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MINI REVIEW

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Designed Bifunctional Ligands in Cooperative Homogeneous Gold Catalysis

Xinpeng Cheng & Liming Zhang*

Department of Chemistry and Biochemistry, University of California, Santa Barbara, CA 93106

*Corresponding author: zhang@chem.ucsb.edu

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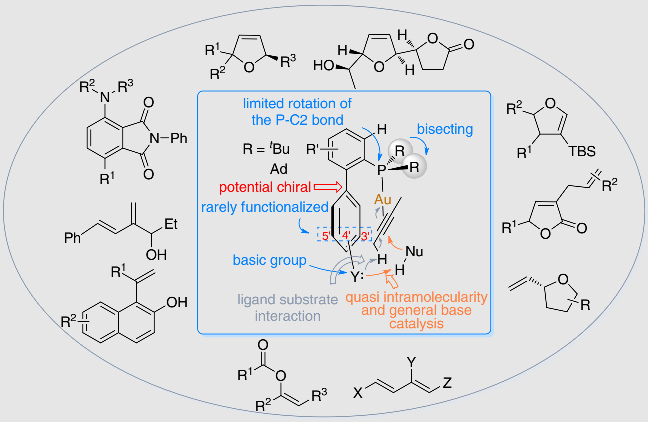
Over the past two decades, homogeneous gold catalysis has experienced exponential development and contributed a plethora of highly valuable synthetic methods to the synthetic toolbox. Metal–ligand cooperative catalysis is a versatile strategy for achieving highly efficient and/or novel catalysis but has seldom been explored in gold chemistry. This minireview summarizes the progress we have made in developing remotely functionalized biaryl-2-ylphosphine ligands and employing them in cooperative gold catalysis that achieves excellent catalytic efficiency or realizes previously unknown reactivities. This approach also provides new venues for implementing asymmetric gold catalysis.



Keywords: **homogeneous gold catalysis, cooperative catalysis, phosphine, bifunctional ligands**

Introduction

In the past 20 years, homogeneous gold catalysis has emerged from a few prior pioneer studies[1–7] to a full-blown research field of high-impact and extraordinary synthetic utility.[8–20] The potent soft Lewis acidity of Au(I) complexes permits the development of various versatile catalytic methods from alkyne and allene substrates. These methods are increasingly employed in the synthesis of natural products and/or bioactive targets.[21–24] Further developments in Au(I) catalysis demand advances in fundamental reactivities and/or new reaction modes.

Ligands are of critical importance in metal catalysis. In addition to their role in modulating the steric environment and the electronic properties of the metal center during the reaction, multifunctional ligands[25] could be engineered to actively participate in bond formation/breaking processes, thereby achieving transformations otherwise unattainable. This type of metal–ligand cooperative catalysis[26–29] could be highly versatile. Many systems of exceptional synthetic values have been developed, including Noyori's ruthenium-catalyzed asymmetric ketone reduction,[30,31] Milstein's electron-rich PNP- and PNN-type Ru pincer complexes for dehydrogenative coupling reactions,[32] the Shvo's Ru catalyst for hydrogenation/dehydrogenation,[33] and first-row transition metal catalysis based on redox noninnocent ligands.[34] However, this highly versatile and valuable ligand cooperation strategy had not been explored in Au(I) catalysis before our initial work in 2014.[35] In this account, we summarize our efforts in the development of bifunctional

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phosphine ligands that enable cooperative Au(I) catalysis of exceptional efficiency and/or with unprecedented reactivities.

Ligand design considerations

Many ligands used in Au(I) catalysis are adopted directly from Pd catalysis. They were initially designed to facilitate the chemistry of square-planar Pd(II) complexes, and hence, are hardly optimal for Au(I) catalysis, which features a distinct and robust linear alignment of ligating atom–Au(I)–π bond. This linear structure of the Au(I) complex poses significant challenges to realizing metal–ligand cooperation due to the spatial separation of the ligand and the alkyne/allene substrate. Moreover, as the incoming nucleophile undergoes *anti*-attack at the substrate, the spatial separation between the ligand and nucleophile could be even larger. However, these spatial constraints for the desired cooperation in catalysis could be overcome by a proper choice of the ligand framework.

In 2014, we initiated a project to develop new biphenyl-2-ylphosphine ligands tailored specifically to the linear Au(I) structure for achieving ligand–substrate/nucleophile interactions, with two design features (Figure 1a): (1) the bottom half of the pendant phenyl ring (i.e., the C3’, C4’, and C5’) was functionalized with a basic Y group; (2) the R groups on phosphorus were made bulky to restrict the free rotation of the C2–P bond and to force the P–Au–alkyne centroid axis to be roughly parallel to the ligand pendant phenyl ring and the Au-coordinated C–C triple bond to lie proximal to C3’, C4’, and C5’. The conformational considerations were corroborated by the density functional theory (DFT)-optimized structure shown in Figure 1b. As outlined in Figure 1a, two types of secondary coordination sphere interactions are envisioned: (1) the ligand basic Y group, being spatially close to the C–C triple bond, able to interact with the alkyne substrate via deprotonation at the propargylic position, and (2) the Y group capable of forming an H-bond with the incoming protic nucleophile and partially deprotonate it during its attack at alkyne (Figure 1a). It is anticipated that allenes could also be suitable substrates. These interactions could enable new transformations, enhance the reaction efficiency, and/or achieve unprecedented selectivity. Moreover, the biphenyl axis could be made chiral by restricting its rotation. Consequently, this metal–ligand cooperation would be made asymmetric, thereby rendering asymmetric Au(I) catalysis.

Notably, despite the popularity of ligands based on the privileged biphenyl-2-ylphosphine framework, most reported ones, including several developed by Buchwald,[36–38] featured only alkyl or simple aryl groups[39] at the C3’, C4’, and C5’ positions (Figure 1c). The only exceptions were a sulfonate group for increasing catalyst aqueous solubility[40] and a phenol moiety for regioselective Pd-catalyzed Kumada coupling[41] (Figure 1c). As such, regardless of the metal employed, our designed bifunctional ligands constituted new members of biaryl-2-ylphosphines and deemed novel in the context of metal–ligand cooperation.

For the past several years, we have prepared a series of bifunctional biaryl-2-ylphosphine ligands to investigate their capability to enable cooperative Au(I) catalysis. Figure 2 depicts the successful ones, which could be divided into two subtypes: one featuring a remote amide group as exemplified by WangPhos and (*R*)-**L1** (Figure 2a) and the other possessing a more basic aniline or tertiary amine moiety at the bottom half of the pendant ring, for example, **L2**–**L8** (Figure 2b). The amide-based ligands tend to accelerate nucleophilic addition to alkynes and allenes by interacting with incoming protic nucleophiles, while the amine-based ones are often deployed to facilitate unprecedented Au(I) catalysis by enabling challenging deprotonative processes.

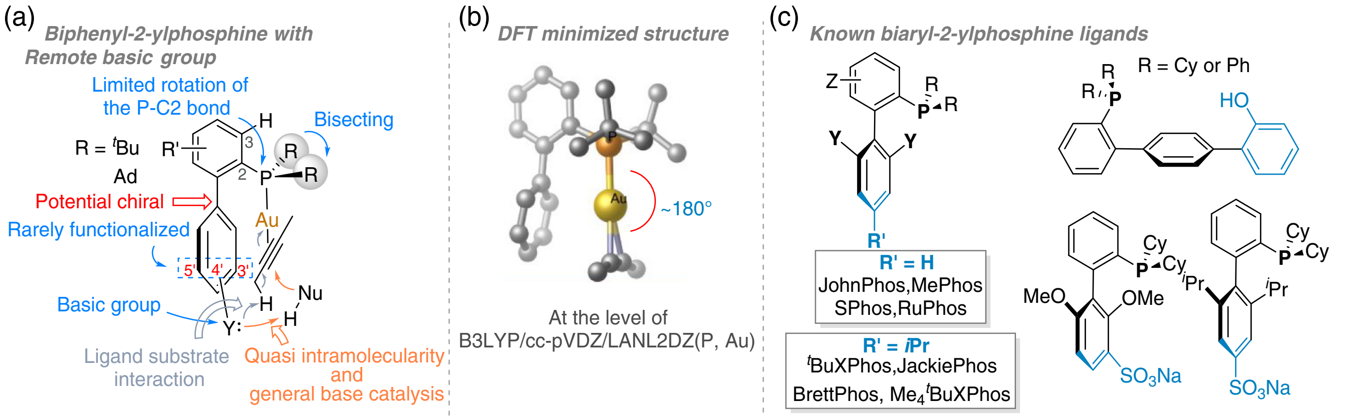

Figure 1 | *Biaryl-2-ylphosphine ligands featuring a remote basic group: design.*

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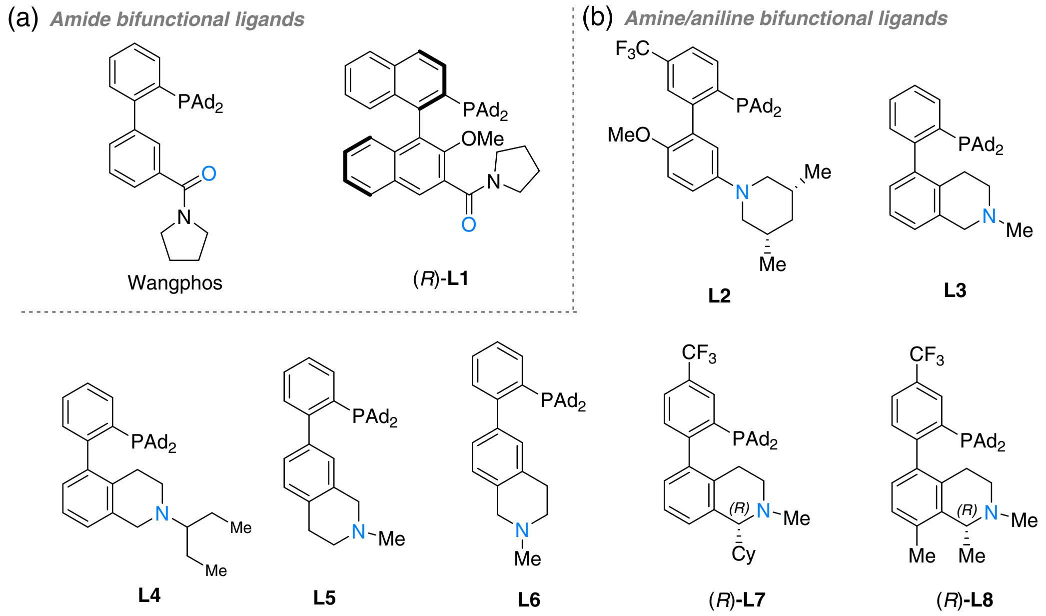
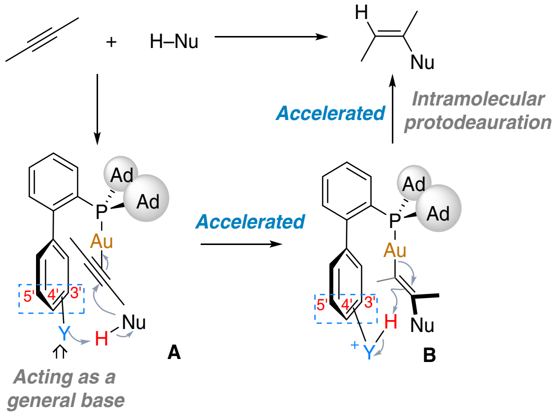


Figure 2 | *A selected list of our reported bifunctional ligands.*

Bifunctional biphenyl-2-ylphosphines for accelerated nucleophilic attack of alkynes and allenes

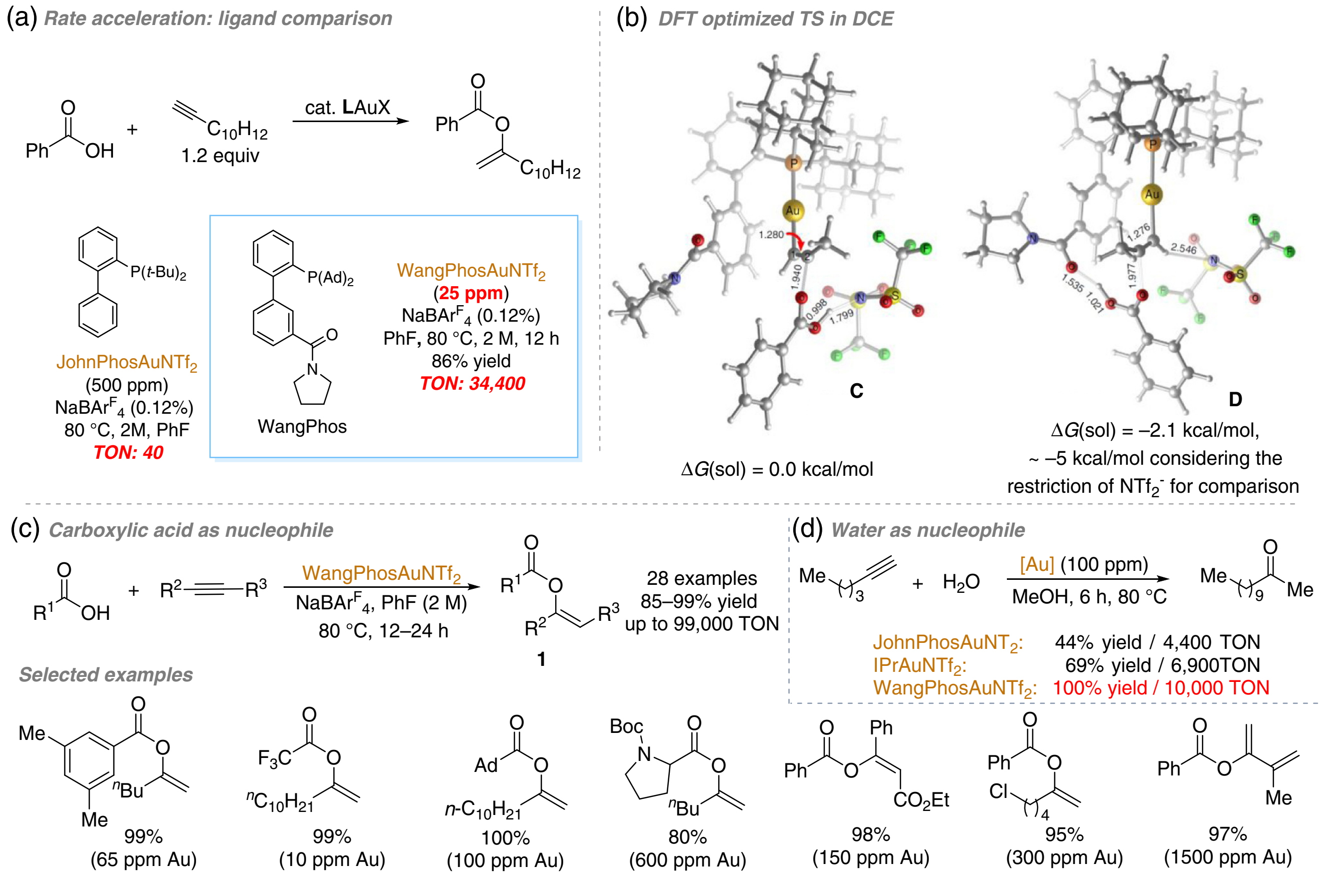
In our initial foray into the ligand design,[35] as shown in Scheme 1, we envisioned that the basic Y group could partially deprotonate the protic nucleophile in the transition state **A**, which would result in a lowered barrier, and hence, accelerated nucleophilic attack at the gold-activated C–C triple bond via a general base catalysis. Furthermore, subsequent protodeauration via **B** could also be accelerated due to its intramolecular nature. Such an addition to allenes should be similarly accelerated. This would lead to enhanced reaction kinetics and increased catalyst turnover frequency, which would likely result in improved turnover numbers and, in turn, lower catalyst loadings.



Scheme 1 | *Ligand designed for accelerated nucleophilic attack using alkyne as an example.*

Accelerated addition to alkynes by oxygen-based nucleophiles

In our first implementation of this design, we examined the Au(I)-catalyzed addition of carboxylic acids to alkynes.[35] We discovered that a carboxamide could be a suitable Y group for achieving the anticipated reaction acceleration. Moreover, WangPhos featuring a 3'-pyrrolidine-1-carbonyl was found to be particularly efficacious. With its cationic Au(I) complex as the catalyst (Scheme 2a), the addition of benzoic acid to 1-dodecyne was estimated to be accelerated 860 times when compared with that by the Au(I) catalyst prepared from JohnPhos, an electronically and sterically similar ligand but only missing the remote amide group. The dramatic rate enhancement was consistent with the co-operation of the amide functionality during catalysis, which was corroborated by DFT calculations. As shown in Scheme 2b, the calculated transition state **D** featuring a H-bonding between the amide oxygen and the carboxylic acid proton is lower in energy by an estimated ~5 kcal/mol than the alternative transition state **C**, in which the proton forms an H-bond with the counteranion NTf_2^-. As a consequence of this substantially enhanced the reaction rate, the catalyst loading was lowered to 25 ppm, and the catalyst TON reached 34,400, due to the addition of a single amide group, which was remarkable. It is noteworthy that the position of the amide moiety, that is, C3', is essential, as a related C4' ligand variant led to less than half of the rate acceleration. Selected

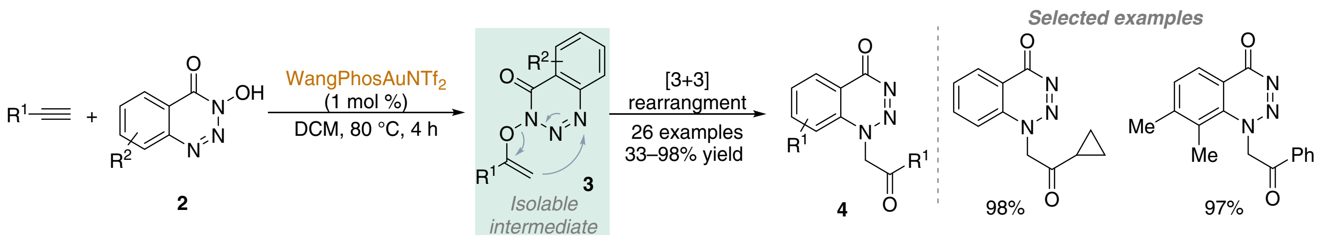


Scheme 2 | *Accelerated addition of carboxylic acid to alkyne and alkyne hydration.*

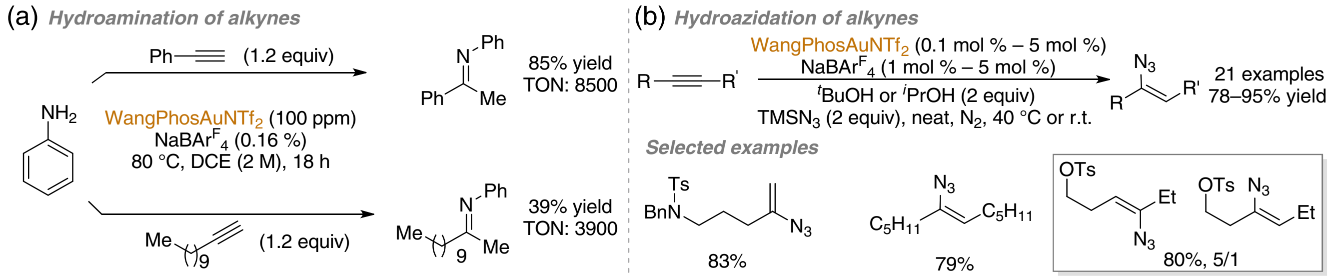
examples of the reaction scope are shown in Scheme 2c. We found that carboxylic acids bearing a myriad range of functional groups, including Bpin, thiophene, diene, different halogens, and *N*-protected proline, were well tolerated, and the desired vinyl esters **1** were formed in nearly quantitative yields with catalysis loadings of 600 ppm or less. Notably, the reaction of much more acidic trifluoroacetic acid (TFA) was achieved using 10 ppm of the Au(I) catalyst, resulting in a catalyst TON of 99,000. Terminal and internal alkynes with various functionalities were also accommodated.

Besides, WangPhos facilitated alkyne hydration. As shown in Scheme 2d, WangPhos was demonstrated to be a more effective ligand than JohnPhos and IPr, despite the reaction conduction in protic methanol; meanwhile, the catalyst TON reached 10,000.

In 2020, Liu's group reported that WangPhos could promote the *O*-nucleophilic addition of *N*-hydroxybenzo [1,2,3]-triazin-4(3 *H*)-ones **2** to alkynes (Scheme 3).[42] The resulting isolable intermediate **3** subsequently underwent a [3+3]-sigmatropic rearrangement to afford 1-(2-oxo-2-arylethyl)benzo [*d*][1,2,3]triazin4(1 *H*)-ones **4** in moderate to excellent yields. During the optimization of the reaction conditions, WangPhos was a much more effective ligand, leading to the desired product in 98% yield, while Ad-JohnPhos and IPr led to 66% and 29% yield, respectively.



Scheme 3 | *Accelerated addition of* N-*hydroxybenzo[1,2,3]-triazin-4(3H)-ones to alkynes.*



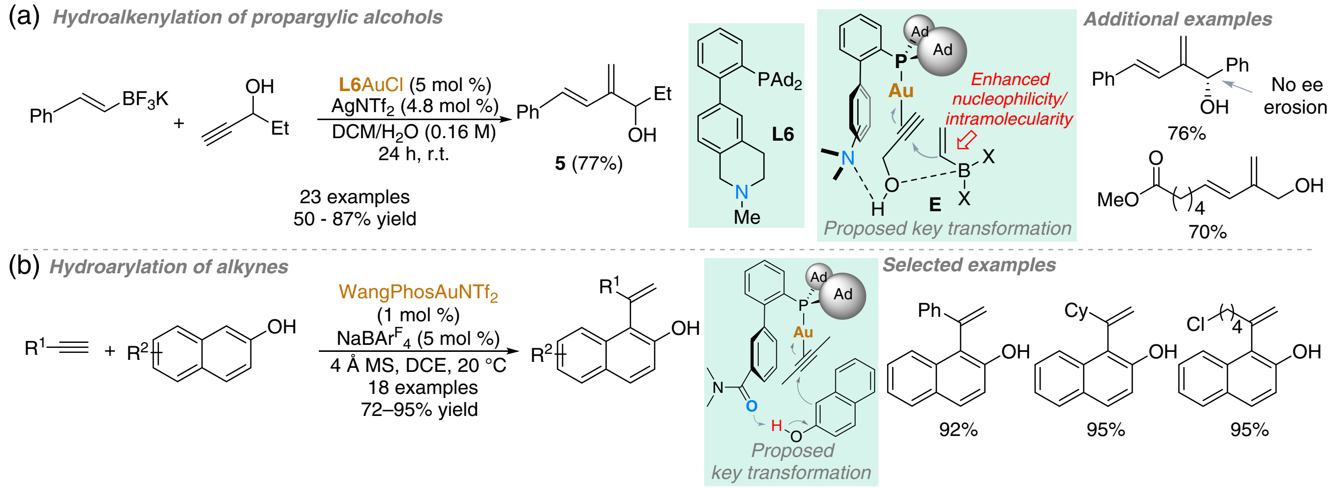
Scheme 4 | *Nitrogen as the nucleophile for the accelerated nucleophilic attack.*

Accelerated addition to alkynes by nitrogen-based nucleophiles

In our initial study,[35] we also explored the hydroamination of alkynes by anilines (Scheme 4a). When phenylacetylene was used as the substrate, the TONs reached 8500. In the case of 1-hexyne, the TONs were 3900. Later, we demonstrated that the Au(I)-catalyzed hydroazidation of alkynes could also be accelerated in the presence of WangPhos to afford vinyl azide products (Scheme 4b).[43] In this chemistry, hydrazoic acid was generated in situ via the reaction between commercially available trimethylsilyl azide (TMSN$_3$) and *t*-butanol or isopropanol. Due to the enhanced reaction rate, most reactions with terminal alkyne substrate require only mild conditions using 0.1 mol% catalyst at 40 °C. Unactivated internal alkynes have not succumbed previously to hydroazidation due to their decreased reactivities, this Au(I) catalysis overcame the limitation, albeit requiring 5 mol% catalyst.

Accelerated addition to alkynes by carbon-based nucleophiles

In 2018, we reported the Au(I)-catalyzed intermolecular hydroalkenylation of propargylic alcohols by alkenyl trifluoroborates (Scheme 5a), resulting in the regioselective formation of dienols (e.g., **5**) in moderate to high yields.[44] Instead of WangPhos featuring a remote amide group, ligand **L6** bearing a remote tertiary amino group was optimal, affording **5** in 77% yield. Conventional ligands, including Ph$_3$P, IPr, JohnPhos, or MorDalPhos, led to a <6% yield of **5**, and the related ligands **L3** and **L5** possessing the same tertiary amine moiety but at slightly different locations led to 18% and 37% yields, respectively. These results highlighted the importance of the tertiary amino group and its discreet location. DFT calculations supported the cooperative model shown as structure **E**, where the remote amino group enhanced the nucleophilicity of the alcohol oxygen via partial deprotonation, which, in turn, interacted with the alkenylboron partner with increased affinity. Consequently, the alkenyl group was more nucleophilic and spatially proximal to the Au(I)-activated alkyne, both of which increased the reaction rate. This strategy of activating a carbon-based nucleophile, such as the alkenylboron species via the relay of the propargylic HO group, is rather unique and achieved the reactivity inaccessible by conventional ligands. Of note, no erosion of the propargylic configuration was observed with a chiral propargylic alcohol substrate.



Scheme 5 | *Hydroalkenylation and hydroarylation of alkyne.*

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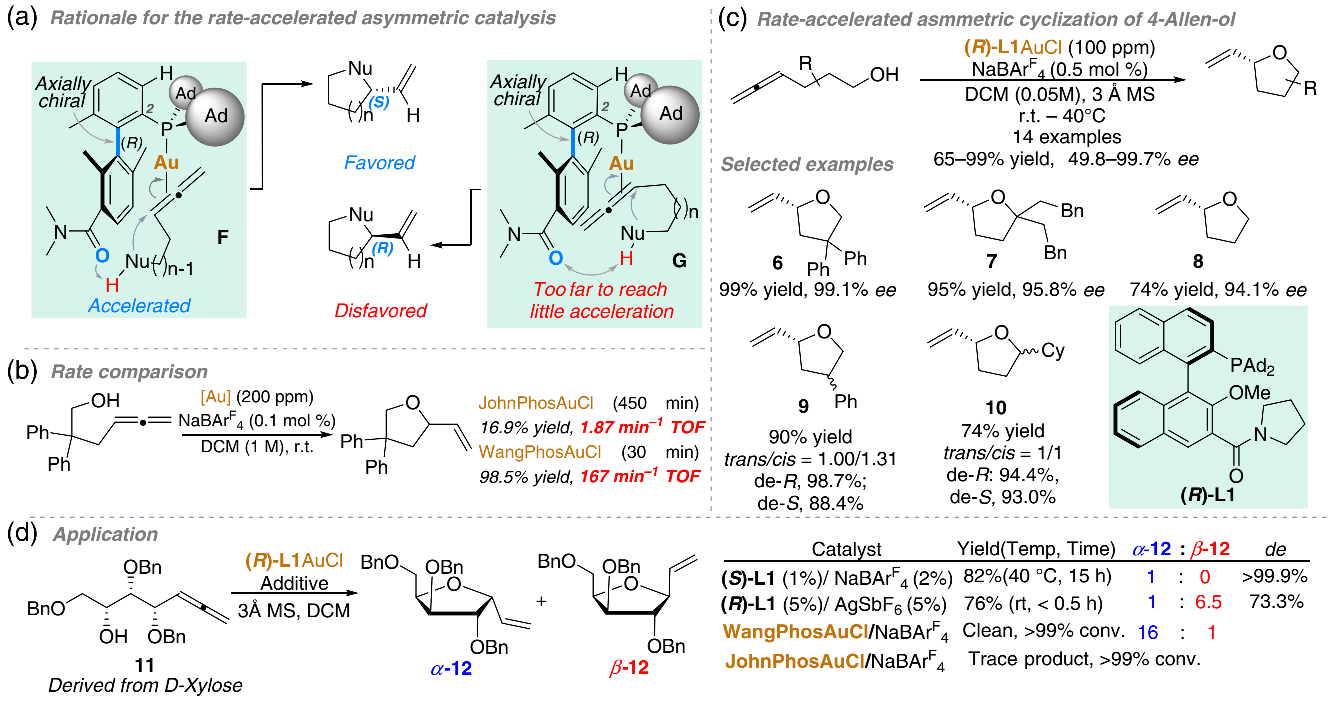
In 2020, we described an Au(I)-catalyzed hydroarylation of terminal alkynes, facilitated by WangPhos (Scheme 5b).[45] Typical ligands such as Ph_3P, IPr, and JohnPhos were ineffective. Thus, we proposed that the substantially accelerated addition of the α-carbon of β-naphthols to the C–C triple bond was due to the partial phenolic deprotonation by the remote amide group of WangPhos in the addition transition state. The essential role of partial deprotonation in the form of H-bonding was substantiated when no apparent reaction was noticeable with 2-methoxynaphthalene.

Ligand-accelerated asymmetric gold catalysis: Cyclization to allenyl alcohols

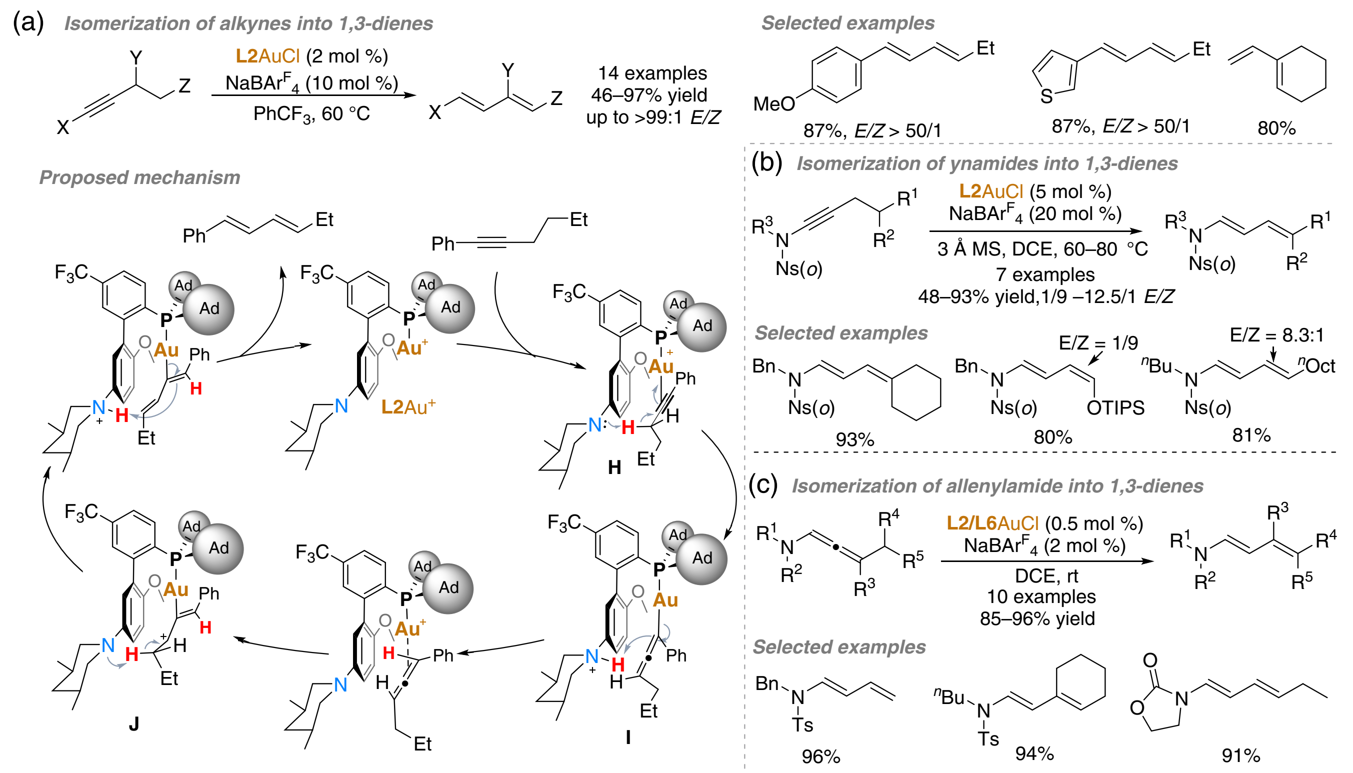
Asymmetric Au(I) catalysis[18,46–51] is mostly achieved by employing chiral Au(I) catalysts featuring atropisomeric bisphosphine, monodentate chiral phosphoramidite or sulfinamidephosphine (SadPhos)[52–55] as the ligands, and in a few cases by using a chiral counteranion.[56–59] These systems rely mainly on the chiral steric environment to achieve asymmetry. Due to rate retardation caused by steric hindrance or the lack of rate acceleration, the reactions tend to require high catalyst loadings (typically 5 mol %), low reaction temperatures, and long reaction times. On the other hand, the accelerated nucleophilic addition shown in Scheme 2 allows the realization of asymmetric induction based on the accelerated formation of one stereoisomer over its enantiomer. This strategy of achieving asymmetric Au(I) catalysis is not previously known; more importantly, due to the overall accelerated reaction, low catalyst loadings could be permitted.[60]

As shown in Scheme 6a, the cyclization of an allenyl nucleophile could generate a new chiral center. With a chiral version of WangPhos featuring a restricted biaryl axis, the corresponding cationic Au(I) complex could bind to a monosubstituted allene to form two competing complexes **F** and **G**, prior to cyclization. With the 3'-amide group positioned optimally to direct the attack of the tethered nucleophile in the case of **F**; the cyclization should be much accelerated. On the contrary, the amide group is far away from the nucleophile in **G**, and hence, little rate increase could be expected. As a result, the cyclization would mostly go through **F**, thereby becoming enantioselective or diastereoselective. This anticipated acceleration was confirmed with WangPhos as the ligand, (Scheme 6b), leading to >88-fold increase in turnover frequency (TOF) over JohnPhos. As shown in Scheme 6c, (*R*)-**L1**, an axially chiral version of WangPhos prepared in a four-step sequence from commercially available (*R*)-binol, indeed enabled highly enantioselective cyclization of achiral allenyl alcohols, affording tetrahydrofurans (THFs) **6**–**8** with >94% ee. Moreover, with chiral substrates, high diastereomeric excesses in **9** and **10** were achieved with each substrate enantiomer regardless of the configuration. This chemistry constituted the first-accelerated asymmetric Au(I) catalysis,[18,51] and due to the fast reaction rate, the catalyst loadings could be as low as 100 ppm.



Catalyst	Yield(Temp, Time)	α-12 : β-12	de
(**S**)-**L1** (1%)/ NaBAr$^F_4$ (2%)	82%(40 °C, 15 h)	1 : 0	>99.9%
(**R**)-**L1** (5%)/ AgSbF$_6$ (5%)	76% (rt, < 0.5 h)	1 : 6.5	73.3%
WangPhosAuCl/NaBAr$^F_4$	Clean, >99% conv.	16 : 1	
JohnPhosAuCl/NaBAr$^F_4$	Trace product, >99% conv.		

Scheme 6 | *Ligand-promoted asymmetric cyclization of 4-allene-1-ol.*



Scheme 7 | *Isomerization of propargylic esters into 1,3-dienyl esters.*

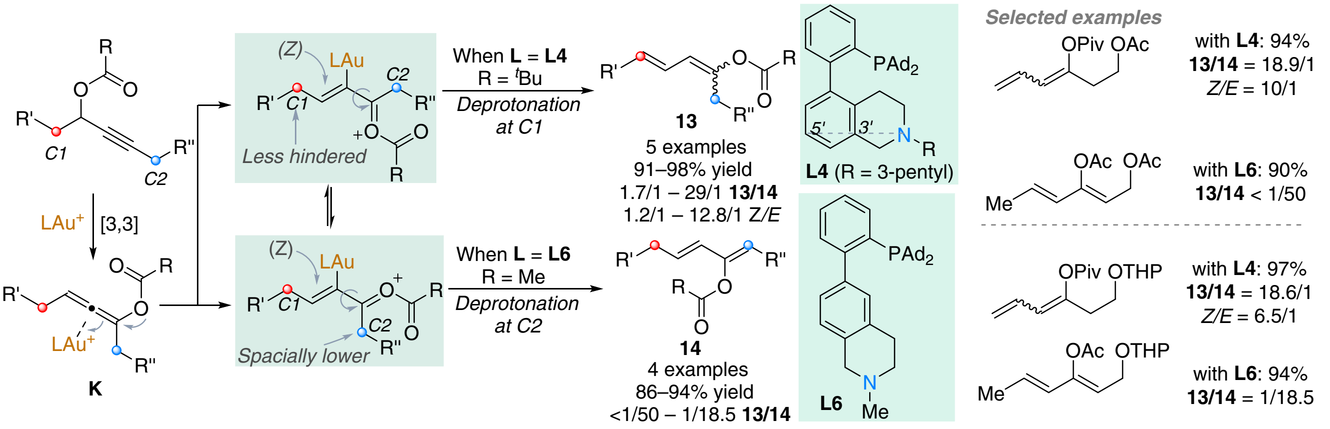
To examine the synthetic utility of this chemistry, the allenyl polyol **11**, prepared from d-xylose, was subjected to the chemistry (Scheme 6d). With WangPhos as the ligand, an intrinsic preference for the α-*C*-glycoside α-**12** over its β-anomer (16:1) was observed. In a matched scenario with (*S*)-**L1** as the ligand, α-**12** was formed exclusively. On the other hand, in the mismatched scenario with (*R*)-**L2**, the large intrinsic preference for the α-anomer was reverted to favor β-**12** by a ratio of 6.5/1. This is valuable in stereoselective access to *C*-glycosides. Additionally, the reaction resulted in a complex and intractable mixturewhen JohnPhos was used as the ligand, revealing that due to the accelerated cyclization, these amide-functionalized ligands also enabled valuable chemoselectivity as side reactions are no longer kinetically competitive.

Amine-Functionalized Bifunctional Phosphine Ligands Enabling Substrate Soft Deprotonation

Another approach to achieving Au–ligand cooperation is to engage a ligand and alkyne substrate interaction. We envisioned that by installing an amino group as Y at the bottom half of the pendant benzene ring as in the cases of **L2–L8,** the amino group might be sufficiently basic to remove the proton at the propargylic position, the acidity of which should be enhanced by the coordination of the cationic and acidic Au center (see Figure 1a). Typically propargylic deprotonation is accomplished by $NaNH_2$ or *n*BuLi. This soft deprotonation by a much less basic amine (pKa: 4–10) was unknown and conceptually similar to, yet more challenging than soft enolization.

Isomerization of alkyne/allene into diene

In the first implementation of this design, alkynes were isomerized into conjugated dienes with good to excellent *E*-selectivities and under mild conditions by employing the 3,5-dimethyl piperidine-functionalized biphenyl-2-ylphosphine **L2** as the ligand (Scheme 7a). The proposed mechanism of this reaction using 1-phenyl-1-hexyne as an example entailed the designed propargylic deprotonation via the cooperation of the ligand nitrogen and the cationic Au, as depicted in the structure **H**, the *ipso* -protodeauration of the thus-generated allenylgold [Au(I)] **I**, and subsequent activation of the allene intermediate by the same Au(I) catalyst to form the Au(I)-substituted allylic cation **J**, which, in turn, underwent a second proton abstraction by the same basic aniline moiety to deliver the diene product upon protodeauration. The overall transformation involved metal–ligand cooperation in each of the two proton shuttling. The deprotonation of a weakly acidic propargylic proton (p*K*a >30)



Scheme 8 | *Ligand-enabled isomerization of propargylic esters into dienyl esters.*

by the ligand aniline (p*Ka* ~4) was remarkable and highlighted the synergy between the cationic Au center and the basic aniline. We termed it as *soft propargylic deprotonation*. A DFT study[61] supported the proposed mechanism of isomerization of alkyne to allene and further revealed that the propargylic deprotonation followed a *syn-periplanar* process.

This isomerization strategy was later applied to ynamides and allenylamides (Scheme 7c) successfully to afford dienylamide products.[62] The reactions of ynamides required heating, while those of allenylamides proceeded at ambient temperature, revealing that the first proton migration was slower.

The isomerization of aliphatic internal alkynes into dienes is plagued by the lack of regiochemical control in both the formation of allene intermediates and their further isomerization to the products. To circumvent the regiochemical issues in the allene formation, we employed the Au(I)-catalyzed [3,3]-rearrangement of propargylic esters to produce the carboxyallenes intermediate **K** regiospecifically (Scheme 8).[63] We found that the isomerization of the in situ generated **K** could be achieved with opposite regioselectivities by positioning the ligand tertiary amino group at different locations and tuning the reaction sterics.[64] As shown in Scheme 8, when ligand **L4**, having a bulky tertiary amine at the C3'–C5' level was employed, and the substrates were pivalates, regioselective deprotonation occurred at the sterically more accessible C1 position of the vinyl oxocarbenium intermediate, leading to the selective formation of the dienyl ester **13**. However, when the ligand **L6** processed methyl-substituted nitrogen at a spatially much lower position and R is a methyl group, regioselective deprotonation occurred at the C2 position of the vinyl oxocarbenium species. This study, along with the hydroalkenylation chemistry shown in Scheme 5, confirmed the importance of optimal positioning of an amino group ligand in achieving cooperative Au(I)-catalysis.

The reaction of allene intermediates other than 1,3-diene formation

As demonstrated in Scheme 7a, allene was generated as an intermediate from alkyne en route to 1,3-diene. When the isomerization to 1,3-diene was impeded or disfavored, alternative reaction outcomes emerged. This approach provided rapid access to functional structures directly from alkyne substrates by circumventing the typically synthetic, more challenging allenes.

To this end, we reported the cycloisomerization of allylic alkynoates to α-allylbutenolides using the *tert*-amino-functionalized **L3** as the ligand (Scheme 9a).[65] The reaction tolerated various substituents and displayed good to excellent yields. Mechanistically, the allene intermediate **15** generated upon the first proton migration underwent cyclization in the presence of the same Au(I) catalyst to generate the cationic species **L**. This pathway was favored over the second proton migration because it was facile and the electron-withdrawing ester group destabilized the formation of the allylic cation intermediate of type **J** (Scheme 7a). The ligand amino group most likely served as a proton shuttle in the deprotonative aromatization of **L** and the subsequent protodeauration. Thus, the generated allyloxyfuran **16** underwent the Claisen rearrangement to form the unconjugated butenolide **17**, which formed the final product **18** upon a third proton migration. Our unpublished results suggest that this last step is also facilitated by metal–ligand cooperation. As such, this chemistry involves three metal–ligand cooperative proton migrations.

Concurrently, we demonstrated that the related cycloisomerization of alkynamides into 2-aminofurans could be realized (Scheme 9b).[65] Furans with an electron-donating 2-*N,N*-dialkylamino group, are highly electron-rich and have seldom been prepared. This work provided expedient access to this challenging class of furans. Indeed, except in one case with a less electron-donating aniline group, the furan intermediates were too sensitive

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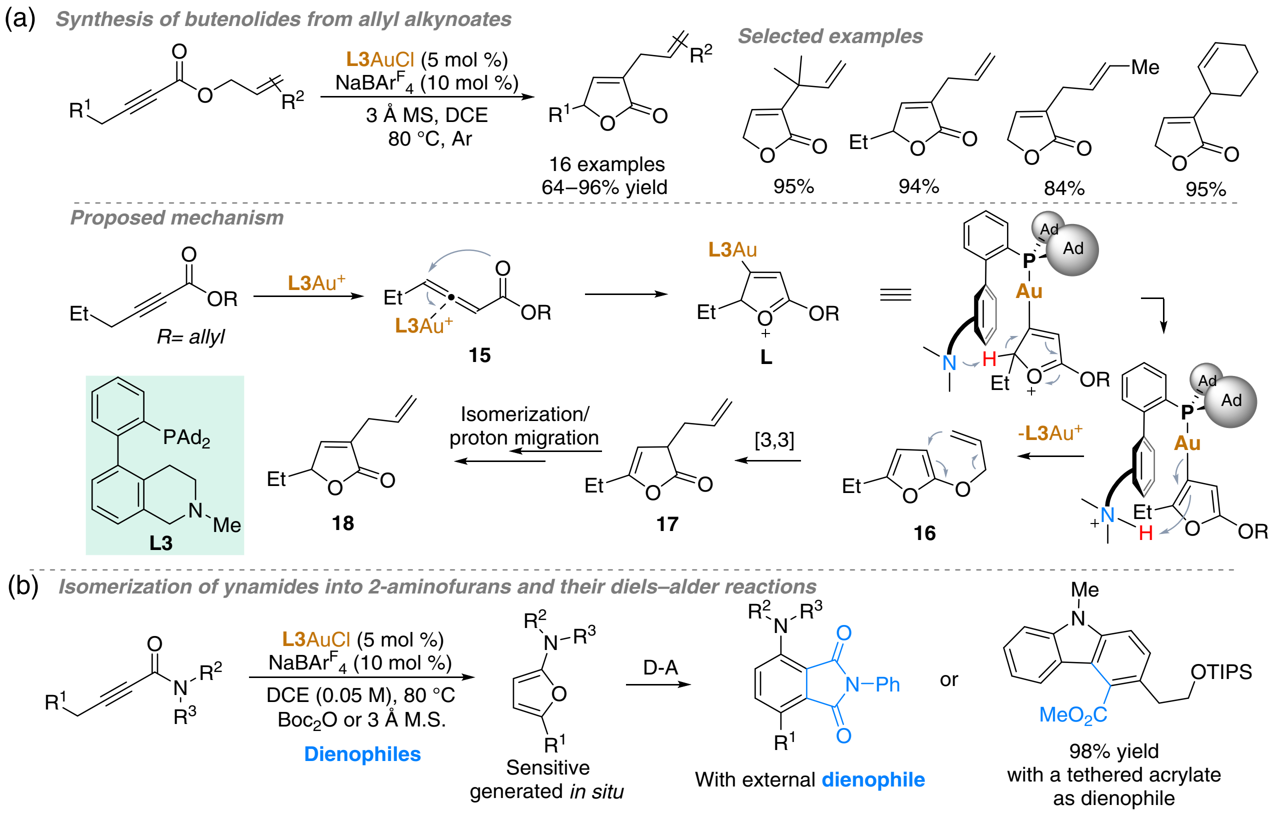
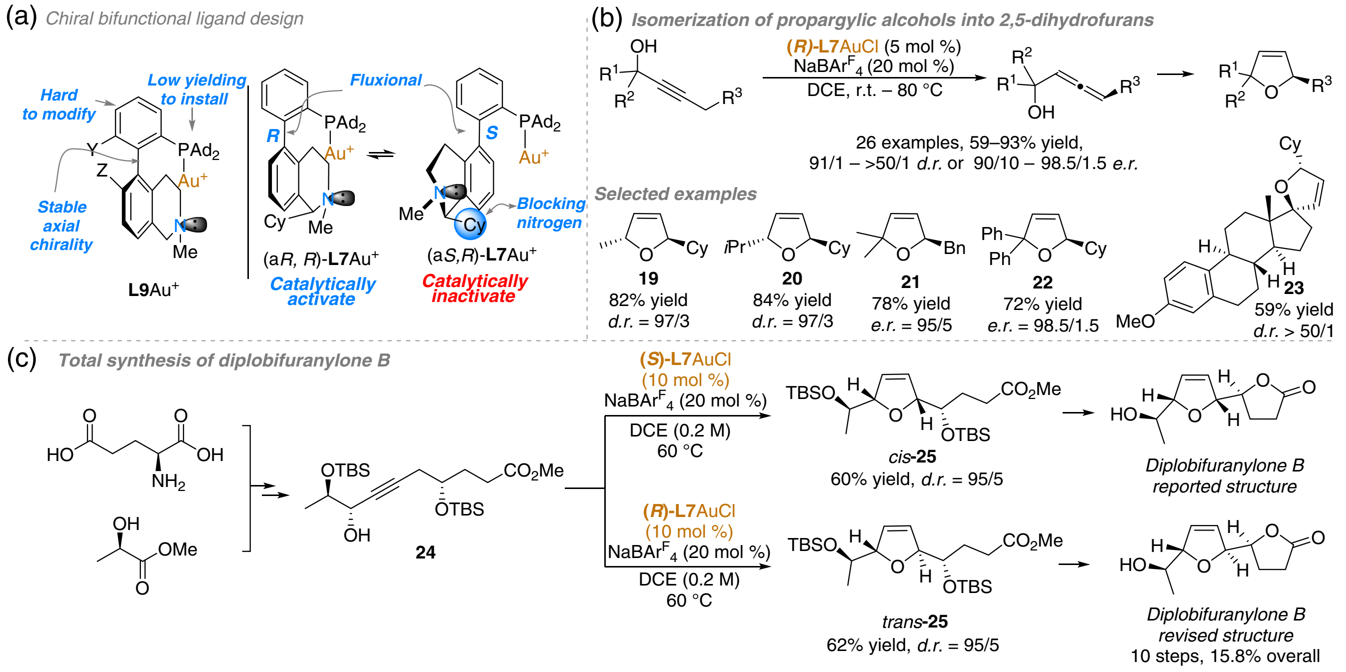


Scheme 9 | *Synthesis of butenolides from allyl alkynoates and access to 2-aminofurans.*

to be isolated. Consequently, they were trapped in situ by an external or tethered dienophile to eventually, functionalized aniline products.

Chiral allenes are versatile intermediates in asymmetric synthesis.[66] The direct isomerization of alkyne to chiral allene, a 100% atom-economic approach, has only been realized with high *ee* values on *t*-butyl 3-butynoates, which have acidic propargylic C–H bonds.[67,68] We anticipated that in the presence of a chiral variant of **L2**–**L6**, the alkyne isomerization to allene (see Scheme 7) would likely become asymmetric for a broad range of propargylic C–H bonds. From a ligand design point of view, the employment of a chiral axis, as in **L9**Au$^+$ (Scheme 10), is the most straightforward strategy. However, our synthesis[69] of **L1** from (*R*)-binol only resulted in a 14% yield during the installation of the bulky Ad$_2$P group[70] due to the requisite steric hindrance around the chiral binaphthyl axis. Consequently, we opted for an alternative yet novel strategy, where center chirality was used to achieve the same performance as a chiral axis. As shown in Scheme 10a, we designed an axially fluxional biphenyl-2-ylphosphine **L7**, which featured a chiral center at C1 in the pendant 1,2,3,4-tetrahydroisoquinoline ring. We expected that the R group in (a*R*, *R*)-**L7** would seldom affect the catalytic activity of the Au$^+$ complex, as it pointed away from the catalytic site. On the other hand, the axial rotation of **L7** by 180° would afford (a*S*, *R*)-**L7**, of which the R group pointed to the catalytic site. It was envisioned that a bulky and/or pseudoaxially oriented R group would provide sufficient steric shielding of the nitrogen lone pair electrons to block its participation in the key deprotonation step. As such, similar to the stable axial chirality in **L9**, this center chirality could make the remote tertiary amino group only available for deprotonation when it is behind the biphenyl framework. The synthesis of (*R*)-**L7**AuCl was readily accomplished with excellent *ee*. We overcame the reversibility between the alkyne and allene by employing propargylic alcohols as substrates, as the chiral allenes generated in situ were trapped in a stereospecific and irreversible 5-*endo*-trig cyclization[71] to deliver chiral dihydrofurans (DHFs; Scheme 10b). To this end, from readily available chiral propargylic alcohols, the chiral 2,5-DHFs (e.g., **19**, **20**, and **23**) possessing a new stereogenic center are formed with good to excellent levels of diastereomeric ratio from chiral substrates, and good to high enantiomeric ratios from achiral substrates as in the cases of **21** and **22** were achieved. Remarkably, by varying the substrate configuration and the ligand chirality, three stereoisomers of the DHF **19** were prepared with excellent stereoselectivities. The mechanistic studies revealed that the biphenyl axis of **L7**Au$^+$ is fluxional, and the axis configuration requisite for the asymmetric catalysis [i.e., (a*R*)] was



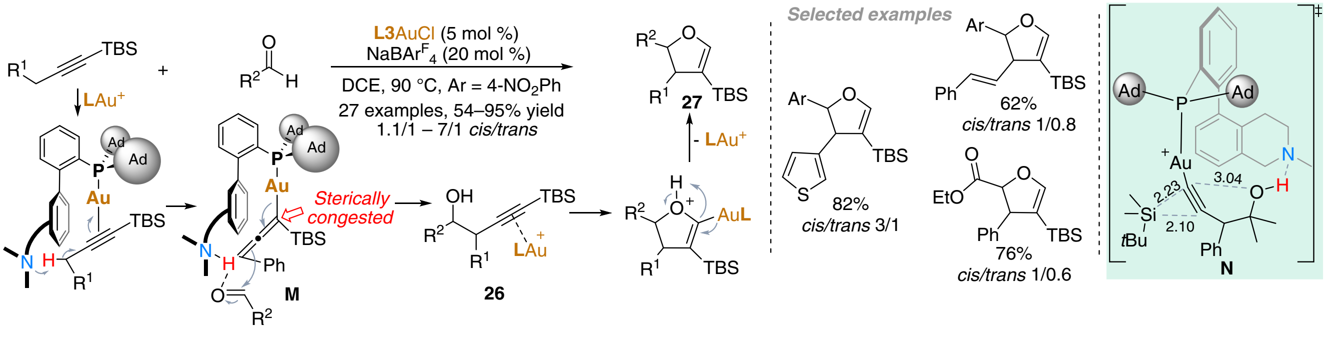
Scheme 10 | *Asymmetric isomerization of propargylic alcohols to access chiral 2,5-dihydrofurans.*

thermodynamically favored. This result suggested that the existence of configurationally stable precatalyst (*R*)-**L7**AuCl axial isomers was inconsequential.

We applied this Au(I) catalysis to the total synthesis of diplobifuranylone B (Scheme 10c).[72] L-Glutamic acid and methyl (*R*)-lactate were used as the starting materials to prepare the propargylic alcohol intermediate **24**. The subsequent construction of the key DHF ring was carried out smoothly under the asymmetric gold catalysis conditions to afford the chiral *cis*-2,5-DHF **25** in 60% yield and with 95/5 diastereoselectivity. Complete desilylation of **25** is accompanied by spontaneous lactonization, and hence, completed the synthesis of the reported structure of diplobifuranylone B,[73] the nuclear magnetic resonance (NMR) spectra of which, however, did not match the reported data. By switching the Au(I) catalyst to its enantiomer, that is, (*S*)-**L7**Au$^+$, the chiral *trans*-**25** was formed in a comparable diastereomeric ratio, and upon deprotection, furnished the correct structure of diplobifuranylone B. Overall, this total synthesis required 10 steps in the longest linear sequence and afforded 15.8% overall yield; moreover, it demonstrated the stereochemical flexibility offered by this Au(I) catalysis.

Nucleophilic reaction of catalytically generated σ-allenylgold

Nucleophilic σ-allenylmetal species[74–76] are typically generated or employed in a stoichiometric manner in propargylation reactions. As shown in Scheme 7a, the allenylgold intermediate **I** could be generated catalytically; however, it appears to undergo prompt *ipso*-protodeauration or reverts back to the gold alkyne complex **H**. Thus, harnessing the unexplored reactivities of these catalytic allenylgold species beyond



Scheme 11 | *Propargylation of aldehydes and silyl-migrative cyclization.*

protonation would dramatically enrich Au(I) catalysis and the chemistry of σ-allenylmetals.[74–76]

We recently discovered that the facile *ipso*-protodeauration of the allenylgold of type **I** could be avoided by installing a bulky silyl group and, in particular, a tert-butyldimethylsilyl (TBS) group at the alkyne terminus (Scheme 11).[77] Consequent, under the catalysis of **L3**Au^+, the TBS-terminated alkynes could react with aldehydes to deliver the silylated DHFs **27** in moderate to high yields and with moderate *cis/trans* ratios. The reaction worked well with activated aldehydes devoid of α-C(sp^3)–H bonds and with alkynes possessing a pi-substituent at the propargylic position. Mechanically, the silylated allenylgold intermediate **M** generated from the metal–ligand cooperation propargylates an aldehyde to afford the homopropargylic alcohol **26**. Its subsequent Au(I)-catalyzed cyclization entailed an unexpected silyl migration to afford the final product. The cyclization of homopropargylic alcohols of type **26** was further studied experimentally, and its mechanism was examined by DFT calculations.[78] The computed transition state **N** revealed that cyclization and silyl migration occurred in a single step, and the steric bulk, as well as the tertiary amino group of the ligand, played critical roles in the process.

Summary

Over the past 6 years, we have developed a range of bifunctional ligands based on the privileged biaryl-2-ylphosphine framework. Rather unique to these new ligands is incorporating a basic functional group on the bottom half of the pendant phenyl or naphthyl ring. Owing to the robust linear configuration of Au(I) complexes and proper positioning of the remote basic group, these bifunctional phosphine ligands permitted secondary coordination sphere interactions, and hence, facilitated metal–ligand cooperation, thereby benefiting homogeneous Au(I) catalysis. These ligands could be divided into two subtypes: those featuring a amide group and the other, a tertiary aniline or amine group. The former ligands could lead to dramatically accelerated additions of protic nucleophiles to alkynes and allenes, and the latter subtype, due to the presence of substantially basic amino groups, could enable unprecedented soft propargylic deprotonation and facilitate other deprotonations in Au(I) catalysis. Consequently, several Au(I) catalysis are achieved at high efficiency and with ultralow catalyst loadings, and transformations that are otherwise not feasible by conventional ligands are enabled. The further evolvement of this ligand design, including the incorporation of remote functional groups beyond the basic ones, should offer new thrusts for advancing Au(I) catalysis. The applications of these ligands to catalysis by metals other than Au(I) would broaden the impact of ligand design and open up new opportunities to enrich metal catalysis in general.

Conflict of Interest

There is no conflict of interest.

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