Remote Cooperative Group Strategy Tailoring Ligands for Accelerative Asymmetric Gold Catalysis

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ABSTRACT: (Word Style "BD_Abstract"). All manuscripts must be accompanied by an abstract. The abstract should briefly state the problem or purpose of the research, indicate the theoretical or experimental plan used, summarize the principal findings, and point out the major conclusions. Abstract length is one paragraph.

In general, an asymmetric transition metal catalyst comprises a metal as the reaction center and a chiral ligand/counter anion associated with the metal to induce reaction asymmetry. In most cases, enantiomeric excess (*ee*) is achieved by installing bulky groups asymmetrically on ligands/counteranions to block/hinder the formation of one of the product enantiomers. The engineered steric congestion must be close to the reaction center and will likely also suppress, though to a lesser extent, the formation of the major enantiomer. As such, the overall reaction rate is slowed in this '*decelerative asymmetric strategy*', which may result in the requirement of higher catalyst loadings and/or longer reaction times (Scheme 1A). This could be costly for large-scale synthesis. In comparison, an '*accelerative asymmetric strategy*' can achieve enantioselectivity by selectively accelerating the formation of one of the product enantiomers. As the overall reaction becomes faster, the catalysis should be more efficient and allow lower catalyst loadings. As a result, the accelerative strategy is in theory superior to the frequently employed decelerative one. However, unlike the universal utility of sterics in hindering reactions, there is a lack of generally applicable strategies to achieve rate acceleration and especially in an asymmetric manner. As such, accelerative asymmetric catalyses have had limited applications in transition metal chemistry, despite its prevalence in enzymatic reactions.

A versatile strategy to achieve reaction acceleration in metal catalysis is the incorporation of ligand metal cooperation,[1] in which the ligand, in addition to directly coordinate to the metal center, cooperation with metal to facilitate bond fragmentation/formation and/or redox process. Applications of this strategy in asymmetric catalysis[2] are limited, and yet most of them have the cooperative functional groups on the first coordination sphere.[2b, c, 2g] A venerable example of this approach is Noyori's asymmetric transfer hydrogenation.[2a] Even in this chiral ruthenium complex-catalyzed reaction, the discrimination of prochiral faces is achieved in many instances via steric hindrance, hence belonging to a decelerative asymmetric approach despite the accelerated nature of the collaborative catalysis.

Asymmetric homogeneous gold catalysis,[3] despite the challenge stemming from the linear structure of Au(I) complexes and the anti attack by incoming nucleophile, has made significant progress. But highly enantioselective ones rely on steric hindrance imposed by chiral ligands[4], counter anions[5], or their combination,[5-6] therefore belonging to decelerative catalysis.

Herein we reported the first accelerative asymmetric gold catalysis, where selective and accelerated formation of one enantiomer is achieved via asymmetric ligand-metal cooperation. The cooperation is realized in the secondary ligand sphere by a remote cooperative Lewis basic group in new chiral binaphthyl-2-ylphosphine ligands.

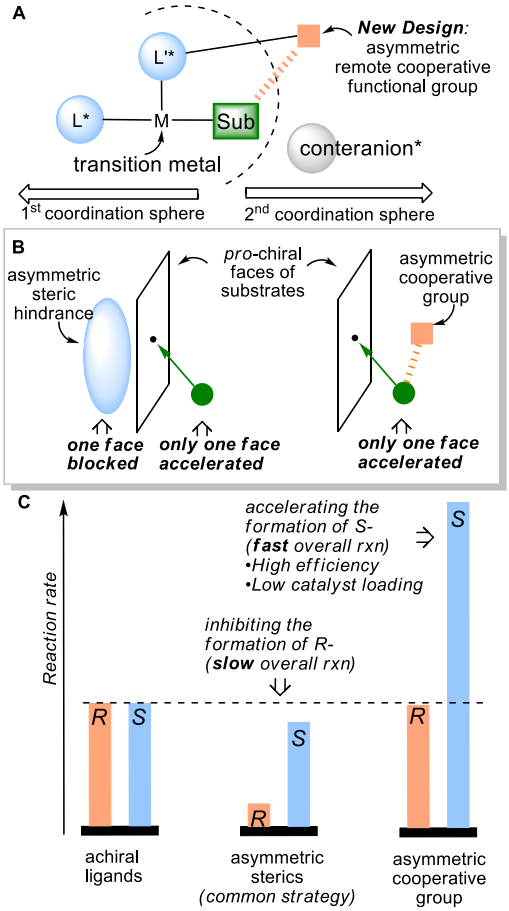
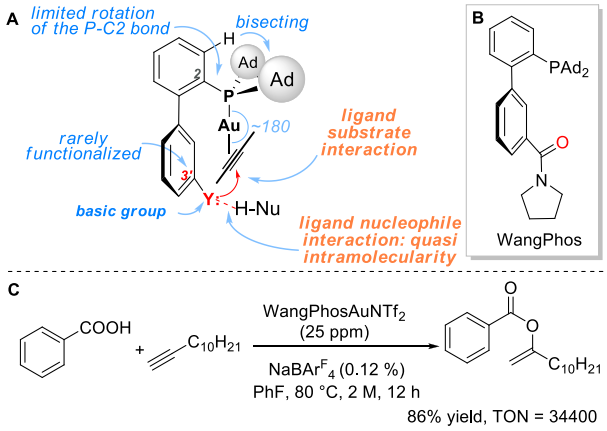


Figure 1. (A) General view of asymmetric transition metal catalysis. Comparison between two ligand design strategy, asymmetric steric hindrance and asymmetric cooperative group: (B) origin of asymmetry. (C) origin of enantio excess and reaction efficiency.

We recently developed a series of novel biphenyl-2-ylphosphine ligands featuring basic functional groups at the rarely explored 3'-position of the privileged ligand framework.[7] Due to the linear nature of P-Au(I)-(alkyne centroid) and the restriction of rotation of the C2−P bond by bulky adamantyl groups, the resulting gold(I) complex projects the coordinated C-C triple bond in proximity of the remote basic groups and therefore enables beneficial interactions between ligand and substrate/nucleophile. With WangPhos featuring a 3'-amide group as ligand, the gold-catalyzed nucleophilic attack of carboxylic acid is accelerated by an estimated 800 fold, comparing to the ligand in its absence, due to the cooperation of the remote amide group in the form of general basic catalysis (Scheme 1C).

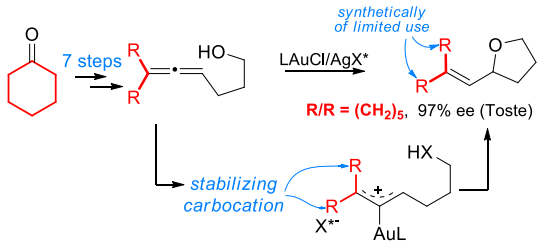
Scheme 1. (A) General Design of Remotely Functionalized Biphenyl-2-ylphosphine Specifically Accommodating Au(I) Catalysis. (B) An Example: WangPhos. (C) Highly Efficient Acid Addition to Alkyne Catalyzed by WangPhos Gold(I) Catalyst.



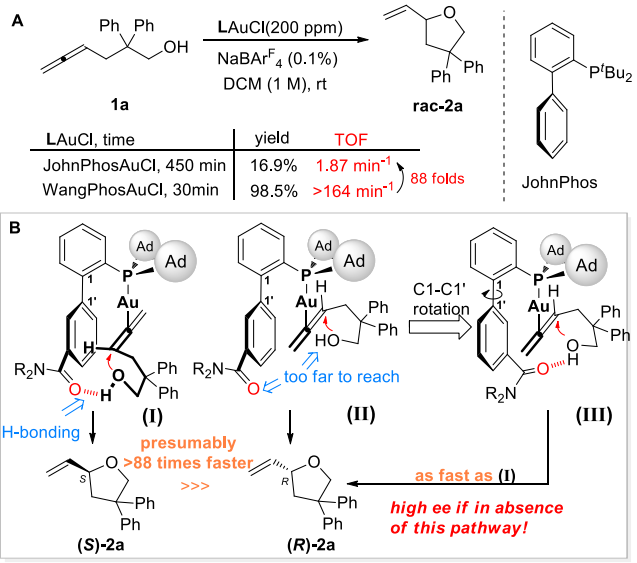
In the context of asymmetric gold catalysis, we envisioned that this cooperative strategy can be applied to the cyclization of 4-allenols such as **1a** (Scheme 3A), where a new chiral center is created. To our delight, comparing to JohnPhos, a sterically and electronically similar ligand but lacking any remote cooperative group, WangPhos promotes the gold-catalyzed cyclization of **1a** to racemic vinyl tetrahydrofuran ***rac*-2a** at a rate at least 88 times faster. This dramatic rate acceleration can be readily rationalized by invoking ligand metal cooperative catalysis and specifically the general base catalysis by the remote amide group. As depicted in Scheme 2B, the coordinated allene would experience minimum, if any, steric interaction with the pendant amide group due to relatively long distance between them and their relatively small sizes. Therefore, the initial coordination would proceed with little facial selectivity, producing similar amount of two diastereomeric complexes **I** and **II**. In contrast to complex **II,** complex **I** places the alcohol adjacent to the pendent amide group and hence permits a general base catalysis in the form of a H-bonding, which would enhance the nucleophilicity of alcohol via partial deprotonation in transition state. As a result, *Si*-face attack that produces **(*S*)-2a** in complex **I** would largely (presumably ≥88 times faster) outcompete *Re*-face attack in complex **II** (similar scenario as JohnPhos). However, due to the low barrier of rotating C1-C1' bond in the ligand and likely its gold complex, WangPhosAu^{+} would exist in equal amount as the enantiomer to that in complex **I**, and the resulting complex **III** would accelerate the *Re*-face attack, which delivers racemic **2a** as a net result. It is anticipated that by using a chiral version of WangPhos with the rotation of C1-C1' locked the cyclization of 4-allenols could become asymmetric.

It is noteworthy that cyclization of allenols have been studied extensively in gold and silver catalysis. Notably, as shown in Scheme 2, most reported 4-allenol cyclizations with >90% *ee* employ trisubstituted allenes as substrate[5], presumably for the purpose of accessing aurated allylic cation and creating favorable steric congestion. However, the distal symmetric disubstitution (shown in red) in the cyclized product has no apparent synthetic utility and may require step(s) for its removal while simple vinyl group could be easily modified to other functional groups. Moreover, the substrate synthesis, as shown in the Scheme 3, requires excessive 7 steps from cyclic ketones; in stark contrast, its R = H counterpart can be prepared in a single step from pent-4-yn-1-ol via the Crabbe allene synthesis.

Scheme 2. Reported Au-catalyzed enantionselective cyclization of allenols and their drawbacks.



Scheme 3. (A) Rate comparison between JohnPhos and WangPhos in cyclization of 4-Allenol. (B) Rationale for the rate acceleration and for enantioselective catalysis.



To this end, we chose the configurationally much more stable binaphthyl as the ligand framework, and targeted the (1,1'-binaphthyl)-2-yldi(adamantan-1-yl)phosphine ligands **L1-L3** (Figure 2A). They can be readily synthesized from commercially available (R)-BINOL in a short sequence of 3-4 steps (see supporting information for details). Much to our delight, initial study with 5 mol% **(*R*)-L1**AuCl as the catalyst precursor delivered **(*R*)-2a** in 98.4% *ee* within 5 min. The absolute configuration of **2a** was assigned as (*R*) based on comparison **(how did you assign the stereochemistry here?)**, and is consistent with the rationale/design shown in Scheme 3B, where the front-orienting amide in **II** leads to the (*S*)-product. This exceptional initial result validated our ligand design concept and, moreover, was achieved with the very first chiral ligand of this type!

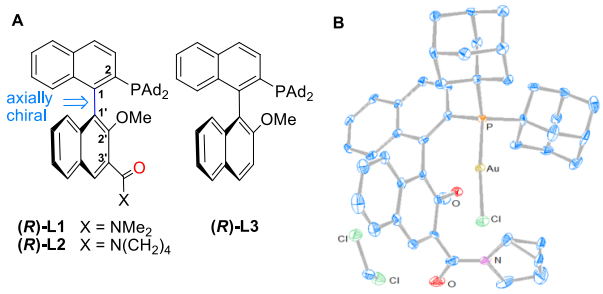
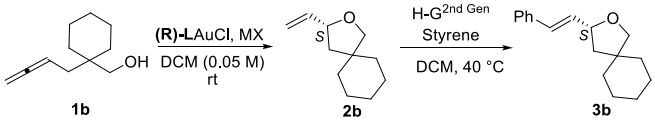


Figure 2. (A) Selected ligands for this study. (B) ORTEP drawings of ***(R)*-L2**AuCl with 50% ellipsoid probability.

The exceptional *ee* with the substrate **1a** hampered our effort of condition optimization and ligand development. To this end, reaction optimization was conducted with 4-allenol **1b** as the substrate. Due to lack of desirable UV absorption for chiral HPLC analysis of the product **2b**, a subsequent olefin metathesis was carried out to install a styryl group as the chromophore. Our control experiment with **2a** established that there is no erosion of stereochemistry in the cross metathesis step. Gladly, treating **1b** with 1% **L1**AuCl as catalyst and 5% $NaBAr^{F}_4$ as chloride scavenger furnished **2b** in 98% yield and 95.5% *ee* within 15 min (Table 1, Entry 1). Moreover, using **L2** with a pyrrolidin-1-ylcarbonyl group, due to its stronger basicity than N,N-dimethylcarbamyl group in **L1**, a better enantioselectivity (96.6% *ee*) is achieved. Whereas ***(R)*-L3** bearing no cooperative amide group was used as control experiment, an expected steep drop of reaction rate and a poor *ee* (-8.8%) were observed, which confirmed the cooperative nature of the amide moiety (Table 1, Entry 3). Replacing BAr^{F}_4- with more coordinative counteranions caused diminished enantioselectivity (Table 1, Entries 4-6). We also observed that the removal water by 3 Å MS improved *ee* to 97.5% (Table 1, entry 7), possibly because the residual water, being able to act as both H-bonding donor and acceptor, would disrupt the H-bonding between the alcohol and amide group. In contrast to the common temperature profiles in asymmetric catalysis, lowering the reaction temperature led to a decreased *ee* while higher temperature didn't cause much *ee* erosion (Table 1, entries 8-10). Owning to the accelerated nature of the catalysis, the catalyst loadings could be dramatically lowered down to 100 ppm without noticeably affecting *ee* (Table 1, entries 11-12). At last, higher concentration was proven to be detrimental to *ee* despite a faster reaction rate (Table 1, entry 13), which can be attributed to the disruption of ligand-substrate H-bonding by unreacted alcohol. To confirm the identity of the optimal catalyst, we ascertained the structure and stereochemistry of ***(R)*-L2**AuCl by X-ray diffraction study (Figure 2B).

Table 1. Optimization of reaction conditions towards enantioselective gold-catalyzed allenol cyclization with low catalyst loading[a].



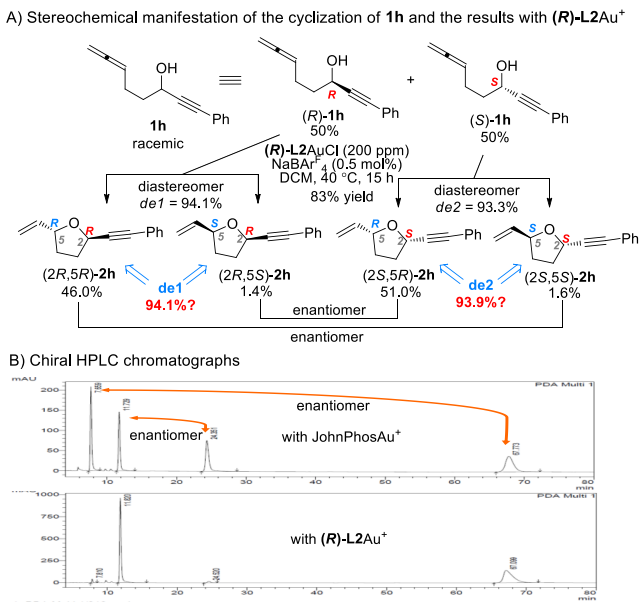
Entry	Cat. (mol%)	MX (mol%)	Temp. (°C) /Time	Yld[b] (%)	*ee*[c] (%)
1	**L1**AuCl (1)	$NaBAr^{F}_4$ (5)	rt/15 min	98	95.5
2	**L2**AuCl (1)	$NaBAr^{F}_4$ (5)	rt/15 min	97	96.6
3	**L3**AuCl (2)	$NaBAr^{F}_4$ (5)	rt/1 h	11	-8.8
4	**L2**AuCl (1.2)	$AgNTf_2$ (1)	rt/15 min	96	93.4
5	**L2**AuCl (1.2)	AgOTf (1)	rt/15 min	95	78.9
6	**L2**AuCl (1.2)	$AgSbF_6$ (1)	rt/15 min	92	94.1
7[d]	**L2**AuCl (1)	$NaBAr^{F}_4$ (5)	rt/15 min	92	97.5
8[d]	**L2**AuCl (1)	$NaBAr^{F}_4$ (5)	-20/30 min	90	95.5
9[d]	**L2**AuCl (1)	$NaBAr^{F}_4$ (5)	40/15 min	89	97.0
10[d,e]	**L2**AuCl (1)	$NaBAr^{F}_4$ (5)	60/15 min	94	97.1
11[d]	**L2**AuCl (0.1)	$NaBAr^{F}_4$ (1)	rt/30 min	94	97.1
12[d]	**L2**AuCl (0.01)	$NaBAr^{F}_4$ (0.5)	rt/2.5 h	92[f]	96.9
13[d,g]	**L2**AuCl (0.01)	$NaBAr^{F}_4$ (0.5)	rt/1 h	92	95.7

[a] Reactions were performed in vials. [b] Yields and conversions were estimated by NMR using 1,3,5-triisopropylbenzene as internal reference. All conversions >99% otherwise noted. [c] *ee* values of olefin metathesis products were determined by HPLC on a chiral stationary phase. [d] 3 Å molecular sieves were added. [e] DCE was used as solvent. [f] 98% NMR conversion. Isolated yield 93%, *ee* 97.1%. [g] 0.25 M in DCM.

With the best conditions in hand, we promptly explored the reaction scope with a range of 4-allenols. As shown in Table 2, entries 1-4, 4-allenols with germinal di-substitutions at the sp^3-carbons generally exhibited excellent yield and enantioselectivity (up to 99.7%, Table 2, entry 3) with 100-ppm catalyst loadings. This includes the tertiary alcohol **1e** (entry 4), indicating the steric hindrance around the HO group is consequential. On the other hand, sterics next to the allene moiety, as in entry 5, led to a moderate *ee* (Table 2, entry 5). In absence of any substitution and the Thorpe-Ingold effect, the cyclization of the parent 4-allenol **1g** remained highly enantioselective (94.1% *ee*, entry 6).

Besides the achiral 4-allenols, we also expand the scope to the ones with preexisting stereogenic centers, which are complicated by diastereoselective outcomes but of high synthetic significance due to their frequent occurrence in complex molecule synthesis. As shown in Scheme 3A, the gold-catalyzed cyclization of the racemic 1-phenylethynyl-substituted 4-allenol **1h** leads to the formation of four stereoisomers, with each **1h** enantiomer leading to a pair of diastereromers. The selectivity of each diastereomeric pair, i.e., de1 or de2, is defined as diastereomeric excess and reflects how well the facial selectivity of the allene being attacked by HO group is realized. In the case of ***(R)*-L2**, these de values would reflect how the chiral ligand can dictate the newly generated chiral center regardless of the preexisting stereogenic one and can be derived upon complete separation of these four stereoisomers on chiral HPLC. As shown in Scheme 3B, they can indeed be separated. Combining the intrinsic *cis*-distereoselectivity with **2h** (albeit small) and the logic assumption of our ligand largely dictating stereochemical outcome (confirmed latter), we can assign all the peaks in the HPLC chromatograph of their stereochemistry and calculate the de values. To this end, the de is 94.1% for the product derived from (*R*)-**1h** and 93.9% from (*S*)-**1h**, confirming the extraordinary control of stereochemical outcome by our ligand even with chiral substrates. It is conceivable that by starting from enantiomerically pure substrates all four isomers can be prepared with high selectivity by simply combining different ligand and substrate enantiomers. This is especially of importance in the synthesis of ubiquitous tetrahydrofurans as often diastereomeric selectivities are often poor.[ref]

Scheme 3. The stereochemical outcomes in the reaction of 4-allenol 1h with a preexisting stereogenic center. **(which one is**

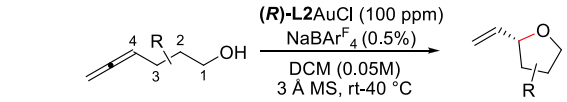


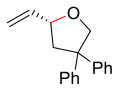
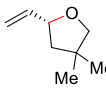
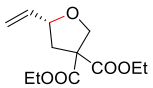
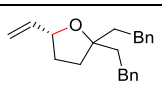
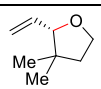
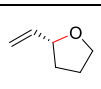
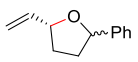
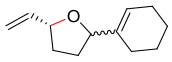
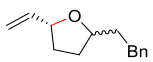
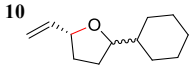
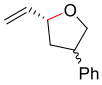
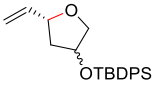
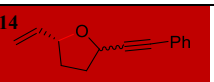
matched case? Should be the cis one, right? Why would the cis one on the right with lower de?

Can you give the drs (in other words, which diastereomers is favored) of the reactions of the 4-allenol substrates in the Table? In this way, we can clearly show people the matched and mismatched scenario.

Besides **1h**, 4-allenols with other substituents at C1 such as phenyl (entry 7), alkenyl (entry 8), phenethyl (entry 9) and cyclohexyl (entry 10) also underwent the reaction smoothly, affording the cyclized products in good yields (74% - 87%) and most importantly exhibited excellent allene facial selectivities (>92% *de*) regardless the preexisting chiral centers. The reaction of a 2-phenyl-substituted 4-allenol, i.e., **1m**, exhibited exceptional 98.7% *de* for one enantiomer (most likely the (*R*)-isomer), and a lower yet still good *de* with the other enantiomer, exhibiting pronounced match and mismatch phenomenon. On the other hand, the reaction of **1n** demanded a higher catalyst loading (0.5%), possibly due to the bulky 2-*tert*-butyldiphenylsilanoxyl group, but the allene facial selectivities are excellent with both substrate enantiomers. Finally, the reaction of a 3-benzyloxy group in **1o** (entry 13) was also highly stereoselective, despite a moderate yield.

Table 2. Reaction scope[a].

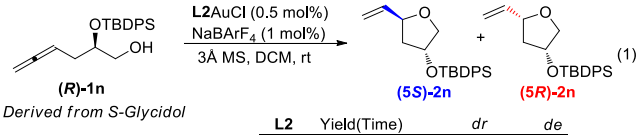


1 	2 	3 
2a, rt, 3 h 99% yield 99.1% *ee*	**2c**, rt, 5 h 59 (89)% yield[b] 97.0% *ee*	**2d**, rt, 6 h 83% yield 99.7% *ee*
4 	5 	6 
2e, rt, 8 h 95% yield 95.8% *ee*	**2f**, rt, 3 d 92% yield[b] 49.8% *ee*	**2g**, rt, 9 h 74% yield[b] 94.1% *ee*
7 	8 	9 
2i[c], rt, 33 h 84% yield 95.8%, 92.1% *de*	**2j**[c], rt, 48 h 87% yield 94.7%, 92.5% *de*	**2k**, 40 °C, 15 h 86% yield 95.9%, 95.4% *de*
10 	11 	12 
2l, rt, 24 h 74% yield 94.4%, 93.0% *de*	**2m**, rt, 55 h 90% yield 98.7%, 88.4% *de*	**2n**[d], rt, 6 h 94% yield 98.9%, 97.5% *de*
13 	14 	
2o[e], 40 °C, 36 h 65% yield 95.3%, 92.4% *de*	**2o**[e], 40 °C, 15 h 83% yield 94.6%, 93.3% *de*	

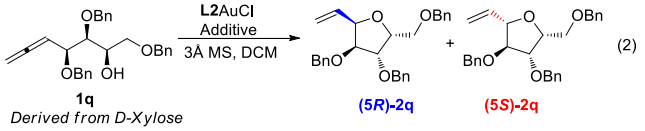
[a]Reactions were performed in vials. Yields given are for the isolated product. Yields in parenthesis are NMR yield by using CD_2Cl_2 as solvent and 1,3,5-triisopropylbenzene as internal reference. For those allenols with a preexisting chiral center, two *de* values are given to describe the *ee* values of the newly formed chiral center with respect to the two allenol enantiomers. [b] Volatile product. [c] 200 ppm catalyst were used. [d] 0.5 mol% catalyst and 1 mol% $NaBAr^F_4$ were used. [e] 0.2 mol % catalyst were used. .

To confirm the exceptional allene facial selectivities with chiral substrates, we prepared the enantiomerically enrich **(*R*)-1n** (>99% *ee*) from *S*-glycidol (>99% *ee*) and subjected it to the gold catalysis with **(*S*)-** and **(*R*)-L2**AuCl as catalyst precursor, respectively. As expected, a complete switch of diastereoselectivity was observed along with excellent yields (Eq. 1); moreover, the *de* values are identical (within margin of error) to those obtained with racemic **1n**.

We attempted to briefly demonstrate the synthetic potential of this chemistry toward the synthesis of *C*-glycosides. As shown in Eq. 2, the partially protected allene-polyol **1q** was prepared from *D*-xylose. When it was subject to the gold catalysis with **(*S*)-L2** as ligand, the vinyl xyloside **(5*R*)-2q** was formed exclusively in 82% yield. With the ligand antipode, **(5*S*)-2q** was obtained in 76% yield and in a 6.5:1 selectivity. As the intrinsic diasterselectivity with ___ favors ___ to a large extent, this moderate yet serviceable selectivity for the minor product is noteworthy and synthetically useful.



L2	Yield(Time)	dr	de
(*S*)	88%(1.5 h)	250 : 1	99.2%
(*R*)	91%(3.75 h)	1 : 86	97.7%



catalyst	Yield(Temp, Time)	(5*R*)-2q : (5*S*)-2q	de
(*S*)-L2 (1%)/$NaBAr^F_4$(2%)	82%(40 °C, 15 h)	Exclusive : -	>99.9%
(*R*)-L2 (5%)/$AgSbF_6$(5%)	76%(rt, < 0.5 h)	1 : 6.5	73.3%
achiral ligand	76%(rt, < 0.5 h)	1 : 6.5	73.3%

In conclusion, This highly efficient and enantioselective cooperative gold(I) catalysis, due to its excellent tolerance of functional

groups and preexisting stereogenic centers, would enable facile access to tetrahydrofura with specific stereochemistry, which are present in a wide array of natural products.

Remote cooperative functional group strategy is a novel and promising ligand design concept that will produce high stereoselectivity and at the same time, avoid the reactivity loss resulting from necessary sterics for asymmetry induction. This approach appears to be particularly attractive in homogeneous gold(I) catalysis since this design projects chiral environment close to the substrates, although the linear coordination nature of gold(I) places the substrates opposite to the ligand. By asymmetrically installing a remote amide group on a sterically less demanding (1,1'-binaphthyl)-2-yldi(adamantan-1-yl)phosphine ligand platform, the derived gold(I) catalyst invokes a beneficial H-bonding interaction with alcoholic substrates, which enables a highly efficient and stereoselective synthesis towards various tetrahydrofuran derivatives in remarkably low catalyst loading (down to 100 ppm). Considering a vast range of weak interactions (hydrogen bonding, charge-charge, π-π stacking, etc.) and a large assortment of chiral ligand-transition metal complexes, we believe that this strategy could be applied in a much broader scope.

This strategy could be very powerful that one can set up the functional groups as well as their stereochemistry in allenols beforehand and select one of **(*R*)-** or **(*S*)-L2** to produce the desired tetrahydrofuran products.

ASSOCIATED CONTENT

Supporting Information

AUTHOR INFORMATION

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Present Addresses

(Word Style "Section_Content"). †If an author's address is different than the one given in the affiliation line, this information may be included here.

Author Contributions

(Word Style "Section_Content"). ‡These authors contributed equally. (match statement to author names with a symbol, if applicable)

Notes

(Word Style "Section_Content"). The authors declare no competing financial interests.
Any additional relevant notes should be placed here.

ACKNOWLEDGMENT

(Word Style "Section_Content"). Generally the last paragraph of the paper is the place to acknowledge people (dedications), places, and financing (you may state grant numbers and sponsors here). Follow the journal's guidelines on what to include in the Acknowledgement section.

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