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Asymmetric Organocatalysis Combined with Metal Catalysis: Concept, Proof of Concept, and Beyond

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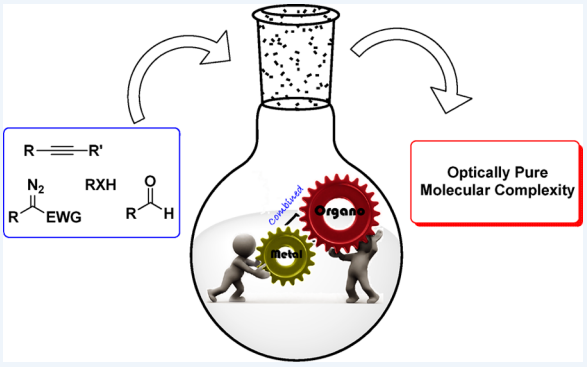
CONSPECTUS: Asymmetric catalysis has been considered to be the most intriguing means for building collections of functionalized optically active compounds. In particular, metal and organocatalysis have been well established to allow many fundamentally different reactions. Metal catalysis has enabled the participation of a much broader scope of chemical bonds in organic transformations than are allowed by organocatalysis, while organocatalysis permits a broader scope of functional groups to undergo a diverse range of enantioselective transformations, individually, simultaneously, or sequentially. Theoretically, the combination of organocatalysts and metal complexes could probably render new transformations through the simultaneous or sequential activation and reorganization of multiple chemical bonds if the superior features of both the catalysts are adopted.



In 2001, both our research group and Takemoto's group separately described an asymmetric allylation of glycine imino esters with allyl acetate catalyzed by palladium complexes and chiral ammonium salts. In these cases, the oxidative addition of palladium complexes to allyl acetate formed the π-allylic fragments, while the chiral ammonium salts were actually responsible for controlling the stereoselectivity. These reactions in fact marked the beginning of asymmetric organo/metal combined catalysis. Since then, asymmetric organocatalysis combined with metal catalysis, including cooperative catalysis, relay catalysis, and sequential catalysis, has been a versatile concept for the creation of unknown organic transformations. Sequential catalysis describes a one-pot reaction involving two or more incompatible catalytic cycles. Alternatively, cooperative and relay catalyses require high compatibility of principally distinct catalysts and will be the focus of this Account. The catalysts in cooperative catalytic reactions must be able to simultaneously and individually activate both substrates to drive a bond-forming reaction, while relay catalysis is basically defined as a cascade process in which two or more sequential bond-forming transformations are independently catalyzed by distinct catalysts.

In the past decade, we have discovered a variety of binary catalytic systems consisting of metals, including Rh(II), Pd(0), Au(I), and Mg(II), and chiral organocatalysts, including chiral phosphoric acids and quinine-based bifunctional molecules, for cooperative catalysis and relay catalysis, allowing the accomplishment of many unprecedented asymmetric transformations. In this Account, these achievements will be summarized, particularly focusing on the description of the concept and proof of the concept, to demonstrate the robustness of combined organo/metal catalysis in the creation of efficient enantioselective transformations.

In addition, elegant studies from other laboratories using chiral phosphoric acid/Au(I) for the establishment of asymmetric cascade reactions involving the carbon−carbon triple bond functionality and typical combined organo/metal catalytic systems, very recently disclosed, will also be highlighted.

1. INTRODUCTION

In contrast to historical approaches, such as chiral pool synthesis and chiral reagents, asymmetric catalysis is a more efficient and economical way to produce optically active chemicals and holds great importance in synthetic organic chemistry.[1] Since the seminal works in the 1960s,[2] asymmetric metal catalysis has long stood at the center of asymmetric synthesis and has received great success, largely because of the emergence of privileged chiral ligands.[1a,b] In recent years, asymmetric organocatalysis has also achieved important advances[3] and has been an additional robust tool for the manufacture of chiral molecules. Although asymmetric organocatalysis has enabled the participation of a broad range of functionalities in numerous enantioselective transformations, extensions of this new chemistry currently suffer from a paucity of efficient modes to activate relatively inactive chemical bonds. In contrast, metals and their complexes are able to activate a wide range of chemical bonds, particularly those

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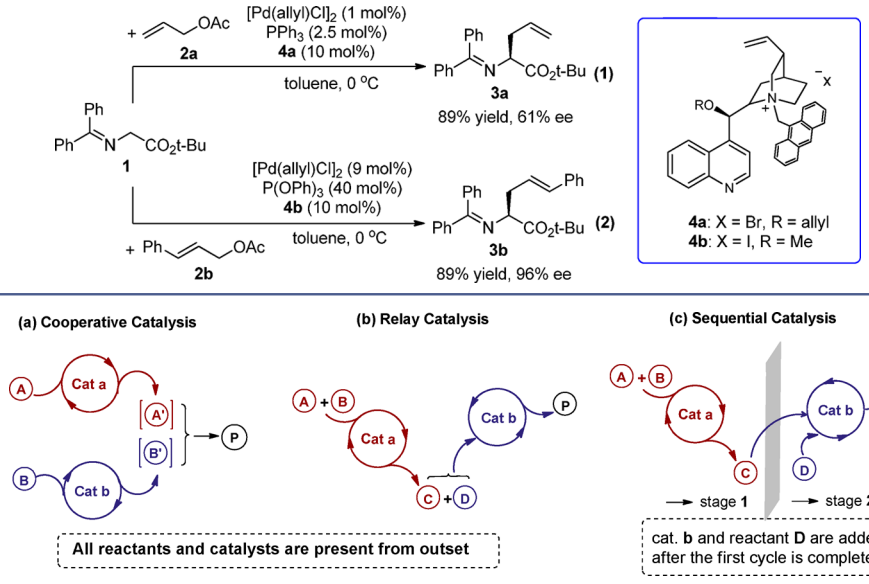

Figure 1. Classifications of organocatalysis combined with metal catalysis.

inactive chemical bonds that organocatalysts are unable to cleave. If the superior qualities of both organocatalysts and metals are combined to promote a reaction system, we may achieve an alternative strategy to create new transformations that neither of the individual chiral catalysts can realize alone.

1.1. Earlier Examples of Asymmetric Organocatalysis Combined with Metal Catalysis

In 2001, we first introduced the concept of combining a palladium catalyst with a cinchona alkaloid-based ammonium salt, **4a**, to promote asymmetric allylic alkylation of a glycine imino ester, **1**. The oxidative addition of the palladium complex to allyl acetate **2a** formed the π-allylic fragment and the chiral phase-transfer catalyst (PTC) **4a** was actually responsible for the control of stereoselectivity by the formation of a chiral ion pair with the glycine imino ester **1**. As anticipated, the use of **4a** as a sole chiral element allowed the allylation product **3a** to be obtained with moderate enantioselectivity (eq 1).[4]

Takemoto and co-workers independently described a similar reaction by using an almost identical strategy. In the presence of 9 mol % allyl palladium chloride dimer, 40 mol % achiral triphenyl phosphite, and 10 mol % chiral PTC **4b**, the asymmetric allylic alkylation of the glycine imino ester **1** with cinnamyl acetate **2b** proceeded cleanly to give **3b** with 96% ee (eq 2).[5]

The aforementioned two reactions in fact marked the beginning of asymmetric organo/metal combined catalysis. Over the past decade, such a concept has drawn increasing attention and has been widely accepted as a productive strategy that enables unique transformations with high efficiency.[6]

1.2. Categories of Asymmetric Organocatalysis Combined with Metal Catalysis

Organocatalysis combined with metal catalysis includes the categories of cooperative catalysis,[7] relay catalysis, and sequential catalysis (Figure 1).[8] Both cooperative and relay catalyses require high compatibility of principally distinct catalysts. Asymmetric cooperative catalysis depends on the catalysts involved being able to simultaneously and individually activate both substrates to drive a bond-forming reaction (Figure 1a), while relay catalysis is defined as a cascade process in which two or more sequential bond-forming events are independently promoted by two or more catalysts in a cascade manner (Figure 1b). Sequential catalysis generally describes a one-pot reaction promoted by different catalysts that are incompatible, and therefore parts of the catalysts or, in some cases, reagents must be added after the previous catalytic reaction is complete. Such a process can be considered as an "artificial" relay catalysis (Figure 1c).[8c]

In this Account, we will summarize typical advances in asymmetric organocatalysis (as shown in Figure 2, three types of

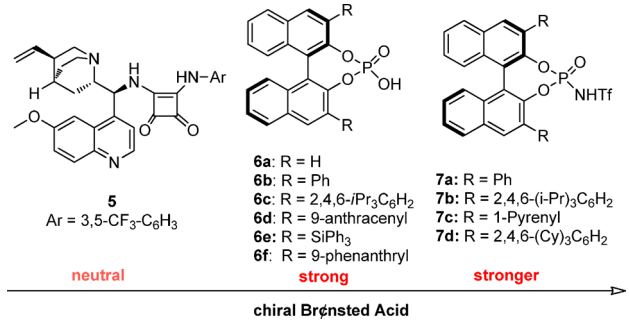

Figure 2. Chiral organocatalysts used in the combined catalysis.

chiral Brønsted acids are involved, quinine-derived squaramide (i.e., a neutral Brønsted acid), BINOL-derived strong chiral phosphoric acids, and the stronger N-triflyl phosphoramides) combined with metal catalysis, mostly developed by our group, and will particularly emphasize the description of the concept and proof of concept, together with the demonstration of applications of asymmetric cooperative and relay catalysis in the creation of unprecedented enantioselective transformations.

2. DESCRIPTIONS OF ORGANOCATALYSTS IN CONJUNCTION WITH METAL CATALYSTS

2.1. Asymmetric Cooperative Catalysis

2.1.1. Rhodium Complex/Chiral Phosphoric Acid Cooperative Catalysis. In 2007, Hu and co-workers established a three-component reaction of diazo esters **8** with alcohols **9** and imines **10** catalyzed by rhodium acetate dimer to

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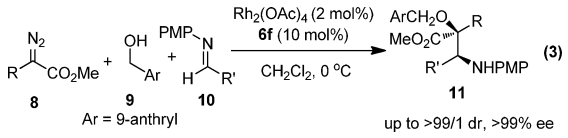
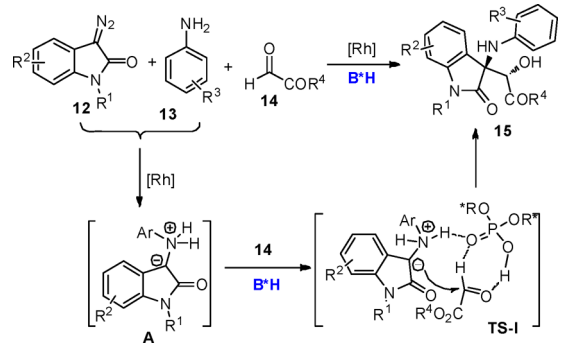
give racemic β-amino esters in high yields.[9] Since chiral phosphoric acids are able to efficiently activate imine-based functionalities by hydrogen-bonding interactions or protonation,[10] they were selected as collaborative chiral organocatalysts to control the stereochemistry. As anticipated, the combination of rhodium acetate dimer and chiral phosphoric acid **6f** allowed the three-component reaction to give chiral β-amino esters **11** with excellent levels of stereoselectivity (eq 3).[11]



Based on a similar concept, we accomplished an enantioselective three-component reaction of 3-diazooxindoles **12** with anilines **13** and glyoxylates **14**, by virtue of the rhodium acetate dimer and chiral phosphoric acid binary catalytic system (Scheme 1). The reaction was proposed to proceed via a

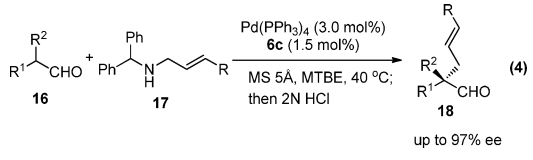
Scheme 1. Cooperatively Catalytic Asymmetric Aldol-Type Reaction



rhodium-catalyzed generation of ammonium ylides **A** from **12** and **13**, followed by an enantioselective aldol-type reaction with glyoxylates **14** catalyzed by a chiral Brønsted acid via the transition state **TS-I** to generate the desired products, wherein multiple hydrogen-bonding interactions would be involved in the catalysis on the basis of the hypothesis of Terada.[10b]

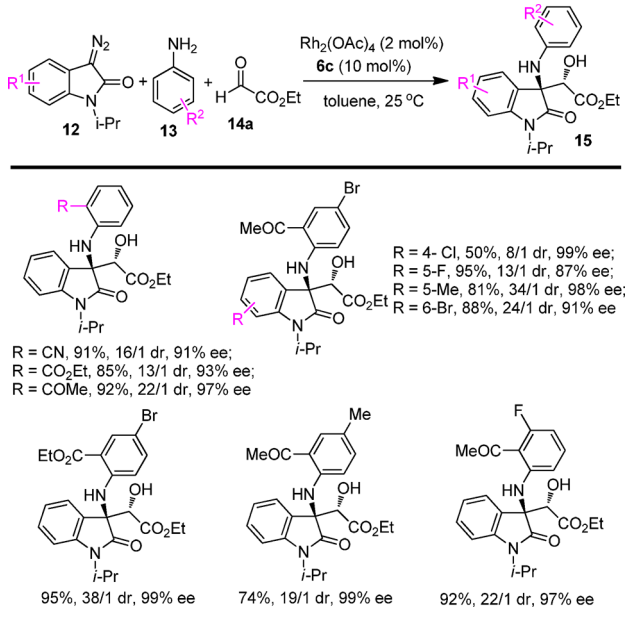
The combination of 2 mol % $Rh_2(OAc)_4$ and 10 mol % chiral phosphoric acid **6c** was really able to effectively catalyze the proposed reaction of *N*-isopropyl 3-diazooxindoles **12** with **13** and **14**, delivering highly functionalized and structurally diverse 3-amino oxindoles **15** in high yields and with excellent levels of diastereo- and enantioselectivities (Scheme 2).[12]

2.1.2. Chiral Pd(0) Complex/Chiral Phosphoric Acid Cooperative Catalysis. List and co-workers first demonstrated that the combination of a palladium(0) complex and a chiral phosphoric acid could efficiently catalyze a highly enantioselective allylic alkylation reaction between α-branched aldehydes and allyl amines (eq 4).[13]



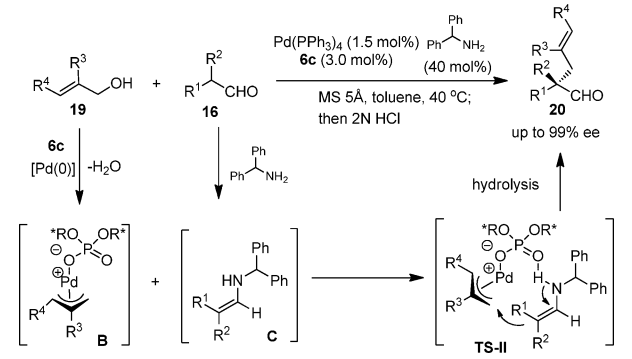
Recently, the same group accomplished a highly enantioselective α-allylation of aldehydes with simple allylic alcohols **19** by

Scheme 2. Substrate Scope of the Asymmetric Aldol-Type Reaction



exploiting the cooperative catalysis of a palladium(0) complex, a chiral phosphoric acid, and diphenylmethanamine (Scheme 3).[14]

Scheme 3. Pd(0)/Brønsted Acid/Amine Cooperatively Catalyzed Asymmetric α-Allylation of Aldehydes with Allylic Alcohols



Mechanistically, all catalysts of this organo-metal tertiary catalytic system were necessary for the reorganization of the chemical bonds: the oxidative addition of the Pd(0) complex to the chiral Brønsted acid-activated allylic alcohol generated a π-allyl-Pd-phosphate **B**, which then underwent a stereoselective allylation with an enamine intermediate **C** generated from a condensation reaction of **16** and diphenylmethanamine via transition state **TS-II**, giving rise to α,α-disubstituted aldehydes **20** with high optical purity after hydrolysis.

Although the combination of enamine catalysis with palladium complexes and chiral Brønsted acids has efficiently promoted highly enantioselective allylic alkylations of enolizable aldehydes or ketones, it is difficult to control the stereoselectivity of similar transformations involving other highly acidic soft nucleophiles, which have commonly been used in classical asymmetric allylic alkylation reactions.[15] To address this issue, we proposed that the π-allylic palladium **E**, generated from the oxidative addition of a Pd(0) complex to the chiral Brønsted acid-activated allylic

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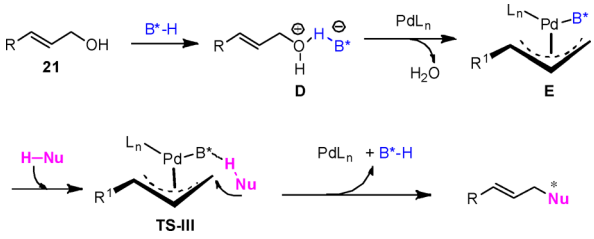
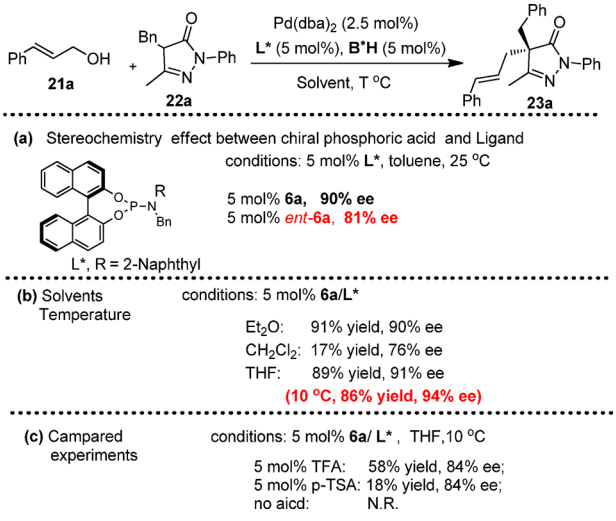
alcohol **D**, in which the chiral couteranion would serve as a conjugate base capable of activating the incoming acidic nucleophiles, would thereby enable the subsequent enantioselective substitution reaction (Scheme 4). On the other hand, if the chiral Brønsted acid is unable to give high enantioselectivity, chiral ligands could be introduced to control the stereoselectivity.

Scheme 4. General Strategy for Pd(0) Complex/Brønsted Acid Cooperative Catalytic Enantioselective Allylation of Acidic Nucleophiles



Extending this consideration, an allylic alkylation of cinnamyl alcohol **21a** with pyrazol-5-one **22a** was investigated by using the combination of a chiral Pd(0) complex and a chiral Brønsted acid (Scheme 5). Indeed, a "match/mismatch" effect between the

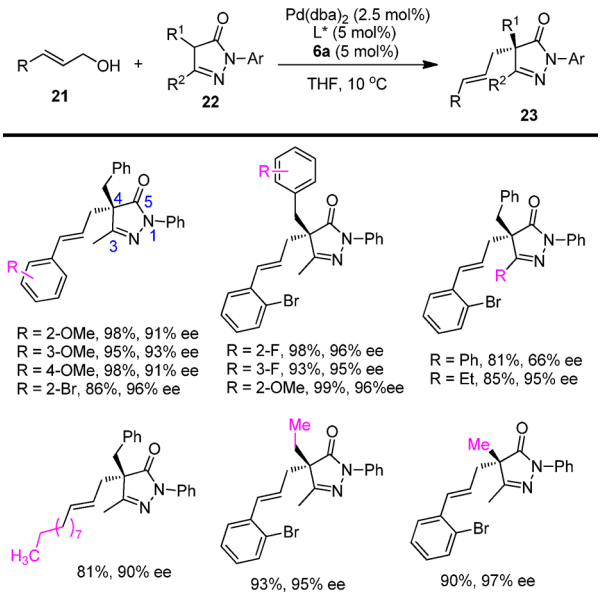
Scheme 5. Asymmetric Allylation of Pyrazol-5-one 22a with Cinnamyl Alcohol



chiral phosphoric acids and the ligands was observed in the control of stereoselectivity: the combination of Brønsted acid **6a** and (*R*)-phosphoramidite **L*** allowed the allylic alkylation to generate **23a** with 90% ee, whereas *ent*-**6a** and (*R*)-phosphoramidite **L*** resulted in a much lower enantioselectivity (Scheme 5a). An enhanced enantioselectivity of 94% ee was achieved by conducting the reaction at 10 °C in THF (Scheme 5b). Notably, achiral Brønsted acids gave significantly diminished yields (Scheme 5c). The reaction did not occur in the absence of Brønsted acids, again indicating the critical role of the cooperative effect between the palladium catalyst and the Brønsted acid in this protocol.[16]

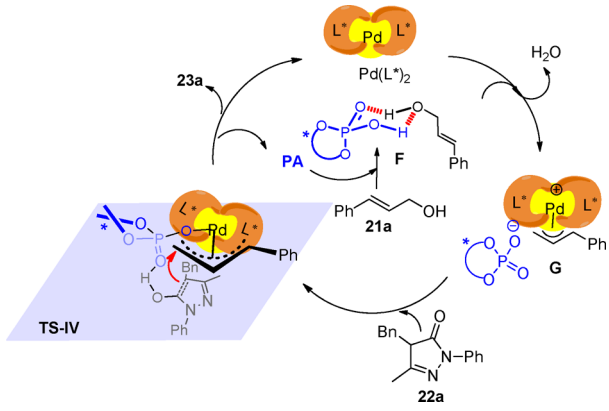
The protocol demonstrated good generality for both substrates. As a consequence, a wide scope of structurally diverse pyrazol-5-ones **22** and allylic alcohols **21** could be coupled in extremely high yields and with excellent levels of enantioselectivity (Scheme 6).

Scheme 6. Generality for Pyrazol-5-ones and Allylic Alcohols



The high-resolution mass spectrometry analysis identified that two chiral phosphoramidite ligands became coordinated to the palladium atom during the catalysis, producing the active catalyst Pd(**L***)$_2$, which initially underwent an oxidative addition to the phosphoric acid-activated allylic alcohol **21a** to generate the crucial chiral π-allyl palladium(II) complex **G** bearing two chiral ligands and a chiral anion. Subsequently, the asymmetric allylic alkylation reaction of **G** with the enolizable pyrazol-5-one **22a** occurred via the transition state **TS-IV**, wherein the pyrazol-5-one **22a** was activated by forming a hydrogen-bond interaction with the chiral phosphate, to stereoselectively generate **23a** (Scheme 7).

Scheme 7. Reaction Mechanism for the Asymmetric Allylation of Pyrazol-5-ones with Allylic Alcohols Cooperatively Catalyzed by Chiral Pd(0) Complex and Chiral Phosphoric Acid



In addition to palladium(0), palladium(II) complex/chiral phosphoric acid cooperative catalysis has also been successfully applied to promote some other enantioselective transformations, such as allylic C–H activation,[17a] oxa-Diels–Alder cycloaddition,[17b] and a palladium carbenoid-associated three-component coupling reaction.[17c]

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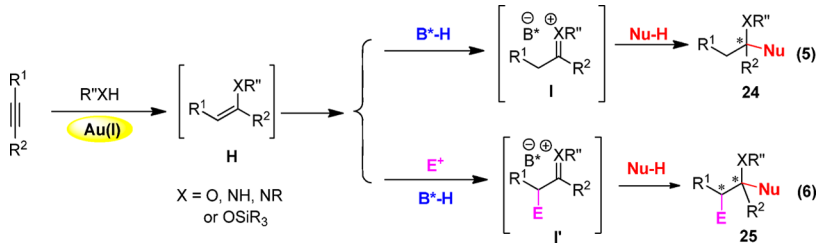
Scheme 8. General Strategy for the Creation of Asymmetric Relay Catalytic Cascade Reactions



2.2. Asymmetric Relay Catalysis

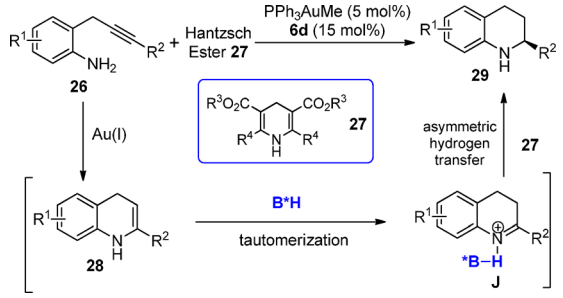
Relay catalysis, first introduced by Rovis in 2007,[18] describes the consecutive catalytic behavior of different catalysts in a cascade reaction.[19] Relay catalysis avoids the additional work-up of either isolable or transient intermediates and thus reduces labor, saves time, and minimizes waste. More importantly, the asymmetric organo/metal relay catalysis provides a general platform to design new protocols for the enantioselective construction of molecular complexity from readily available starting materials.

2.2.1. General Strategy for the Creation of Gold Complex/Chiral Brønsted Acid Relay Catalysis. The past decade has witnessed an impressive development of homogeneous gold catalysis, which exhibits incomparable efficiency for the activation of carbon−carbon multiple bonds, leading to numerous synthetically useful transformations.[20] As shown in Scheme 8, the nucleophilic addition of functional groups, including hydroxyl, amine, and silanol, onto gold-activated alkynes generates active species **H**, which, under the influence of a Brønsted acid, would principally be converted into electrophiles **I** capable of participating in subsequent addition reactions with various nucleophiles to generate compounds **24** (Scheme 8, eq 5). On the other hand, the intermediates **H** are actually active nucleophiles capable of being trapped by electrophiles E^+ to generate electrophiles **I′**, which would then undergo a similar reaction as **I** does to generate products **25** (Scheme 8, eq 6). As such, the combination of gold catalysis with Brønsted acid catalysis would provide a general platform to convert the carbon−carbon triple bond functionality into divergent optically pure complex molecules.

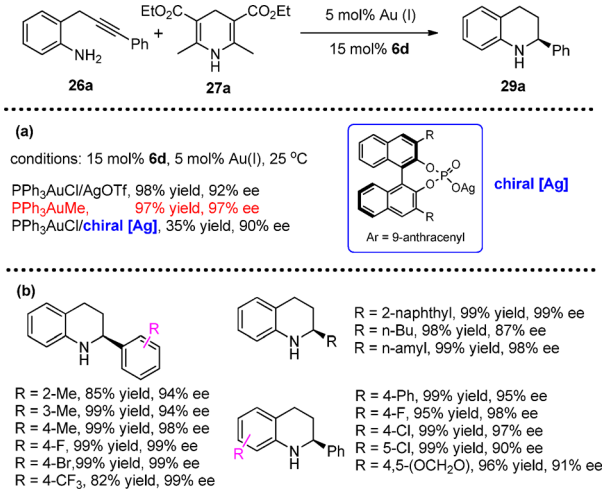
2.2.2. Early Reports. In 2009, we first demonstrated that a gold complex, combined with a chiral phosphoric acid, was able to directly convert the carbon−carbon triple bond into a stereogenic center by the asymmetric relay catalytic strategy.[21] We initially proposed that the propargylic anilines **26** would first undergo an intramolecular hydroamination under gold(I) catalysis to furnish a 1,4-dihydroquinolines **28**. Afterward, the 1,4-dihydroquinolines **28** might be protonated by a chiral Brønsted acid to form iminium intermediates **J**, which would undergo an asymmetric transfer hydrogenation to produce optically active tetrahydroquinolines **29** (Scheme 9).

Gratifyingly, 5 mol % PPh_3AuOTf_2 and 15 mol % **6d** rendered the consecutive intramolecular hydroamination/asymmetric transfer hydrogenation of **26a** to deliver the 2-phenyl tetrahydroquinoline (**29a**) in 98% yield and with 92% ee. Ph_3PAuMe was found to be a better partner of **6d**, providing 97% yield and 97% ee. A chiral gold phosphate prepared from PPh_3AuCl and chiral silver phosphate was also able to catalyze this tandem reaction but with an eroded yield (35%) and with lower enantioselectivity (90% ee), indicating that the enantioselective transfer hydrogenation step was predominantly catalyzed by the chiral phosphoric acid **6d** (Scheme 10a).

Scheme 9. Relay Catalytic Consecutive Hydroamination/Asymmetric Transfer Hydrogenation of Propargylic Anilines



Scheme 10. Generality of the Consecutive Intramolecular Hydroamination/Asymmetric Transfer Hydrogenation



The relay catalytic process was highly efficient and amenable to a wide range of the propargylic anilines **26**, leading to the generation of corresponding tetrahydroquinolines **29** in very high yields and with excellent levels of enantioselectivities (up to 99% yield and 99% ee, Scheme 10b).

A similar concept was independently reported by Liu and Che. They established a relay catalytic intermolecular hydroamination/asymmetric transfer hydrogenation reaction of alkynes **30**, anilines **13**, and the Hantzsch ester **27a** by using cationic JohnPhosAuOTf complex and the *ent*-**6d** as the combined catalyst, leading to direct generation of chiral secondary amines **31** in very high yields and with excellent levels of enantioselectivity (eq 7).[22]

Almost simultaneously, Dixon and co-workers reported a gold complex/Brønsted acid relay catalytic cascade cycloisomerization/asymmetric Friedel−Crafts reaction (Scheme 11).[23] In this process, the gold complex first catalyzed a cycloisomerization of

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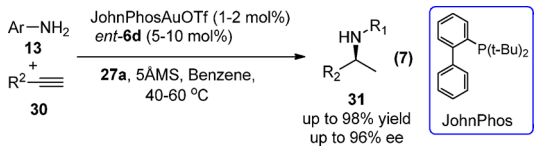
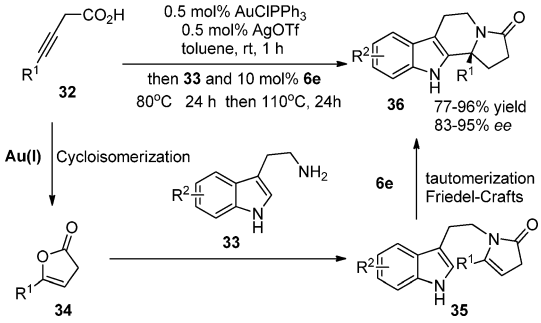


Scheme 11. Asymmetric Relay Catalytic Synthesis of Polycyclic Indole Derivatives



alkynoic acids **32** to generate enol lactones **34**, which then participated in the chiral phosphoric acid **6e**-catalyzed cyclization cascade with tryptamines **33**, furnishing optically active polycyclic indole derivatives **36** in good yields and with high ee values.

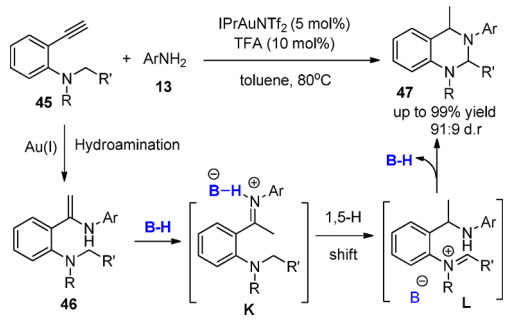
2.2.3. Cycloaddition/Hydroamination Cascade. Under the promotion of the combined catalyst of 10 mol % JohnPhosAuMe complex and 15 mol % chiral phosphoric acid **6d**, the propargylic anilines **26** first condensed with aldehydes to generate aldimines **39**, which then underwent asymmetric Povarov reaction with an enamide **38** at −40 °C catalyzed by **6d** to produce tetrahydroquinoline derivatives **40**. Afterward, the gold(I) complex prompted the tetrahydroquinoline derivatives **40** to undergo an intramolecular hydroamination at room temperature to access polycyclic compounds **41**, which could be diastereoselectively reduced into julolidine derivatives **42** (Scheme 12).[24] A broad scope of propargylic anilines **26** and aldehydes **37** were amenable to the relay catalytic three-component reaction to furnish polycyclic heterocycles with excellent enantioselectivities.

The ^{31}P NMR spectral analysis disclosed that the JohnPhosAuMe complex quickly reacted with **6d** at room temperature (complete within 30 min) to produce a gold phosphate complex **43** (eq 8). To find out whether the gold phosphate generated *in situ* was able to catalyze the [4 + 2] reaction, a control reaction of **26a** and 4-bromobenzaldehyde **37a** with enamide **38** in the presence of 10 mol % chiral gold phosphate **43**, generated from silver phosphate **44** and the JohnPhosAuCl complex, was conducted at −40 °C (eq 9). However, no reaction was observed, suggesting that the phosphoric acid **6d** solely catalyzed the asymmetric Povarov reaction at low temperature.

Kinetic studies found that the gold phosphate **43** rather than the methyl gold complex served as the real catalyst for the intermolecular hydroamination while the presence of additional amounts of phosphoric acid **6d** allowed the reaction to proceed a little faster.

The direct functionalization of sp^3-hybridized C−H bonds has a broad scope of synthetic applications but remains a formidable challenge. In the presence of a gold(I) complex and a Brønsted acid, a cascade hydroamination/isomerization would proceed to convert 2-ethynylaniline derivatives **45** into imine intermediates **K**, which would undergo 1,5-hydride transfer/cyclization to generate cyclic aminals **47**.[25] Indeed, the employment of 5 mol % IPrAuNTf$_2$ and 10 mol % TFA enabled the proposed multiple cascade reaction to afford multifunctionalized aminals **47** in excellent yields (Scheme 13).[26]

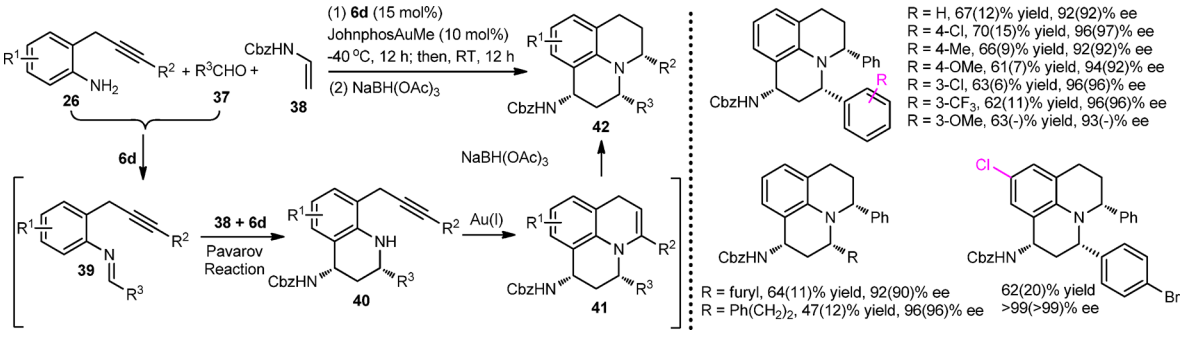
Scheme 13. Cascade Hydroamination/Redox Reaction



The replacement of trifluoroacetic acid (TFA) by a chiral phosphoric acid led to an enantioselective cascade reaction. However, the catalytic amount of **6c** was not sufficient to completely control the stereoselectivity. Thus, we envisioned that the use of an excess amount of chiral phosphoric acid **6c** would compete with the gold(I)-catalyzed nonselective background reaction and thereby improve the stereoselectivity. Indeed, a positive correlation was found between the enantioselectivity and the loading of **6c**; 2 equiv of chiral phosphoric acid **6c** were required to allow the desired product **47a** to be isolated in excellent enantioselectivity (eq 10).

2.2.4. Intramolecular Hydroalkoxylation/Aldol-Type Reaction Cascade. The nucleophilic addition of a hydroxyl group onto a gold-activated carbon−carbon triple bond furnishes an enol ether that upon contact with Brønsted acids undergoes

Scheme 12. Enantioselective Relay Catalytic Synthesis of Julolidine Derivatives



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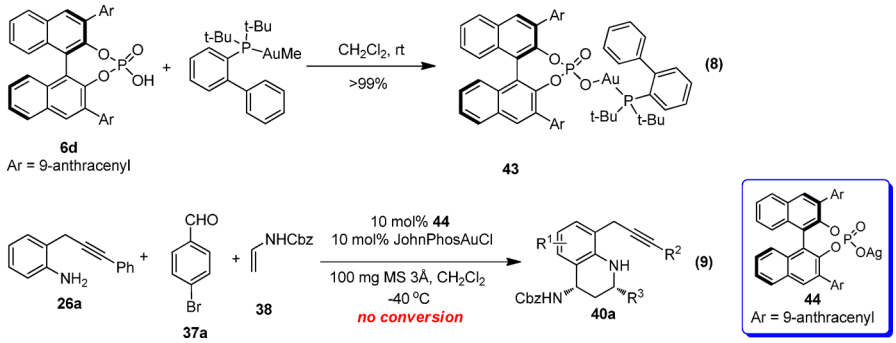
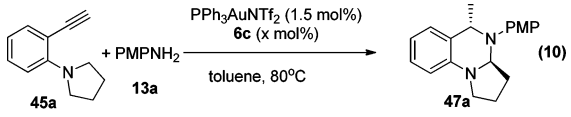




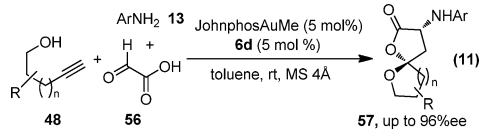
x = 20, 78% yield, 63:37 d.r, 19%/25% ee;
x = 60, 75% yield, 63:37 d.r, 49%/42% ee;
x = 100, 65% yield, >95:5 d.r, 64%/58% ee;
x = 200, 61% yield, 63:37 d.r, 99%/95% ee

protonation, leading to the generation of an oxonium ion electrophile capable of being trapped by nucleophiles (Scheme 8). With azlactones **49** as nucleophiles, the gold(I) complex of *t*-BuXPhos, combined with chiral Brønsted acid *ent*-**6c**, facilitated a variety of alkynols **48** to participate in a cascade intramolecular hydroalkoxylation/aldol-type reaction to deliver conformationally restricted amino acid precursors **50** in excellent yields and with high levels of enantioselectivity (Scheme 14).[27]

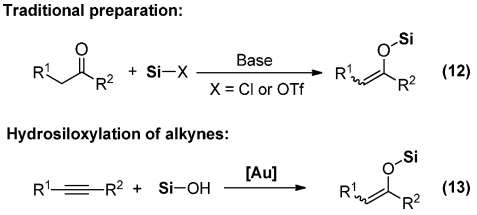
In this case, the enol ethers **51** generated from the cyclization of **48** catalyzed by the gold(I) complex could react with either chiral phosphoric acid or gold phosphate to generate oxonium ion intermediates **M** or **M′**. Subsequently, the oxonium ion species underwent an enantioselective aldol-type reaction with the azlactones **49** via either transition state **TS-V** or **TS-V′** to give the final products, wherein the stereoselectivity was solely controlled by the chiral phosphate (Scheme 15).

2.2.5. Intramolecular Hydroalkoxylation/Mannich-type Reaction/Acetalization Cascade. As mentioned in Scheme 8, the enol ethers are active nucleophiles, capable of attacking appropriate electrophiles to form oxonium ions that can subsequently be trapped by another nucleophile. As shown in Scheme 16, the enol ethers **54** formed from the gold(I)-catalyzed cyclization of alkynols **52** smoothly underwent a Mannich-type reaction with salicylaldehydimines **N** activated by a chiral phosphoric acid to give an intermediate **O**, which immediately participated in an intramolecular acetalization to afford the final spiroacetals. The combination of the gold(I) complex and chiral phosphoric acid **6e** was able to assemble alkynols **52**, anilines **13**, and salicylaldehydes **53** into spiroacetals **55** with high stereoselectivities (up to >25/1 dr, 95% ee).[28a]

Independently, Fañanás and Rodríguez established a similar three-component protocol of alkynols **48**, anilines **13**, and glyoxylic acid **56**, using the combined catalysts of JohnPhosAuMe and chiral phosphoric acid **6d**, to give optically active [5,5]-spiroacetals **57** in high yields (eq 11).[28b]

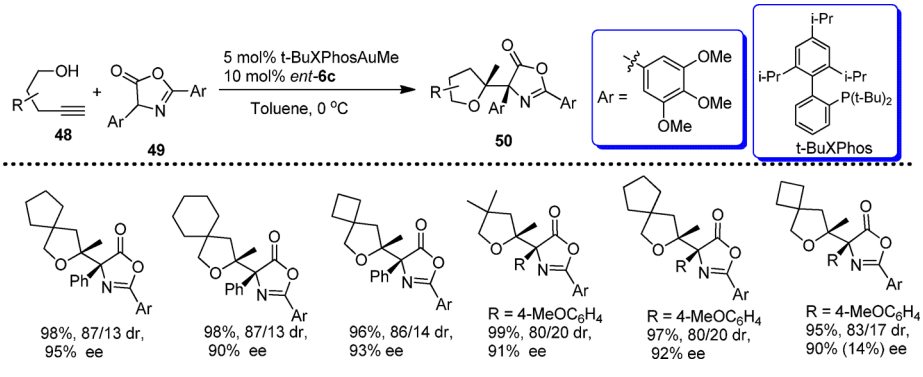


2.2.6. Hydrosiloxylation/Aldol Reaction Cascade. Silyl enolates have a wide scope of applications in organic synthesis as versatile starting materials. The traditional methods to prepare silyl ethers generally require stoichiometric or more amounts of strong base and additional laborious work-up and purification processes (eq 12).[29] Gaunt and co-workers first demonstrated



that the activated alkynes could serve as latent silyl enolates via Lewis acid-catalyzed hydrosiloxylation reaction, which has great

Scheme 14. Cyclization of Alkynols Triggered Asymmetric Addition of Azlactones



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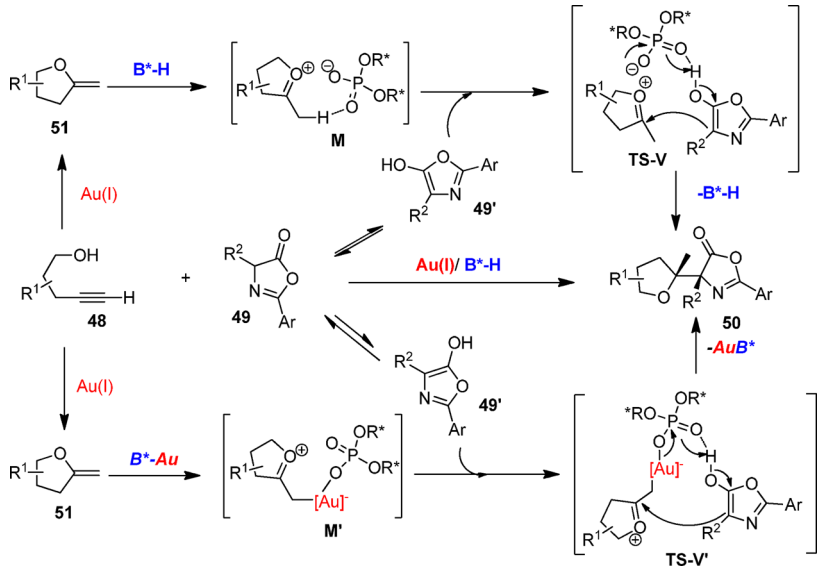
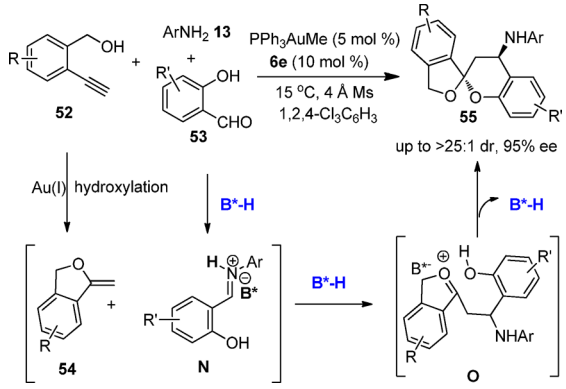
Scheme 15. Plausible Mechanism for Cascade Alkynol Cyclization/Asymmetric Aldol-Type Addition



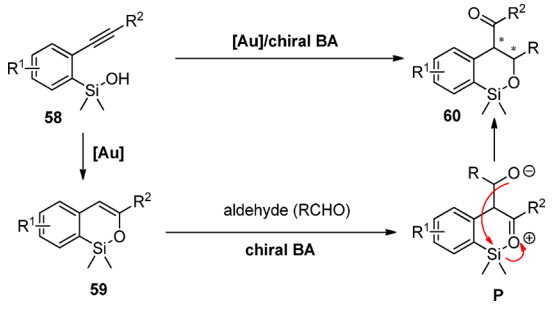
Scheme 16. Relay Catalytic Synthesis of Enantioenriched Spiroacetals



potential in modern synthetic chemistry, especially in tandem reactions (eq 13).[30]

Based on our previous success in the gold/chiral phosphoric acid relay catalysis,[21,24] we proposed a tandem hydrosiloxylation/Mukaiyama aldol reaction for the synthesis of chiral β-hydroxyl carbonyls. As shown in Scheme 17, an intramolecular hydrosiloxylation of **58** might occur under gold catalysis, forming silyl enolates **59**, which could undergo Mukaiyama aldol reaction with aldehydes. After Si−O bond recombination,

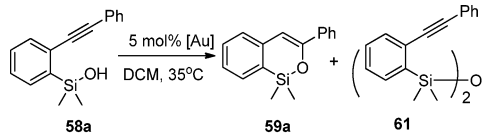
Scheme 17. Mukaiyama Aldol Reaction of *in Situ* Generated Silyl Enolates



products **60** with two continuous stereogenic centers would be anticipated.[31]

In this cascade reaction, the initial intramolecular hydrosiloxylation of **58a** largely relied on the ligands and counteranions of the gold complexes. The use of 5 mol % IPrAuMe complex and *N*-triflyl phosphoramide **7b** successfully suppressed the formation of self-condensation byproduct **61**, giving rise to silyl enolate **59a**, quantitatively (Scheme 18).

Scheme 18. Gold-Catalyzed Intramolecular Hydrosiloxylation



Au(I)	*t* [h]	Conv. [%]	**59a/61**
[AuCl(PPh$_3$)]/AgNTf$_2$	0.5	>99	40:60
[AuMe(t-BuXPhos)]/**7a**	16	64	>99:1
[AuMe(t-BuXPhos)]/**7b**	8	>99	>99:1
[AuMe(IPr)]/**7b**	4	>99	>99:1

The presence of 5 mol % IMesAuMe complex and 15 mol % *N*-triflyl phosphoramide **7b** efficiently promoted the sequential intramolecular hydrosiloxylation, asymmetric Mukaiyama aldol reaction, and cyclization of arylacetylenes **58** with fluorenyl glyoxylate **62** to give **60** in high yields and with excellent enantioselectivities (Scheme 19).

More importantly, the relay catalytic cascade reaction could be scaled up. As a result, commencing with a gram scale cascade hydrosiloxylation/Mukaiyama aldol reaction of **58b** with fluorenyl glyoxylate hydrate **62′**, Wu and co-workers accomplished an enantioselective synthesis of (−)-5-*epi*-eupomatilone-6 (Scheme 20).[32]

2.2.7. Hydrosiloxylation/Diels−Alder Reaction Cascade. The gold-catalyzed hydrosiloxylation also enables structurally unique enynes to be latent 1,3-silyloxydienes, which are principally able to participate in the Diels−Alder reactions (eq 14). The cationic gold(I) complex was the most active

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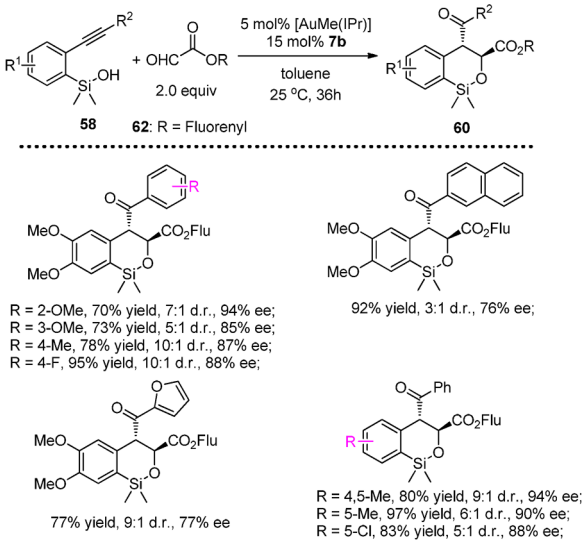
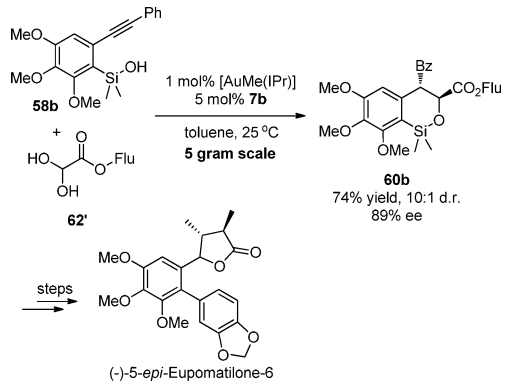
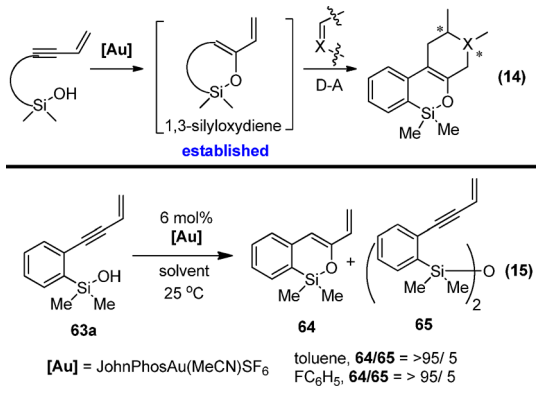
Scheme 19. Highly Enantioselective Hydrosiloxylation/ Mukaiyama Aldol Reaction/Cyclization Cascade



Scheme 20. Enantioselective Synthesis of (−)-5-*epi*-Eupomatilone-6

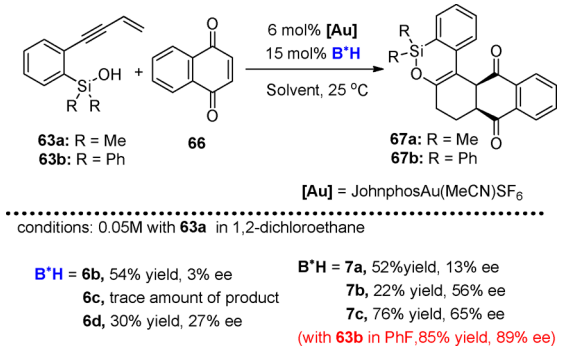




catalyst for the intramolecular hydrosiloxylation reaction to generate the 1,3-silyloxydienes **64** in perfect chemoselectivity and the formation of undesired product **65** was significantly suppressed (eq 15).[33]

An initial attempt found that the relay catalytic cascade intramolecular hydrosiloxylation/asymmetric Diels−Alder reaction of either enyne **63a** or enyne **63b** with benzoquinone **66** could indeed be established under the catalysis of the chiral phosphoric acid, combined with the JohnPhosAu(MeCN)SF_6 complex. However, the desired products were isolated in low yields and with poor stereoselectivity. The more acidic *N*-triflyl phosphoramide **7c** allowed the cascade reaction to proceed cleanly at room temperature in fluorobenzene to give polycyclic product **67b** in an 85% yield and with 89% ee (Scheme 21).

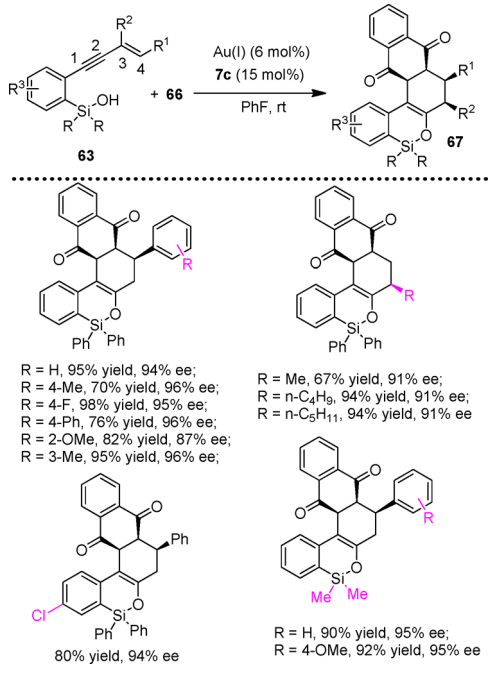
Scheme 21. Relay Catalytic Hydrosiloxylation/Asymmetric Diels−Alder Reaction



A wide range of enynyl disubstituted silanols **63** bearing either an electron-donating or electron-withdrawing aryl substituent at C4 were applicable to the relay catalytic cascade reaction, leading to the generation of polycyclic compounds **67** in high yields and with high levels of enantioselectivity. Moreover, the enynyl diphenylsilanols with an alkyl substituent at C3 also underwent the cascade reaction, cleanly (Scheme 22).

Additionally, a cascade hydrosiloxylation/asymmetric hetero-Diels−Alder reaction of enynyl diphenylsilanols **63** with fluorenyl glyoxylate **62** catalyzed by 1 mol % IPrAu(MeCN)SbF_6 and 15 mol % **7d** proceeded smoothly to produce chiral

Scheme 22. Substrate Scope of the Asymmetric Cascade Hydrosiloyation/Diels−Alder Reaction



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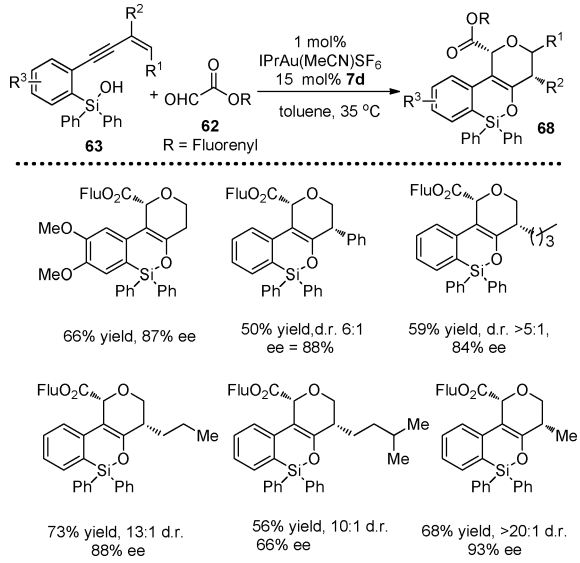
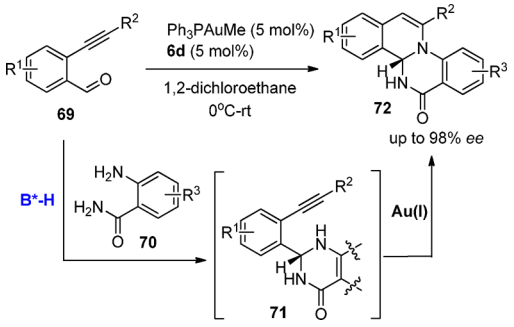
dihydropyranone derivatives **68** in good yields and with high levels of stereoselectivity (Scheme 23).[34]

Scheme 23. Asymmetric Cascade Hydrosiloxylation/Hetero-Diels–Alder Reaction



The gold/chiral phosphoric acid relay catalysis has been a general concept to create new cascade reactions.[35] For instance, Patil developed a cascade condensation/hydroamination reaction of 2-alkynylbenzaldehydes **69** with 2-aminobenzamides **70** catalyzed by the combined catalysts of Ph_3PAuMe and chiral Brønsted acid **6d**, providing a unique and efficient route to optically pure nitrogen-fused 1,2-dihydroisoquinolines **72** (Scheme 24).[35a]

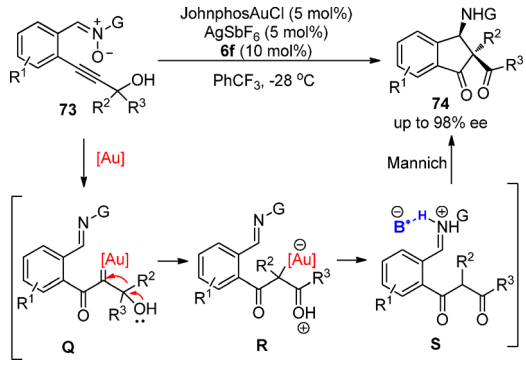
Scheme 24. Relay Catalytic Enantioselective Condensation/Hydroamination Process



Zhang and co-workers reported a gold/chiral phosphoric acid relay catalytic approach for the synthesis of highly optically active β-amino spirocyclic diketone derivatives **74** (Scheme 25).[35b] In this transformation, the gold-catalyzed intramolecular oxo-transfer process initially occurred to form the α-hydroxyl gold carbenoid intermediates **Q**. Semipinacol rearrangement of the intermediates **Q** then proceeded, affording the β-keto esters **R**, which would undergo an enantioselective Mannich reaction under the catalysis of chiral phosphoric acid to furnish products **74**.

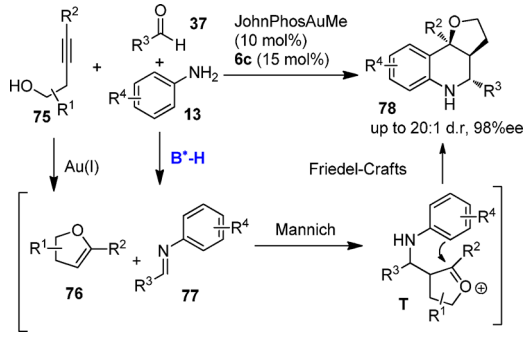
Most recently, Fañanás and Rodríguez established a three-component coupling reaction of alkynols **75**, aldehydes **37**, and anilines **13** catalyzed by a gold(I) complex and the chiral

Scheme 25. Relay Catalytic Redox-Pinacol-Mannich Reaction



phosphoric acid **6c**, providing a straightforward method for the enantioselective synthesis of hexahydrofuro[3,3-*c*]quinolones **78** (Scheme 26).[35c] The computational study of this reaction

Scheme 26. Enantioselective Synthesis of Hexahydrofuro-[3,3-*c*]quinolones



suggested a sequential Mannich/intramolecular Friedel–Crafts process of *in situ* generated enol ethers **76** with imines **77** rather than a concerted Povarov reaction.

2.2.8. Rhodium Complex/Bifunctional Organocatalyst Relay Catalysis. The rhodium/strong chiral Brønsted acid relay catalysis has recently been established by Terada and co-workers.[36] In contrast, neutral Brønsted acids, especially nitrogen or sulfur containing bifunctional organocatalysts, have not been exploited in transition metal-involved relay catalysis, presumably due to the deactivation effect of both catalytic cycles.

The diazo esters **79** oxidatively add to a metal complex to generate metal carbene species **U**, which very quickly undergo semipinacol rearrangement to yield β-keto esters **81**.[37] Under the promotion of a chiral bifunctional organocatalyst, the β-keto esters **81** would undergo asymmetric Michael addition to nitroolefins **80** (Scheme 27).

The combination of $Rh_2(OAc)_4$ and bifunctional squaramide **5** proved to be the best binary catalysts and provided the best results in terms of yields and enantioselectivity. Importantly, the relay catalytic process between β-hydroxy α-diazo esters **79** and nitroolefins **80** was able to tolerate a diverse range of substrates, offering direct access to highly functionalized chiral nitro compounds **82** that were essentially impractical otherwise (Scheme 28). Moreover, the nitro group and the tethered functionalities in the products would allow further transformations to access biologically interesting optically pure molecules.[38]

2.2.9. δ-Lewis Acid/Chiral Phosphoric Acid Relay Catalysis. The Friedländer reaction, a reliable and easily

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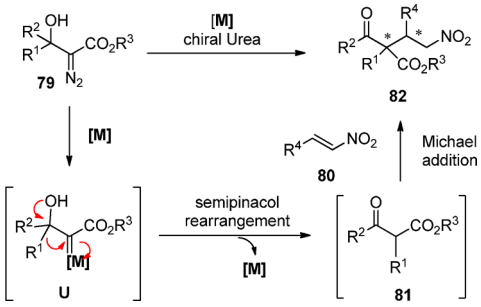
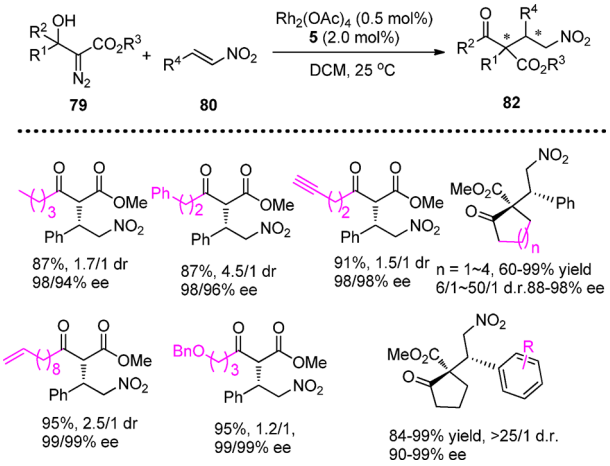
Scheme 27. Cascade Semipinacol Rearrangement/Michael Addition Reaction



Scheme 28. Cascade Semipinacol Rearrangement/ Asymmetric Michael Addition Reaction



operative approach to access quinolines, could be accelerated by either Brønsted or Lewis acid.[39] The chiral phosphoric acids have been excellent catalysts for the enantioselective transfer hydrogenation of quinolines.[40] Thus, the combination of a Lewis acid and a chiral phosphoric acid would render a cascade reaction that would directly transform the starting materials of the Friedländer reaction into optically active tetrahydroquinolines.

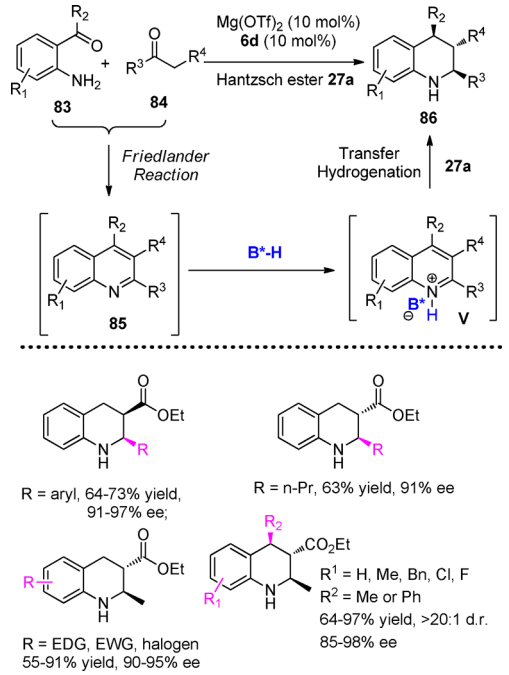
The presence of 10 mol % $Mg(OTf)_2$ and 10 mol % chiral phosphoric acid was found to most efficiently promote the cascade Friedländer condensation/transfer hydrogenation. Both 2-amino benzaldehydes and 2-amino phenyl ketones were accommodated to give a broad scope of highly substituted tetrahydroquinoline derivatives **86** with concomitant generation of multiple stereogenic centers in excellent levels of stereochemical control (Scheme 29).[41]

Kinetic studies revealed that although the Friedländer step could be accelerated by either $Mg(OTf)_2$ or Brønsted acid **6d**, a much faster and cleaner reaction was observed in the presence of the binary catalyst system, due to the synergistic effect between the Lewis and Brønsted acids.[42] As for the asymmetric hydrogen transfer process, the chiral phosphoric acid **6d** was determined to be the sole catalyst.

3. CONCLUSION

We have demonstrated, both conceptually and practically, the fascinating capabilities of asymmetric organocatalysis combined with metal catalysis, a robust strategy that permits the creation of unprecedented asymmetric transformations by using either cooperative or relay catalysis. Through simultaneous activations

Scheme 29. Step-Economical Synthesis of Tetrahydroquinolines



of both nucleophiles and electrophiles, asymmetric cooperative catalysis using palladium(0) complexes combined with chiral phosphoric acids has afforded highly enantioselective allylic alkylation reactions. The binary catalyst systems consisting of rhodium acetate and chiral phosphoric acids have allowed a diverse range of multicomponent reactions to be accessed by the electrophilic trapping rhodium-associated ylides. Based on gold(I)/chiral Brønsted acid relay catalysis, a broad scope of unprecedented asymmetric cascade reactions have been developed, leading to the efficient preparation of structurally complex and diverse chiral molecules by taking advantage of the rich chemistry in gold-activated alkynes and the robustness of the chiral phosphoric acids in the control of stereochemistry. The Lewis acid/chiral phosphoric acid and rhodium/bifunctional squaramide binary catalyst systems have shown great potential in the creation of step-economical protocols for the direct installation of ubiquitous functionalities into structurally diverse molecules with potential synthetic applications.

Because of plentiful activation modes and unique ability to activate inactive chemical bonds demonstrated by metal catalysis, together with the excellent functionality tolerance of organocatalysis, asymmetric organocatalysis combined with metal catalysis should therefore create new chemistry that we have not yet imagined. This hypothesis is supported by not only the examples highlighted in this Account but also some other typical examples recently developed from worldwide research teams.[6,43] It can be anticipated that asymmetric organocatalysis combined with metal catalysis will be a booming field among homogeneous catalysis in the future.

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Notes

The authors declare no competing financial interest.

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Zhi-Yong Han received his B.S. degree in 2004 and Ph.D. degree in 2011 from University of Science and Technology of China under the direction of Prof. Gong. His Ph.D. research focused on asymmetric relay catalysis consisting of organo/metal binary systems. Currently, he is a postdoctoral fellow in Arndtsen's group at McGill University.

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Liu-Zhu Gong graduated from Henan Normal University in 1993 and received his Ph.D. in 2000 from Institute of Chemistry, Chinese Academy of Sciences. He became an associate professor of Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, in 2000 and was promoted to full professor in 2001. Since 2006, he has been a full professor of University of Science and Technology of China. He was appointed the Cheung Kong Scholar Chair Professor of organic chemistry in 2008. His current research interest is focused on organo- and transition metal-catalyzed asymmetric synthesis and total synthesis of natural products.

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