Communication

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# Remote Cooperative Group Strategy Enables Ligands for Accelerative Asymmetric Gold Catalysis

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*Supporting Information Placeholder*

**ABSTRACT:** An accelerative asymmetric gold catalysis is achieved for the first time via chiral ligand metal cooperation. An asymmetrically positioned remote amide group in the designed chiral binaphthyl-based ligand plays the essential role of a general base catalyst and selectively accelerates the cyclizations of 4-allen-1-ols into one prochiral allene face. The reactions are mostly highly enantioselective with achiral substrates, and due to the accelerated nature of the catalysis catalyst loadings as low as 100 ppm are allowed. With a preexisting chiral center at any of the backbone $sp^3$-carbons, the reaction remained highly efficient and most importantly maintained excellent allene facial selectivities regardless of the substrate stereochemistry. By using different combinations of ligand and and substrate enantiomers, it is now possible to access all four stereoisomers of versatile 2-vinyltetrahydrofurans with exceedingly high selectivity. The underpinning design of this chemistry reveals a novel and conceptually distinctive strategy to tackle challenging asymmetric gold catalysis, which to date has relied on decelerative asymmetric steric hindrance approaches.

Ligand accelerated catalysis (LAC)[1] offers a versatile platform in metal catalysis for achieving efficient asymmetric catalysis. An often-practiced approach to realizing enantioselectivity in LAC is to introduce asymmetric steric hindrance to selectively slow down the formation of one of the enantiomers, albeit it may still be faster than the non-accelerated scenario (Figure 1C vs. 1A).[2] This is a superior strategy to those based only on steric retardation (Figure 1B) due to faster reactions and lower catalyst loadings. Alternatively but relatively rare in transition metal catalysis, high enantioselectivity could be achieved by selectively accelerating the formation of only one of the enantiomers via asymmetric ligand substrate interactions[3] and/or ligand metal cooperation[4] (Figure 1D). In comparison to the scenario in Figure 1C, this latter approach does not accelerate the formation of the minor enantiomer and hence offers enhanced chances of achieving excellent enantioselectivity.

Asymmetric gold catalysis, despite the challenge stemming from the linear structure of Au(I) complexes and the *anti* attack by incoming nucleophile, has experienced significant progress.[5] However, highly enantioselective ones hardly deploy ligand accelerated catalysis[3e] and mostly rely on decelerative and hence efficiency-lowering steric hindrance (i.e., Figure 1B) imposed by chiral ligands,[6] counter anions,[7] or their combination.[8] As such, these reactions typically requires relatively high catalyst loadings due to decreased reaction rates.

Herein we reported a first asymmetric ligand-accelerated gold catalysis, where the formation of one enantiomer is selectively accelerated via asymmetric ligand substrate interaction. This interaction enables ligand metal cooperation[4] and is realized in the secondary ligand sphere by a remote and asymmetrically positioned Lewis basic group in new chiral binaphthyl-2-ylphosphine ligands. The utility of this accelerative strategy is demonstrated by the very low catalyst loadings (as low as 100 ppm) and the generally excellent stereoselectivities in the cyclization of 4-allen-1-ols. Importantly, it demonstrates a new and highly efficient strategy to achieve challenging asymmetric gold catalysis, which to date has mostly been limited to the scenario depicted in Figure 1B.

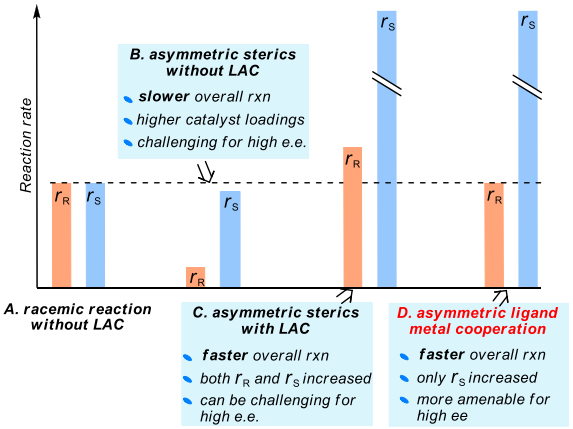
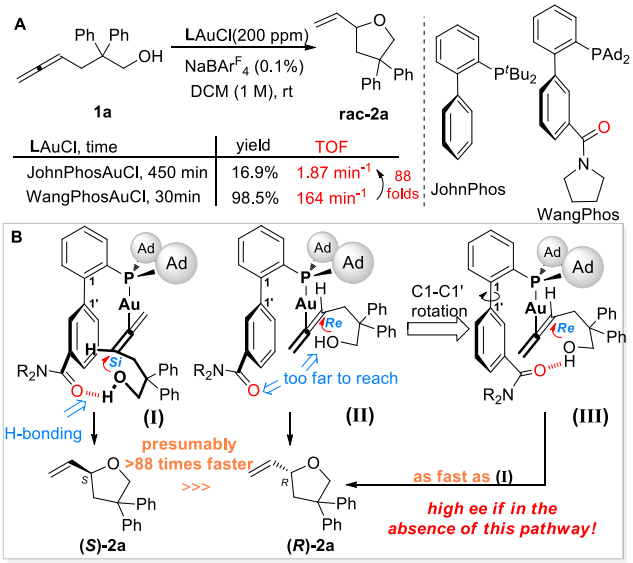



**Figure 1.** Common scenarios of asymmetric catalysis.

We recently developed a series of novel biphenyl-2-ylphosphine ligands[9] featuring basic functional groups at the bottom half of the pendant phenyl ring.[10] With WangPhos (Scheme 1A)[10a,10c] possessing a 3'-amide group as ligand, the gold-catalyzed nucleophilic attack of carboxylic acid is accelerated by an estimated 800 fold, comparing to non-functionalized JohnPhos, due to the cooperation of the remote amide

group in the form of general basic catalysis.[10b] In the context of asymmetric gold catalysis, we envisioned that this cooperative strategy can be applied to the cyclization of 4-allen-1-ols such as **1a** (Scheme 1A), where a new chiral center is created. To our delight, comparing to JohnPhos, a sterically and electronically comparable ligand but lacking any remote cooperative group, WangPhos promotes the gold-catalyzed cyclization of **1a** to racemic 2-vinyltetrahydrofuran *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 1B, the coordinated allene would lead to 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 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**, where the amide group is too far from the alcohol HO group to allow H-bonding and hence should undergo cyclization in a similar rate to that with JohnPhos as ligand. 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 or enantiomeric conformer to that in complex **I**. The resulting complex **III** would equally 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.

**Scheme 1.** (A) Rate comparison between JohnPhos and WangPhos in cyclization of 4-allen-1-ol **1a**. (B) Rationale




for the rate acceleration and for enantioselective catalysis.

It is noteworthy that cyclization of allenols have been studied extensively in asymmetric gold[5] and silver catalysis.[11] Most highly enantioselective cyclizations of 4-allenols **1** employ non-stereogenic trisubstituted allenes as substrate,[7,8b,12] with one exception,[6a] the distal symmetric disubstitution of which, however, require excessive steps for installation[13] and of no apparent synthetic utility. On the contrary, mono-substituted allenes such as **1a** is easily accessible via the Crabbe allene synthesis,[14] and the vinyl group in cyclization product can be readily manipulated.

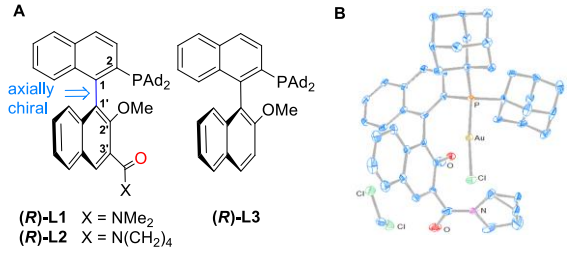
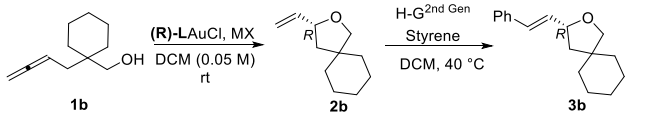



**Figure 2**. (A) Selected ligands for this study. (B) ORTEP drawings of (*R*)-**L2**AuCl with 50% ellipsoid probability.

At the outset, 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 literature precedent,[11a] and is consistent with the rationale/design shown in Scheme 1B, where the front-orienting amide in **I** 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!

**Table 1.** Optimization of reaction conditions towards enantioselective gold-catalyzed 4-allen-1-ol cyclization.[a]




| Entry | Cat. (mol%) | MX (mol%) | Temp. /Time | Yld[b] (%) | *ee*[c] (%) |
|---|---|---|---|---|---|
| 1 | (*R*)-**L1**AuCl (1) | NaBAr$^F_4$ (5) | rt/15 min | 98 | 95.5 |
| 2 | (*R*)-**L2**AuCl (1) | NaBAr$^F_4$ (5) | rt/15 min | 97 | 96.6 |
| 3 | (*R*)-**L3**AuCl (2) | NaBAr$^F_4$ (5) | rt/1 h | 11 | -8.8 |
| 4 | (*R*)-**L2**AuCl (1.2) | AgNTf$_2$ (1) | rt/15 min | 96 | 93.4 |
| 5 | (*R*)-**L2**AuCl (1.2) | AgOTf (1) | rt/15 min | 95 | 78.9 |
| 6 | (*R*)-**L2**AuCl (1.2) | AgSbF$_6$ (1) | rt/15 min | 92 | 94.1 |
| 7[d] | (*R*)-**L2**AuCl (1) | NaBAr$^F_4$ (5) | rt/15 min | 92 | 97.5 |
| 8[d] | (*R*)-**L2**AuCl (1) | NaBAr$^F_4$ (5) | -20 °C /30 min | 90 | 95.5 |
| 9[d] | (*R*)-**L2**AuCl (1) | NaBAr$^F_4$ (5) | 40 °C /15 min | 89 | 97.0 |
| 10[d,e] | (*R*)-**L2**AuCl (1) | NaBAr$^F_4$ (5) | 60 °C /15 min | 94 | 97.1 |
| 11[d] | (*R*)-**L2**AuCl (0.1) | NaBAr$^F_4$ (1) | rt/30 min | 94 | 97.1 |
| 12[d] | (*R*)-**L2**AuCl (0.01) | NaBAr$^F_4$ (0.5) | rt/2.5 h | 92[f] | 96.9 |
| 13[d,g] | (*R*)-**L2**AuCl (0.01) | NaBAr$^F_4$ (0.5) | rt/1 h | 92 | 95.7 |

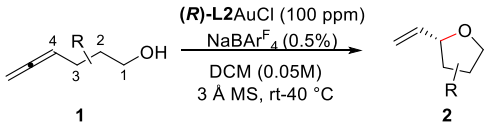
[a] Reactions were performed in vials. [b] Yields and conversions were estimated by NMR using 1,3,5-triisopropylbenzene as internal reference. All conversions >99% otherwise noted. [c] *ee* values of olefin metathesis products were determined by HPLC on a chiral stationary phase. [d] 3 Å molecular sieves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

The exceptional *ee* with the substrate **1a** left little room for 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 mol% **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). Consistent with the case of **2a**, its configuration is assigned as (*R*). Moreover, using **L2** with a pyrrolidin-1-ylcarbonyl group, which is more basic than *N,N*-dimethylcarbamyl group in **L1**, a better enantioselectivity (96.6% *ee*) was 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 counter anions caused diminished enantioselectivities (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 temperatures did not 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, a 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 ligand (*R*)-**L2**, we ascertained the structure and stereochemistry of its gold complex by X-ray diffraction studies (Figure 2B). With the best conditions in hand, we promptly explored the reaction scope. 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%, entry 3) with 100-ppm catalyst loadings. This includes the tertiary alcohol **1e** (entry 4), indicating the steric hindrance around the HO group is inconsequential. 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 the Thorpe-Ingold effect, the cyclization of the parent 4-allenol **1g** remained highly enantioselective (94.1% *ee*, entry 6).

Besides the achiral 4-allen-1-ols, 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 entries 7-11, 4-allen-1-ols with various substituents at C1 such as phenylethynyl (entry 7), phenyl (entry 8), alkenyl (entry 9), cyclohexyl (entry 10) and phenethyl (entry 11) underwent the cyclization smoothly, affording the cyclized products in good yields (74% - 87%). Most importantly, these reactions exhibited excellent allene *Re* face selectivities regardless the substrate configurations. In each entry, the *de-R* and *de-S* values reflect the diastereomeric excesses of the products derived from the (*R*)- and (*S*)-substrates, respectively, and are calculated based on complete separation of the four product stereoisomers by chiral HPLC. The reaction of a 2-phenyl-substituted 4-allen-1-ol, i.e., **1m**, exhibited exceptional 98.7% *de-R*, and a lower yet still good *de-S* (entry 12). On the other hand, the reaction of **1n** demanded a higher catalyst loading (0.5 mol %), possibly due to the bulky 2-*tert*-butyldiphenylsilanoxyl group, but the allene facial selectivities are excellent with both substrate enantiomers (entry 13). Finally, the reaction of a 3-benzyloxy group in **1o** (entry 14) was also highly stereoselective, despite a moderate yield. Notably, in all these cases using racemic substrates (entries 7-14), the reactions exhibited poor *cis*/*trans* selectivities, confirming that the cyclization stereochemical outcomes can be little controlled by the substrate preexisting chiral centers.

**Table 2. Reaction scope[a].**

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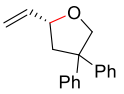
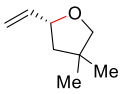
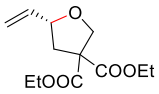
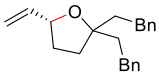
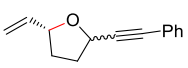
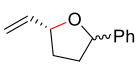
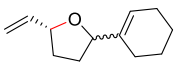
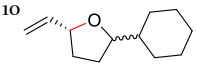
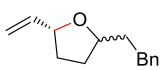
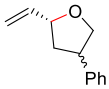
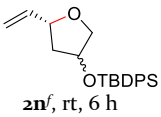
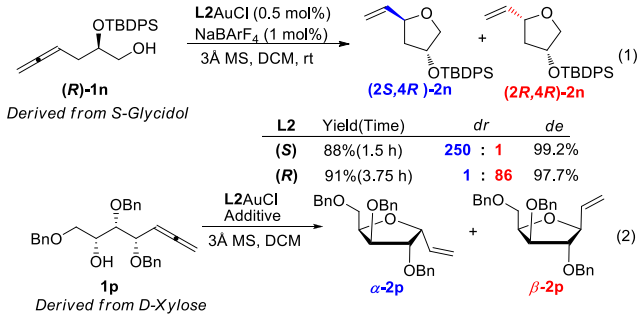
| 1  | 2  | 3  | |
| **2a**, rt, 3 h<br>99% yield<br>99.1% *ee* | **2c**, rt, 5 h<br>59 (89)% yield[b]<br>97.0% *ee*[c] | **2d**, rt, 6 h<br>83% yield<br>99.7% *ee*[c] | |
| 4  | 5  | 6  | |
| **2e**, rt, 8 h<br>95% yield<br>95.8% *ee* | **2f**, rt, 3 d<br>92% yield[b]<br>49.8% *ee*[c] | **2g**, rt, 9 h<br>74% yield[b]<br>94.1% *ee*[c] | |
| 7  | 8  | 9  | |
| **2h**[d], 40 °C, 15 h<br>83% yield<br>*trans*/*cis* = 1.11/1.00<br>*de-R*, 94.6%;<br>*de-S*, 93.3% | **2i**[e], rt, 33 h<br>84% yield<br>*trans*/*cis* = 1.04/1.00<br>*de-R*, 95.8%;<br>*de-S*, 92.1% | **2j**[e], rt, 48 h<br>87% yield<br>*trans*/*cis* = 1.35/1.00<br>*de-R*, 94.7%;<br>*de-S*, 92.5%[c] | |
| 10  | 11  | 12  | |
| **2k**, rt, 24 h<br>74% yield<br>*trans*/*cis* = 1/1<br>*de-R:* 94.4%,<br>*de-S*, 93.0%[c] | **2l**, 40 °C, 15 h<br>86% yield<br>trans/cis = 1.06/1.00<br>*de-R*, 95.9%;<br>*de-S*, 95.4%[c] | **2m**, rt, 55 h<br>90% yield<br>*trans*/*cis* = 1.00/1.31<br>*de-R*, 98.7%;<br>*de-S*, 88.4% | |
| 13  | 14  | | |
| **2n**[f], rt, 6 h<br>94% yield<br>*trans*/*cis* = 1.33/1.00<br>*de-S*, 98.9%;<br>*de-R*, 97.5% | **2o**[g], 40 °C, 36 h<br>65% yield<br>*trans*/*cis* = 1.00/1.01<br>*de-R*, 95.3%;<br>*de-S*, 92.4% | | |

[a] Reactions were performed in vials. Yields given are for the isolated product. For allenols with a preexisting chiral center, the *de* value is given for each enantiomeric substrate and designated by its configuration. [b] Volatile product. [c] The product was converted into its styryl derivative via olefin cross metathesis for subsequent chiral HPCL analysis. [d] 500 ppm catalyst were used. [e] 200 ppm catalyst were used. [f] 0.5 mol% catalyst and 1 mol% $NaBAr^F_4$ were used. [g] 0.2 mol % catalyst was used.

To confirm the exceptional allene facial selectivities with chiral substrates, we prepared the enantiomerically enriched (*R*)-**1n** (98.8% *ee*) from (*S*)-glycidol 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 nearly identical 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 **1p** was prepared from *D*-xylose. When it was subject to the gold catalysis with (*S*)-**L2** as ligand, the vinyl *C*-xyloside *α*-**2p** was formed exclusively in 82% yield. With the ligand antipode, *β*-**2p** was obtained in 76% yield and in a 6.5:1 diastereoselectivity. As the intrinsic diastereoselectivity with WangPhos favors *α*-**2p** by a ratio of 16:1, this fair yet serviceable selectivity for the much disfavored *β*-isomer is noteworthy and can be synthetically useful. Notably, when JohnPhos was used as gold ligand, the reaction was messy and little **2p** was formed, which reveals the versatility of our designed ligands for cyclizations regardless asymmetric induction.




| 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) | α-2p : β-2p | 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% |
| WangPhosAuCl/NaBAr$^F_4$ | clean rxn, >99% conv. | 16 : 1 | |
| JohnPhosAuCl/NaBAr$^F_4$ | messy reaction, trace product, >99% conv. | | |

In conclusion, we have achieved for the first time an accelerative asymmetric gold catalysis via chiral ligand metal cooperation. An asymmetrically positioned remote amide group in the designed chiral binaphthyl-based ligand plays the essential role of a general base catalyst and selectively accelerates the cyclizations of 4-allen-1-ols into one prochiral allene face. The reactions are mostly highly enantioselective with achiral substrates, and due to the accelerated nature of the catalysis catalyst loadings as low as 100 ppm are allowed. With a preexisting chiral center at any of the backbone sp$^3$-carbons, the reaction remained highly efficient and most importantly maintained excellent allene facial selectivities regardless of the substrate stereochemistry. Of exceptional synthetic significance is that all four stereoisomers of versatile 2-vinyltetrahydrofurans can be prepared with exceedingly high selectivity by using different combinations of ligand and substrate enantiomers. The underpinning design of this chemistry offers new yet rational strategies to tackle challenging asymmetric gold catalysis, which to date has relied on decelerative chiral steric approaches.

## ASSOCIATED CONTENT

### Supporting Information

Experimental details, compound characterization and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interests.

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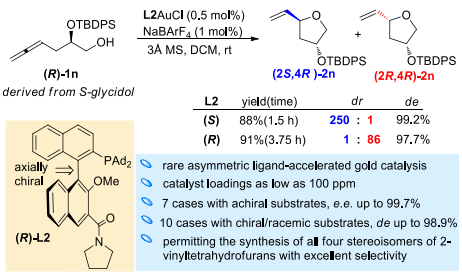
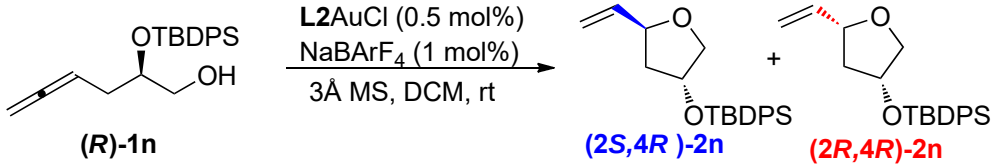

OTBDPS
OH
(R)-1n
derived from S-glycidol
L2AuCl (0.5 mol%)
NaBArF4 (1 mol%)
3Å MS, DCM, rt
OTBDPS
(2S,4R)-2n
OTBDPS
(2R,4R)-2n
L2 yield(time) dr de
(S) 88%(1.5 h) 250 : 1 99.2%
(R) 91%(3.75 h) 1 : 86 97.7%
axially chiral
PAd2
OMe
O
N
(R)-L2
rare asymmetric ligand-accelerated gold catalysis
catalyst loadings as low as 100 ppm
7 cases with achiral substrates, e.e. up to 99.7%
10 cases with chiral/racemic substrates, de up to 98.9%
permitting the synthesis of all four stereoisomers of 2-vinyltetrahydrofurans with excellent selectivity

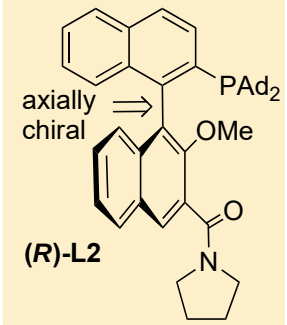



**(*R*)-1n**

*derived from S-glycidol*

**(2*S*,4*R*)-2n** **(2*R*,4*R*)-2n**

| **L2** | yield(time) | *dr* | *de* |
|---|---|---|---|
| **(*S*)** | 88%(1.5 h) | **250** : **1** | 99.2% |
| **(*R*)** | 91%(3.75 h) | **1** : **86** | 97.7% |




- rare asymmetric ligand-accelerated gold catalysis
- catalyst loadings as low as 100 ppm
- 7 cases with achiral substrates, *e.e.* up to 99.7%
- 10 cases with chiral/racemic substrates, *de* up to 98.9%
- permitting the synthesis of all four stereoisomers of 2-vinyltetrahydrofurans with excellent selectivity