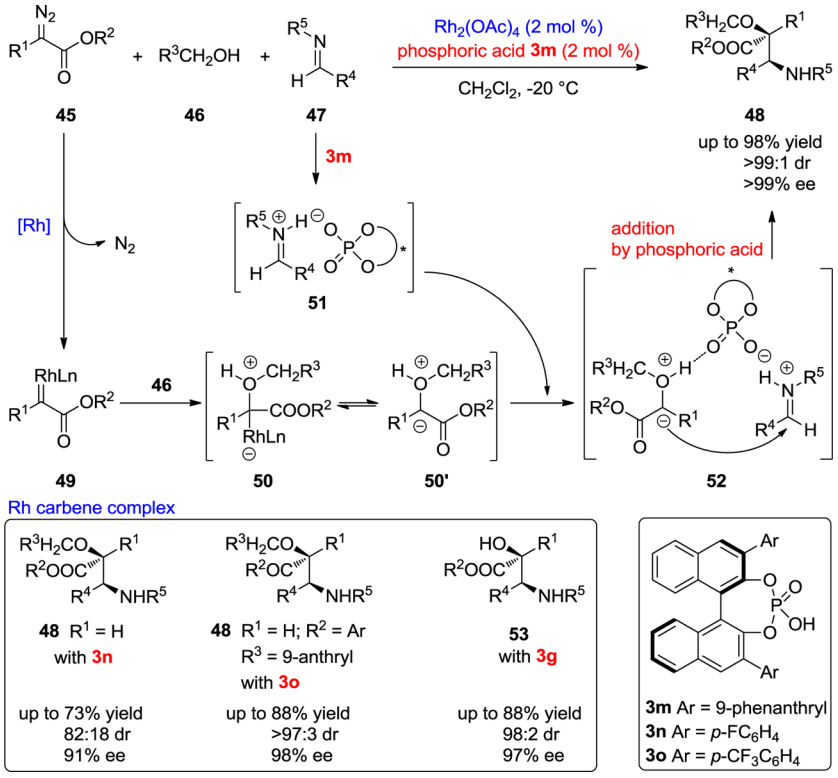
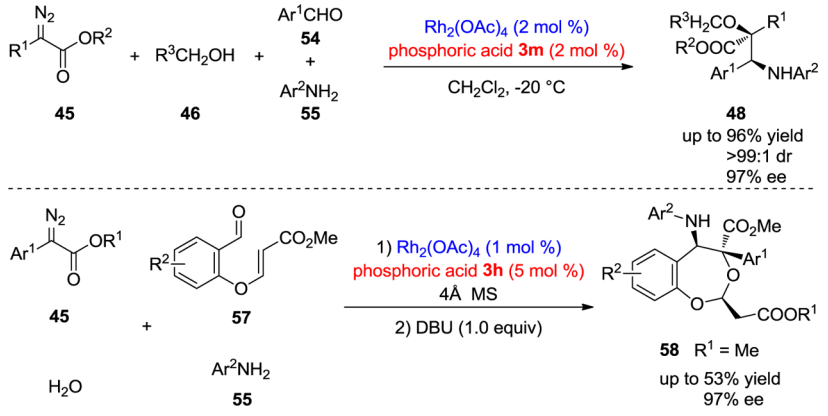
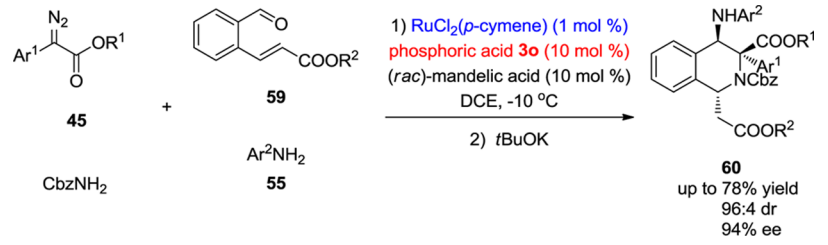
Scheme 12. Rh/Phosphoric Acid Catalyzed Three-Component Reactions



Scheme 13. Rh/Phosphoric Acid Catalyzed Four-Component Reactions



Scheme 14. Ru/Phosphoric Acid Catalyzed Four-Component Reactions



expanded the scope of the process.[33,34] In the sequence, shown in Scheme 13 (bottom), a base-promoted oxa-Michael addition cooperates with Rh-catalyzed oxonium ylide formation, and oxonium ylide trapping by an imine yields the seven-membered ring products **58.**

In addition to Rh complexes, Ru complexes also participate in four-component cascade Mannich/aza-Michael addition reactions with the cooperation of chiral phosphoric acids.[35] As shown in Scheme 14, multisubstituted tetrahydroisoquinolines **60** bearing a quaternary stereogenic carbon are obtained by using the synergistic catalytic system.

In 2011, by using a cooperative catalysis strategy, Hu and co-workers were able to generate and trap unstable and highly reactive secondary protic ammonium ylides.[36] As shown

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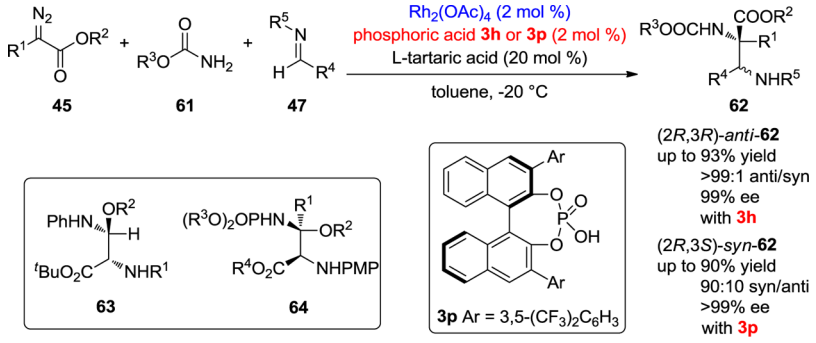
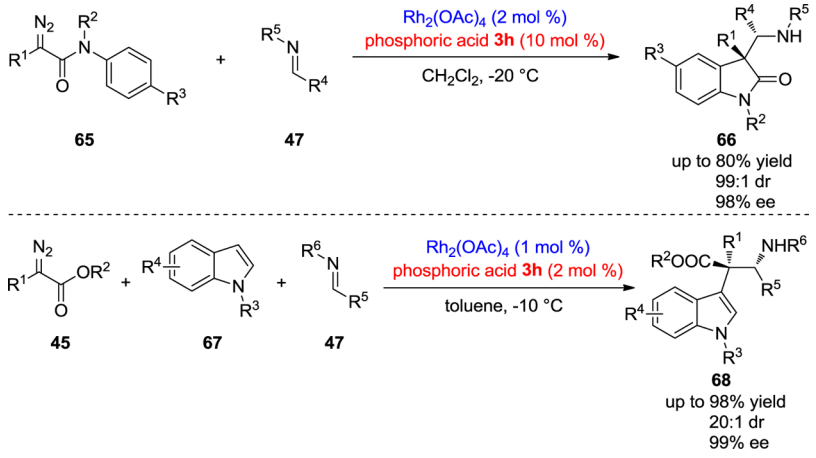
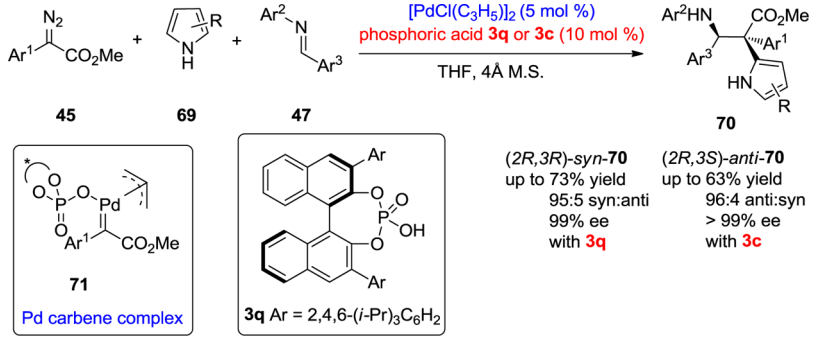
Scheme 15. Rh/Phosphoric Acid Catalyzed Three-Component Reactions



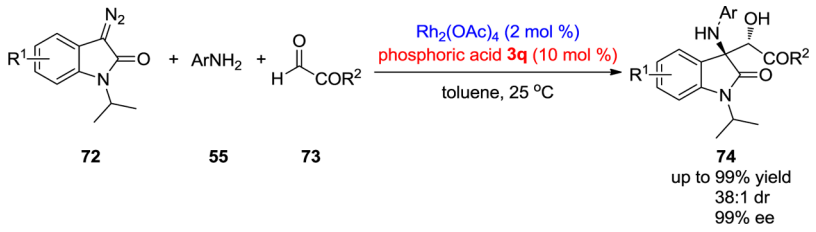
Scheme 16. Rh/Phosphoric Acid Catalyzed Multicomponent Reactions in Which Aromatic Compounds Act as Nucleophiles



Scheme 17. Pd/Phosphoric Acid Catalyzed Three-Component Reactions



Scheme 18. Rh/Phosphoric Acid Catalyzed Three-Component Reactions



in Scheme 15 (top), the presence of a chiral phosphoric acid increases the reactivity of imine **47**, not only by inhibiting the undesired 1,2-proton transfer process but also by providing excellent control of enantioselctivity. Notably, varying chiral phosphoric acids enables preparation of all four stereoisomers of the products. Therefore, this process serves as a brand new method to synthesize enantiopure biologically important *α,β*-diamino acid derivatives **62**. Very recently, this protocol has been employed to prepare enantiomerically pure *α,β*-bis(arylamino) acid derivatives **63**[37] and 2,3-diaminosuccinic acid derivatives **64**[38] (bottom, Scheme 15).

Besides alcohols and amines, aromatic compounds have also been employed as nucleophiles in well-designed cascade reactions. In 2012, Hu and co-workers designed efficient

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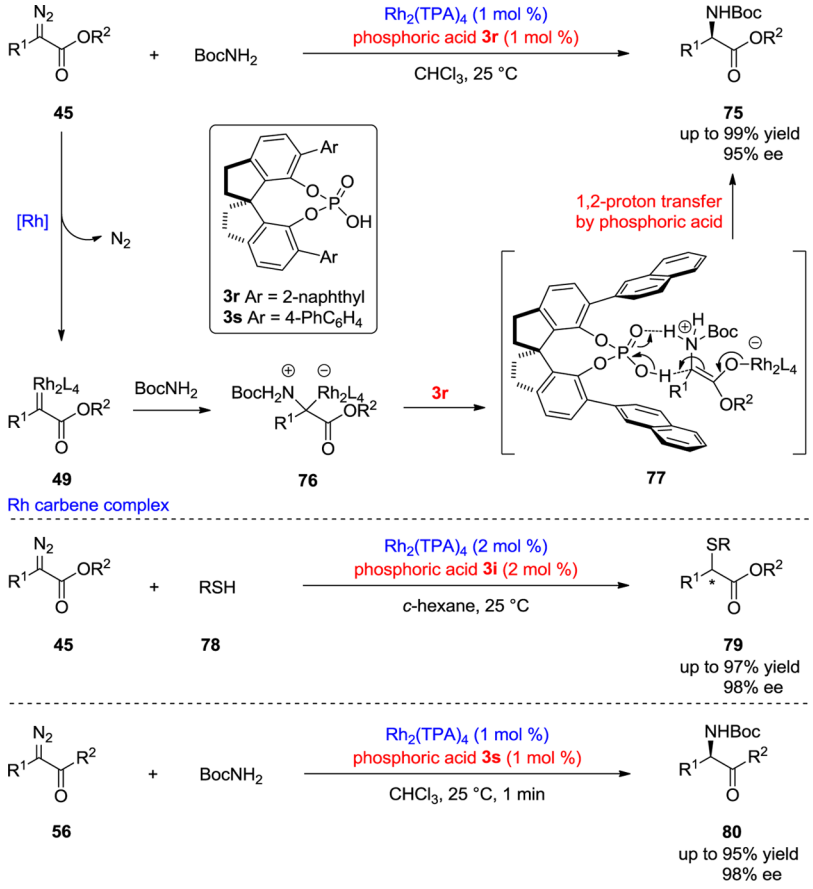
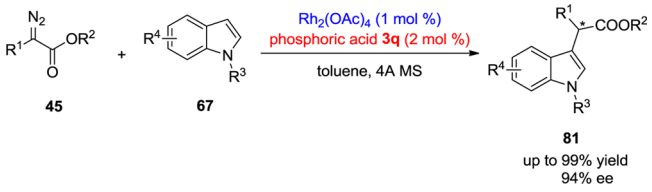
Scheme 19. Rh/Phosphoric Acid Catalyzed X−H Insertion Reactions



Scheme 20. Rh/Phosphoric Acid Catalyzed C−H Insertion Reactions



intramolecular and intermolecular protocols to synthesize oxindole and indole derivatives (Scheme 16).[39] The processes serve as single-step approaches to access polyfunctionalized products in excellent yields and stereoselectivities.

Recently, Hu and co-workers developed a new multicomponent reaction that produces α-pyrrole substituted β-amino acid esters and utilizes pyrroles as nucleophiles (Scheme 17).[40] The results of initial studies showed that in contrast to Rh complexes that are unable to catalyze this reaction, Pd catalysts promote reactions that proceed with high yields and levels of diastereoselectivity and enantioselectivity. On the basis of the results arising from the HRMS (high-resolution mass spectrometry) studies, the authors surmised that chiral palladium(II) phosphate **71** is the active metal catalyst in this process.

In 2013, Gong and co-workers developed a three-component reaction involving sequential catalysis by a Rh complex and a chiral phosphoric acid (Scheme 18).[41] The ammonium ylide generated from anilines **55** serves as a nucleophile in the reaction with **73**, which produces the aldol-type product **74** with excellent levels of diastero- and enantioselectivity.

Zhou reasoned that if an aldehyde electrophile is not included in the mixture employed for reaction of diazoesters **45** with $BocNH_2$, the zwitterionic intermediate derived from **76** would not serve as a nucleophile but instead would be trapped by N−H insertion (top, Scheme 19).[42] Using this plan, Zhou developed an asymmetric N−H insertion reaction that utilizes cooperative catalysis by a Rh complex and chiral phosphoric acid. The key step in this pathway involves proton transfer through a seven-membered transition state in which a chiral environment is created by the phosphoric acid. In a later effort, an enantioselective S−H insertion process was uncovered by the same group (middle, Scheme 19).[43] Recently, these workers also described an elegant N−H insertion reaction of α-diazoketones **56** that is a more challenging carbene precursor (bottom, Scheme 19).[44]

In 2012, Hu and co-workers described a new method for enantioselective C−H functionalization of indoles that utilizes sequential catalysis (Scheme 20).[45] The results of initial mechanistic studies suggested that the process takes place through a route involving proton-transfer followed by Rh-promoted C−H functionalization of the indoles.

The reactions described above proceed through metal carbene intermediates, and since they are catalyzed in a cooperative fashion they can be easily incorporated into relay catalytic systems. In 2012, Terada and Toda demonstrated the viability of this proposal in the form of a relay catalytic system consisting of carbonyl ylide formation and enantioselective transfer hydrogenation.[46] As shown in Scheme 21, Rh-promoted intramolecular reaction of the α-azoketones **82** provides carbonyl ylides **85** and **85′**, both of which are protonated to generate isobenzopyrylium phosphate **86**. Transfer hydrogenation of **86**

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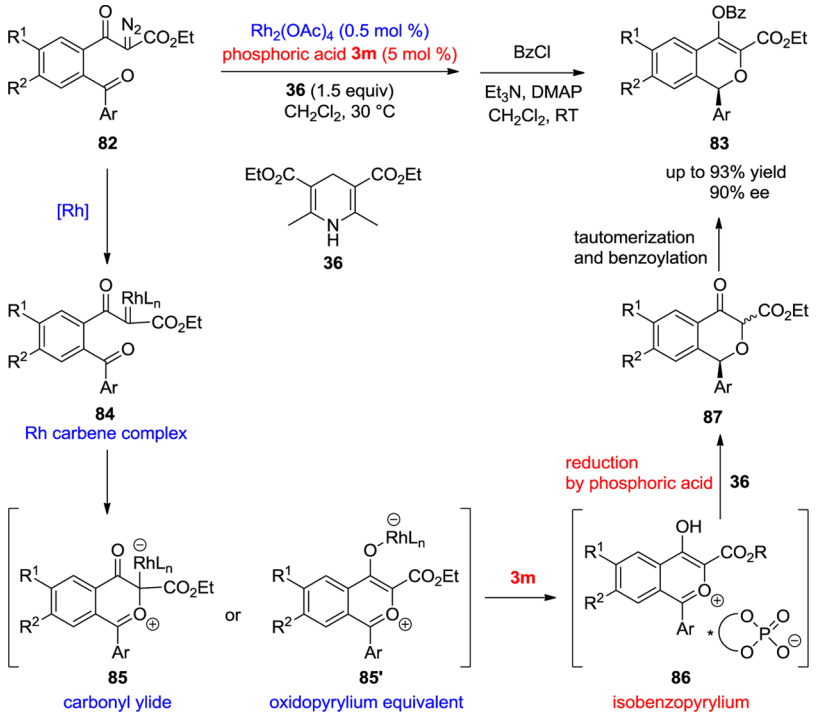
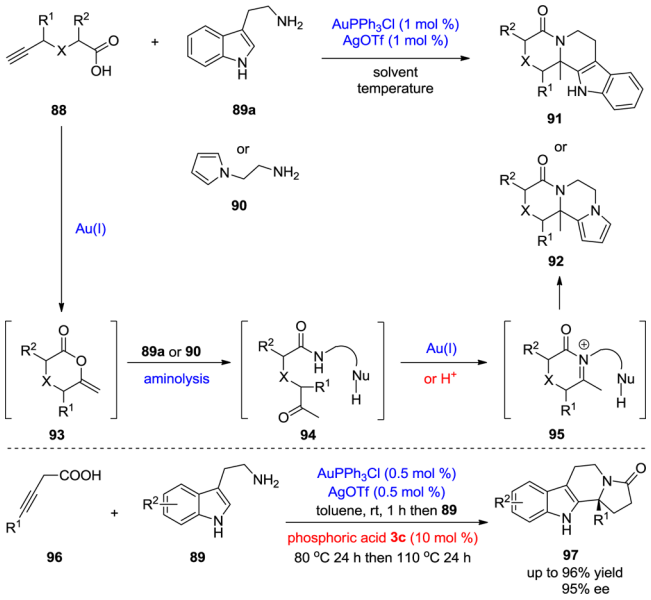
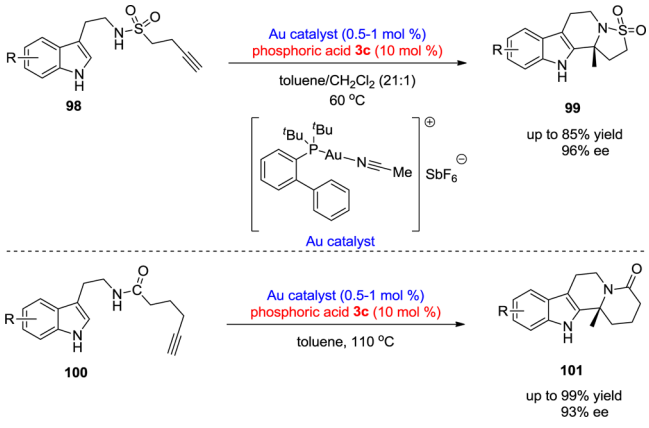
Scheme 21. Rh/Phosphoric Acid Catalyzed Relay Reactions



Scheme 22. Au/Phosphoric Acid Catalyzed *N*-Acyliminium Ion Cyclization Reactions



Scheme 23. Au/Phosphoric Acid Catalyzed Hydroamination/Isomerization/Cyclization Reactions



catalyzed by phosphoric acid **3m** then gives the precursor of *O*-benzoylbenzopyrans **83**.

SEQUENTIAL CATALYSIS WITH GOLD COMPLEXES

Inspired by the studies of Au-catalyzed cycloisomerization reactions of acetylenic acids carried out by Michelet and co-workers,[47] Dixon and co-workers designed a highly efficient Au-catalyzed *N*-acyliminium ion cyclization cascade that starts with alkynoic acids **88** (top, Scheme 22).[48] Mechanistic studies of this process reveal that the Brønsted acidity and not Lewis acidity of the Au complex facilitates generation of *N*-acyliminium ion **95**. This finding serves as the basis for the design of an enantioselective version of the process, described in studies reported in 2009.[49] Specifically, the use of an Au complex and chiral phosphoric acid promotes enantioselective reactions, as exemplified by the process depicted in Scheme 22 (bottom), in which a relay catalytic system promotes generation of highly enantioenriched (up to 95% ee) tetracyclic indole derivatives.

Recently, Dixon and co-workers reported an intramolecular relay reaction consisting of Au-catalyzed hydroamination of sulfonamides **98** and subsequent *N*-sulfonyliminium cyclization catalyzed by a chiral phosphoric acid (top, Scheme 23).[50] This dual catalytic system is also applicable to amide analogues **100**, which are converted to the corresponding lactams **101** in high yields and levels of enantioselectivity (bottom, Scheme 23).

A highly efficient and enantioselective method for the synthesis of tetrahydroquinoline derivatives **103** was described in 2009 by Gong and co-workers.[51] As shown in Scheme 24, the binary catalytic system is composed of an Au-catalyzed

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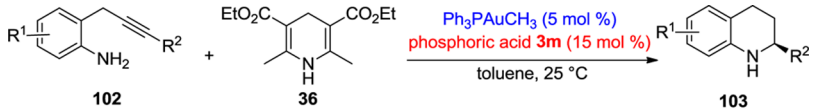
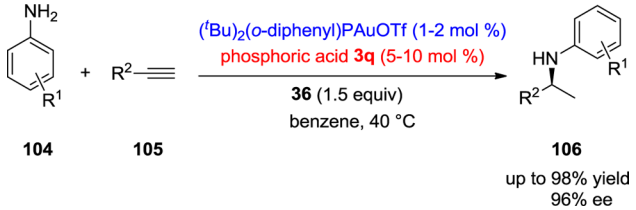
Scheme 24. Au/Phosphoric Acid Catalyzed Intramolecular Hydroamination/Isomerization/Transfer Hydrogenation Reactions



intramolecular hydroamination reaction and a chiral phosphoric acid catalyzed asymmetric transfer hydrogenation reaction.

At almost the same time, Che and co-workers reported a highly similar intermolecular version of this tandem process (Scheme 25).[52]

Scheme 25. Au/Phosphoric Acid Catalyzed Intermolecular Hydroamination/Isomerization/Transfer Hydrogenation Reactions



In later studies, Gong and co-workers applied the relay catalysis protocol to the synthesis of structurally diverse and complex julolidine derivatives (Scheme 26).[53] This transformation commences by condensation between aniline and aldehyde substrates to give an iminium intermediate that subsequently undergoes asymmetric Diels–Alder reaction catalyzed by chiral phosphoric acid **3b**. The final step in the process involves Au-catalyzed hydroamination reaction. The results of kinetic studies show that chiral phosphoric acid **3b** is both a catalyst for the asymmetric Diels–Alder reaction and a promoter for the hydroamination reaction.[54] Observations made in ^{31}P NMR and kinetic studies conducted to probe the active Au species revealed that gold phosphate **111** is the in situ generated catalyst for the hydroamination reaction.

In 2011, Gong and co-workers applied the relay catalysis strategy to the preparation of substances bearing vicinal quaternary stereogenic centers (Scheme 27).[55] Studies by this group show that a pathway, involving an oxonium ion forming cyclization reaction catalyzed by the Au complex and an isoxazolidinone addition reaction catalyzed by chiral phosphoric acid, produces the conformationally restricted coupling products **114** in high levels of stereoselectivity.

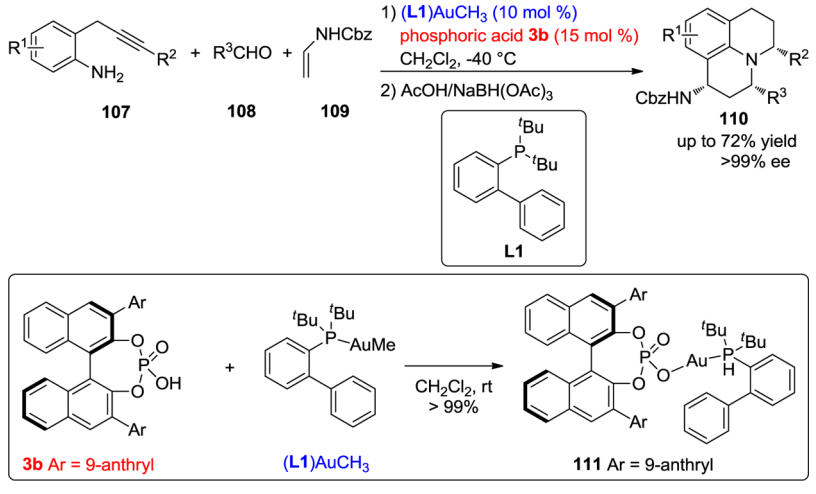
In 2012, Gong and co-workers described an intramolecular hydrosiloxylation/Diels–Alder reaction sequence that generates highly enantioenriched pentacyclic substances **117** (top, Scheme 28).[56] Slightly different than in their previous studies, this group employed *N*-triflylphosphoramide **3t** as the relay catalyst owing to its excellent performance in the asymmetric Diels–Alder reaction step. In a later effort, an intramolecular hydrosiloxylation/Mukaiyama aldol reaction sequence was also developed by the same research group. The process employs an Au complex and *N*-triflylphosphoramide **3u** as the dual catalytic system (bottom, Scheme 28).[57]

The spiroacetal moiety is a privileged scaffold found in a wide range of natural products. Recently, Gong and co-workers designed a new, relay catalysis based method for the synthesis of highly enantioenriched spiroacetals (Scheme 29).[58]

In 2013, Gong and co-workers developed a novel relay catalysis method involving a redox process[59] in which simple 2-alkynylaniline derivatives are transformed to benzopyrimidines **126** in high yields. As shown in Scheme 30, the process is composed of three steps including an Au-catalyzed hydroamination reaction, a Brønsted acid catalyzed 1,5-hydride-transfer redox reaction, and a Brønsted acid catalyzed intramolecular Mannich reaction. However, the results of subsequent studies of the asymmetric version of this reaction showed that the level of enantioselectivity is not satisfactory when a catalytic amount of chiral phosphoric acid **3q** is used and that use of higher amounts of **3q** (up to 200 mol %) leads to improved enantioselectivities.

A novel approach to produce chiral fused 1,2-dihydroisoquinolines was developed by Patil and co-workers in 2012.[60] As shown

Scheme 26. Au/Phosphoric Acid Catalyzed Condensation/Diels–Alder Cyclization/Hydroamination Reactions



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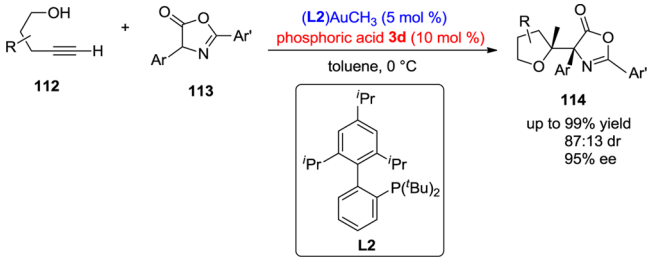
Scheme 27. Au/Phosphoric Acid Catalyzed Cyclization/Isomerization/Addition Reactions



in Scheme 31, the transformation is composed of an enantioselective condensation reaction of 2-alkynylbenzaldehydes with 2-aminobenzamides promoted by chiral phosphoric acid **3j** and an intramolecular hydroamination reaction promoted by Ph_3PAuMe.

In 2013, Zhang and co-workers described a novel cascade reaction catalyzed by an Au complex and a chiral phosphoric acid (Scheme 32).[61] Through the sequence, involving a redox-pinacol reaction and a Mannich process, optically pure β-amino spirocyclic and quaternary diketone derivatives **135** are produced in up to 95% yield. Control experiments revealed that chiral phosphoric acid **3b** is the real catalyst for the Mannich reaction step.

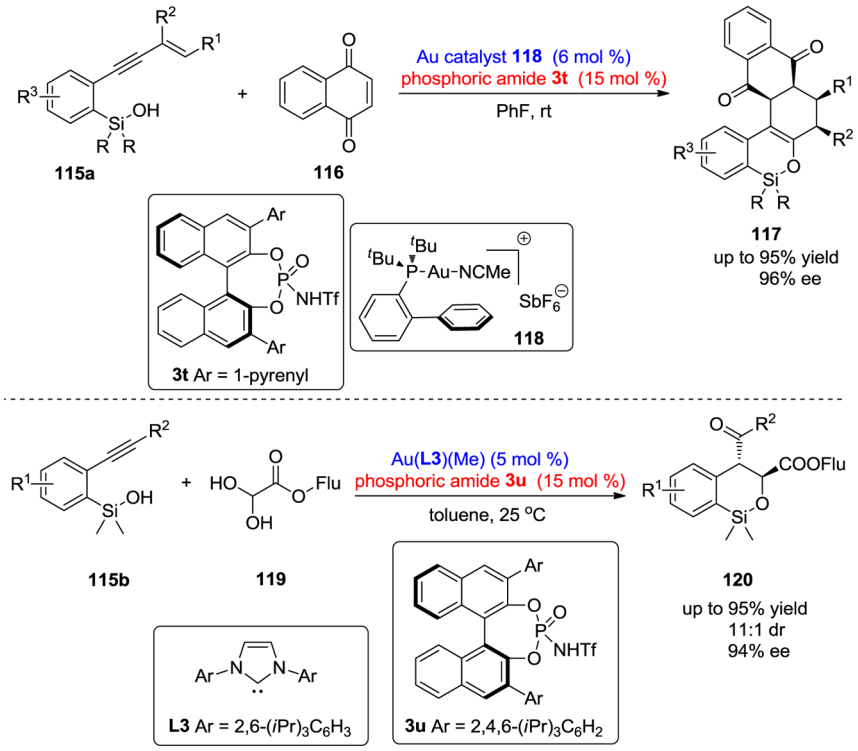
SEQUENTIAL CATALYSIS WITH LEWIS ACID

Apart from those promoted by using a combination of transition metal and chiral phosphoric acid, dual catalytic systems consisting of a Lewis acid and phosphoric acid have been also applied to relay catalysis. An example of this approach, described in 2012 by Gong and co-workers, proceeds through a unique sequence involving Friedlander condensation and transfer hydrogenation reactions (Scheme 33).[62] To shed light on the mechanism of this process, a series of kinetic experiments were performed. The results indicate that the Friedlander condensation reaction is catalyzed by both the chiral phosphoric acid and Lewis acid, the latter being more effective. More importantly, a mixture of the two catalysts accelerates the Friedlander condensation reaction, implying that they act in a synergistic manner to promote this transformation. Furthermore, the results of kinetic experiments reveal that transfer hydrogenation step is catalyzed solely by the chiral phosphoric acid.

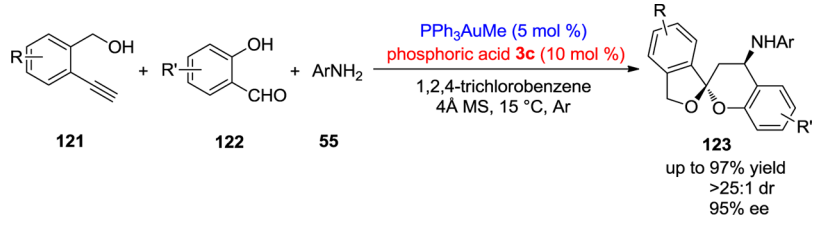
CONCLUSION

The development of processes that involve sequential catalysis, promoted by a combination of two or more catalysts, has

Scheme 28. Au/Phosphoric Amide Catalyzed Hydrosiloxylation/Diels–Alder or Mukaiyama Aldol Reactions



Scheme 29. Au/Phosphoric Acid Catalyzed Hydroalkoxylation/Addition Reactions



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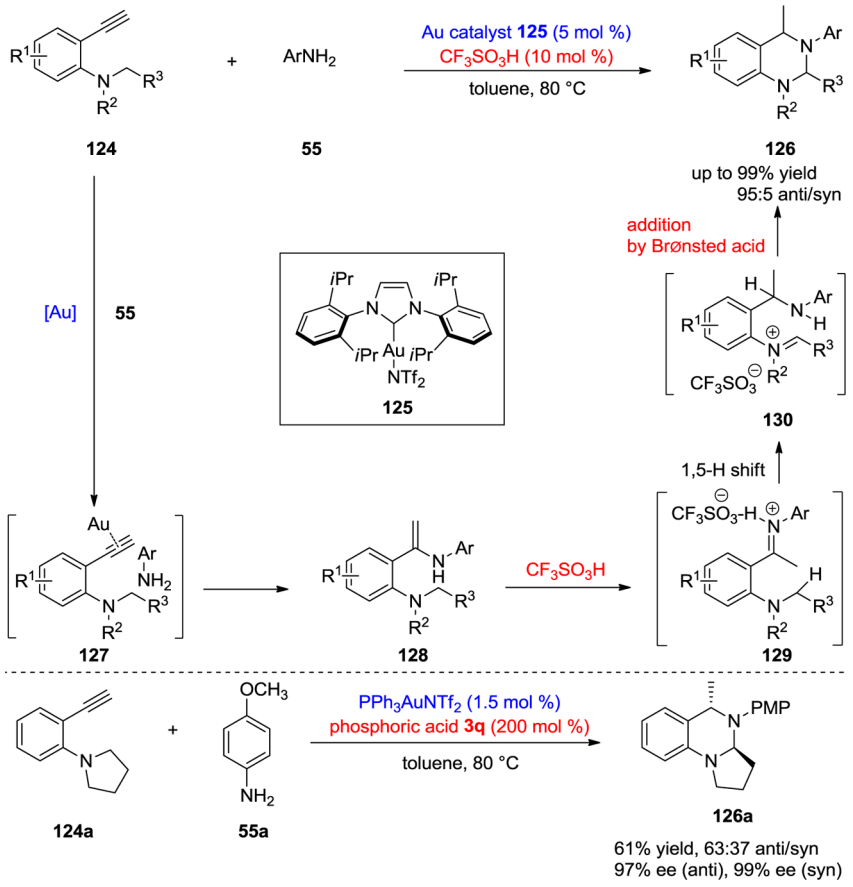
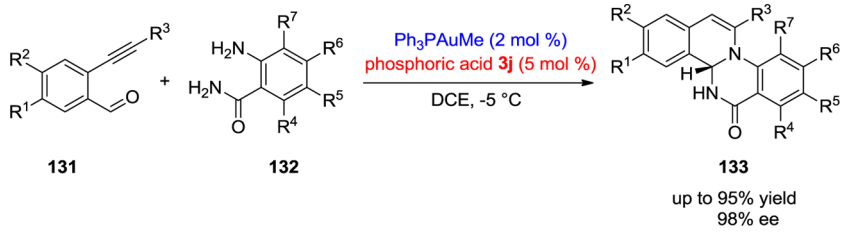
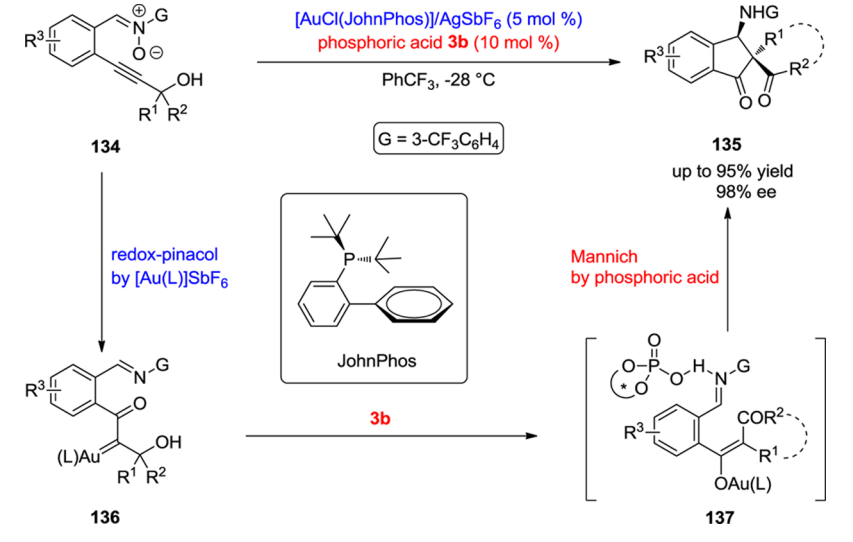
Scheme 30. Au/Phosphoric Acid Catalyzed Hydroamination/1,5-Hydride Transfer/Addition Reactions



Scheme 31. Au/Phosphoric Acid Catalyzed Condensation/Hydroamination Reactions



Scheme 32. Au/Phosphoric Acid Catalyzed Redox-Pinacol/Mannich Reaction



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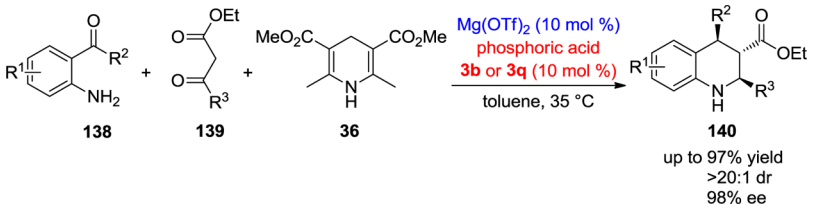
Scheme 33. Mg/Phosphoric Acid Catalyzed Condensation/Transfer Hydrogenation Reactions



seen rapid progress in recent years. More than the advantages associated with the utilization of simpler substrates and the avoidance of isolation of intermediates, sequential catalysis can lead to new and unique reactions. It is noteworthy that some of the unprecedented enantioselective sequential reactions uncovered in the efforts described above do not take place when either of the component chiral catalysts are used alone. Moreover, the synergistic effects observed in some sequential catalytic systems are another beneficial characteristic that leads to more highly efficient cascade processes compared to the simple sum of the outcomes of individual reactions.

As highlighted in this paper, recent progress made in the development of sequential catalytic processes consisting of metal complexes and chiral phosphoric acids represent outstanding achievements. However, notable challenges remain in this area. First, because only a small number of metal complexes are compatible with phosphoric acids, the range of sequential catalytic processes that rely on these catalysts is limited. Second, the occurrence of side reactions is problematic, especially when they use achiral metal catalysts which negatively impact levels of enantioselectivity. Third, the efficiencies of sequential catalytic processes studied to date are only moderate, and consequently, catalysts loadings are relatively high. Finally, more detailed studies are needed to elucidate the mechanistic intricacies of these processes that should facilitate the design of new reactions.

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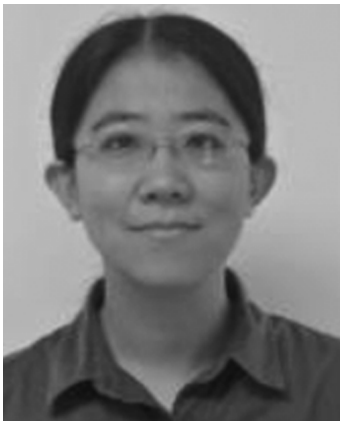
Notes

The authors declare no competing financial interest.

Biographies

Ze-Peng Yang was born in Shanxi, China, in 1990. He received his B.Sc. in chemistry from Tongji University in 2011. He then joined Professor Shu-Li You's group at the Shanghai Institute of Organic Chemistry (SIOC) as a Ph.D. student. His current work focuses on transition-metal-catalyzed allylic dearomatization reactions.



Wei Zhang was born in Tianjin, China, in 1978. She received her B.Sc. in chemistry from the University of Science and Technology of China in 2000. In 2007, she received her Ph.D. from the University of Chicago under the direction of Prof. Hisashi Yamamoto. She then spent three years doing postdoctoral studies at Northwestern University in medicinal chemistry with Prof. Richard B. Silverman. In 2010, she joined the You Group as an associate professor. Her research interest is focused on asymmetric catalysis.

Shu-Li You received his B.Sc. in chemistry from Nankai University in 1996 and his Ph.D. from the Shanghai Institute of Organic Chemistry (SIOC) in 2001 under the supervision of Prof. Li-Xin Dai. Following postdoctoral studies with Prof. Jeffery W. Kelly at The Scripps Research Institute, he worked at the Genomics Institute of the Novartis Research Foundation as a Principal Investigator before returning to SIOC as a full professor in 2006. His research interests include asymmetric catalysis, synthetic methodology, natural product synthesis, as well as medicinal chemistry.

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