

Synthesis of Chiral Bifunctional NHC Ligands and Survey of Their Utilities in Asymmetric Gold Catalysis

Jun-Qi Zhang,^{†,‡} Yunkui Liu,^{†,§} Xing-Wang Wang,^{†,§} and Liming Zhang^{*,†,§}

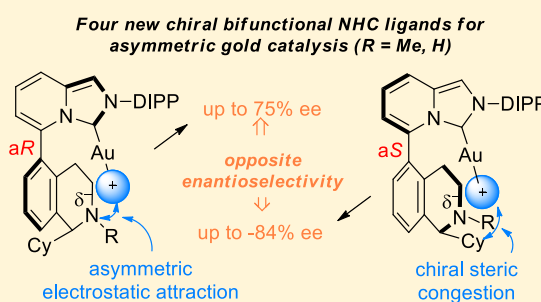
[†]Department of Chemistry and Biochemistry, University of California, Santa Barbara, California 93106, United States

[‡]Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou 215123, P. R. China

[§]State Key Laboratory Breeding Base of Green Chemistry-Synthesis Technology, Zhejiang University of Technology, Hangzhou 310014, P. R. China

Supporting Information

ABSTRACT: The synthesis and characterization of the chiral bifunctional NHC ligands based on the imidazo[1,5-*a*]pyridine (ImPy) scaffold are described. These ligands possess a fluxional biaryl axis and a chiral center. The configurational stability of the biaryl axis in their gold(I) complexes is investigated. The application of these axially chiral ImPy-based AuCl complexes in a series of gold catalysis is explored, and varying degrees of asymmetric induction are observed. In most cases, the ligand (a*S*,*R*)-**L8-H** with its cyclohexyl group pointing to the reaction site and hence exerting asymmetric steric influence is more effective in asymmetric induction.



INTRODUCTION

For the past several years, our lab has developed several remotely functionalized biaryl-2-ylphosphines [i.e., WangPhos and **L1**–**L7** (Figure 1)] for gold catalysis.¹ These novel ligands feature a basic substituent at the bottom half of the pendant aryl ring. Because of the approximately linear arrangement of the P–Au–substrate coordination and the restricted rotation of the P–C2 bond imposed by the bulky adamantyl groups, they enable beneficiary second-coordination sphere interactions

between the basic group and substrates and/or nucleophiles in homogeneous gold catalysis (Figure 1A). As such, a range of versatile and/or new gold catalyses have been developed.¹ For example, WangPhos, the first ligand of this type and one that features a 3'-carboxamide, can accelerate the gold-catalyzed addition of carboxylic acid to alkyne >800-fold by comparison to JohnPhos, a ligand of similar steric and electronic characteristics but without the remote basic group (eq 1).¹ⁱ As a result, the loading of the gold catalyst in this reaction mixture can be decreased to a level of tens of parts per million. This accelerative gold catalysis is also applied to achieve for the first time accelerative asymmetric gold catalysis, in which hexa-4,5-dien-1-ols are cyclized with an excellent enantiomeric excess in the presence of as little as 100 ppm of the chiral cationic gold(I) catalyst² prepared from the binaphthyl ligand (*R*)-**L1** (eq 2).^{1e} Replacing the amide group of WangPhos with a more basic aniline or tertiary amino group led to ligands **L2**–**L7**, among others, that are capable of engaging novel interactions with alkyne substrates via the basic groups and thereby enable gold catalysis^{1a–d,f,h} that cannot be achieved by conventional ligands. The first study in this context is the isomerization of alkynes into 1,3-dienes (eq 3). In this case, the remote anilinic group (*pK_a* ~ 4) of ligand **L2** is capable of effectively deprotonating the propargylic C–H bond (*pK_a* > 30) due to the synergistic Au(I) activation and the

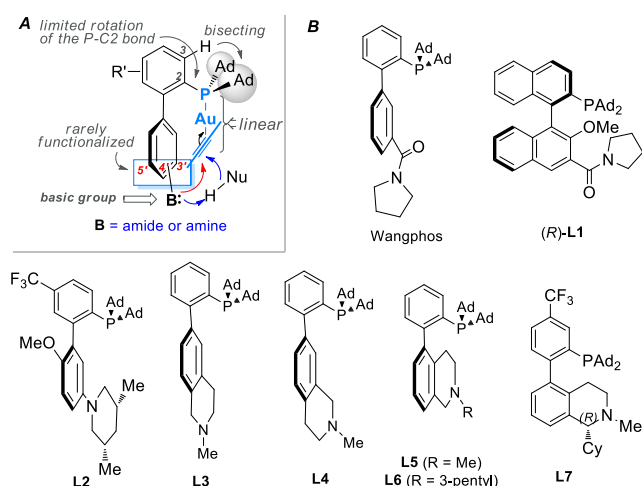


Figure 1. Novel biaryl-2-ylphosphines featuring a remote basic functional group specifically designed for homogeneous gold catalysis: (A) design and (B) a selected list of our reported ligands.

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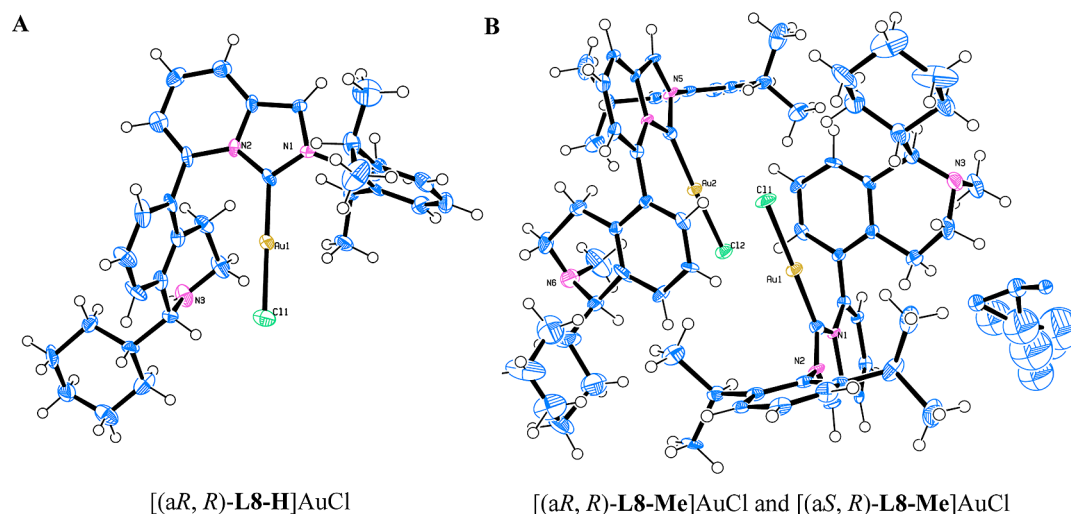


Figure 3. ORTEP drawings of [(aR,R)-L8-H]AuCl (A, solvent omitted) and [(aR,R)-L8-Me]AuCl and [(aS,R)-L8-Me]AuCl (B, solvent shown) showing 50% thermal ellipsoid probabilities. Selected bond distances (angstroms) and angles (degrees) for [(aR,R)-L8-H]AuCl: Au1–C1, 1.977(15); Au1–Cl1, 2.268(4); C1–N1, 1.352(19); C1–N2, 1.361(18); C7–C8, 1.45(2); C1–Au1–Cl1, 177.9(5); N1–C1–N2, 104.2(12). Selected bond distances (angstroms) and angles (degrees) for [(aR,R)-L8-Me]AuCl: Au2–C37, 2.00(3); Au2–Cl2, 2.294(8); C37–N4, 1.36(4); C37–N5, 1.37(3); C40–C44, 1.49(4); C37–Au2–Cl2, 178.3(9); N4–C37–N5, 99(2). Selected bond distances (angstroms) and angles (degrees) for [(aS,R)-L8-Me]AuCl: Au1–C1, 1.93(3); Au1–Cl1, 2.266(7); C1–N1, 1.39(4); C1–N2, 1.32(3); C4–C8, 1.47(4); C1–Au1–Cl1, 177.9(9); N1–C1–N2, 107(2).

Synthesis of Chiral Bifunctional NHC Ligands and the Structural Data of Their Au(I) Complexes. Our synthesis of the gold(I) complexes of (R)-L8 commenced with the condensation between 6-bromopicolinaldehyde and 2,6-diisopropylaniline, followed by the reaction with paraformaldehyde in the presence of TMSBr.¹¹ Upon workup, 5-bromo-2-(2,6-diisopropylphenyl)imidazo[1,5-a]pyridin-2-ium **1** was obtained as a white powder. Its Suzuki–Miyaura coupling with the boronate (R)-**2**, the synthesis of which we reported previously,^{1a} yielded the biaryl NHC precursor salt (R)-**3** by employing a modified literature procedure.⁴ The gold complex [(R)-L8-Boc]AuCl was prepared first by the synthesis of its silver complex as a crude product from (R)-**3** by using the combination of AgCl and KOH in dichloromethane in the dark and then by its transmetalation with AuCl·SMe₂. As expected, [(R)-L8-Boc]AuCl exhibits a mixture of diastereomeric atropisomers (3:2 dr) due to the restricted rotation of the biaryl axis in the presence of AuCl. To our delight, they could be readily separated by regular silica gel flash column chromatography. Subsequently, the Boc groups of the separated NHC–Au(I) complexes [(aS,R)-L8-Boc]AuCl and [(aR,R)-L8-Boc]AuCl were quantitatively removed upon exposure to TFA at 0 °C, affording complexes [(aS,R)-L8-H]AuCl and [(aR,R)-L8-H]AuCl, respectively, as white solids upon subsequent aqueous NaHCO₃ washing. These solids are fully air and moisture stable. Furthermore, they underwent reductive amination in the presence of paraformaldehyde and NaBH(OAc)₃ without incident to smoothly deliver [(aS,R)-L8-Me]AuCl and [(aR,R)-L8-Me]AuCl, respectively, in excellent yields. Single crystals of [(aR,R)-L8-H]AuCl and of the 1:1 mixture of [(aR,R)-L8-Me]AuCl and [(aS,R)-L8-Me]AuCl were successfully cultivated and subsequently subjected to X-ray diffraction studies. Their molecular structures and selected structural data are shown in Figure 3. As expected, the C_{carbene}–Au–Cl connection is nearly linear, with the angle ranging from 177.9° to 178.3°. The Au–Cl

distances range from 2.266 to 2.294 Å, and their Au–carbene bond lengths range from 1.93 to 2.00 Å.

Fluxional Nature of the Ligand Biaryl Axis. Inspired by our previously reported work on the related phosphine ligands,^{1a} we speculated that these chiral ImPy-based AuCl complexes, upon removal of the chloride, could rotate along its biaryl axis under heating conditions. Thus, we first examined [(aS,R)-L8-H]AuCl using our previously employed protocol: heating a mixture of 1 equiv of the complex, 4 equiv of NaBARF₄, and 20 equiv of 6-dodecyne in DCE at the specified temperature and then quenching the reaction with tetrabutylammonium chloride (4 equiv) after the specified time (Figure 4A). We note that this complex has the cyclohexyl group

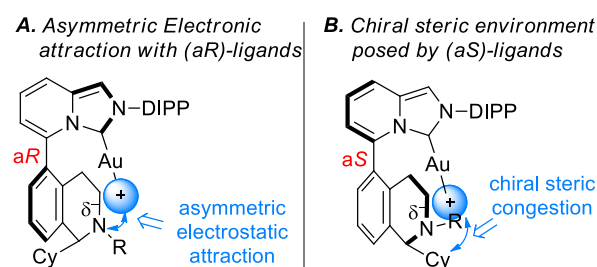
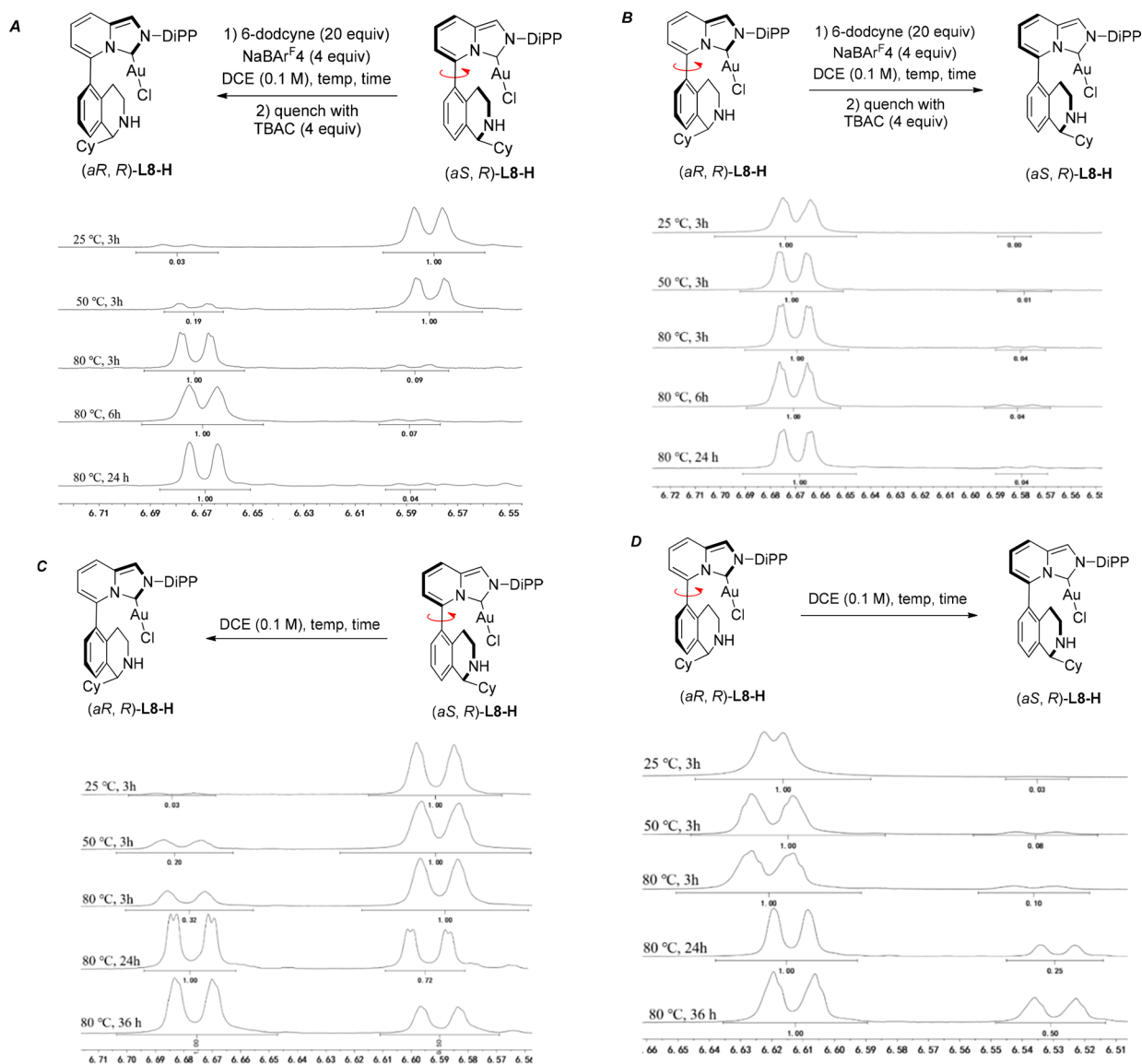


Figure 4. Rationales for inducing chirality by the chiral bifunctional ImPy–Au complexes.

intrude into the space of AuCl. This protocol is intended to examine the biaryl axis fluxionality of the in situ-generated cationic [(aS,R)-L8-H]Au⁺ complex. As shown in Figure 4A, a small amount of [(aR,R)-L8-H]AuCl was observed when the rotation was conducted at room temperature for 3 h. With a further increase in temperature to 50 °C, more [(aR,R)-L8-H]AuCl was detected with an (aR)/(aS) ratio of 0.19/1.00. The ratio increased to 1.00/0.09 when the conversion was performed at 80 °C for 3 h. Eventually, after 24 h, the (aR)/(aS) ratio was further increased to 1.00/0.04, which appears to be the equilibrium point. This conclusion was supported by

Scheme 2. Studying the Biaryl Axis Rotation of ImPy-Based Gold Complexes [(*R*)-L8-H]Au⁺ and [(*R*)-L8-H]AuCl

reaching the same ratio when [(*aR*,*R*)-L8-H]AuCl was employed as the starting point (Figure 4B). This result confirms that the biaryl axis is indeed fluxional and is consistent with our previous observation, where the presumed cationic Au(I) intermediate with the cyclohexyl group pointing toward the gold center, i.e., with the (*aS*) configuration, is thermodynamically less stable than that with the (*aR*) configuration. We propose that the electrostatic attraction between cationic gold and the partially negatively charged and unhindered nitrogen in the case of the (*aR*) configuration is responsible for the difference in stability.

To our surprise, during the protracted cultivation of single crystals for X-ray studies, we detected epimerization of [(*R*)-L8-H]AuCl at its chiral axis in solution, which is in contrast to the configuration stability of L7AuCl.^{1a} Subjecting either [(*R*)-L8-H]AuCl atropisomer in DCE to an elevated temperature confirmed it (Scheme 2C,D) and revealed (a) their rates of epimerization are similar to those of the cationic counterpart (i.e., Scheme 2A,B) and (b) the preference for the (*aR*) configuration over the (*aS*) configuration is only 2-fold, much lower than that of the cationic counterparts (~25-fold),

suggesting the predominating role of electronic attraction in favoring [(*aR*,*R*)-L8-H] in the cationic scenarios. We did not observe, however, that either atropisomer of [(*R*)-L8-H]AuCl in the solid state had undergone any epimerization while stored at 0 °C for 1 month.

Applications in Asymmetric Gold Catalysis. Having the four chiral ImPyAu(I) complexes in hand, we then survey their efficacy in enabling asymmetric gold catalysis,¹² albeit the semifluxional nature of their biaryl axes. It is surmised, as shown in Figure 4A, that with (*aR*,*R*)-L8-H as the ligand, the electrostatic attraction between the partially negatively charged ligand nitrogen and the cationic intermediates ubiquitous in gold catalysis might introduce the necessary asymmetric interaction to effectively induce product chirality. Alternatively, as shown in Figure 4B, the chiral steric environment posed by the protruding cyclohexyl group in the case of (*aS*,*R*)-L8-H could likewise be conducive to asymmetric catalysis.

We first investigated the gold-catalyzed alkoxymercuration of 1,6-enyne **4a** [X = C(CO₂Me)₂],¹³ and the results are summarized in Table 1 (entries 1–6). With [(*aR*,*R*)-L8-H]AuCl as the catalyst precursor and AgSbF₆ as the chloride

Table 1. Au-Catalyzed Alkoxymercuration of 1,6-Enynes^a

		4a: X = C(CO₂Me)₂ 4b: X = NTs		5a: X = C(CO₂Me)₂ 5b: X = NTs	
entry	enyne	catalyst	chloride scavenger	yield ^b (%)	ee ^c (%)
1	4a	[(aR,R)-L8-H]AuCl	AgSbF ₆	52	33
2	4a	[(aR,R)-L8-Me]AuCl	AgSbF ₆	trace	—
3	4a	[(aS,R)-L8-H]AuCl	AgSbF ₆	99	−73
4	4a	[(aS,R)-L8-Me]AuCl	AgSbF ₆	99	−66
5	4a	[(aS,R)-L8-H]AuCl	NaBARF ₄	82	−18
6	4a	[(aS,R)-L8-H]AuCl	[Ag(CH ₃ CN) ₂] ⁺ BARF [−]	97	−77
7	4b	[(aS,R)-L8-H]AuCl	AgSbF ₆	trace	—
8	4b	[(aR,R)-L8-H]AuCl	AgSbF ₆	71	21

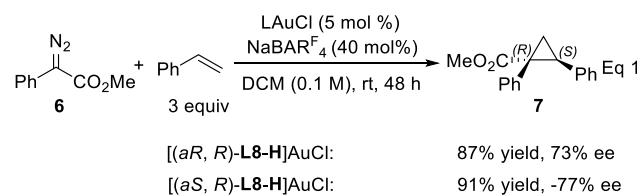
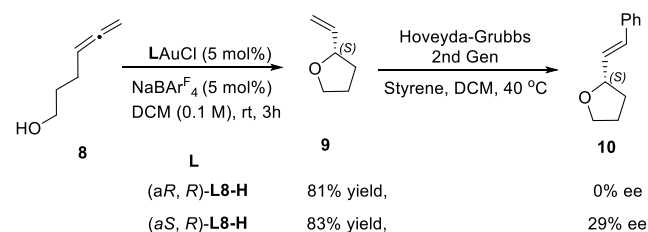
^aReaction conditions: 0.1 mmol scale, 5 mol % catalyst based on Au center, 5 mol % chloride scavenger, 1 mL of mixed solvent (1:1 DCM/MeOH). ^bIsolated yields. ^cDetermined by chiral HPLC. The absolute stereochemistry is assigned upon the comparison of its specific rotation to the literature data, and the negative ee values indicate the opposite configuration of the product.

scavenger, desired product **5a** was formed in 52% yield and with 33% ee (entry 1). On the other hand, the *N*-methyl counterpart of [(aR,R)-L8-H]AuCl, i.e., [(aR,R)-L8-Me]AuCl, led to only a trace amount of reaction (entry 2). Significant increases in enantioselectivity and yield in the presence of either of the (aS) ligands, i.e., [(aS,R)-L8-H] or [(aS,R)-L8-Me], were observed (entry 3 or 4, respectively). We note that the sense of chirality is opposite and the ee can reach a respectable value of −73%. The chloride scavenger appears to be important, as NaBARF₄ led to poor ee (entry 5) but [Ag(CH₃CN)₂]⁺BARF[−] improved it to −77% (entry 6). Because (R)-L8-H performed better than (R)-L8-Me, the former ligands were employed in the subsequent studies.

Sulfonamide substrate **4b**,^{11c,12} however, reacted quite differently, with (aR,R)-L8-H performing instead much better than [(aS,R)-L8-H] in terms of reaction yield (entries 7 and 8), but the ee remained poor.

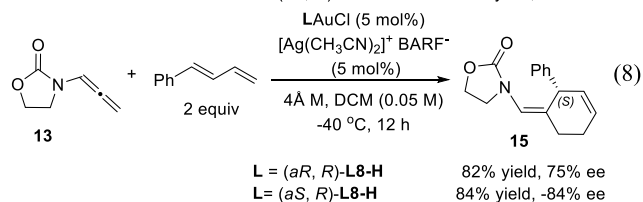
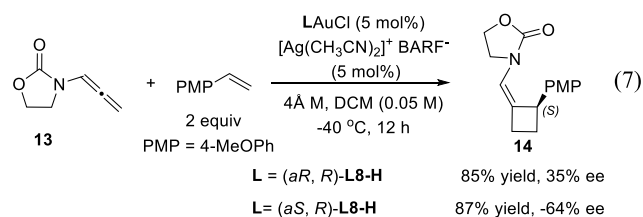
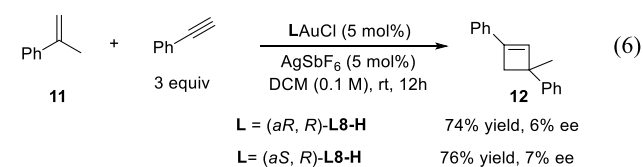
We then evaluated the asymmetric cyclopropanation of styrene by the gold carbene generated from methyl phenyldiazoacetate **6**. Despite this reaction has been widely reported by employing chiral Rh catalysts,¹⁴ the gold counterpart¹⁵ has not been achieved with good enantiomeric excess, despite success in related studies.¹⁶ To our delight, both ligands (aS,R)-L8-H and (aR,R)-L8-H could promote the reaction with high efficiency and decent enantiomeric excess. The absolute stereochemistry of **7** is assigned upon the comparison of its specific rotation to the literature data.¹⁴ Again, the ligand atropisomers led to the selective formation of the enantiomer of **7** and hence to the negative ee value (eq 5).

The asymmetric cyclizations of 4-allen-1-ol **8** was next examined. As shown in Scheme 3, [(aR,R)-L8-H]AuCl with its

Scheme 3. Gold-Catalyzed Enantioselective Cyclization of 4-Allen-1-ol **7**

cyclohexyl group pointing away from gold induced no chirality; on the other hand, its atropisomer [(aS,R)-L8-H]AuCl led to the formation of vinyltetrahydrofuran **9** with 29% ee, which was determined by chiral HPLC analysis of its cross-coupling product **10**. We previously reported that with a remotely amide-functionalized binaphthyl-2-ylphosphine as the ligand an accelerative asymmetric gold catalysis permits the cyclization of **8** with excellent ee.^{1e} In that chemistry, the amide group, behaving as a general base, enables the drastic rate acceleration and thereby the asymmetric induction. The lack of such acceleration in the case of (aR,R)-L8-H is not entirely surprising as the basic nitrogen is most likely positioned too far from the HO group during cyclization.

The [2+2] cycloaddition between α -methylstyrene and phenylacetylene has been realized asymmetrically by using non-C₂-chiral Josiphos digold(I) complexes as the catalyst.¹⁷ However, neither (aR,R)-L8-H nor (aS,R)-L8-H was able to induce much chirality in this reaction; however, the reaction was efficient (eq 6). Notably, in this case, the same enantiomer was preferred.

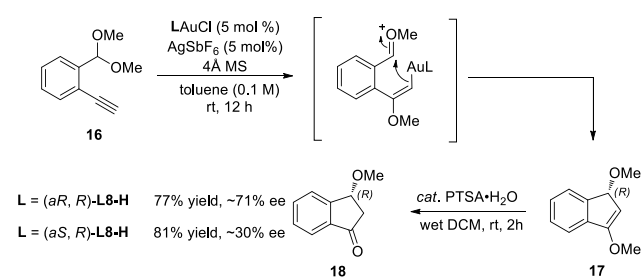


We next turned to the reactions of allenamides, which have been subjected to asymmetric gold catalysis in several

reports.¹⁸ As shown in eq 7, both atropisomers of (R)-L8-H smoothly promoted the intermolecular [2+2] cycloaddition between allenamide **13** and *p*-methoxystyrene to afford the cyclobutane **14** in >80% yields. For the asymmetric induction, similar to the observations in Table 1, they led to opposite stereoselectivities and (aS,R)-L8-H was substantially better than its (aR) counterpart. The reaction of **13** with 1-phenyl-1,3-butadiene was the most enantioselective with either of the (R)-L8-H isomers among the screened reactions (eq 8). Again, (aS,R)-L8-H is better, albeit moderately, and an 84% unoptimized ee was achieved for cyclohexene product **15**. In these two cases, the product absolute configurations were also assigned upon comparison of their specific rotations to literature data.¹⁸

With acetal **16** as the substrate, the gold-catalyzed cycloisomerization led to indanone product **17** upon hydrolysis in good yields (Scheme 4).¹⁹ Interestingly, in this case, (aR,R)-

Scheme 4. Gold(I)-Catalyzed Enantioselective Carboalkoxylation of Alkyne



L8-H induced much higher enantiomeric excesses than that of its (aS,R) counterpart, in contrast to the trend observed in Table 1, Scheme 3, and eqs 5, 7 and 8, where the latter ligand was more effective in asymmetric induction. The configuration of **18** was assigned on the basis of chiral HPLC behavior comparable to that of the literature.¹⁹

These results reveal that both the attractive interaction and the steric repulsion outlined in Figure 4 can indeed provide asymmetric induction. In most cases, the chiral steric environment posed by (aS,R)-L8-H is more effective in controlling the stereochemical outcomes. However, in the case of Scheme 4, the development of a discrete oxocarbenium intermediate prior to the enantiodetermining step apparently allows better stereocontrol by the electronic mode, therefore affording a much higher ee in the case of (aR,R)-L8-H.

CONCLUSIONS

We have synthesized and characterized four new chiral bifunctional NHC ligands based on the imidazo[1,5-a]pyridine (ImPy) scaffold. These ligands possess a fluxional biaryl axis, a chiral center, and a remote alkylamino group. Upon coordination to Au(I), the rotation around the biaryl axis is hindered, but the equilibria between the atropisomers can be established upon moderate heating. Despite the semistable axial chirality, these gold complexes are demonstrated to induce chirality with a range of gold-catalyzed transformations, and enantiomeric excesses can reach 84%. Two modes of imparting asymmetry by these ligands are chiral steric hindrance and asymmetric electrostatic attraction, the choice of which is dictated by the ligand axial chirality and often leads to opposite asymmetric induction. In most cases, ligand (aS,R)-L8-H with its cyclohexyl group pointing to the reaction

site and hence posing a chiral steric environment is more effective in inducing chirality than its atropisomer (aR,R)-L8-H, which relies on electrostatic attraction for enantioselectivity.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organo-met.9b00400.

General procedures, procedure for the preparation of gold complexes, Au-catalyzed enantioselective transformations, X-ray structures of gold catalysts, ¹H and ¹³C NMR spectra, HPLC chromatograms, and references (PDF)

Accession Codes

CCDC 1910598 and 1913712 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Author

*E-mail: zhang@chem.ucsb.edu.

ORCID

Yunkui Liu: 0000-0001-8614-458X

Xing-Wang Wang: 0000-0002-6004-8458

Liming Zhang: 0000-0002-5306-1515

Notes

The authors declare no competing financial interest.

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