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Chiral Bifunctional Phosphine Ligand Enables Gold-Catalyzed Asymmetric Isomerization and Cyclization of Propargyl Sulfonamide into Chiral 3-Pyrroline

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Abstract

This work details an asymmetric gold-ligand cooperative catalysis that transforms readily accessible chiral/achiral propargylic sulfonamides into chiral 3-pyrrolines. A bifunctional biphenyl-2-ylphosphine ligand featuring a chiral tetrahydroisoquinoline fragment is essential for the observed metal−ligand cooperation and the asymmetric induction. 2,5-*cis*-3-Pyrrolines are formed with excellent diastereoselectivities in a “matched” scenario. The “mismatched” scenario by using the ligand enantiomer delivers 2,5-*trans*-3-pyrrolines with >5/1 diastereoselectivity. The synthetic utilities of this chemistry are demonstrated.

Graphical Abstract

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Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02896.

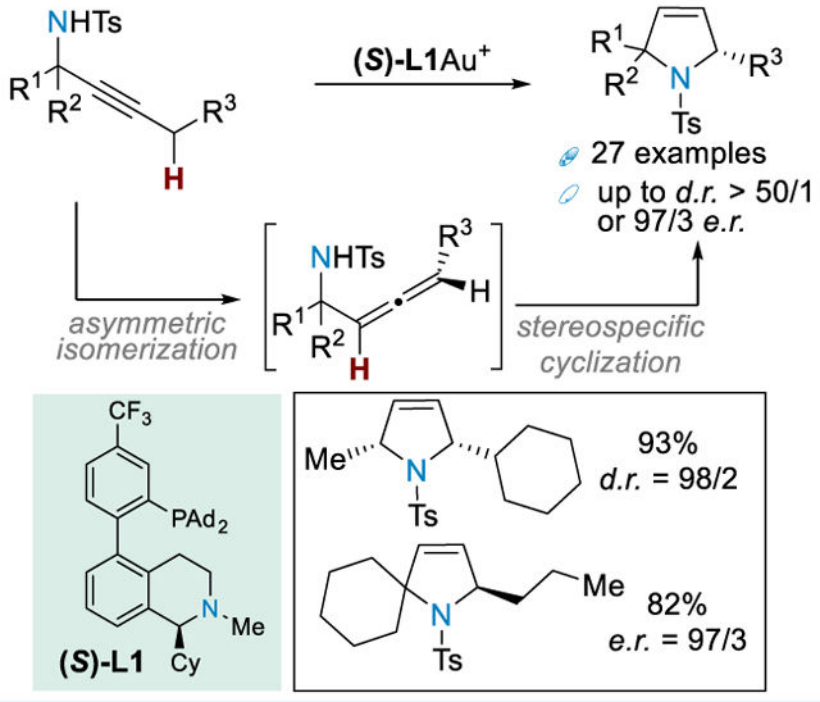
Experimental procedures, characterization data, and spectral data (PDF)

Accession Codes

CCDC 1992021 contains 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.

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c02896

The authors declare no competing financial interest.



For the past several years, we[1] have implemented a metal−ligand cooperation strategy[2] in homogeneous gold catalysis.[3] The bifunctional ligands were developed based on the general design shown in Scheme 1A, where the basic group installed on the bottom half of the pendant benzene ring of the biaryl-2-ylphosphine framework can behave as a general base interacting with the incoming protic nucleophile[4] or engage challenging substrate deprotonation.[5] The metal−ligand cooperation has facilitated the development of various efficient or novel gold catalyses[4,5] and offered new strategies to achieve asymmetric transformations.[4b,5b,d] In 2019, we reported that a chiral tertiary amine-functionalized ligand, that is, (*R*)-**L1**, can enable the asymmetric isomerization of alkyne to chiral allene.[5d] As shown in Scheme 1B, from a propargylic alcohol substrate, this isomerization delivers a chiral allenol via the initial cooperative propargylic deprotonation by the ligand tertiary amino group followed by *ipso*-protodeauration of the allenylgold intermediate **A**. The allenol thus generated subsequently undergoes one-pot gold-catalyzed stereospecific cyclization to afford the chiral dihydrofuran product.[6] This chemistry is applied as a key step in the synthesis of diplobifuranylone B.[7] We envisioned that this approach could be applied to the synthesis of chiral 3-pyrrolines if propargylic sulfonamides were employed (Scheme 1C). Despite the fact that the reaction mechanism is similar, the sulfonamide moiety is much larger than its HO counterpart and may hinder the desired gold catalysis. Of significance is that pyrrolidines are structural motifs prevalent in alkaloid natural products, as exemplified by those shown in Scheme 1D. This chemistry, if successfully implemented, would provide expedient synthesis to chiral 3-pyrrolines and, upon manipulation, chiral pyrrolidines from readily accessible propargylic sulfonamides.[8]

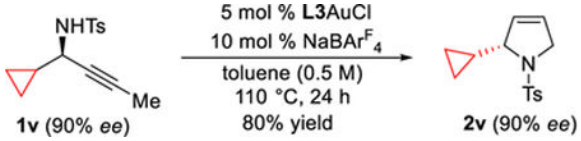
At the outset, we chose (*R*)-4-methyl-*N*-(oct-3-yn-2-yl)-benzenesulfonamide (**1a**) as the model substrate for the designed reaction. As shown in Table 1, JohnPhos led to little

conversion (entry 1), as expected, and the addition of catalytic DIPEA did not improve the reaction result (entry 2). When the achiral tertiary amine-functionalized ligand **L3** was employed, the gold catalysis resulted in the formation of the desired 3-pyrroline **2a** as a diastereomeric mixture in 92% yield (entry 3). In comparison with the 2,5-dihydrofuran chemistry,[5d] where the reaction was completed in 2 h at 80 °C, the higher reaction temperature (i.e., 95 °C) and the much longer reaction time (i.e., 48 h) reflect the challenge posed by the sterically bulky toluenesulfonamide moiety. In the product mixture, *cis*-**2a** was favored by a 3/1 ratio over its *trans* counterpart, revealing a moderate level of innate diastereoselectivity. In contrast with the lack of reactivity in entry 1, this result confirmed the role of the ligand remote amino group in enabling this reaction. To our delight, when the chiral ligand (*S*)-**L1** was employed, the reaction went smoothly to afford **2a** in 97% yield with an outstanding cis/trans ratio of 96/4 (entry 4). The absolute stereochemistry of *cis*-**2a** was confirmed by an X-ray diffraction study. (See the figure in Table 1.) This excellent result is consistent with the "matched" nature of the asymmetric induction between the inherent *cis* preference and the chiral ligand-induced (*S*)-configuration at the nascent chiral center. When the temperature was decreased to 80 °C, the reaction became sluggish, and low conversion was observed (entry 5). It was found the solvent toluene was optimal for the reaction (entry 7), as $PhCF_3$ and chlorobenzene led to slightly lower diastereoselectivities (entries 4 and 6). The reaction carried out under neat conditions gave significantly lower yields (entry 8). After the reaction temperature was increased to 110 °C, the reaction time was shortened to 14 h without compromising the reaction yield or diastereoselectivity (entry 9). Further increasing the reaction temperature to 120 °C and using chlorobenzene as the solvent led to a faster reaction but a lower diastereoselectivity (i.e., 95/5, entry 10). On a preparative scale, *cis*-**2a** was isolated in 93% yield by following the conditions in entry 9. With the ligand enantiomer, that is, (*R*)-**L1**, employed in the gold catalysis, the ligand-induced asymmetry mismatches the inherent *cis* preference. As such, the observed diastereomeric ratio (i.e., 92/8, entry 11) was expectedly lower than that achieved with (*S*)-**L1** (see entry 9), but the ligand induction remained dominant, and *trans*-**2a** was the major diastereomer. Likely the consequence of the "mismatch", the reaction was sluggish, needing 72 h to achieve completion. The reaction gave slightly lower yields and diastereoselectivities with (*R*)-**L2**[5b] as the ligand (entry 12). Nevertheless, the ability to access the disfavored trans isomer as the predominant product is valuable in synthesis. By performing this reaction on a preparative scale, we isolated *trans*-**2a** in 91% yield (entry 11).

With the optimized reaction conditions (Table 1, entries 9 and 11) in hand, we set out to explore the reaction scope. The synthesis of chiral *cis*-3-pyrrolines was first studied (Scheme 2A). For the R^2 group in the chiral propargylic amide substrate **1**, a benzyl group was allowed, affording the *cis*-3-pyrrolines *cis*-**2b** in 96% yield with 96/4 diastereoselectivity. More steric demanding groups such as isopropyl and cyclohexyl groups lead to even higher *cis* selectivities of the products (e.g., *cis*-**2c** and *cis*-**2d**) while maintaining excellent reaction efficiency. Several functionalized R^2 groups were tolerated. An incomplete conversion was observed in the presence of a primary chloride in the case of **2e**. We attributed it to the deactivation of the gold catalyst by leached chloride. The yield based on conversion (88%), however, remains excellent. In addition, a silyl ether (**2f**) and a phthalimide (**2g**) group were allowed. We then varied the propargylic R^1 group while fixing R^2 as isopropyl. Alkyl groups

including *n*-propyl (**2h**), isopropyl (**2i**), and cyclopropyl (**2j**) reacted uneventfully to deliver the desired *cis*-3-pyrroline products in good yields and with >50/1 diastereomeric ratios. However, a *tert*-butyl group proved to be too bulky to permit any detectable conversion, even at 130 °C using chlorobenzene as the solvent (**2k**). A phenyl group and its electronically modified variants were readily tolerated, and the *cis*-pyrroline products **2l**−**2n** were formed in 74−79% yields with >50/1 diastereoselectivity. Electron-rich heteroaryl groups including 2-furyl (**2o**), 2-thienyl (**2p**), and *N*-tosylindol-3-yl (**2q**) were accommodated, and the preference for the cis products remained excellent. The yields of **2o** and **2p** were moderate, which is likely due to side reactions related to their electron-rich arene moieties. A similar phenomenon was observed in the formation of the *cis*-pyrroline **2r** featuring a *β*-styryl as the R^1 group.

We then examined several representative cases of the formation of disfavored *trans*-3-pyrrolines besides *trans*-**2a**. As shown in Scheme 2B, **2b**, **2c**, **2d**, and **2e** were formed in synthetically useful trans/cis ratios of around (5 to 6)/1 and in mostly good yields. A second batch of catalysts was added to consume all of the substrates in the first three cases. In the formation of the chlorinated 3-pyrroline **2e**, the reaction similarly did not proceed to completion, even with 10 mol % catalyst loading. Lastly, we subjected achiral propargylic tosylamides to the reaction. As shown in Scheme 2C, the reaction worked well in the case of **2s**, where the propargylic substituents in the substrate are part of a cyclohexane ring, and an enantiomeric ratio of 97/3 was achieved. In this case, (*R*)-**L2** performed better and was used, and the reaction was performed in $PhCF_3$ and at 95 °C. When the propargyl substituents were phenyl groups, the desired **2t** was not formed, probably due to steric hindrance. In the absence of a propargylic substituent, the formation of the monosubstituted chiral 3-pyrroline product **2u** was slow, leading to an only 38% yield (83% based on conversion), even with the loading of (*S*)-**L1**AuCl doubled, despite the fact that the enantioselectivity (i.e., 94/6) was good. To establish a complementary and yet more efficient access to this class of chiral monosubstituted 3-prolines, we subjected the chiral sulfonamide substrate (*R*)-**1v** (90% *ee*) to the gold catalysis (eq 1). Because no new stereocenter was generated in the product **2v**, the achiral ligand **L3** was employed. The reaction was efficient, and full retention of the propargylic chiral center was observed.



Eq. 1

To probe the synthetic utility of this asymmetric gold catalysis, we employed the propargylic amide substrate **1w** featuring an iodinated phenyl group for further transformation. As shown in Scheme 3A, its gold catalysis smoothly afforded **2w** in 86% yield as a diastereomeric mixture with a *cis/trans* ratio of 93/7. Subjecting *cis*-**2w** to radical reaction conditions and two different radical trapping strategies led to the synthesis of the chiral tricyclic allylated pyrroline **3** and its alcohol counterpart **4** in moderate yields and as single

stereoisomers. This gold catalysis allows the synthesis of a homologue of a late-stage intermediate in the synthesis of (+)-preussin.[9] As shown in Scheme 3B, the iodine-less version of *cis*-**2w**, that is, *cis*-**2x**, was synthesized with a similar efficiency from (*R*)-**1x**. It then underwent diastereoselective epoxidation and regioselective reductive ring opening by lithium triethylborohydride to afford the 3-hydroxypyrrolidine **6** in a combined 57% yield. Dess-Martin oxidation of **6** arrived at the pyrrolidinone **7**. The homologue of **7** with R being *n*-nonyl instead of *n*-heptyl, that is, **7′**, serves as an intermediate[10] in the total synthesis[10,11] of (+)-preussin in three steps.

In conclusion, we have developed gold-catalyzed asymmetric access to chiral 3-pyrrolines from readily available propargylic tosylamides. This catalysis is achieved via metal−ligand cooperation enabled by a bifunctional biphenyl-2-ylphosphine ligand featuring a chiral tetrahydroisoquinoline moiety. 2,5-*cis*-3-Pyrrolines can be synthesized with excellent selectivities over their trans counterparts due to the “matched” scenario. With the ligand enantiomer, this cooperative catalysis overcomes “mismatching” and delivers disfavored 2,5-*trans*-3-pyrrolines with >5/1 diastereoselectivities. The synthetic utilities of this chemistry are demonstrated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

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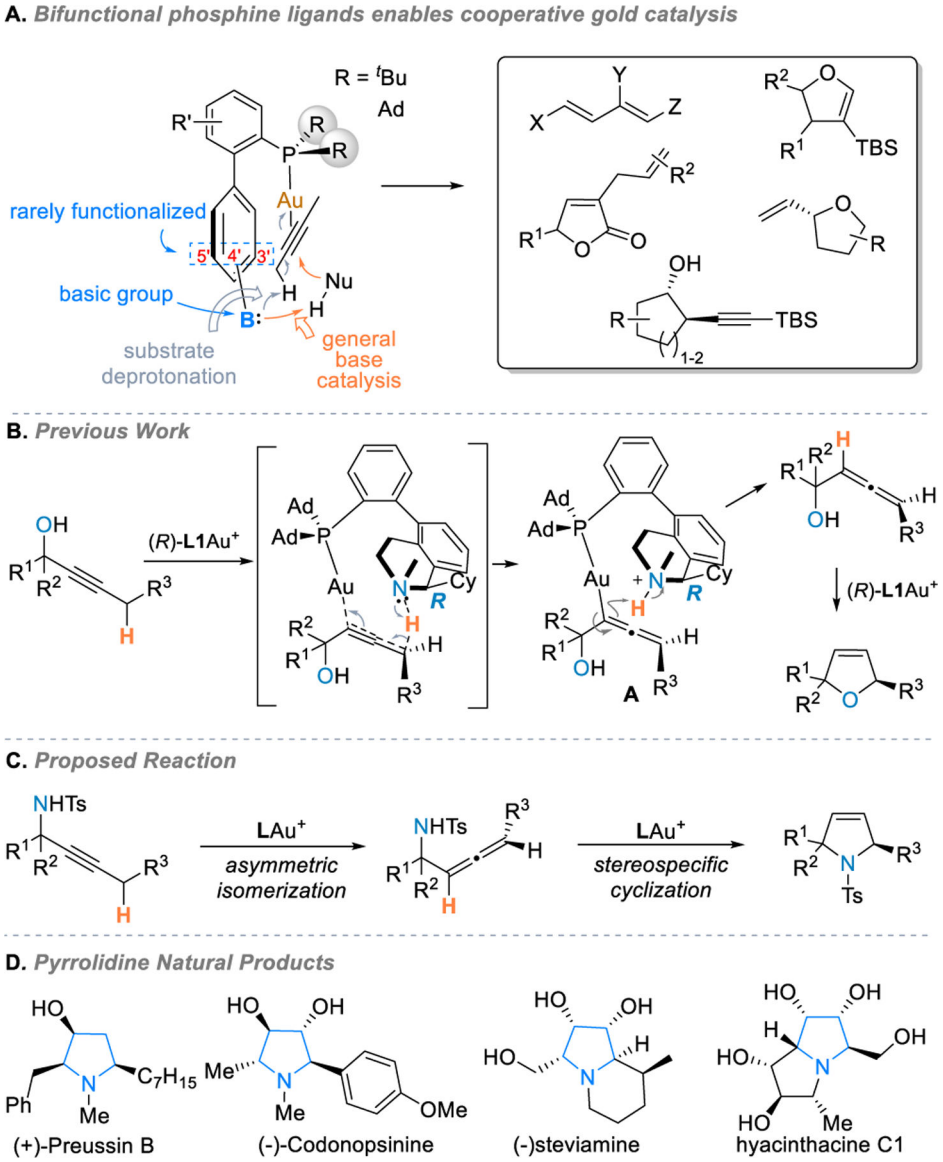
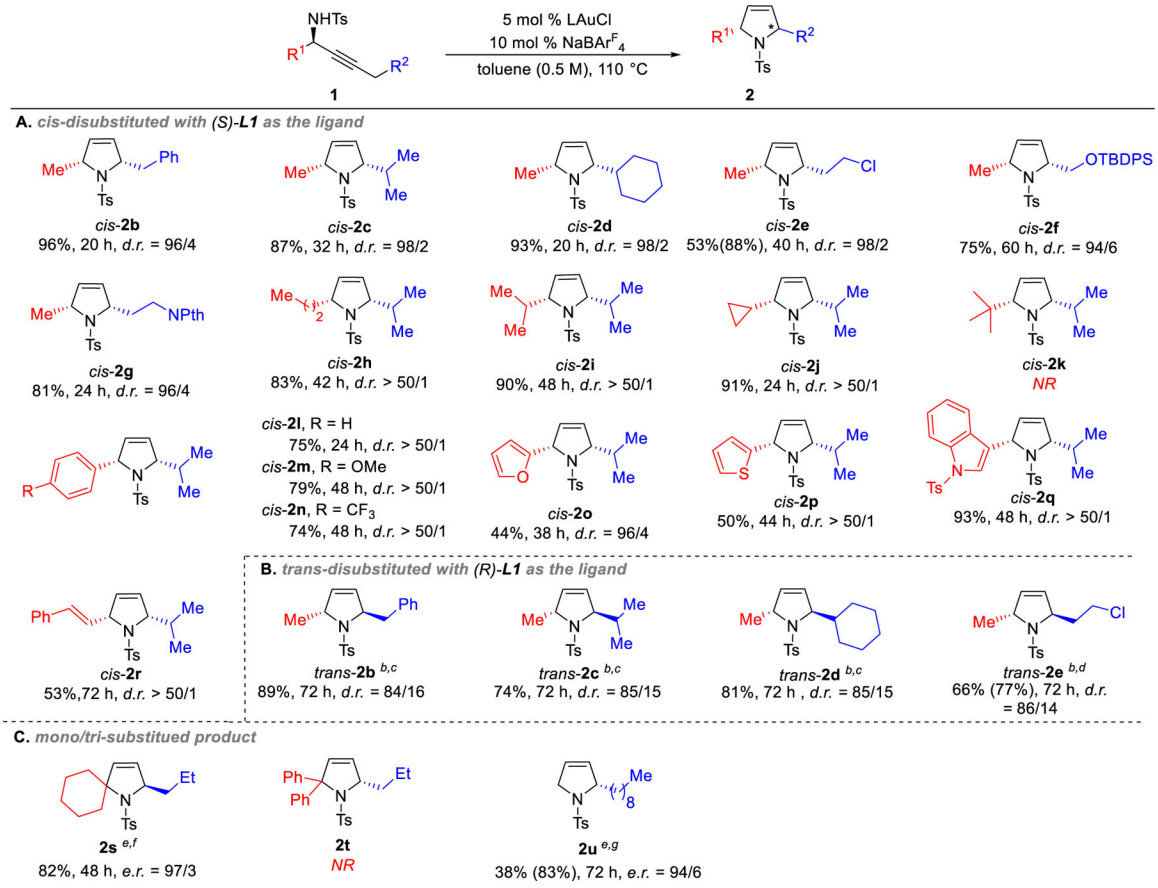


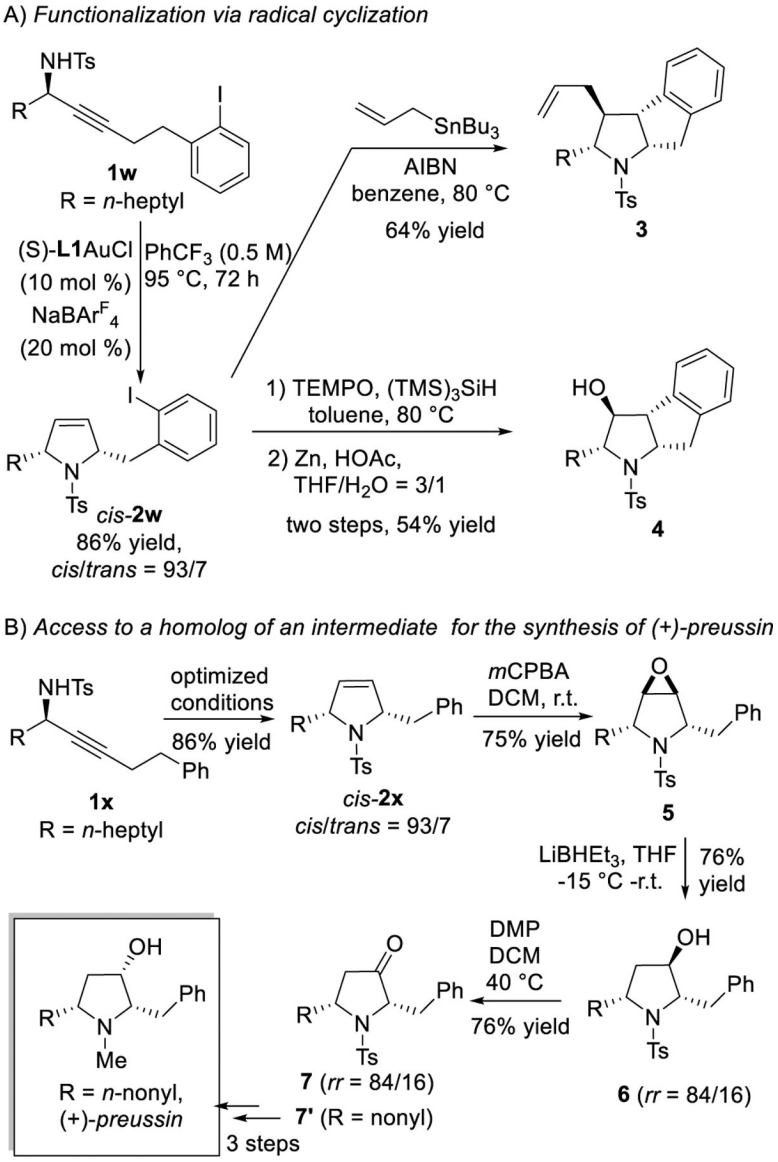
Scheme 1.
Reaction Design



Scheme 2.

Reaction Scope[a]

[a]Reaction was performed on a 0.2 mmol scale in a 2-dram sealed vial if not specified. Yields based on conversion are reported in parentheses. [b]Toluene (0.2 M). [c]Second batch of (*R*)-**L1**AuCl (5 mol %) and $NaBAr^F_4$ (10 mol %) was added after 24 h. [d]10 mol % (*R*)-**L1**AuCl and 20 mol % $NaBAr^F_4$. [e]$PhCF_3$ (0.5 M) at 95 °C. [f]5 mol % (*R*)-**L2**AuCl and 10 mol % $NaBAr^F_4$. [g]10 mol % (*S*)-**L1**AuCl and 20 mol % $NaBAr^F_4$.



Scheme 3.
Synthetic Application

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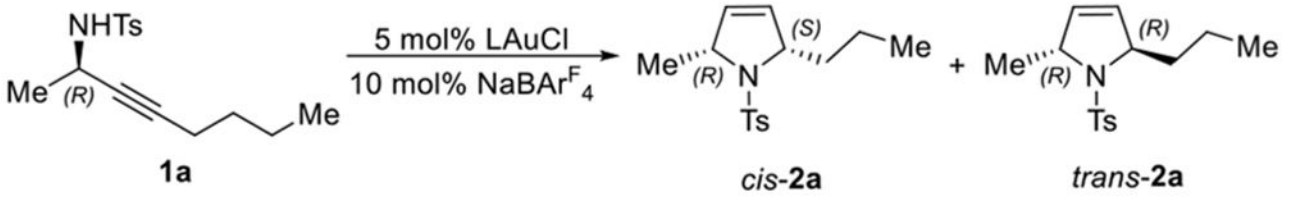
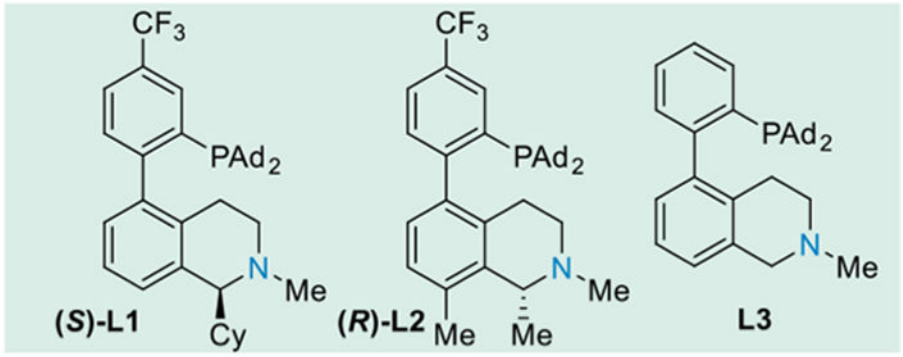
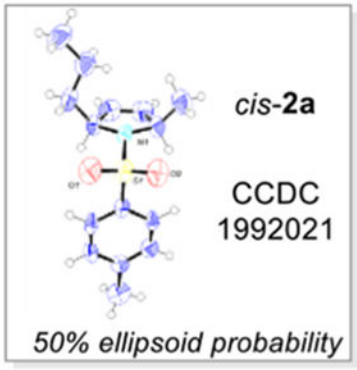
Table 1.

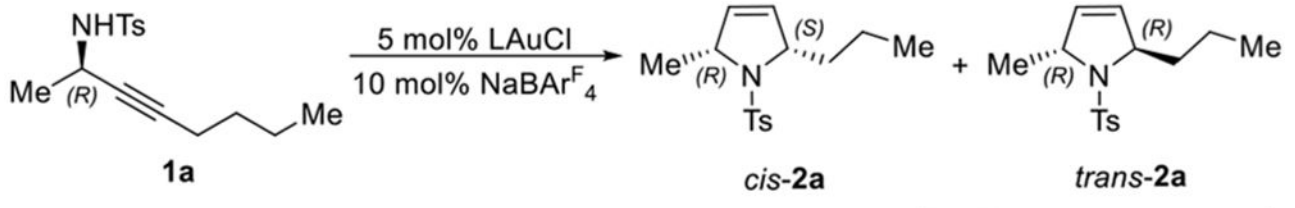
Reaction Condition Optimization[a]

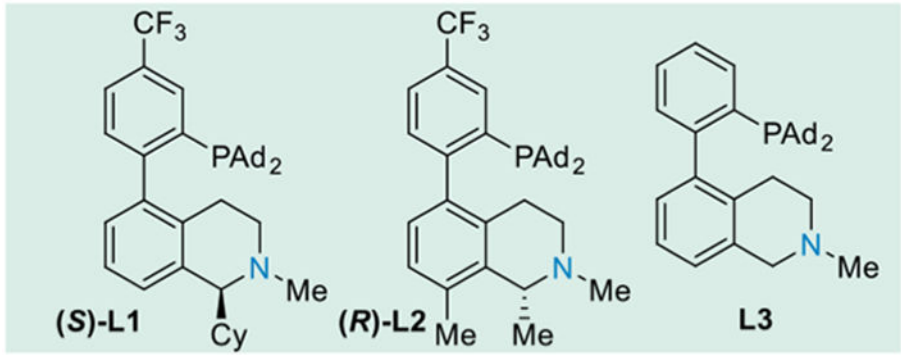


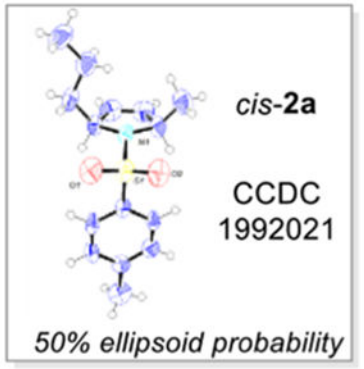




entry	ligand	solvent	temp/time	conv. (%)	yield (%)[b]	*d.r.*
1	**JohnPhos**	$PhCF_3$/0.5 M	95 °C/48 h	7	2	
2[c]	**JohnPhos**	$PhCF_3$/0.5 M	95 °C/48 h	4	<2	
3	**L3**	$PhCF_3$/0.5 M	95 °C/48 h	>99	92	3/1
4	(*S*)-**L1**	$PhCF_3$/0.5 M	95 °C/48 h	>99	97	96/4
5	(*S*)-**L1**	$PhCF_3$/0.5 M	80 °C/48 h	5	4	
6	(*S*)-**L1**	PhCl/0.5 M	95 °C/48 h	>99	98	96/4
7	(*S*)-**L1**	PhMe/0.5 M	95 °C/48 h	>99	96	97/3
8	(*S*)-**L1**	neat	95 °C/24 h	>99	35	97/3
9	(*S*)-**L1**	**PhMe/0.5 M**	**110 °C/14 h**	**>99**	**96**[d]	**97/3**
10	(*S*)-**L1**	PhCl/0.5 M	120 °C/7 h	>99	98	95/5







entry	ligand	solvent	temp/time	conv. (%)	yield (%)[b]	*d.r.*
11	(*R*)-**L1**	**PhMe/0.2 M**	**110 °C/72 h**	**>99**	**89** [e]	**8/92**
12	(*R*)-**L2**	PhMe/0.2 M	110 °C/72 h	>99	81	9/91

[a] Conditions: **1a** (0.05 mmol), 5 mol % LAuCl, and 10 mol % NaBAr$^F_4$.

[b] NMR yield was determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal reference.

[c] 5 mol % *N,N*-diisopropylethylamine (DIPEA) was added.

[d] 93% isolated yield.

[e] 91% isolated yield.