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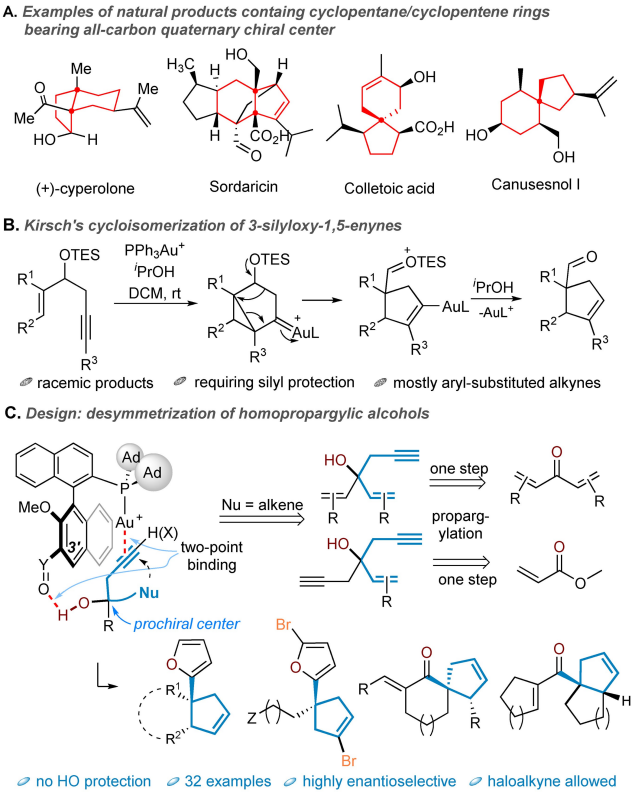
# Gold(I)-Catalyzed Desymmetrization of Homopropargylic Alcohols *via* Cycloisomerization: Enantioselective Synthesis of Cyclopentenes Featuring a Quaternary Chiral Center

*Philip Kohnke and Liming Zhang**

**Abstract:** Cyclopentene rings possessing a chiral quaternary center are important structural motifs found in various natural products. In this work, we disclose expedient and efficient access to this class of synthetically valuable structures *via* highly enantioselective desymmetrization of prochiral propargylic alcohols. The efficient chirality induction in this asymmetric gold catalysis is achieved *via* two-point bindings between a gold catalyst featuring a bifunctional phosphine ligand and the substrate homopropargylic alcohol moiety—an H-bonding interaction between the substrate HO group and a ligand phosphine oxide moiety and the gold-alkyne complexation. The propargylic alcohol substrates can be prepared readily *via* propargylation of enoate and ketone precursors. In addition to monocyclic cyclopentenes, spirocyclic and bicyclic ones are formed with additional neighboring chiral centers of flexible stereochemistry in addition to the quaternary center. This work represents rare gold-catalyzed highly enantioselective cycloisomerization of 1,5-enynes. Density functional theory (DFT) calculations support the chirality induction model and suggest that the rate acceleration enabled by the bifunctional ligand can be attributed to a facilitated protodeauration step at the end of the catalysis.




***Scheme 1.*** Cyclopentane/cyclopentenes & reaction design.

Cyclopentane rings featuring a quaternary center are found in many bioactive natural products,[1] including those of fused rings and spirocycles (Scheme 1A). Despite various creative approaches to their construction, new synthetic methods affording excellent enantioselectivity remain desirable.

Although there are inherent challenges in achieving asymmetric Au(I) catalysis[2] due to the linear structure of Au(I) complexes, we recently demonstrated that enantioselective metal-ligand cooperation[3] offers a viable and versatile strategy to overcome them.[4] This type of cooperative catalysis[3c] can be enabled by chiral binaphthylphosphine ligands featuring a 3′-basic group. To further advance the utility of these ligands in achieving value-added asymmetric gold catalysis, we surmised that the two-point binding—gold-substrate coordination and H-bonding interaction between the ligand basic group and an H-bond donor in a substrate—may offer an opportunity to desymmetrize prochiral homopropargylic alcohols, as outlined in Scheme 1C. It is envisioned that a facile cyclization by a tethered nucleophile would then create a chiral center by breaking substrate symmetry. In this context, we considered the use of a tethered alkene as the nucleophilic group. 1,5-enyne cycloisomerizations are known to be facile,[5] but highly enantioselective ones are rare.[6] Moreover, in 2007, Kirsch reported that 3-silyloxy-1,5-enynes undergo cycloisomerization to form racemic cyclopentenes possessing a quaternary center (Scheme 1B).[7] The reaction mechanism entails cascade 1,5-enyne cyclization, semi-pinacol rearrangement, and desilylation. The silyl protecting group in this chemistry is thought to prevent competitive HO group 5-*endo*-dig

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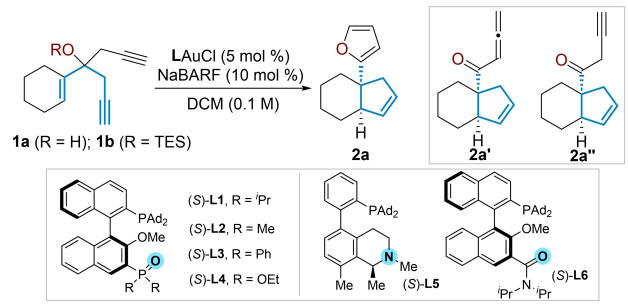
cyclization to form labile dihydrofurans.[8] In light of the importance of structures featuring chiral quaternary centers, we surmised that our bifunctional ligands, due to the H-bonding interaction with the HO group, might prevent the dihydrofuran formation and hence enable the use of unprotected substrates. Besides the omission of the substrate silylation step, the H-bond interaction, as discussed previously, might also offer the needed chiral induction to promote an asymmetric transformation. In this work, we disclose a highly enantioselective desymmetrization[9] of prochiral homopropargylic alcohols *via* a facile enyne cycloisomerization (Scheme 1C). Besides the expedient access to a range of versatile cyclopentene frameworks featuring chiral quaternary centers, the substrates, being dienynols or enediynols, are readily prepared *via* simple propargylation of easily available materials.

We began our study by employing the prochiral enediynol **1a** as the substrate. This compound was prepared in one step from commercially available methyl 1-cyclohexene-1-carboxylate *via* double propargylation. The conditions optimization results of its desymmetric cycloisomerization are shown in Table 1. Initially, we screened different ligands in DCM, using NaBARF as the halide scavenger (entries 1–8). The full consumption of **1a** was achieved in each case. The best ligand is (*S*)-**L1**, which is a new ligand and possesses a 3′-diisopropylphosphoryl group, and the

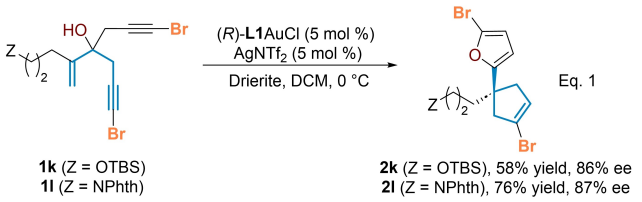
***Table 1:*** Reaction optimization.[a]




| entry | ligand | temp/time | yield of **2a** | ee of **2a** |
|---|---|---|---|---|
| 1 | JohnPhos | rt/12 h | 40% | N/A |
| 2 | IPr | rt/16 h | 0% | N/A |
| 3 | (*S*)-**L1** | rt/0.5 h | 65% | 91% |
| 4 | (*S*)-**L2** | rt/0.5 h | 67% | 82% |
| 5 | (*S*)-**L3** | rt/16 h | 17% | 50% |
| 6 | (*S*)-**L4** | rt/1 h | 62% | 63% |
| 7 | (*S*)-**L5** | rt/16 h | 52% | ~0% |
| 8 | (*S*)-**L6** | rt/6 h | 0% | N/A |
| 9[b] | (*S*)-**L1** | rt/6 h | 68% | 87% |
| 10[c] | (*S*)-**L1** | rt/6 h | 59% | 92% |
| 11[d] | (*S*)-**L1** | rt/0.5 h | 69% | 92% |
| 12[d,e] | (*S*)-**L1** | rt/0.5 h | 75% | 92% |
| **13**[d,e] | **(*S*)-L1** | **0 °C/3 h** | **81%** | **94%** |
| 14[d] | (*S*)-**L1** | −20 °C/18 h | 73% | 93% |
| 15[d,f] | (*S*)-**L1** | rt/16 h | – | N/A |

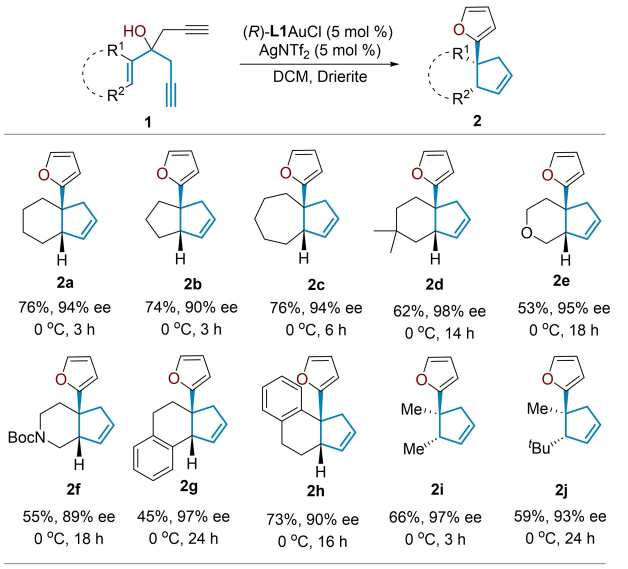
[a] Reactions run with **1a** as the substrate and quenched by $^{n}Bu_4N^+Cl^-$, isolated yield reported, the *ee* values determined by chiral HPLC analysis. [b] Toluene as solvent. [c] $PhCF_3$ as solvent. [d] 5 mol% $AgNTf_2$ instead of NaBARF used. [e] Drierite used as a drying agent. [f] **1b** used as the substrate, and the conversion was 43%.

furanyl hexahydroindene **2a** was formed in 65% yield and with 91% ee (entry 3). In comparison, JohnPhos led to a substantially slower reaction and a lower yield (entry 1), and the NHC ligand IPr resulted in a complex mixture (entry 2). The dimethyl and diphenyl counterparts of (*S*)-**L1**, i.e., (*S*)-**L2** (entry 4) and (*S*)-**L3** (entry 5), and the phosphonate ligand (*S*)-**L4** (entry 6) were less effective in chiral induction. In the case of (*S*)-**L3**, the reaction was sluggish and low yielding. In addition, the tertiary amine phosphine ligand (*S*)-**L5** did lead to the desired product, but the reaction was slow and exhibited no enantioselectivity (entry 7). Finally, the amide ligand (*S*)-**L6** gave an intractable mixture of products. Further optimization of the reaction conditions, including the use of toluene (entry 9) and trifluorotoluene (entry 10) as the solvent, $AgNTf_2$ as the chloride scavenger (entry 11), and the addition of Drierite (entry 12) eventually resulted in the increase of yield to 75% and a marginal enhance of the ee value to 92% (entry 12). By lowering the reaction temperature to 0 °C, the reaction was further improved, affording **2a** in 81% yield and with 94% ee (entry 13). However, further lowering the temperature led to a much slower reaction, a lower yield, and surprisingly a slightly lower ee (entry 14). During some of the optimizations, when the reaction was stopped prematurely, the allenyl ketone **2a′** and the alkynyl ketone **2a″** were observed along with **2a** and could be isolated as an inseparable mixture. **2a′**/**2a″** are the precursors to **2a** and were converted to the latter under the reaction conditions. When the TES-protected substrate **1b**—analogous to the work by Kirsch[7]—was subjected to the conditions of entry 11, the substrate consumption was incomplete after 16 h, and the desired product **2a** was not formed (entry 15). These results suggest that the H bond between the **L1** diisopropylphosphoryl moiety and the substrate HO group plays a key role in promoting the reaction and enabling high levels of enantioselectivity.




With the optimized reaction conditions (Table 1, entry 13) in hand, we set out to investigate the scope of this desymmetric enediynol cycloisomerization. As shown in Table 2, a variety of cyclic alkene substrates were tolerated, and chiral *cis*-fused cyclopentenes (**2a**–**2h**) were formed in moderate to good yield and with mostly excellent enantioselectivity. This chemistry provides expedient access to synthetically versatile bicyclic frameworks including 5/5-fused (**2b**), 7/5-fused (**2c**), and 6/5-fused with heterocyclic 6-membered rings (**2e** and **2f**). Moreover, conjugated cyclic alkenes such as dihydronaphthalenes were also tolerated, affording isomeric furan products **2g** and **2h** possessing an angularly fused tricyclic skeleton with 97% ee and 90% ee, respectively. The moderate yield of **2g** was attributed to the labile nature of the tertiary alcohol substrate under acidic

**Table 2:** The reaction scope with enediynol substrates.[a]

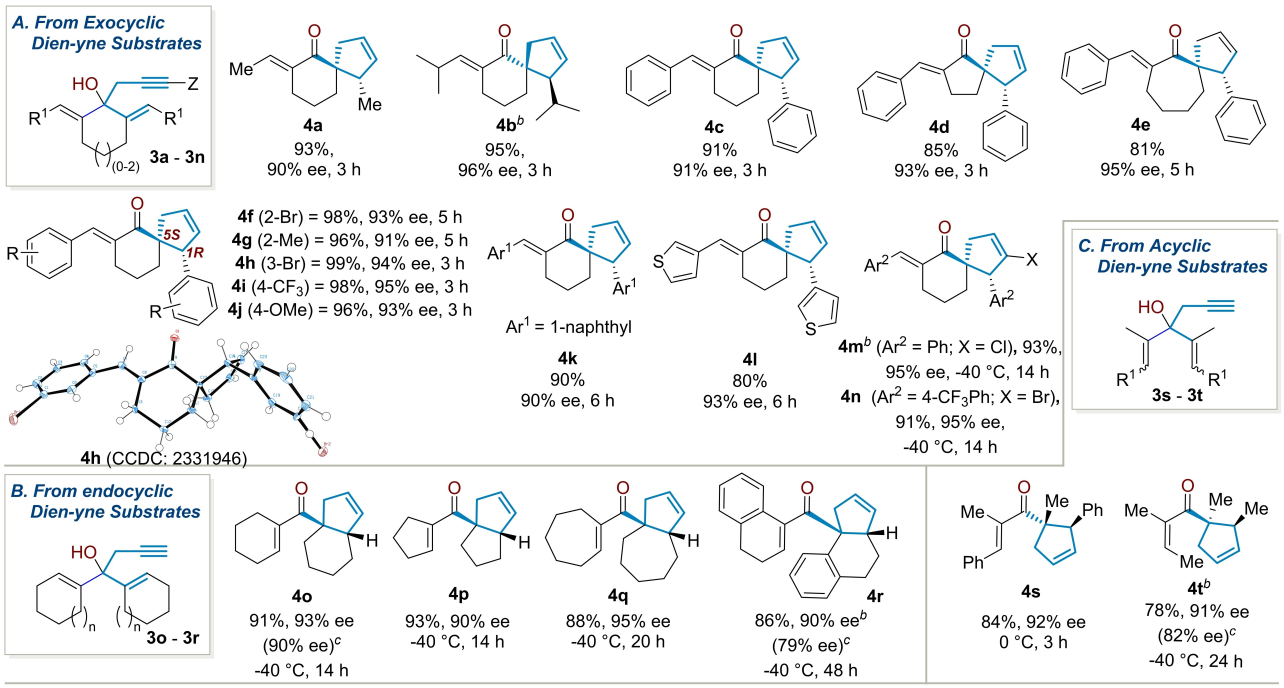



[a] solated yields are reported, and the ee values were determined by chiral HPLC.

conditions. Acyclic alkene substrates were also tolerated, and the furan-substituted cyclopentene products **2i** and **2j** featuring two adjacent chiral centers—one of quaternary—were formed with 97 % ee and 93 % ee, respectively. Of note is that the sterically hindered *tert*-butyl group in the case of **2j** was readily allowed. We also examined 1,1-disubstituted alkene substrates. As shown in Eq. 1, the bromoalkyne substrates **1k** and **1l** were used in place of the usual terminal alkynes, as the products would otherwise be achiral. To our delight, the halogenated C–C triple bond participated in the desymmetric gold catalysis smoothly, furnishing the chiral bromocyclopentenes **2k** and **2l** in good yields and with serviceable 86 % and 87 % ee, respectively.

To expand the reaction scope, we next investigated the reaction scope with prochiral dienynols. The results are shown in Table 3. In comparison to the enediynol cases (Table 2), this series exhibited significantly increased efficiency, with yields ranging from 78 % to 98 %. Exocyclic dienyne substrates **3a**–**3l** (Table 3A) were prepared in one step from the corresponding cyclic dienones *via* propargylation. They underwent highly stereoselective desymmetrization to afford a range of spirobicyclic ketones (**4a**–**4l**) with 90–97 % ee. The alkene substituent $R^1$ can be methyl (**4a**), isopropyl (**4b**), phenyl (**4c**) and variously substituted ones (**4f**–**4j**), 1-naphthyl (**4k**), and thiophenyl (**4l**). In addition, five- and seven-membered substrates (**4d**–**4e**) were readily accommodated. The alkyne termini of **3c** and **3i** were chlorinated or brominated, and their reactions, similar to those shown in Eq. 1, proceeded smoothly to deliver the halogenated cyclopentene product **4m** or **4n** with 95 % ee. However, the iodine variant of **3i** was labile, and no conversion was observed due to catalyst quenching. For the dienynol substrates having cyclic alkene functionalities (**3o**–**3r**), the reactions accommodated 5–7 membered rings and were again highly efficient and enantioselective. In some

**Table 3:** The reaction scope with enediynol substrate.




[a] Reaction conditions: (*R*)-**L1**AuCl (5 mol %), $AgNTf_2$ (5 mol %), DCM (0.1 M), Drierite. Yields are isolated. [b] (*S*)-**L1** used instead. [c] The ee value in parenthesis from reaction run at 0 °C.

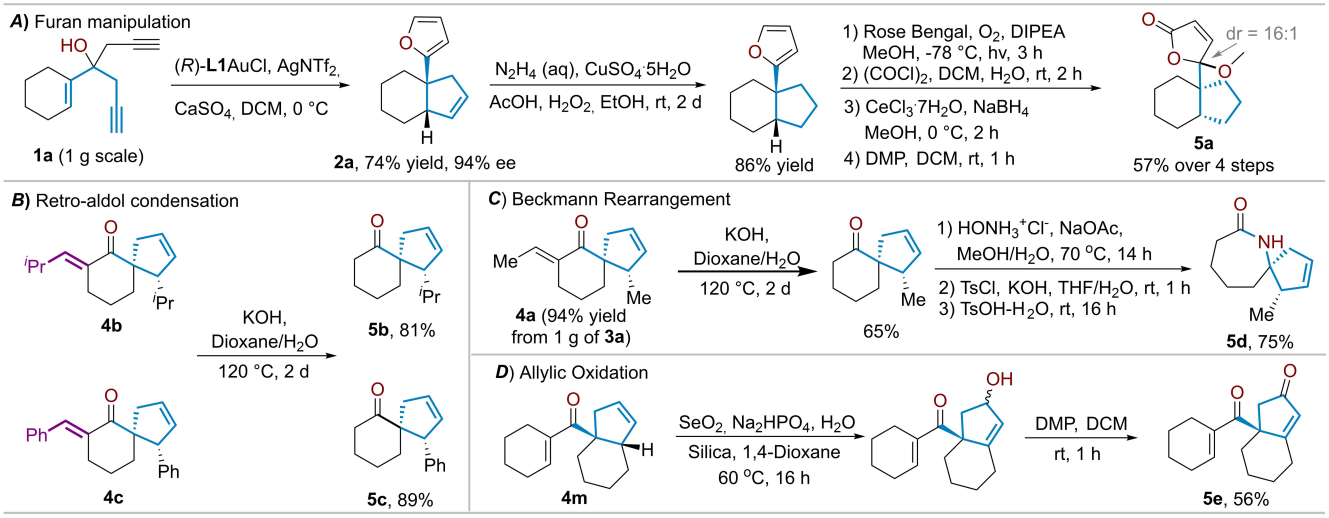
cases (**4p**–**4r**), the reactions were run at −40 °C instead of 0 °C to increase the ee value to ≥90 %. With **3s** possessing acyclic alkene moieties, the reaction smoothly afforded the chiral cyclopentenyl ketone **4s** with 92 % ee. As anticipated, the diastereomer of **4s** was not detected. In the case of **4t**, the substrate **3t** is a 7:1 mixture of the (*Z*,*Z*)-isomer and the (*Z*, *E*)-isomer. The methyl groups of the major (*Z*,*Z*)-**3t** remain *trans* on the cyclopentene ring of the product **4t**, which exhibits 91 % ee. An inseparable minor diastereomer of **4t** was formed and still possesses a *Z*-alkene, suggesting that the minor (*Z*,*E*)-**3t** reacts selectively *via* its sterically more accessible *E*-alkene moiety. In comparison, **2i** was formed from a substrate possessing a C–C double bond substituted by two *cis* methyl groups, these methyl substituents on the product cyclopentene ring are *cis* to each other. These results confirm the stereospecific nature of the cycloisomerization chemistry and reveal flexible control of the adjacent ring tertiary chiral center by substrate alkene geometry.

The absolute configuration of the brominated product **4h** was determined by single crystal x-ray diffraction studies[10] to be (*1R*,*5S*). The absolute configurations of the other products are assigned accordingly.

We next explored synthetic applications of this chemistry. As shown in Scheme 2A, we were able to perform a 1 g-scale synthesis of **2a** with 0.5 mol % catalyst loading in 74 % yield and with an identical ee value. Upon double bond reduction and the manipulation of the furan ring, **2a** was converted to the butenolide **5a** in five steps in a good overall yield. Both the spirocyclic enones **4b** and **4c** underwent efficient retro-aldol condensation to afford the chiral cyclohexanones **5b** and **5c**, respectively, in good yields (Scheme 2B). We also performed a gram-scale synthesis of **4a** by using only 0.5 % catalyst, which was then subjected to sequential retro-aldol condensation and Beckmann rearrangement to yield the lactam **5d** in a 49 % overall yield (Scheme 2C). Finally, we executed regioselective allylic oxidation of **4m** by $SeO_2$ followed by DMP oxidation to furnish the richly functionalized bis-enone product **5e** in a 56 % overall yield.

We performed DFT calculations of the reaction of **3a** with (*R*)-**L1** as the metal ligand. The reaction potential energy surface is shown in Figure 1. In the gold-substrate complex **3a-Au** leading to the major product enantiomer a strong H-bond (d = 1.696 Å) between the ligand phosphine oxide and the substrate HO group is formed. Dictated by this H-bonding interaction, **3a-Au** undergoes desymmetric 6-*endo-dig* cyclization *via* **TS1** with a free energy barrier of 9.72 kcal/mol, forming initially the tertiary cationic intermediate **Int1** and then the cyclopropyl gold carbene **Int2**. In this process, the hydrogen bond is maintained throughout, which is consistent with the lack of 5-*endo-dig* cyclization of the homopropargylic moiety. The subsequent semi pinacol-type rearrangement traverses through **TS2** with a free energy barrier of 8.58 kcal/mol. The ensuing cyclopentyl gold intermediate **Int3** then undergoes intramolecular protodeauration *via* **TS3** to form the product **4a** with the correct stereochemistry upon subsequent ligand exchange. The initial stereodetermining cyclization step could alternatively traverse through **3a-Au′** and **TS1′** en route to the enantiomer of **4a**. **3a-Au′** also possesses a longer H-bond (d = 1.736 Å) and is 3.56 kcal/mol higher in free energy than **3-Au**, and **TS1′** is 1.92 kcal/mol higher in free energy than **TS1**. These energy differences are consistent with **4a** being the major enantiomer formed in this chemistry. Of note is that the ligand phosphine oxide moiety also serves as an intramolecular proton shuttle in **TS2** and **TS3**, which should lower both barriers. The protodeauration step *via* **TS3** has the largest free energy barrier of 17.12 kcal/mol and is the turnover-limiting step. This is consistent with the observation that the reaction using phosphine oxide-functionalized **L1** is substantially faster than that using an otherwise sterically and electronically similar JohnPhos.

In conclusion, an efficient desymmetrization of prochiral 3-hydroxy-1,5-enynes was realized to access spirocyclic, bicyclic, and monocyclic cyclopentenes in mostly good to




***Scheme 2.*** Synthetic applications. Isolated yields are reported, and the ee values were determined by chiral HPLC.

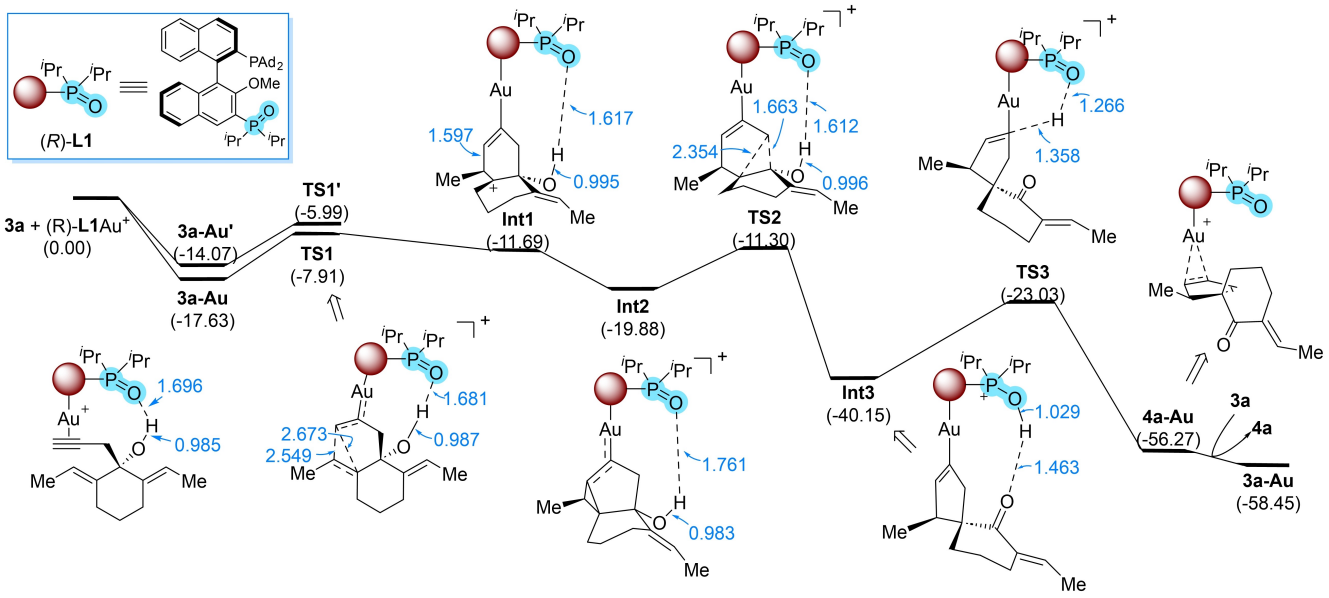



***Figure 1.*** DFT-calculated reaction potential energy surface at the M06/6-311g(d,p)/LANL2DZ(Au)/SMD(DCM) level. The bond lengths are shown in Å and the free energies in kcal/mol.

excellent yield and with excellent enantiomeric excesses. This chemistry represents a rare implementation of gold-catalyzed highly enantioselective 1,5-enyne cycloisomerization and is enabled by a cationic gold(I) complex possessing a new chiral bifunctional binaphthylphosphine ligand featuring a distal diisopropylphosphoryl moiety. This gold catalyst forms two-point binding with the substrate homopropargylic alcohol moiety and achieves excellent chirality induction during the cyclization step while minimizing competing 5-*endo-dig* cyclization. Owing to easy access to prochiral alcohol substrates, the chemistry offers expedient access to structurally diverse chiral cyclopentenes featuring a quaternary center. Moreover, an adjacent ring tertiary chiral center can be flexibly controlled by substrate alkene geometry. In addition to terminal alkyne substrates, halo-terminated alkynes are allowed. The chirality induction model is supported by DFT calculations and opens new venues for achieving asymmetric gold catalysis in the presence of properly designed bifunctional phosphine ligands.

## Supporting Information

The authors have cited additional references within the Supporting Information (Ref. [11–18]).

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## Conflict of Interest

The authors declare no conflict of interest.

## Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

**Keywords:** Cycloisomerization · Quaternary Center · Enantioselectivity · Gold · Reaction Mechanisms

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[10] Deposition Number 2331946 (for 4 h) contain(s) the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

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