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Chiral Bifunctional Phosphine Ligand Enabling Gold-Catalyzed Asymmetric Isomerization of Alkyne to Allene and Asymmetric Synthesis of 2,5-Dihydrofuran

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Supporting Information

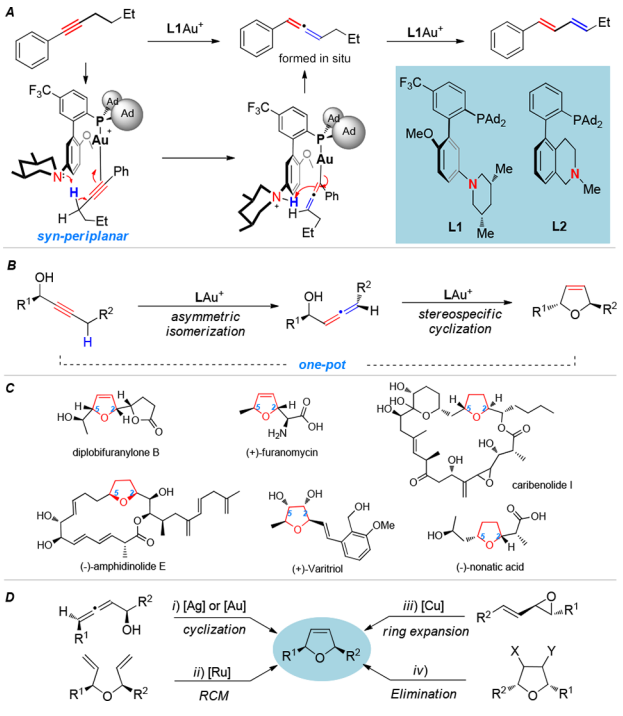
ABSTRACT: The asymmetric isomerization of alkyne to allene is the most efficient and the completely atom-economic approach to this class of versatile axial chiral structure. However, the state-of-the-art is limited to *tert*-butyl alk-3-ynoate substrates that possess requisite acidic propargylic C−H bonds. Reported here is a strategy based on gold catalysis that is enabled by a designed chiral bifunctional biphenyl-2-ylphosphine ligand. It permits isomerization of alkynes with nonacidic α-C−H bonds and hence offers a much-needed general solution. With chiral propargylic alcohols as substrates, 2,5-disubstituted 2,5-dihydrofurans are formed in one step in typically good yields and with good to excellent diastereoselectivities. With achiral substrates, 2,5-dihydrofurans are formed with good to excellent enantiomeric excesses. A novel center-chirality approach is developed to achieve a stereocontrol effect similar to an axial chirality in the designed chiral ligand. The mechanistic studies established that the precatalyst axial epimers are all converted into the catalytically active cationic gold catalyst owing to the fluxional axis of the latter.

Axially chiral allenes are versatile and highly valuable intermediates in asymmetric synthesis.[1] Various preparative methods have been documented.[2] Notwithstanding, the direct isomerization of alkyne to chiral allene, the arguably simplest and the most atom-economic approach, has only been reported with alkynes featuring rather acidic propargylic hydrogens,[3] such as 1,3-diphenylpropyne[3c,f] and *t*-butyl alk-3-ynoates[3d,e], and moreover, high e.e. values are only realized with the latter substrates. To date, there is no asymmetric isomerization of a vast range of other alkynes and especially those devoid of acidic propargylic hydrogens.

We previously reported the isomerization of arylalkynes into 1-aryl-1,3-dienes via the intermediacy of an allene (Scheme 1A).[4] This reaction is enabled by a bifunctional biphenyl-2-ylphosphine (i.e., **L1**) that features a remote aniline moiety and was specifically designed to permit the basic aniline group to deprotonate an Au(I)-activated alkyne. Later on, we reported that ligands featuring a more basic remote tertiary amino group such as **L2** are likewise effective in promoting the alkyne-to-allene isomerization.[5]

It is envisioned that with a chiral version of **L1** or **L2** as ligand the isomerization of alkyne into chiral allene could be realized. Of high significance is that this approach would for the first time be of general utility due to the demonstrated accommodation of alkyne substrates with nonacidic α-C−H bonds.[4,5]

Scheme 1. Soft Propargylic Deprotonation and Chiral 2,5-Dihydrofuran Synthesis



To overcome the inherent equilibrium between alkyne and allene in the isomerization process, we envisioned that the chiral allene generated in situ could be trapped in a stereospecific cyclization of allenylmethanol[6] (Scheme 1B). As such, a readily available chiral propargylic alcohol[7] could be directly converted to a chiral 2,5-dihydrofuran possessing a new stereogenic center. Chiral 2,5-disubstituted 2,5-dihydrofuran and the related tetrahydrofuran are structural motifs presented in various bioactive natural products (for examples, see Scheme 1C).[8] The typical approaches[9] to the construction of the former, however, do not feature increase of stereochemical complexity as the two requisite chiral centers are either preinstalled (i.e., Scheme 1D, approaches ii[9a] and iv[9b])

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or derived from existing chiral elements via stereoselective/stereospecific processes (i.e., approaches i[9c] and iii[9d]). An asymmetric approach starting from only one chiral element, as in the case of a chiral propargylic alcohol in Scheme 1B, leads to enhanced stereochemical complexity and is inherently advantageous but has yet to be realized. Herein, we report an implementation of Scheme 1B enabled by a designed chiral version of **L2**.

The traditional and obvious approach to developing a chiral version of the biphenyl-2-ylphosphine **L2** is to employ a biaryl framework with a stable chiral axis (e.g., Scheme 2A). Our previous work on a related system,[10] however, revealed that the installation of the bulky PAd_2 group via a Pd-catalyzed cross coupling[11] can be low yielding (~14%) due to the requisite steric congestion around a stable chiral axis. As such, we envisioned a new design, which is depicted in Scheme 2B. Instead of relying on axial chirality to orient the remote basic nitrogen, e.g., behind the top benzene ring as depicted in **L3**Au^+ in Scheme 2A, we designed an axially fluxional biphenyl-2-ylphosphine **L4**, which features a chiral center at C1 in the pendant 1,2,3,4-tetrahydroisoquinoline ring. A R group in (a*R*,*R*)-**L4** would largely not affect the catalytic activity of the Au^+ complex as it points away from the catalytic site. On the other hand, axial rotation of **L4** by 180° would afford (a*S*,*R*)-**L4**, which has the R group pointing to the catalytic site. A bulky 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 **L3**, this center chirality could also make the remote tertiary amino group only available for deprotonation when it is behind the biphenyl framework. While the gold complexes (a*R*,*R*)-**L4**Au^+ and (a*S*,*R*)-**L4**Au^+ might not be interconvertible and hence (a*S*,*R*)-**L4**Au^+, catalytically inactive, could be wasted; the ease of constructing center chirality and the anticipated high efficiency in installing the PAd_2 group ortho to a sterically unencumbered axis propelled us to explore this novel design.

On the basis of the design, the chiral ligands **L4-1**–**L4-4** were prepared,[12] and their structures are shown underneath the Table 1 equation. We then set out to study the designed cycloisomerization by using (*R*)-dodec-3-yn-2-ol (**5a**, 99% ee) as the substrate (Table 1). The pre-existing stereocenter of **5a** permits expedient analysis of the stereoselectivity at the newly generated chiral center by ^{1}H NMR. Instead of the desired cycloisomerization, JohnPhos led expectedly only to the well-precedented Meyer–Schuster rearrangement (entry 1). With the achiral **L2** as ligand, the desired 2,5-dihydrofuran **7a** was indeed formed in 79% yield but with little diastereoselectivity (entry 2). This result confirmed again the essential role of the remote amino group in enabling this reaction and revealed that

Scheme 2. Our Design of Chiral Bifunctional Biphenyl-2-ylphosphine Ligands Relying on Center Chirality

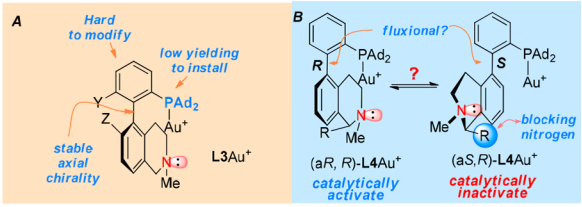
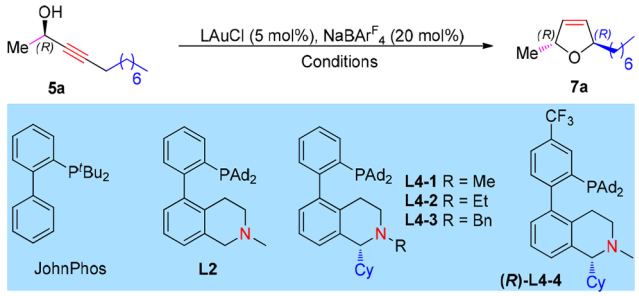


Table 1. Reaction Optimization[a,b]



entry	ligand	solvent	temp/time	conv.	yield	trans/cis
1	JohnPhos	DCE (0.1 M)	60 °C/7 h	>99%	<1%	
2	**L2**	DCE (0.1 M)	60 °C/4 h	>99%	79%	54:46
3	(*R*)-**L4-1**	DCE (0.1 M)	60 °C/7 h	>99%	70%	92:8
4	(*R*)-**L4-2**	DCE (0.1 M)	60 °C/7 h	48%	16%	89:11
5	(*R*)-**L4-3**	DCE (0.1 M)	60 °C/7 h	58%	3%	
6	(*R*)-**L4-4**	DCE (0.1 M)	60 °C/7 h	>99%	76%	93:7
7	(*R*)-**L4-4**	DCE (0.1 M)	40 °C/18 h	>99%	48%	94:6
8	(*R*)-**L4-4**	DCE (0.1 M)	80 °C/2 h	>99%	83%	93:7
9	(*R*)-**L4-4**	DCE (0.25 M)	80 °C/2 h	>99%	75%	93:7
10	**(*R*)-L4-4**	**DCE (0.05 M)**	**80 °C/2 h**	**>99%**	**85%**	**93:7**
11[c]	(*R*)-**L4-4**	DCE (0.05 M)	80 °C/2 h	>99%	79%	92:8
12[d]	(*R*)-**L4-4**	DCE (0.05 M)	80 °C/2 h	93%	69%	92:8
13	(*R*)-**L4-4**	toluene (0.05 M)	80 °C/2 h	>99%	13%	91:9
14	(*R*)-**L4-4**	$PhCF_3$ (0.05 M)	80 °C/2 h	>99%	68%	93:7
15	(*R*)-**L4-4**	PhF (0.05 M)	80 °C/2 h	>99%	51%	93:7

[a]0.05 mmol reaction scale. [b]Conversion and yield determined by using 1,3,5-trimethoxybenzene as NMR internal standard. Except entries 1 and 13, <5% of the Meyer–Schuster rearrangement product formed. [c]10 mol % NaBAr$^F_4$ used. [d]5 mg of 3 Å MS used.

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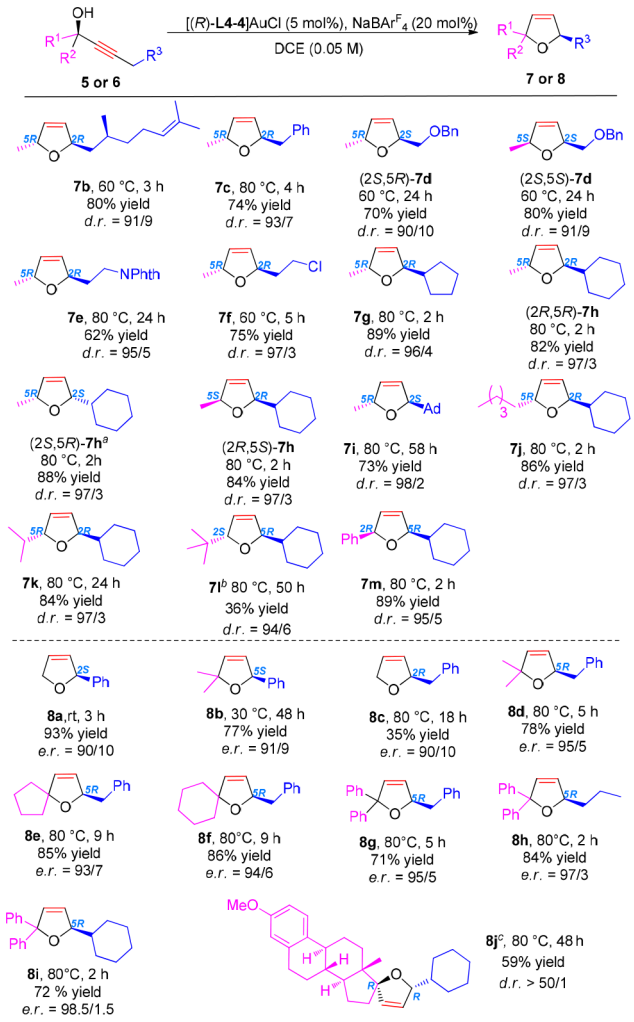
the pre-existing stereocenter has little directing effect on the configuration of the newly generated stereocenter and likely the proceeding allene chirality. To our delight, with (*R*)-**L4-1** featuring a sterically demanding cyclohexyl group at its chiral center, the gold catalysis afforded **7a** in 70% yield and with a trans/cis ratio of 92/8 (entry 3). This amounts to >11:1 preference for the (*R*)-configuration at the new chiral center. Changing the ligand *N*-substituent from methyl in (*R*)-**L4-1** to bulkier ethyl in (*R*)-**L4-2** or benzyl in (*R*)-**L4-3** resulted in a significant decrease in conversion and, moreover, reaction yields (entries 4 and 5). The installation of an inductively electron-withdrawing CF_3 group on the C4 of (*R*)-**L4-1** delivered the ligand (*R*)-**L4-4**, which led to a better yield (76%) and a slightly improved diastereoselectivity (trans/cis = 93:7, entry 5). Further studies (entries 6−10) with (*R*)-**L4-4** as ligand revealed that a better yield (85%) could be achieved by running the gold catalysis at 80 °C and in a lower substrate initial concentration of 0.05 M (entry 10). A lower loading of $NaBAr^F_4$ or the addition of 3 Å MS led to a slightly lower yield (entries 11 and 12). It was also found that the solvent DCE was important for the optimal yield as $PhCF_3$, toluene, and PhF led to lower yields (entries 13−15). Of note, except entries 1 and 13, little Meyer−Schuster product (<5%) was detected in all the other entries.

With the optimized reaction conditions in hand, we set out to investigate the reaction scope (Table 2). Initially, a series of chiral secondary propargylic alcohols (**5**, R^1 = Me, R^2 = H) were examined. Various functional groups such as C−C double bond (**7b**), phenyl (**7c**), benzyloxy (**7d**), phthalimide (**7e**), and chloro (**7f**) were all readily tolerated at the R^3 group, and moderate to high yields and good diastereoselectivities were realized. Changing R^3 from linear chains to more steric hindered cyclopentyl (**7g**), cyclohexyl (**7h**), and 1-adamantyl (**7i**) groups led to excellent diastereoselectivities without compromising the reaction yields. Switching the R^1 group from methyl to *n*-pentyl (**7j**), isopropyl (**7k**), or phenyl (**7m**) also resulted in excellent yield and diastereoselectivity. A *tert*-butyl group, however, appeared detrimental and led to a much lower yield of **7l**, albeit the trans/cis selectivity remained excellent. Importantly, the cis-counterpart of (2*S*,5*R*)-**7d**, i.e., (2*S*,5*S*)-**7d**, was readily accessed from the corresponding substrate enantiomer in a higher 80% yield and with a slightly improved cis/trans selectivity. Notably, (2*S*,5*S*)-**7d** is a key intermediate employed in the total synthesis of (−)-varitriol.[13] A similar phenomenon was observed in the cases of (2*R*,5*S*)-**7h** and (2*R*,5*R*)-**7h**. Moreover, by employing the ligand enantiomer, i.e., (*S*)-**L4-4**, (2*S*,5*R*)-**7h** was isolated in 88% yield and with an identical 97/3 diastereomeric ratio. These results established that by using different combinations of **L4-4** and substrate enantiomers, all four stereoisomers of 2,5-disubstituted 2,5-dihydrofuran can be accessed with high to excellent levels of stereoselectivity.

We turned our attention next to achiral propargylic alcohol substrates **6**. The enantioselective cycloisomerization occurred smoothly. In the cases of **8a** and **8b**, despite that chiral arylallenes are known to undergo rapid epimerization under gold catalysis,[14] the products were still obtained with good enantiomeric ratios, suggesting the HO 5-*endo-trig* cyclization must be rapid. **8c** with a 2-benzyl group was formed in a low yield, which could be due to a competitive isomerization toward a 1,2-dien-1-ol intermediate, but its homologues derived from achiral tertiary propargylic alcohols such as **8d**−**8g** were all formed in good to excellent yields and with

Table 2. Reaction Scope[a,b]



[a][(*S*)-**L4-4**]AuCl used. [b]<5% Meyer−Schuster rearrangement product. [c]10 mol % [(*R*)-**L4-4**]AuCl used.

high enantiomeric ratios. The tolerance of steric hindrance in these cases is notable. Outstanding asymmetric inductions by our chiral ligand were observed in the cases of **8h**, **8i**, and **8j** due largely to increased steric bulk around the C−C triple bond. In the last case where the substrate was derived from estrone, the reaction was slow, likely due to steric hindrance, and required a higher catalyst loading and a longer reaction time. However, the cycloisomerization is exceptionally diastereoselective (>50:1).

To probe how the ligand works, we first attempted to separate the two precatalyst atropisomers. To our delight, they form crystals of different shapes and could be manually separated. X-ray diffraction studies confirmed their epimeric structures (Scheme 3A). In the case of [(a*S*,*R*)-**L4-4**]AuCl, the cyclohexyl group clearly intrudes into the space occupied by Cl and should block the binding of π-substrates during catalysis. In the case of [(a*R*,*R*)-**L4-4**]AuCl, the cyclohexyl group points away from the metal. Though an inversion of the pyramidal nitrogen in [(a*R*,*R*)-**L4-4**]AuCl is needed in order to point its lone pair electrons to Au, such a process should have an easily surmountable barrier. When a 1:1.7 mixture of [(a*R*,*R*)-**L4-4**]AuCl and [(a*S*,*R*)-**L4-4**]AuCl was heated at 80 °C in DCE for 1 h, the ratio did not change, revealing that the ligand axial

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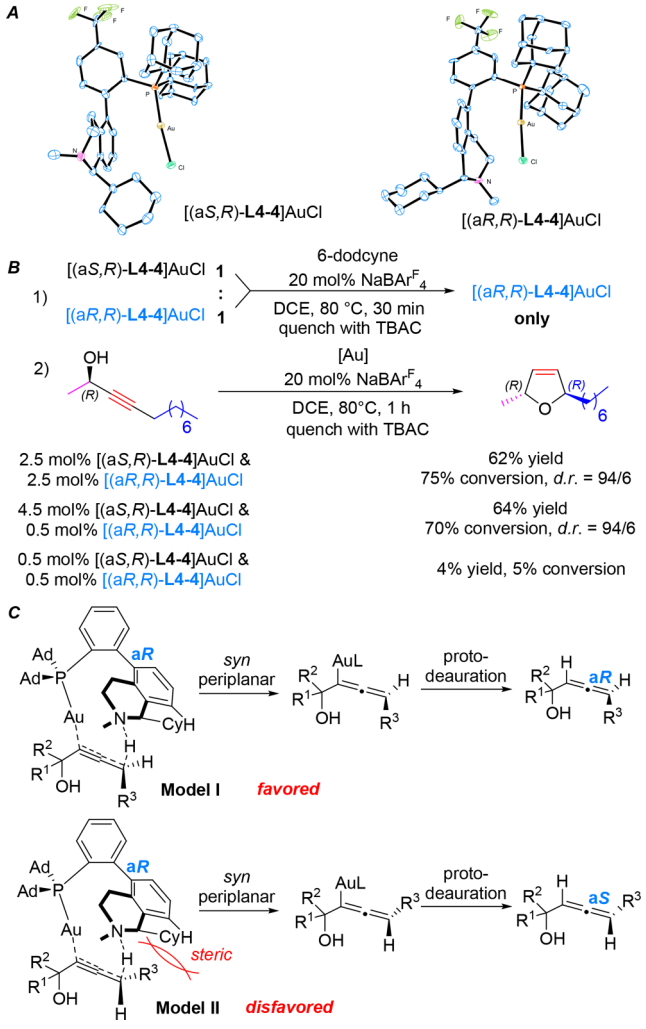
Scheme 3. Study of the Axial Chirality of Gold Catalysts and the Stereochemical Model



configuration is stable when ligated to AuCl. Interestingly, as shown in Scheme 3B, eq 1, a 1:1 mixture of [(a*R*,*R*)-**L4-4**]AuCl and [(a*S*,*R*)-**L4-4**]AuCl was completely converted into [(a*R*,*R*)-**L4-4**]AuCl when a solution of it in DCE was first treated with $NaBAr^F_4$, a chloride abstractor, and 6-dodecyne, then heated at 80 °C and at last quenched with tetrabutylammonium chloride. This experiment suggests that the ligand biaryl axis, most likely in the sterically minimum form of cationic (**L4-4**)Au$^+$, could rotate at 80 °C and, moreover, its configuration requisite for our asymmetric catalysis is thermodynamically much favored. This result suggests that the existence of stable precatalyst axial isomers is inconsequential. This conclusion is nicely supported by the experiments shown in Scheme 3B, eq 2, where the conversions and the yields correlate to the total amounts of (**L4-4**)AuCl instead of that of [(a*R*,*R*)-**L4-4**]AuCl alone.

Previous DFT calculations[15] suggest the reaction should go through a syn-periplanar deprotonation. As such, two competing models leading to opposing allene configurations can be constructed. As in Scheme 3C, Model II experiences destabilizing steric interaction between the R^3 group and the ligand pendant arene ring, while Model I does not. Consequently, the deprotonation will favor the latter model. The predicted product is consistent with our experiment outcome, assuming that the subsequent protodeauration is stereoretentive, which is well documented.[16]

In conclusion, for the first time a generally applicable asymmetric isomerization of alkynes to chiral allenes is realized via a homogeneous gold catalysis enabled by a designed chiral bifunctional biphenyl-2-ylphosphine ligand. Instead of relying on a chiral biaryl axis to achieve asymmetry, this catalysis employs a more readily installed center chirality in the designed ligand. With chiral or achiral propargylic alcohols as substrates, chiral 2,5-dihydrofurans are directly formed in mostly good yields and importantly with good to excellent levels of stereoselectivity at the newly generated stereocenter.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b12833.

Experimental details, compound characterization, and spectra (PDF)

CIF file for [(a*S*,*R*)-**L4-4**]AuCl (CIF)

CIF file for [(a*R*,*R*)-**L4-4**]AuCl (CIF)

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Notes

The authors declare no competing financial interest.

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