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Gold(III)-Catalyzed Enynamine−Cyclopentadiene Cycloisomerization with Chirality Transfer: An Experimental and Theoretical Study Indicating Involvement of Dual Au(III) Push−Pull Assisted *cis*−*trans* Isomerism

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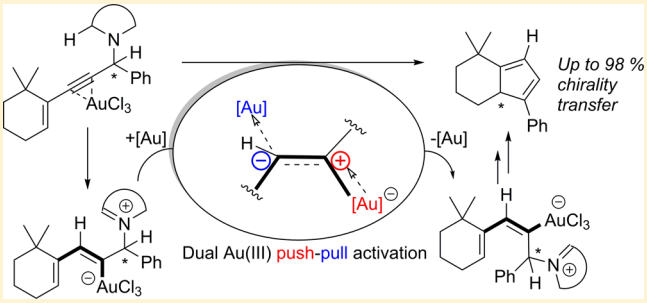
Supporting Information

ABSTRACT: A synthetic approach for asymmetric ring-fused cyclopentadienes (Cps) with a chiral carbon at the ring junction has been established from chiral enynamines by achiral Au(III) catalysis. On the basis of experimental and theoretical data, the proposed mechanistic pathway from enynamines to Cps occurs via a Au(III) ene *cis*−*trans* isomerization step. Computational studies at DFT and NEVPT2 levels advocate that the *cis*−*trans* isomerization step proceeds via a dual Au(III) push−pull assisted intermediate with a low computed rotation barrier. The chirality transfer occurs through a helical-shaped transition state with allenic character. The scope of the catalysis encompasses sterically bulky enynamines including terpene natural products.



1. INTRODUCTION

Cyclopentadienes (Cps) are key synthetic intermediates, widely used in organic and organometallic chemistry. Most notably, they are the direct ligand precursors in the assembly of metallocenes, a very important and well-known class of metal complexes, extensively employed as homogeneous catalysts in many single- or multistep chemical processes. In addition to simpler symmetrical metallocenes, access to more sophisticated asymmetric derivatives is often achieved by endowing the cyclopentadiene ligand precursors with a chiral center.[1] Significantly, there are several natural products possessing cyclopentadiene moieties, which can be foreseen as a functional Cp ligand in metallocene assembly.[2−4] Another prominent area of application of Cps is in the construction of complex natural and related biologically active products, where Cps can offer a phase selective platform for intermolecular Diels−Alder cycloadditions; once again, enantiopurity of the chiral Cp moiety represents an extraordinary advantage in terms of stereocontrol over the resulting chiral product.[2,5−8] Despite their relevance and multipurpose roles, there are very few direct accesses to chiral Cps from acyclic substrates,[9−12] with most synthetic protocols still relying on multistep postmodification of cyclic derivatives.[5,6,13−16]

Homogeneous Au(I) and Au(III) catalysis has been shown to be a powerful tool in various asymmetric cycloisomerization reactions, where alkyne or allene groups may be activated for internal nucleophilic addition by, e.g., alkenes or heteroatoms.[17−22] For instance, related compounds to Cps, cyclopentenones, have been enantioselectively cycloisomerized from 1-ethynyl-2-propenyl pivalates by cationic Au(I) catalysis, where the asymmetry from the pivalate moiety is transferred to the carbon at the β-ketoposition.[23] On the other hand, in the pioneering Au(I)-catalyzed cyclopentadiene synthesis reported by Toste and Lee, chiral enallene led to a racemic mixture of product.[24] Remarkably, a fresh report by Sanz and co-workers describes the synthesis of asymmetric β-alkoxy-Cps for many substrates with good yields and with high to excellent e.r. by use of cationic Au(I) catalysts bearing chiral biphosphine ligands.[11]

In our previous work, we documented a Au(III) salt-catalyzed synthetic route from enynamines to Cps through a Au(III)metallacycle intermediate, whose existence was also confirmed by single-crystal X-ray diffraction.[25] In the present work, after optimizing the reaction conditions and improving yields to synthetically significant levels, we have established the center-to-center chirality transfer and studied the scope and mechanism of the reaction. A combination of extensive experimental work and thorough theoretical study allowed us to confidently reveal the features of the key *cis*−*trans* isomerization step.

2. RESULTS AND DISCUSSION

Synthetic Scope. We began our study by screening different reaction conditions for the cyclopentadiene (**2a**) synthesis from chiral enynamines (**1a**), which were prepared from alkenyltriflates (**3**) and propargylic amines (**4**) (Scheme

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Scheme 1. Synthesis of Enynamines and Cyclopentadienes

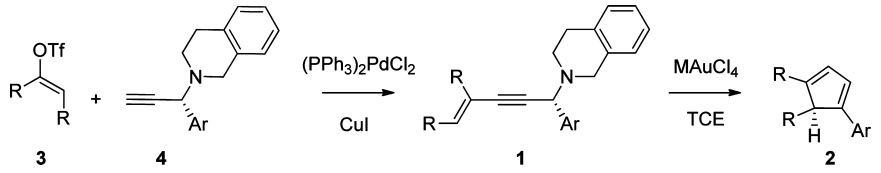
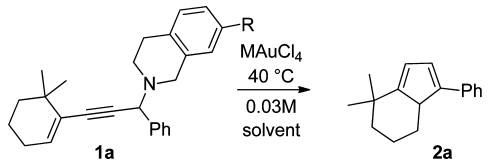


Table 1. Screening of Reaction Conditions



entry	solvent	catalyst (mol %)	R	conditions (equiv)	time (h)	yield (%)
1	MeCN	$KAuCl_4$ (10)	H		16	15
2	MeCN	$KAuCl_4$ (10)	NO_2		16	11[a]
3	MeCN	$KAuCl_4$ (10)	NMe_2		16	<4
4	TCE	$KAuCl_4$ (10	NO_2		18	
5	TCE	$KAuCl_4$ (10	NMe_2		18	
6	DCE	$KAuCl_4$ (10)	H		16	42
7	DCE	$KAuCl_4$ (5)	H		20	21
8	DCE	$KAuCl_4$ (10)	H	AcOH (10)	20	52
9	AcOH	$KAuCl_4$ (10)	H		18	
10	PhMe	$KAuCl_4$ (10)	H		20	12
11	TCE	$KAuCl_4$ (10)	H		18	35
12	TCE	$HAuCl_4$ (5)	H		18	36
13	TCE	$HAuCl_4$ (10)	H		18	56
14	TCE	$HAuCl_4$ (15)	H		18	59
15	TCE	$HAuCl_4$ (10)	H	dg	16	70
16	TCE	$KAuCl_4$ (10)	H	dg	18	67
17	TCE	$KAuCl_4$ (10)	H	0.01 M, dg	18	43
18	TCE	$KAuCl_4$ (10)	H	0.1 M, dg	18	52
19	TCE	$HAuCl_4$ (10)	H	dg, r.t.	18	52

[a]Yield Determined by ^{1}H NMR, dg = degassed, r.t. = room temperature

1). The propargylic amines were synthesized from propargylic acetates (**5**) with enantioselective copper-catalyzed amination.[26] To our delight, we observed chirality transfer from the propargylic position of the enynamine to the ring junction of the cyclopentadiene, which inspired us to further study the scope and mechanism of the reaction.

Initial screening results (Table 1) revealed that the chlorinated solvents, in particular tetrachloroethane, afford best yields, whereas poor product recovery was obtained in nonchlorinated media (entries 1−14).

Tuning the electronics of the isoquinoline moiety with either an electron withdrawing (NO_2) or donating group (NMe_2) lowered the yield in MeCN (entries 2, 3), whereas, in tetrachloroethane, no formation of cyclopentadiene was observed (entries 4, 5). Interestingly, enallene was obtained as a major product (1.0:0.3) when the NMe_2 derivative was used as a starting material in MeCN. The optimum catalyst loading was found to be 10 mol %. Higher loadings had only little effect on the yield (entry 14), whereas lower loadings resulted in decreased yields (entry 12). Chloroauric acid, $HAuCl_4$, gave slightly better yields than $KAuCl_4$, but the latter was chosen as catalyst because, in some cases, the use of $HAuCl_4$ (entry 15) led to undesired double bond isomerization. The reaction turned out to be moderately sensitive to concentration and temperature (entries 17−19), while careful degassing of the reaction solvent almost doubled the yield (entries 11, 16). We conclude that the removal of air is beneficial due to the sensitivity of the starting material that readily decomposes on standing at room temperature.

Investigation of the scope of the reaction (Table 2) indicates that the reaction is applicable to the synthesis of various acyclic and ring-fused chiral Cps from low to good yields. The best yields and highest retention of chirality were associated with cyclohexene rings substituted with alkyl groups. Remarkably, the highest chirality retention was obtained for **2e**, where a quaternary stereocenter is formed. The electronic nature of the aromatic ring was found to have an impact on both enantioselectivity and yield (**2b** and **2c**). Both electron withdrawing and donating substituents in the *para*-position decrease the yield, whereas a decrease in enantioselectivity is associated only with electron donating groups. Formation of enallene as a side product in a 1:1 ratio with the Cp was observed only with **1f** as the starting material. Remarkably, the reaction could also be applied to the synthesis of the extended ring-fused system of natural betuline (**2j**). As expected, for the betuline derivative, the stereochemistry of the formed asymmetric carbon was fully dictated by the rigid terpene scaffold.

The absolute configuration of cyclopentadienes was established with NMR NOE experiments using substrates **2h** and **2i**

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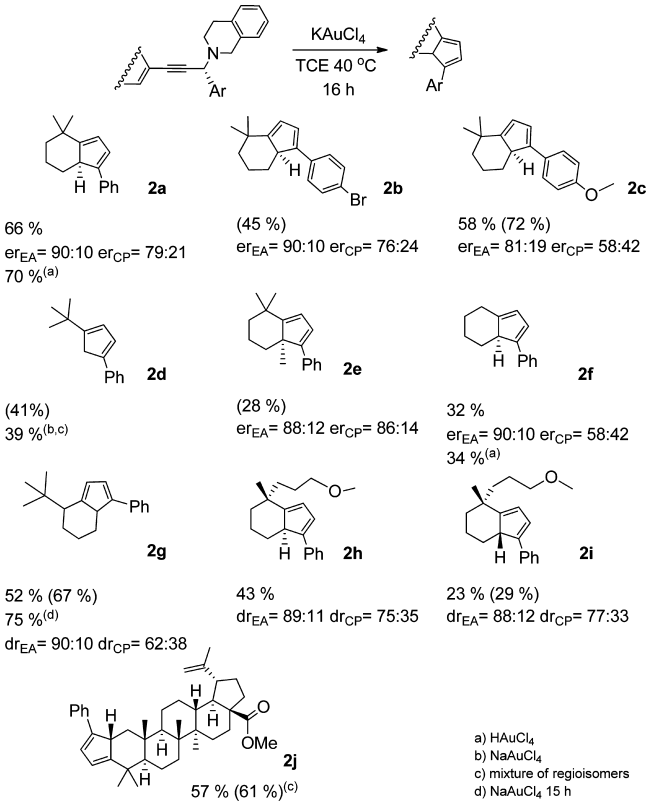
Table 2. Scope of Reaction[a]



[a]Products with isolated yields (NMR yields in parentheses) and stereomeric ratio of enynamine (EA) and cyclopentadiene (CP).

(Supporting Information), which were prepared from commercially available enantiopure (+)-methyl-(*R*)-3-(1-methyl-2-oxocyclohexyl)propionate (**6**) by protecting the carbonyl group as a 1,3-dioxolane (**7**), followed by reduction with LAH (**8**) (Scheme 2). The formed alcohol was then methylated with NaH/MeI and deprotected to afford ketoether (**9**), which was then converted to the corresponding triflate (**10**). The triflate (**10**) was coupled with chiral ynamines (**4**) to form (*R*,*R*) and (*R*,*S*)-enynamines that gave two diastereomeric Cps (**2h**, **2i**) upon treatment with $KAuCl_4$ in TCE.

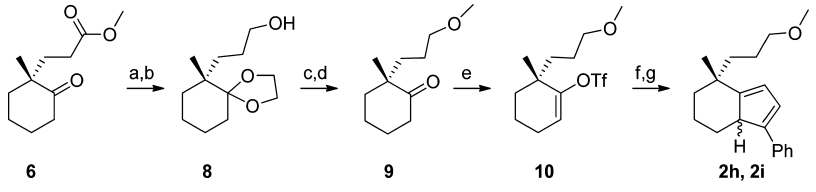
Mechanistic Aspects. Previously, we have shown that the reaction proceeds from activated enyneamine **I** via 1,5-hydride shift to form a vinyl−Au(III)complex **II-*cis***, which can C−H activate R^1 to form Au(III)−metallacycle **III** (Scheme 3).[25] We have ruled out the involvement of this species in the mechanism by performing successfully the reaction with the methylated analogue where R^1 = Me (**2e**, Table 2). Thus, the complex **III** is not likely a reactive intermediate in the catalytic cycle. On the other hand, the cleavage of $AuCl_3$ at this stage together with 3,4-dihydroisoquinoline elimination would lead to formation of enallene **IV**.

As discussed above, the formation of the enallene was only observed in the Au(III) catalysis of substrate **1f**. In this case, the chirality transfer was also significantly lower. Previously, Toste et al. have demonstrated that a rasemic mixture of cyclopentadiene is obtained in Au(I)-catalytic cyclization of chiral enallene.[24] In addition, Che et al. have synthesized **IV-f** from similar enynamine using Au(III)- and Ag-salts as catalysts; noteworthy, the Ag-based system led to 99% enantiomeric excess, whereas the latter only gave 50% *ee* with no reported formation of cyclopentadiene.[27,28] This finding implies that $KAuCl_4$ is capable of racemizing **IV-f** under similar reaction conditions prior to cyclization. Moreover, we observed slightly more racemized enallene (e.r. 54:46) than the Cp (e.r. 58:42) in the reaction mixture of **IV-f** (Scheme 4). We consider that the formation of the enallene occurs enantioselectively by the cleavage of gold and 3,4-dihydroisoquinoline, while the racemization is caused by a recoordination/decoordination process of gold to enallene. In agreement with this hypothesis, several other studies have shown the occurrence of rapid isomerization of allenes under Au(I)/Au(III) catalysis in ambient conditions.[29−35] In our fresh computational study, we discovered that the racemization of enallene **IV-f** occurs through a gold-activated intermediate in the *cis*-conformation prior to the cyclization from the *trans*-conformation.[36] When the system was studied according to the transition state theory using several methods, and with molecular dynamics at the DFT level without any constrains, the results pointed out that the time scale for racemization is fast compared to that of the cyclization.

Considering again the enallene formation from **1f**, we note that this starting substrate only differs from **1a** by the R^2-substitution (Scheme 3). In this respect, if the two-step route through enallene would be operational in all of the cases, one could anticipate to observe at least some of the other corresponding enallenes, too. To rule out the involvement of enallene in the reaction mechanism, we pursued the synthesis of enantiopure enallene **IV-a**. Unfortunately, we were only able to receive a complex mixture of products in a minor yield when **1a** was reacted together with $AgBF_4$. Changing the hydride source to prolinol and catalyst to $KAuCl_4$ led to the formation of cyclopentadiene **2a** exclusively. This is somewhat surprising as **1f** has been successfully converted to enallene in the same reaction conditions.[27,28] Despite that all our other numerous attempts to obtain **IV-a** were not successful, we consider the two-step allene route to be an improbable pathway for all the substrates based on the discussion above.

On the basis of the experimental data (see additional data in the Supporting Information), an alternative mechanism is considered to justify the chirality transfer and the absence of enallenes. In this route, the gold is protodeaurated as the last step, after diastereoselective formation of **V**. However, prior to this, the vinyl−Au(III) complex **II-*cis*** should isomerize to the corresponding **II-*trans*** for steric reasons. On the basis of these

Scheme 2. Preparation of Starting Materials for Determining Absolute Configuration



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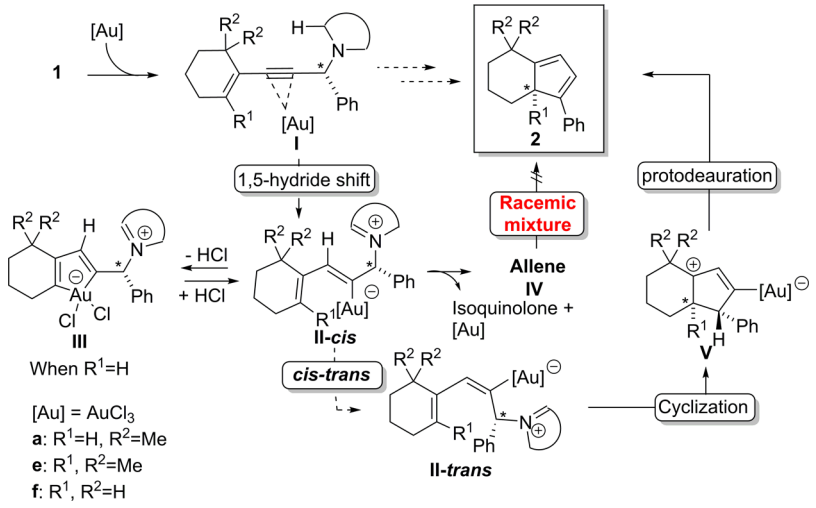
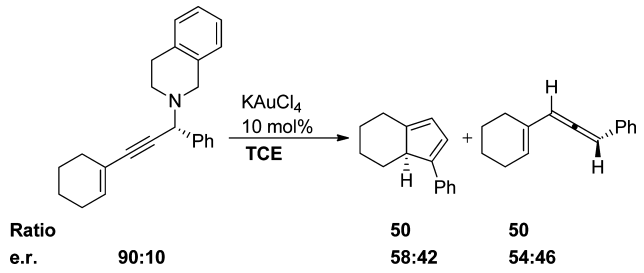
Scheme 3. Possible Pathways to Resting State Au(III)−Metallacycle, Enallene, and Chiral Cyclopentadiene via *cis*−*trans* Isomerization Step



Scheme 4



findings, we performed computational studies to provide theoretical insights into the *cis*−*trans* isomerization and the enantioselectivity determining cyclization step. All computations were carried out using TPSS-D3/def2-TZVP[37−39] in tetrachloroethane (COSMO) unless otherwise noted (see the Experimental Section for details). The corresponding computational level has provided an accurate description of gold complexes compared to high-level ab initio benchmark data as well as experimental results.[40−42]

Transfer of Chirality. To examine our hypothesis on the required *cis*−*trans* isomerization step, we began by exploring the transition states (TS) that determine the stereochemical outcome of the reaction. The **II-*trans*** cyclizes via two diastereomeric TS **TSII-V-syn** and **TSII-V-anti**, with activation free energies of 19.3 and 24.8 kcal/mol, respectively (Figure 1). These TS seem to predict a wrong stereochemical outcome; namely, the formed product should be R-**2a**, whereas we experimentally found S-**2a** as the main product (88%). Closer examination of the TS showed the 3,4-dihydroisoquinoline leaving group to be already over 3.1 Å away from the reaction center. The analysis of vibrational frequencies of the TS confirmed that the leaving group has diverged the system. We consider that, in our model, the 3,4-dihydroisoquinoline moiety stays loosely attached by dispersions with the $AuCl_3$ group because of the unsuitable description of the competitive *van der Waals* forces of the solvent environment. Optimization of these transition states without D3-dispersion correction, and, therefore, neglecting the internal attractive dispersions, inverted the $\Delta\Delta G$ value between the corresponding transition states, and, therefore, gave a "better" result. However, we do not consider this to be a satisfactory option to improve our model.

In order to disclose a more realistic description of the transition states, the system was optimized without the 3,4-dihydroisoquinoline group. The removal of this group allowed the **TSII-V-anti** to relax into a helical-shaped TS. Interestingly,

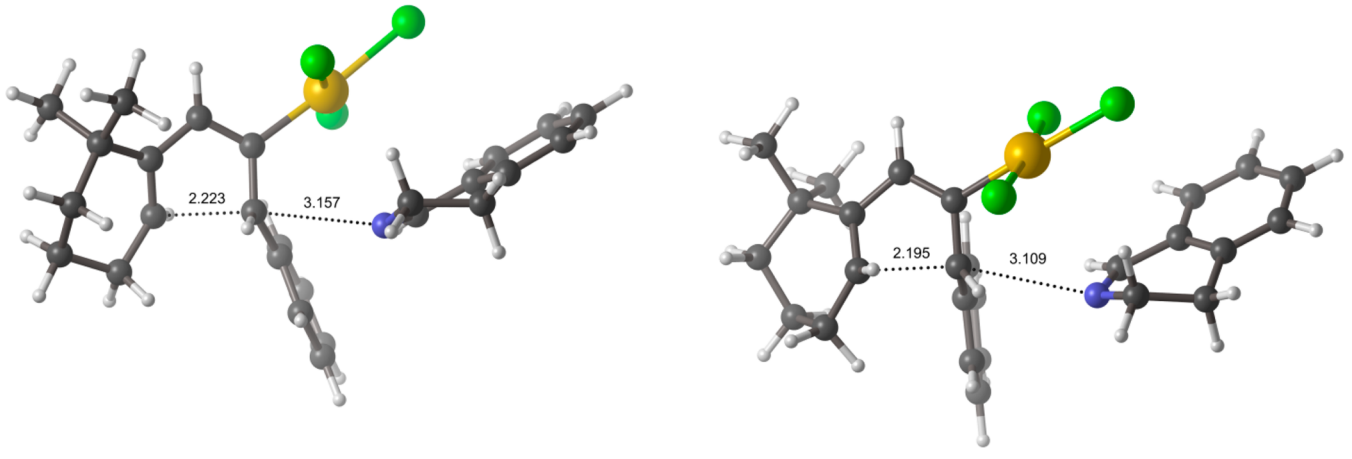


Figure 1. TPSS-D3/def2-TZVP optimized structures of **TSII-V-anti** and **TSII-V-syn**.

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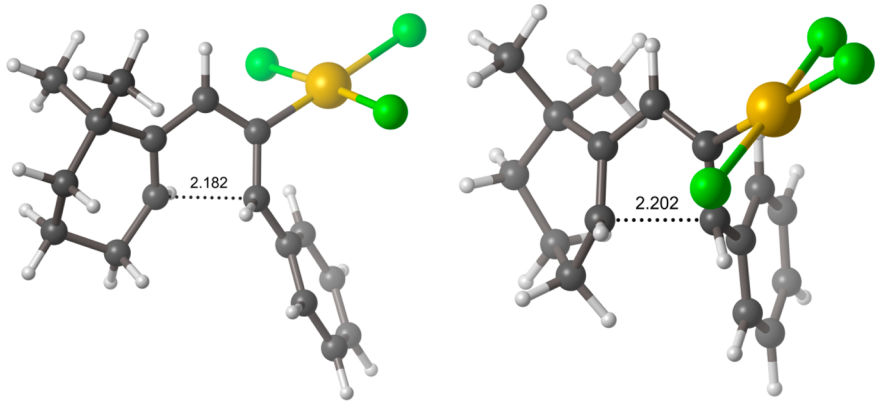


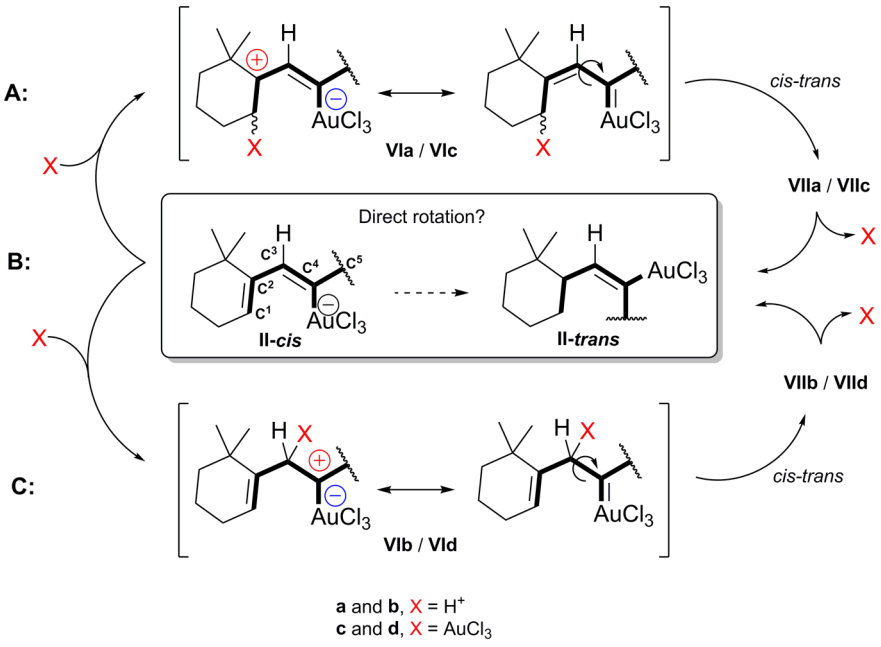
Figure 2. TPSS-D3/def2-TZVP optimized transition states **TSII-V-anti** and **TSII-V-syn** without the isoquinolone group.

Table 3. Comparison of Experimental and Computed Values for Transfer of Chirality[b]

substrate	$\Delta G^{\ddagger}$ (syn−anti) (kcal/mol)	computed (%)[a]	experimental (%)
1a	1.5	92	88
1c	2.5	98	72
1e	4.2	100	98
1f	1.5	92	64

[a]TPSS-D3/def2-TZVP in solution. [b]Populations are calculated from ΔG (298 K) values according to Boltzmann distribution at 313 K.

Scheme 5



a similar conformation has also been reported previously in the enantioselective Rautenstrauch cyclization (Figure 2).[43] The $\Delta G^{\ddagger}$ value for the cyclization to the *S*-enantiomer is 13.6 kcal/mol, and the respective value for the *R*-enantiomer is 15.1 kcal/mol. The computed enantiomeric ratio according to Boltzmann distribution at 313.5 K is 92%, which is in excellent correspondence with the experimental value for the studied substrate (88%). This was also verified using a number of dispersion corrected DFT-D3 functionals (Supporting Information).

According to our computational analysis, the 3,4-dihydroisoquinoline group is cleaved from the system just prior to the transition state, providing a Au-stabilized cationic reaction center. The TS itself is identical to that of the gold-activated enallene, but we reason that the late cleavage of the 3,4-dihydroisoquinoline prevents the racemization.

Experimentally, slightly different enantioselectivities were observed for substrates **1a** and **1e**, whereas distinctly lower selectivities were received for **1c** and **1f** (Table 3). Satisfactorily, the computed values correlate excellently with the values for substrates **1a** and **1e**, but poorly for **1c** and **1f** (Table 3). The drop in the transfer of chirality for **1c** and **1f** compared to **1a** (72% and 64% vs 88%) is somewhat unexpected, while the only exclusive difference between the compounds lies in the R^2 substitutions (R^2 = H/Me) or in the *para*-substitution of the phenyl, both of which are located relatively far away from the

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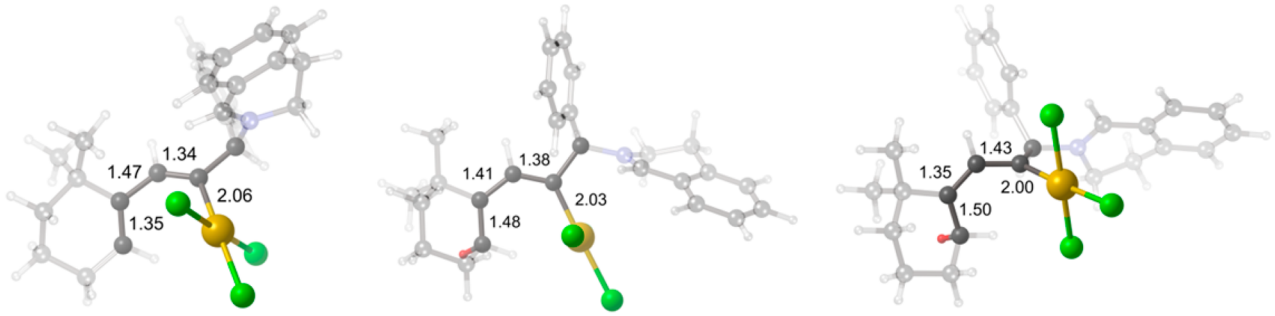

Figure 3. Structures showing the carbene behavior from **II-*cis*** via protonation to the transition state (TPSS-D3/def2-TZVP).

reaction center. Therefore, we considered alternative mechanistic routes that could explain the decreased enantioselectivity for **1c** and **1f**.

For this purpose, we inspected the cyclopentadiene−enallene ratio in the catalysis: the **1a** yielded high selectivity on cyclopentadiene with no enallene observed, whereas, for the substrate **1f** (R^2 = H), this ratio is 50:50 (Scheme 4). Together, this suggests that, for substrate **1f**, there are two operating pathways: one proceeding through the enallene intermediate, leading to a racemic mixture of cyclopentadiene, and the other progressing through the *cis*−*trans* isomerization that provides the chiral product. The competing enallene route explains, therefore, the poor enantioselectivity for substrate **1f**. For **1c**, we did not observe any enallene in the product mixture, but this might be due to a more rapid activation of electron rich enallene compared to enynamine. An alternative explanation is that the methoxy-substituted phenyl ring assists earlier cleavage of the 3,4-dihydroisoquinoline moiety in the cyclization step through resonance effects and allows partial racemization. Meanwhile, the excellent correlation of the chirality transfer between computational and experimental studies for substrates **1a** and **1e** suggests that, in these cases, the mechanism operates chiefly through a chirality transferring *cis*−*trans* isomerization step in the optimized reaction conditions.

Mechanism of Au−Vinyl *cis*−*trans* isomerization. We envisioned that the *cis*−*trans* isomerization can, in principle, proceed via three possible pathways **A**−**C** in Scheme 5. First, we considered the most straightforward route **B**, i.e., direct rotation around the π-system to find out if Au(III), as a formal d^8 metal, would be able to stabilize the triplet character of such a transformation. Because of the pseudo-Jan−Teller origin of the isomerization,[44] this step was studied with the NEVPT2-(6,6)/def2-TZVP method in gas phase (see comprehensive data and discussion in the Supporting Information). We found a high activation energy barrier of 43.1 kcal/mol that seems to exclude this route. Also, light-induced direct rotation of an excited state of the system can be ruled out as the reactions were also performed in the dark.

Thus far, several mechanistic studies have focused on the nature of the gold-carbocation species, where either a carbene or a carbenoid character is possible.[45−48] Experimental and theoretical investigations have suggested that cationic liganded Au(I) predominantly stabilizes the carbocation in an electrostatic carbenoid manner rather than via genuine carbene bonding.[46] The *cis*−*trans* isomerization in the Ph_3P−Au(I)−vinyl ketal cation has been proven conclusively by NMR evidence. Respectively, a nonclassical propargylic gold stabilized carbocation has been reported for alkynes with terminal Au(I) binding, in which stabilization takes place through resonance with the Au(I)−allenylidene form.[47] In these cases, the back-donation from the filled d-shell occurs, thus stabilizing the cationic system. We investigated computationally the acid-activated pathways **A** and **C** to yield a carbocation on the γ- or α-position compared to gold, by activation of the C^1−C^2 (**VIa**, **VIc**) or C^3−C^4 (**VIb**, **VId**) π-system, respectively. As acid additives, we took into consideration a simple protonation or activation of the π-system with another Lewis acidic $AuCl_3$.

Route A. The protonation of C^1 to yield a carbocation at the γ-position (**VIa** and **VIc**) increases the back-donation (Figure 3). The Au−C^4 bond length is decreased by 3 pm, and the C^3−C^4 bond length is increased by 4 pm. Overall, the whole conjugated π-system is affected, and we do not consider this Au−C^4 bond length shortening to correspond to "true" gold−carbene, as was also recently proposed by Seidel and Fürstner.[48] However, while studying the TS for the *cis*−*trans* isomerization (**TSVIa-VIIa**), we observed a more pronounced carbene character: The Au−C^4 distance is shortened by an additional 3 pm, which makes the total decrease of the bond length to be 6 pm when considering **II-*cis***. The C^2−C^3 and C^3−C^4 distances are also notably affected. On the basis of these computational findings, we consider the carbene character to be more likely a phenomenon related to the TS rather than the ground state in this studied system.

The observed TS behavior accounts for the relatively low rotational energy barrier: the $\Delta G^{\ddagger}$ value for the proton-assisted route **A** is 20.2 kcal/mol. When considering the same activation as described, but with another $AuCl_3$, we noted the carbene character not to be as pronounced as in the case of proton assistance. This is in accordance with the calculated bond lengths and higher activation free energy, which, in the dual $AuCl_3$ route **A**, is 27.9 kcal/mol.

Route C. In this route, intermediates **VIb** or **VId** are formed when the C^3−C^4 π-system of **II-*cis*** is activated with a proton or another $AuCl_3$, respectively. Intermediate **VIb** is 16.1 kcal/mol higher in energy than **VIa** (route A), and similarly, **VId** is 11.8 kcal/mol higher in energy than **VIc** when considering the dual gold activation. From a thermodynamic point of view, it is, therefore, clear that the acid (proton or $AuCl_3$) favors the coordination to the C^1−C^2 over the C^3−C^4 π-system, but on the other hand, the sp^3-hybridization of C^3 should provide a low activation energy barrier for this rotation. In this respect, both proton-assisted routes should have similar energetics. The dual gold activation in route **C** provides a low rotational barrier of 10 kcal/mol, when the reaction is overall exothermic by 4.4 kcal/mol (Supporting Information). The transition state for the rotation (Figure 4, **TSVId-VIId**) suggests the covalently bound

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gold to act as a Lewis base, pushing electrons, whereas the new additive is a coordinative Lewis acid.

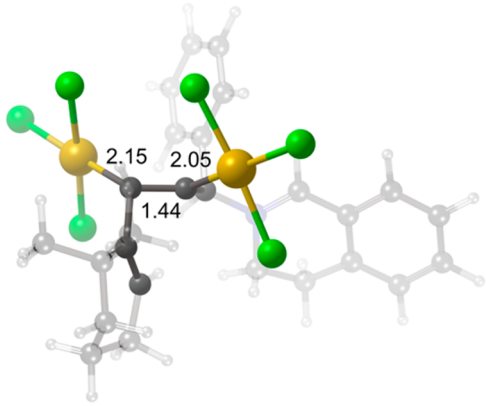
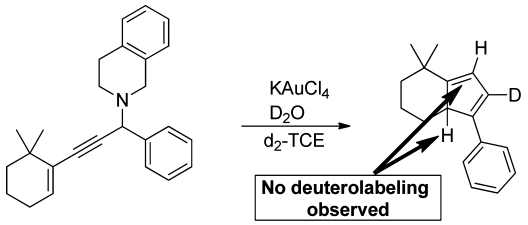


Figure 4. TPSS-D3-def2-TZVP optimized dual gold transition state.

Energetically, we can rule out the dual-activated route **A** as the activation energy of 28 kcal/mol is too high when compared to experimental reaction conditions. On the other hand, the same activation to route **C** goes through route **A** (**VIc** → **VId** → **TSVId-VIId**), giving a total activation energy of approximately 22 kcal/mol. Both proton-assisted routes have barriers of approximately 20 kcal/mol. The energy required for the acid activation itself was not computed because it is dependent on the acid species present in the reaction media. In particular, the nature of gold species in the solution has been shown to depend on the concentration of reagents that can compete for the coordination.[35] Some potential reagents or byproducts in our system include the 3,4-dihydroisoquinoline and the final product cyclopentadiene.

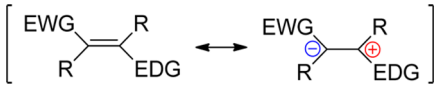
Although the proton assistance seems to be a plausible solution for the *cis*–*trans* isomerization, this was ruled out on the basis of ^{2}H-labeling experiments (Scheme 6). Experimentally, under catalysis conditions using D_2O as an additive, no proton–deuterium exchange was observed in either C^1 or C^3 positions. The fact that C^4 became labeled indicates only that the protodeauration step is solvent-assisted. For additional evidence, we also performed the reaction in the presence of pyridine as a proton sequestering agent and still observed the successful proceeding of the reaction, which is in contrast with a possible proton-assisted catalysis.

Scheme 6. Deuterolabeling Experiments



On the basis of the presented data, we propose the dual-activated route **C** with a second gold species as the operating pathway. The role of the second gold in the *cis*–*trans* isomerization can be rationalized in analogy with the push–pull effect in ethylene substituted with an electron donating and an electron withdrawing group at the two ends to the double bond (Scheme 7). Such a double bond exhibits some zwitterionic character, which may significantly lower the rotational barrier.[49−51]

Scheme 7. Push–Pull Effect by Electron Withdrawing and Donating Groups Lowers Ethylene Rotation Barrier[49−51]



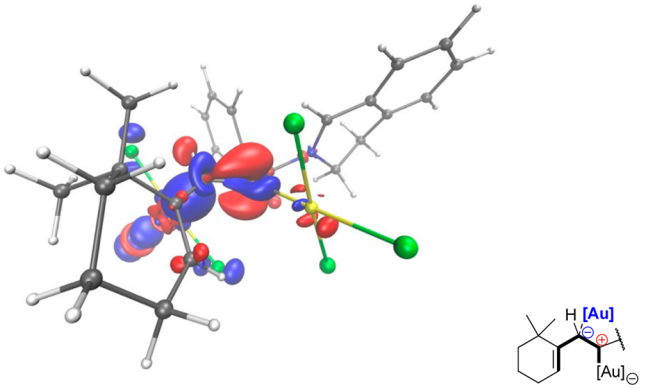


Figure 5. Electron density effect of the second gold (blue [Au] in the inset = $AuCl_3$, of which the influence on the electron density is visualized) to the total electron density of the system in dual gold ground state intermediate **VId**. Blue indicates increased and red decreased electron density.

In Figure 5, we present the computed effect of the second $AuCl_3$ on the electron density of **VId**. Inspection of this electron density difference plot reveals polarization of the bond in a similar manner to that represented in Scheme 7; a decrease in electron density is observed in the p-orbital close to the carbon bound covalently to gold, whereas an increase in electron density appears in the surrounding of the carbon of the second coordinated gold. This leads to a weakening of the π-system. Furthermore, an addition of electron density to σ-type orbitals of the carbon atom is observed. The second gold gains electron density in the Au–C^3 region, and this is an indication of the Lewis acidity of this unit. The covalently bound gold is also affected. Electron density is lost from its filled 5d orbital, and the surrounding toward C^4 is slightly negatively polarized. Taking into account the small change in Au–C^4 bond length by addition of the second gold, and the small polarization effect, we regard the covalently bound gold as a carbocation stabilizing center. The carbene behavior was only observed in the transition state of the computationally studied proton-assisted route **A**.

The Toste, Nolan, Zhang, and Hashmi groups have recently reported dual gold activation pathways for allenyne and 1,2-bialkynephenyl cycloisomerizations.[52−56] A common feature for these reactions is that (at least) one Au(I) converts a terminal alkyne to a nucleophile, while another Au(I) activates the neighboring π-system for this nucleophile. The present experimental and computational evidence implies that a distinct dual Au(III) push–pull activation pathway operates for the studied *cis*–*trans* isomerization. Unfortunately, the fast decomposition of the catalyst and inability to monitor the concentration of gold in the reaction mixture prevented us to perform reliable kinetic studies. However, this investigation takes into account all the feasible pathways, which pinpoint the dual activation as the most probable.

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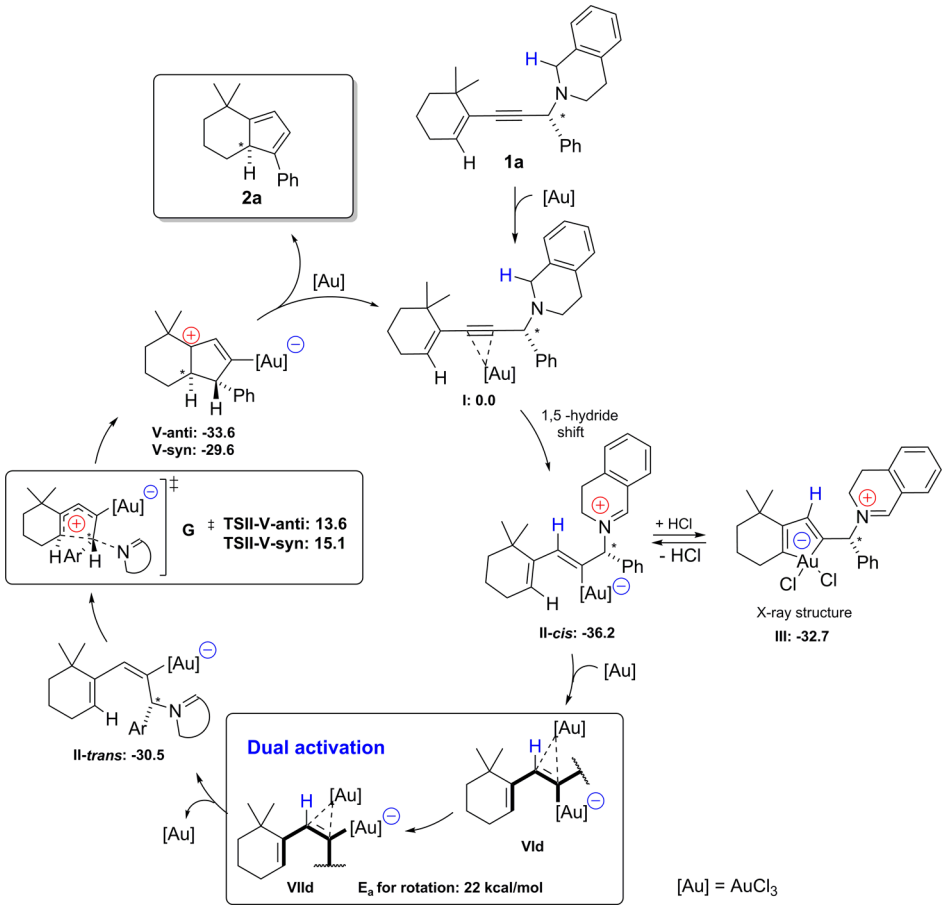
Scheme 8. Proposed Reaction Mechanism[a]



[a]All energies are ΔG (298.15 K) values in kcal/mol, except rotation is reported as ΔE.

Overall, the computational and experimental results support the mechanism presented in Scheme 8. The gold-activated complex **I** is converted to structure **II-*cis*** via 1,5-hydride shift. This may lead to metallacycle **III** or the catalysis proceeds from the *cis*-Au–vinyl complex to the corresponding *trans*-complex by a dual gold activation of **II-*cis*** when another $AuCl_3$ coordinates to the vinyl group producing intermediate **VId**. For this complex, the *cis*–*trans* isomerization is possible with a low rotational energy barrier of 10 kcal/mol, although the total activation energy needed for this transformation is 22 kcal/mol due to gold favoring thermodynamically the C^1–C^2 π-system.

The following cyclization step determines the chirality of the product. A diastereomeric intermediate **V-anti/syn** is formed with the $\Delta G^{\ddagger}$ value for **V-anti** of 13.6 kcal/mol. The last step of the mechanism involves cleavage of the benzylic proton to the reaction media (Supporting Information, Scheme S3) and solvent-assisted protodeauration.

Inspection of the computed energetics at the different stages of the mechanism indicates that the *cis*–*trans* isomerization step is the rate-limiting step. The fact that we failed to experimentally detect any intermediates after the hydride shift in the ^{1}H NMR studies is in agreement with our studied free energy profile for the catalytic cycle. Practically all reactions are endothermic after formation of **II-*cis***, indicating that the population of these species is small and, therefore, out of ^{1}H NMR detection range at the tested concentration levels. Alternatively, the rate-limiting step may be the activation of **II-*cis*** by the second gold depending on the concentration of free gold in solution.

3. CONCLUSIONS

We have established a Au(III) catalytic methodology to convert enynamines to various acyclic and cyclic cyclopentadiene derivatives with low to good yields. The chirality of the propargylic position of the enynamine is transferred to the ring junction of the cyclopentadiene through a helical-shaped transition state with allenic character, at its best with a high degree of preservation. Our extensive experimental and computational studies indicate the *cis*–*trans* isomerization to involve two Au(III) species in a traditional push–pull manner.

We expect that these symmetric or asymmetric cyclopentadiene derivatives have the potential to be attractive synthetic platforms in phase-selective Diels–Alder retro-Diels–Alder cascades in natural product synthesis, as key intermediates in organic synthesis or utilizing ring extended terpene natural products, e.g., betuline as a bulky asymmetric ligand in metallocene assembly.

4. EXPERIMENTAL SECTION

General Remarks. Unless otherwise specified, all commercial materials were used as received without further purification. Reactions involving use of air- and moisture-sensitive materials were carried out in an atmosphere of dry argon using Schlenk techniques or in a conventional argon-filled glovebox. THF and methanol were distilled, respectively, from sodium/benzophenoneketyl and CaH_2 under a

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positive pressure of argon prior to use or taken directly from the solvent purifier. ^{1}H and ^{13}C{^{1}H} NMR spectra were recorded with either a 300 or a 500 MHz spectrometer. ^{1}H spectra were referenced to tetramethylsilane (TMS, 0.00 ppm) and are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). Chemical shifts of the ^{13}C{^{1}H} NMR spectra were referenced to $CDCl_3$ (77.16 ppm). NMR yields were determined using nitrobenzene or 1,3,5-trimethoxybenzene as an internal standard. HR-MS spectral data were acquired with EI ionization mode with a sector analyzer. Column chromatographic purifications were performed on silica gel (230−400 mesh). Brine refers to a saturated water solution of NaCl. Known compounds were prepared according to the literature procedures.

General Procedure for Cyclopentadiene Synthesis. Freshly purified enynamine (1 equiv) was dissolved in tetrachloroethane (0.03M), and the mixture was degassed with three freeze−pump−thaw cycles and by keeping the solution exposed to high vacuum (oil pump) for a minute. The solution was added to gold salt (0.1 equiv), and the temperature was brought to 40 °C under Ar in the absence of light. After 16 h, the solvent was evaporated. Purification of the crude by column chromatography using *n*-hexane or pentane and ethyl acetate as eluent afforded the desired product.

*(S)-3-(4-Bromophenyl)-7,7-dimethyl-4,5,6,7-tetrahydro-3aH-indene (**2b**).* Following the general procedure with 68.2 mg (0.157 mmol) of **1b**, with 5.9 mg (0.0157 mmol) of $KAuCl_4$ and with 5.3 mL of TCE. Purification of the crude by column chromatography using *n*-hexane and ethyl acetate (40:1) as eluent afforded 25.3 mg (0.0832 mmol, 53%) of the desired product.**^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.46−7.38 (m, 2H), 7.30−7.24 (m, 2H), 6.72 (dd, J = 2.2, 0.9 Hz, 1H), 6.05 (d, J = 2.2 Hz, 1H), 3.22 (dd, J = 12.8, 5.8 Hz, 1H), 2.42−2.22 (m, 1H), 1.90−1.58 (m, 4H), 1.26 (s, 3H), 1.19 (s, 3H), 0.72 (qd, J = 12.8, 3.5 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 162.5, 148.2, 135.0, 131.7, 127.3, 127.1, 120.4, 119.8, 49.0, 43.7, 35.3, 34.2, 28.8, 28.5, 22.7. **IR** (cm^{-1}, neat): 3059, 2958, 2926, 1537, 1484, 1073, 1007, 812. **HRMS** (EI$^+$) calcd for $[C_{17}H_{19}Br]^+$ m/z 302.0670, found: 302.0672. **e.r.** (HPLC): 76:24.

*(S)-7,7-Dimethyl-3-phenyl-4,5,6,7-tetrahydro-3aH-indene (**2a**).* Following the general procedure (with 18 h heating) with 42.9 mg (0.121 mmol) of **1a**, with 4.6 mg (0.0122 mmol) of $KAuCl_4$ and with 4.2 mL of TCE. Purification of the crude by column chromatography using *n*-hexane and ethyl acetate (40:1) as eluent afforded 17.8 mg (0.0799 mmol, 66%) of the desired product. Spectral data were found to match literature values.[12] Missing spectroscopic data are reported: **IR** (cm^{-1}, neat): 3057, 2956, 2924, 2858, 872, 753, 691. **e.r.** (HPLC A): 79:21.

*(S)-3-(4-Methoxyphenyl)-7,7-dimethyl-4,5,6,7-tetrahydro-3aH-indene (**2c**).* Following the general procedure with 82.8 mg (0.215 mmol) of **1c**, with 8.1 mg (0.0215 mmol) of $KAuCl_4$ and with 7.2 mL of TCE. Purification of the crude by column chromatography using *n*-hexane and ethyl acetate (20:1) as eluent afforded 25.3 mg (0.125 mmol, 58%) of the desired product. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.39−7.31 (m, 2H), 6.92−6.83 (m, 2H), 6.58 (dd, J = 2.2, 0.8 Hz, 1H), 6.03 (d, J = 2.2 Hz, 1H), 3.80 (s, 3H), 3.22 (dd, J = 12.8, 5.8 Hz, 1H), 2.41−2.30 (m, 1H), 1.90−1.60 (m, 4H), 1.26 (s, 3H), 1.19 (s, 3H), 0.72 (qd, J = 12.8, 3.7 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 160.8, 158.3, 149.2, 129.2, 126.7, 124.6, 120.3, 114.1, 55.4, 49.1, 43.9, 35.2, 34.4, 28.9, 28.5, 22.9. **IR** (cm^{-1}, neat): 3055, 2927,1609, 1505, 1277, 1250, 1177, 1040, 819. **HRMS** (EI$^+$) calcd for $[C_{18}H_{22}O]^+$ m/z 254.1671, found: 254.1665. **e.r.** (HPLC): 58:42.

*(4-(tert-Butyl)cyclopenta-1,3-dien-1-yl)benzene (**2d**).* *Method A*: Following the general procedure (with 18 h heating) with 47 mg (0.143 mmol) of **1d**, with 5.7 mg (0.0143 mmol) of $NaAuCl_4 \times 2H_2O$ and with 4.8 mL of TCE. Purification of the crude by column chromatography using *n*-pentane as eluent afforded 12 mg (0.058 mmol, 41%) of the desired product as a mixture of regioisomers (1.0:0.5:0.07). *Method B*: Freshly purified **1d** (10.5 mg, 0.029 mmol) was dissolved in d_2-tetrachloroethane (1 mL, 0.03 M), and the mixture was degassed by three freeze−pump−thaw cycles and keeping the solution exposed to high vacuum for a minute. The solution was added to $KAuCl_4$ (1.2 mg, 0.031 mmol), and temperature was brought to 40 °C under Ar. After 16 h, the resulting mixture of regioisomers (1.0:0.38:0.07) was analyzed with NMR using 1,3,5-trimethoxybenzene as internal standard. NMR yield 42%. **^{1}H NMR** (300 MHz, $CDCl_3$): Common peaks: δ 7.59−7.44 (m), 7.35−7.23 (m), 7.21−7.11 (m). Common peaks of regioisomers 1 + 2: 3.40−3.26 (m). Regioisomer 1: 6.75 (dt, J = 2.3, 1.1 Hz), 6.20 (dt, J = 2.3, 1.1 Hz), 1.22 (s). Regioisomer 2: 6.94 (dd, J = 2.7, 1.5 Hz), 5.98 (q, J = 1.5 Hz), 1.21 (s). Regioisomer 3: 6.56−6.54 (m, 1H), 6.48 (dd, J = 3.5, 1.9 Hz), 3.16 (dd, J = 1.9, 1.1 Hz), 1.23(s). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.5, 143.9, 136.7, 128.7, 128.0, 127.3, 126.7, 126.3, 126.0, 125.0, 124.8, 124.7, 122.2, 40.7, 40.0, 33.5, 31.0, 29.9. **IR** (cm^{-1}, neat): 3060, 2961, 750, 691. **HRMS** (EI$^+$) calcd for $[C_{15}H_{18}]^+$ m/z 198.1409, found: 198.1400.

*(S)-3a,7,7-Trimethyl-3-phenyl-4,5,6,7-tetrahydro-3aH-indene (**2e**).* Following the general procedure with 27.7 mg (0.0750 mmol) of **1e**, with 2.8 mg (0.0074 mmol) of $KAuCl_4$ and with 2.8 mL of TCE. Purification of the crude by column chromatography using *n*-hexane and ethyl acetate (40:1) as eluent afforded 8 mg of product and unknown side/decomposition product that could not be separated with column chromatography. The analytical sample was purified with preparative HPLC, and the yield was determined with NMR using $PhNO_2$ as an internal standard. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.46 (d, J = 7.5 Hz, 2H), 7.31 (t, J = 7.5 Hz, 2H), 7.19 (t, J = 7.5 Hz, 1H), 6.62 (s, 1H), 6.06 (s, 1H), 2.44 (d, J = 12.9 Hz, 1H), 2.02−1.82 (m, 1H), 1.69−1.58 (m, 2H), 1.26 (s, 3H), 1.24 (s, 3H), 1.23 (s, 3H), 1.20−1.02 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.1, 155.8, 136.8, 128.4, 126.7, 126.3, 125.8, 120.8, 54.8, 43.0, 37.9, 35.8, 31.5, 25.8, 21.0, 20.0. **IR** (cm^{-1}, neat): 3057, 2926, 839, 759, 692. **HRMS** (EI$^+$) calcd for $[C_{18}H_{22}]^+$ m/z 238.1722, found: 238.1715. **e.r.** (HPLC): 86:14.

*(S)-3-Phenyl-4,5,6,7-tetrahydro-3aH-indene (**2f**).* Following the general procedure with 36.6 mg (0.112 mmol) of **1f**, with 4.3 mg (0.0114 mmol) of $KAuCl_4$ and with 3.7 mL of TCE. Purification of the crude by column chromatography using *n*-hexane and ethyl acetate (40:1) as eluent afforded 13.8 mg (0.0694 mmol, 62%) of the desired product and the corresponding enallene as a 1:1 mixture. The pure analytical sample was then purified with column chromatography using *n*-hexane as eluent. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.46−7.37 (m, 2H), 7.36−7.26 (m, 2H), 7.21−7.12 (m, 1H), 6.74−6.72 (m, 1H), 6.08 (t, J = 1.9 Hz 1H), 3.08 (dd, J = 12.8, 5.9 Hz, 1H), 2.79−2.64 (m, 1H), 2.50−2.26 (m, 2H), 2.09−1.94 (m, 1H), 1.88−1.74 (m, 1H), 1.63−1.41 (m, 1H), 1.37−1.14 (m, 1H), 0.82 (qd, J = 12.8, 3.4 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 153.7, 149.3, 136.0, 128.7, 127.0, 126.1, 125.6, 122.4, 51.6, 33.9, 30.0, 29.5, 25.8. **IR** (cm^{-1}, neat): 3055, 2929, 2853, 2350, 1597, 1541, 1491, 1444, 829, 756, 692. **HRMS** (EI$^+$) calcd for $[C_{15}H_{16}]^+$ m/z 196.1252, found: 196.1254. **e.r.** (HPLC): 58:42.

*7-(tert-Butyl)-3-phenyl-4,5,6,7-tetrahydro-3aH-indene (**2g**).* *Method A*: Following the typical procedure with 100.2 mg (0.261 mmol) of **1g**, with 9.9 mg (0.0261 mmol) of KAuCl4 and with 8.7 mL of TCE. Purification of the crude by column chromatography using *n*-hexane and ethyl acetate (40:1) as eluent afforded 34.3 mg (0.136 mmol, 52%) of the desired product as a mixture of diastereomers (62:38). *Method B*: Following the general procedure (with 15 h heating) with 81.5 mg (0.212 mmol) of **1g**, with 8.5 mg (0.0213 mmol) of $NaAuCl_4 \times 2H_2O$ and with 7.1 mL of TCE. Purification of the crude by column chromatography using *n*-hexane and ethyl acetate (40:1) as eluent afforded 40.1 mg (0.159 mmol, 75%) of the desired product as a mixture of diastereomers (62:38). Spectroscopic data for the mixture of diastereomers: **^{1}H NMR** (300 MHz, $CDCl_3$) Diastereomer 1: 6.73 (s), 6.22 (s), 3.04 (dd, J = 12.7, 5.6 Hz), 1.10 (s). Diastereomer 2: 6.78 (s), 6.14 (s), 3.28 (dd, J = 12.2, 6.2 Hz), 0.98 (s). Undistinguished peaks: δ 7.46−7.26 (m), 7.15 (t, J = 7.2 Hz), 2.57 (d, J = 6.9 Hz), 2.43−2.31 (m), 2.22 (d, J = 12.4 Hz), 2.12 (d, J = 12.8 Hz), 1.84 (1.95−1.70), 1.66−1.38 (m), 0.93−0.67 (m). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 154.6, 154.5, 150.2, 148.3, 136.0, 135.8, 128.6, 127.2, 126.7, 126.6, 126.1, 125.7, 125.5, 122.5, 54.3, 51.9, 50.4, 48.2, 34.9, 34.4, 33.0, 31.5, 29.7, 28.9, 28.7, 28.5, 28.3, 26.9, 24.1. **IR** (cm^{-1}, neat): 3055, 2942, 2863, 832, 755, 692. **HRMS** (EI$^+$) calcd for $[C_{19}H_{24}]^+$ m/z 252.1878, found: 252.1884. **d.r.** (^{1}H NMR): 62:38.

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*(3aS,7R)-7-(3-Methoxypropyl)-7-methyl-3-phenyl-4,5,6,7-tetrahydro-3aH-indene (**2h**).* Following the general procedure with 38.5 mg (0.093 mmol) of **1h**, with 3.5 mg (0.0093 mmol) of $KAuCl_4$ and with 3.1 mL of TCE. Purification of the crude by column chromatography using *n*-hexane and ethyl acetate (20:1 → 10:1 → 5:1) as eluent afforded 13.4 mg (0.0474 mmol, 51%) of the desired product as a mixture of diastereomers. The major diastereomer was separated with preparative HPLC. **^{1}H NMR** (500 MHz, $CDCl_3$, −5 °C) δ 7.43 (d, J = 7.5 Hz, 2H), 7.33 (t, J = 7.5 Hz, 2H), 7.18 (t, J = 7.5 Hz, 1H), 6.75 (d, J = 1.5 Hz, 1H), 6.09 (d, J = 1.5 Hz, 1H), 3.38−3.32 (m, 2H), 3.31 (s, 3H), 3.19 (dd, J = 13.0, 5.8 Hz, 1H), 2.41−2.34 (m, 1H), 1.89−1.73 (m, 3H), 1.64−1.51 (m, 2H), 1.39 (td, J = 12.6, 4.3 Hz, 1H), 1.33−1.22 (m, 2H), 1.23−1.17 (m, 3H), 0.74 (qd, J = 13.0, 3.5 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$, −5 °C) δ 160.2, 149.3, 135.8, 128.6, 126.4, 126.1, 125.5, 122.5, 73.5, 58.7, 48.5, 42.8, 38.1, 36.3, 33.9, 25.4, 24.9, 22.1. **IR** (cm^{-1}, neat): 3057, 2927, 2858, 1596, 1447, 1117, 891, 756, 693. **HRMS** (EI^+) calcd for $[C_{20}H_{26}O]^+$ m/z 282.1984, found: 282.1981. **d.r.** (^{1}H NMR): 75:35.

*(3aR,7R)-7-(3-Methoxypropyl)-7-methyl-3-phenyl-4,5,6,7-tetrahydro-3aH-indene (**2i**).* Following the general procedure with 42.1 mg (0.102 mmol) of **1i**, with 3.9 mg (0.0103 mmol) of $KAuCl_4$ and with 3.4 mL of TCE. Purification of the crude by column chromatography using *n*-hexane and ethyl acetate (20:1 → 10:1 → 5:1) as eluent afforded 6.7 mg (0.0235 mmol, 23%) of the desired product as a mixture of diastereomers. The major diastereomer was separated with preparative HPLC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.42 (d, J = 7.6 Hz, 2H), 7.31 (t, J = 7.6 Hz, 2H), 7.16 (t, J = 7.6 Hz, 1H), 6.71 (d, J = 1.9 Hz, 1H), 6.07 (d, J = 1.9 Hz, 1H), 3.44 (t, J = 6.3 Hz, 2H), 3.38 (s, 3H), 3.29 (dd, J = 12.9, 5.7 Hz, 1H), 2.43−2.33 (m, 1H), 1.89−1.55 (m, 8H), 1.19 (s, 3H), 0.73 (qd, J = 12.9, 3.6 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 161.1, 149.4, 136.0, 128.6, 126.5, 126.2, 125.6, 120.8, 73.9, 58.8, 49.2, 40.9, 37.8, 37.7, 34.3, 25.8, 24.2, 22.6. **IR** (cm^{-1}, neat): 3056, 2925, 2855, 1738, 1445, 1116, 1018, 837, 754, 692. **HRMS** (EI^+) calcd for $[C_{20}H_{26}O]^+$ m/z 282.1984, found: 282.1977. **d.r.** (^{1}H NMR): 77:33.

*Betulonic Acid Methyl Ester 3-Phenyl Cyclopentadiene (**2j**).* Following the typical procedure with 70 mg (0.101 mmol) of **1j**, with 3.8 mg (0.0101 mmol) of $KAuCl_4$ and with 3.3 mL of TCE. Purification of the crude by column chromatography using *n*-hexane and ethyl acetate (20:1) as eluent afforded 32.5 mg (0.0576 mmol, 57%) of the desired product as a mixture of regioisomers. The regioisomers were separated with preparative HPLC. Fraction 3: **^{1}H NMR** (500 MHz, $CDCl_3$, −5 °C) δ 7.37−7.30 (m), 7.17 (t, J = 7.1 Hz), 6.73 (d, J = 1.6 Hz), 6.12 (d, J = 1.6 Hz), 4.67 (s), 4.51 (s), 3.68 (s), 3.44 (dd, J = 13.2, 5.5 Hz), 3.05−2.92 (m), 2.33 (dd, J = 12.6, 5.6 Hz), 2.26−2.13 (m), 1.92−1.80 (m), 1.69−1.62 (m), 1.62−1.57 (m), 1.55−1.45 (m), 1.44−1.19 (m), 1.18−1.13 (m), 1.08 (s), 0.97 (s), 0.88 (t, J = 6.9 Hz), 0.85 (s), 0.79 (d, J = 11.6 Hz), 0.35 (t, J = 13.2 Hz). **^{13}C NMR** (126 MHz, $CDCl_3$, −5 °C) δ 176.8, 163.7, 150.5, 150.2, 135.6, 128.7, 126.3, 126.2, 125.5, 120.5, 109.9, 59.7, 56.4, 51.5, 50.2, 49.3, 47.1, 45.2, 42.5, 41.0, 38.8, 38.1, 38.1, 37.0, 34.3, 32.2, 31.7, 30.4, 29.7, 28.2, 25.3, 24.9, 22.8, 21.0, 19.1, 16.6, 16.2, 14.5, 14.4. **IR** (cm^{-1}, neat): 3061, 2944, 2868, 1727, 1490,1135, 863, 760, 739, 693. **HRMS** (EI^+) calcd for $[C_{40}H_{54}O_2]^+$ m/z 566.4124, found: 566.4113. Fraction 1: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.37−7.33 (m), 6.27 (t, J = 1.6 Hz), 4.74 (d, J = 2.5 Hz), 4.61 (dd, J = 2.5, 1.4 Hz), 3.67 (s), 3.00 (d, J = 2.8 Hz), 2.38−2.17 (m), 1.88 (dd, J = 13.5, 6.0 Hz), 1.73−1.65 (m), 1.50−1.37 (m), 1.21 (t, J = 8.8 Hz), 1.14 (s), 1.04 (s), 1.00 (s), 0.95 (s), 0.77 (s). **IR** (cm^{-1}, neat): 2944, 2869, 1726, 1451, 1376, 1364, 1153, 886, 735, 698. **HRMS** (EI^+) calcd for $[C_{40}H_{54}O_2]^+$ m/z 566.4124, found: 566.4113. Fraction 2: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.37−7.31 (m), 6.14 (s), 4.76 (d, J = 1.5 Hz, 1H), 4.67−4.62 (m), 3.67 (s), 3.57−3.45 (m), 3.22−3.11 (m), 3.07−2.93 (m), 2.35−2.16 (m), 2.01−1.82 (m), 1.74−1.66 (m), 1.49−1.36 (m), 1.22 (s), 1.14 (s), 1.05−1.00 (m), 0.98 (s), 0.94 (s), 0.77 (d, J = 3.3 Hz), 0.69 (s). **IR** (cm^{-1}, neat): 2945, 2869, 1727, 1492, 1453, 1187, 1173, 1154, 884, 755, 740, 696. **HRMS** (EI^+) calcd for $[C_{40}H_{54}O_2]^+$ m/z 566.4124, found: 566.4111.

*(R)-2-(1-(4-Bromophenyl)-3-(6,6-dimethylcyclohex-1-en-1-yl)-prop-2-yn-1-yl)-1,2,3,4-tetrahydro-3,4-dihydroisoquinoline (**1b**).* $(PPh_3)PdCl_2$ (18 mg, 0.0256 mmol), CuI (9.8 mg, 0.0515 mmol), and 6,6-dimethylcyclohex-1-en-1-yl trifluoromethanesulfonate (131 mg, 0.507 mmol) were dissolved in 4 mL of degassed THF:DEA (50:50). After 5 min, propargylic amine (166 mg, 0.671 mmol) in 2 mL of THF:DEA (50:50) was added to the mixture, and the temperature was brought to 40 °C. After 16 h, the solvent was evaporated. Purification of the crude by column chromatography (SiO_2) using *n*-hexane and ethyl acetate as eluent (20:1) afforded 168 mg (0.294 mmol, 58%) of the desired product. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.58−7.52 (m, 2H), 7.49−7.44 (m, 2H), 7.12−7.06 (m, 3H), 7.01−6.95 (m, 1H), 6.10 (t, J = 4.1 Hz, 1H), 4.92 (s, 1H), 3.75, 3.74 (ABq, J = 14.9 Hz, 2H), 2.95−2.74 (m, 4H), 2.11−2.01 (m, 2H), 1.68−1.56 (m, 2H), 1.55−1.47 (m, 2H), 1.15 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 138.2, 135.4, 134.8, 134.5, 131.4, 130.3, 130.0, 128.8, 126.8, 126.1, 125.7, 121.6, 89.0, 82.9, 61.1, 52.4, 47.3, 37.7, 33.8, 29.8, 29.1, 26.3, 19.0. **IR** (cm^{-1}, neat): 3023, 2928, 1689, 1588, 1484, 1455, 1071, 1011, 739. **HRMS** (EI^+) calcd for $[C_{26}H_{28}NBr]^+$ m/z 433.1405, found: 433.1417. **e.r.** (HPLC): 90:10.

*(R)-2-(3-(6,6-Dimethylcyclohex-1-en-1-yl)-1-(4-methoxyphenyl)-prop-2-yn-1-yl)-1,2,3,4-tetrahydro-3,4-dihydroisoquinoline (**1c**).* $(PPh_3)PdCl_2$ (24 mg, 0.0342 mmol), CuI (12.6 mg, 0.0662 mmol), and 6,6-dimethylcyclohex-1-en-1-yl trifluoromethanesulfonate (173 mg, 0.670 mmol) were dissolved in 4 mL of degassed THF:DEA (1:1). After 5 min, propargylic amine (186 mg, 0.725 mmol) in 2 mL of THF:DEA (1:1) was added, and the temperature was brought to 40 °C. After 16 h, the solvent was evaporated. Purification of the crude by column chromatography (SiO_2) using *n*-hexane and ethyl acetate as eluent (20:1) afforded 213 mg (0.550 mmol, 82%) of the desired product. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.60−7.54 (m, 2H), 7.10−7.05 (m, 3H), 7.01−6.95 (m, 1H), 6.91−6.85 (m, 2H), 6.09 (t, J = 4.1 Hz, 1H), 4.93 (s, 1H), 3.79 (s, 3H), 3.76 (s, 2H), 2.97−2.73 (m, 4H), 2.10−2.01 (m, 2H), 1.67−1.57 (m, 2H), 1.55−1.47 (m, 2H), 1.16 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.1, 135.7, 134.7, 134.4, 131.1, 130.2, 129.7, 128.8, 126.9, 126.0, 125.6, 113.6, 88.3, 83.9, 61.1, 55.4, 52.3, 47.2, 37.8, 33.8, 29.9, 29.1, 26.3, 19.0. **IR** (cm^{-1}, neat): 3022, 2929, 1610, 1585, 1508, 1455, 1245, 1172, 1036, 739. **HRMS** (EI^+) calcd for $[C_{27}H_{31}NO]^+$ m/z 385.2406, found: 385.2398. **e.r.** (HPLC): 81:19.

*2-(5,5-Dimethyl-4-methylene-1-phenylhex-2-yn-1-yl)-1,2,3,4-tetrahydro-3,4-dihydroisoquinoline (**1d**).* $(PPh_3)PdCl_2$ (14 mg, 0.0199 mmol) and CuI (7.6 mg, 0.0399 mmol) were dissolved in 2 mL of degassed THF:DEA (1:1). 6,6-Dimethylcyclohex-1-en-1-yl trifluoromethanesulfonate (99.5 mg, 0.428 mmol) was added in 2 mL of THF:DEA (1:1), followed by propargylic amine (104 mg, 0.420 mmol) in 1.05 mL of THF after 5 min. The temperature was brought to 40 °C. After 19 h, the solvent was evaporated. Purification of the crude by column chromatography (SiO_2) using *n*-hexane and ethyl acetate as eluent (40:1) afforded 101 mg (0.308 mmol, 72%) of the desired product. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.70−7.64 (m, 2H), 7.39−7.27 (m, 3H), 7.13−7.06 (m, 3H), 7.02−6.97 (m, 1H), 5.38 (d, J = 1.4 Hz, 1H), 5.29 (d, J = 1.4 Hz, 1H), 5.00 (s, 1H), 3.79 (s, 2H), 2.96−2.77 (m, 4H), 1.18 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 141.6, 138.8, 135.6, 134.7, 128.8, 128.6, 128.3, 127.7, 126.9, 126.1, 125.6, 118.1, 88.5, 85.7, 61.7, 52.4, 47.4, 36.1, 29.9, 29.3. **IR** (cm^{-1}, neat): 3025, 2965, 1602, 1449, 899, 737, 700. **HRMS** (EI^+) calcd for $[C_{24}H_{27}N]^+$ m/z 329.2143, found: 329.2144.

*(R)-2-(1-Phenyl-3-(2,6,6-trimethylcyclohex-1-en-1-yl)prop-2-yn-1-yl)-1,2,3,4-tetrahydro-3,4-dihydroisoquinoline (**1e**).* $(PPh_3)PdCl_2$ (7.7 mg, 0.0110 mmol), TEA (67 mg, 0.67 mmol), and propargylic amine (56 mg, 0.226 mmol) were dissolved in 3 mL of degassed DMF. 2,6,6-Trimethylcyclohex-1-en-1-yl trifluoromethanesulfonate (60 mg, 0.220 mmol) in 3 mL of DMF was added to the mixture, and the temperature was brought to 75 °C. After 23 h, the solvent was evaporated. Purification of the crude by column chromatography (SiO_2) using *n*-hexane and ethyl acetate as eluent (20:1) afforded 62 mg (0.167 mmol, 76%) of the desired product. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.72−7.68 (m, J = 7.5 Hz, 2H), 7.35 (t, J = 7.5 Hz, 2H), 7.28 (t, J = 7.5 Hz, 1H), 7.12−7.06 (m, 3H), 6.99 (d, J = 7.0 Hz, 1H), 5.05 (s, 1H), 3.81, 3.79 (ABq, J = 15.1 Hz, 2H), 2.96−2.80 (m, 4H), 2.03 (t, J = 6.2 Hz, 2H), 1.92 (s, 3H), 1.64−1.58 (m, 2H), 1.50−1.46

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(m, 2H), 1.15 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 140.9, 139.3, 135.7, 134.7, 128.8, 128.7, 128.2, 127.6, 126.9, 126.0, 125.6, 124.0, 88.4, 87.3, 61.9, 52.4, 47.4, 37.9, 34.1, 32.1, 29.9, 29.4, 29.4, 23.2, 19.1. **IR** (cm^{-1}, neat): 3293, 2960 2926, 2864, 1493, 1450, 1262, 1086, 1049, 1029, 798, 740, 700, 648. **HRMS** (EI^+) calcd for $[C_{27}H_{31}N]^+$ m/z 369,2457, found: 369.2454. **e.r.** (HPLC): 88:12.

*(R)-2-(3-(Cyclohex-1-en-1-yl)-1-phenylprop-2-yn-1-yl)-1,2,3,4-tetrahydro-3,4-dihydroisoquinoline (**1f**).* $(PPh_3)PdCl_2$ (14 mg, 0.0199 mmol) and CuI (7.6 mg, 0.0399 mmol) were dissolved in 2 mL of degassed THF:DEA (1:1). Cyclohex-1-en-1-yltrifluoromethanesulfonate (92 mg, 0.400 mmol) was added in 2 mL of THF:DEA (1:1), followed by propargylic amine (104 mg, 0.420 mmol) in 1.05 mL of THF after 5 min. The temperature was brought to 40 °C. After 48 h, the solvent was evaporated. Purification of the crude by column chromatography (SiO_2) using *n*-hexane and ethyl acetate as eluent (40:1) afforded the 99.7 mg (0.304 mmol, 76%) of the desired product. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.68−7.62 (m, 2H), 7.38−7.22 (m, 3H), 7.12−7.04 (m, 3H), 7.01−6.94 (m, 1H), 6.18−6.13 (m, 1H), 4.94 (s, 1H), 3.76 (s, 2H), 2.96−2.71 (m, 4H), 2.25−2.02 (m, 4H), 1.70−1.49 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 138.8, 135.6, 134.8, 134.6, 128.8, 128.6, 128.3, 127.7, 126.9, 126.0, 125.6, 120.6, 90.6, 82.0, 61.6, 52.3, 47.3, 29.8, 25.7, 22.5, 21.7. **IR** (cm^{-1}, neat): 3024, 2925, 1492, 1448, 733, 698. **e.r.** (HPLC): 90:10.

*2-(3-(6-(tert-Butyl)cyclohex-1-en-1-yl)-1-phenylprop-2-yn-1-yl)-1,2,3,4-tetrahydro-3,4-dihydroisoquinoline (**1g**).* $(PPh_3)PdCl_2$ (17 mg, 0.0242 mmol) and CuI (9 mg, 0.0473 mmol) were dissolved in 2 mL of degassed THF:DEA (1:1). 6-(*tert*-Butyl)cyclohex-1-en-1-yl trifluoromethanesulfonate (140 mg, 0.486 mmol) was added in 2 mL of THF:DEA (1:1), followed by propargylic amine (129 mg, 0.522 mmol) in 1.3 mL of THF after 5 min. The temperature was brought to 40 °C. After 19 h, the solvent was evaporated. Purification of the crude by column chromatography (SiO_2) using *n*-hexane and ethyl acetate as eluent (40:1) afforded 137.6 mg (0.360 mmol, 74%) of the desired product as a mixture of diastereomers. Spectral data for the mixture of diastereomers: **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.68−7.62 (m, 2H), 7.38−7.26 (m, 3H), 7.12−7.06 (m, 3H), 7.01−6.95 (m, 1H), 6.40−6.34 (m, 1H), 4.92 (s, 1H), 3.77 (s, 2H), 2.94−2.75 (m, 4H), 2.17−1.99 (m, 3H), 1.80−1.41 (m, 4H), 1.07 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 140.0, 139.9, 139.1, 135.6, 134.7, 128.8, 128.6, 128.2, 127.6, 126.9, 126.0, 125.6, 123.3, 92.8, 83.6, 61.8, 52.5, 47.5, 47.5, 46.9, 46.9, 34.6, 29.9, 29.5, 26.1, 25.6, 20.8. **IR** (cm^{-1}, neat): 2952, 1449, 740, 698. **HRMS** (EI^+) calcd for $[C_{28}H_{33}N]^+$ m/z 383.2615, found: 383.2598. **d.r.** (HPLC): 90:10.

*2-((R)-3-((R)-6-(3-Methoxypropyl)-6-methylcyclohex-1-en-1-yl)-1-phenylprop-2-yn-1-yl)-1,2,3,4-tetrahydro-3,4-dihydroisoquinoline (**1h**).* $(PPh_3)PdCl_2$ (4.4 mg, 0.00627 mmol) and CuI (2.4 mg, 0.0126 mmol) were dissolved in 4 mL of degassed THF:DEA (1:1). **9** (39.5 mg, 0.125 mmol) was added in 2 mL of THF, followed by propargylic amine (39 mg, 0.158 mmol) in 2 mL of THF after 5 min. The temperature was brought to 50 °C. After 15 h, the solvent was evaporated. Purification of the crude by column chromatography (SiO_2) using *n*-hexane and ethyl acetate as eluent (10:1) afforded 49.2 mg (0.0938 mmol, 75%) of the desired product. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.66 (d, J = 7.5 Hz, 2H), 7.35 (t, J = 7.5 Hz, 2H), 7.28 (t, J = 7.5 Hz, 1H), 7.12−7.06 (m, 3H), 6.99 (d, J = 6.3 Hz, 1H), 6.17 (t, J = 3.9 Hz, 1H), 4.97 (s, 1H), 3.78, 3.76 (ABq, 2H, J_{AB} = 15.1 Hz), 3.34−3.26 (m, 2H), 3.25−3.23 (m, 3H), 2.94−2.76 (m, 4H), 2.10−1.98 (m, 2H), 1.68−1.37 (m, 8H), 1.14 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 139.0, 135.8, 135.6, 134.6, 129.2, 128.8, 128.6, 128.2, 127.6, 126.9, 126.0, 125.6, 88.5, 83.6, 73.7, 61.7, 58.6, 52.4, 47.3, 37.5, 36.6, 33.6, 29.9, 27.5, 26.2, 24.7, 18.8. **IR** (cm^{-1}, neat): 2928, 2866, 2826, 1493, 1449, 1261, 1115, 1086, 802, 737, 699. **HRMS** (EI^+) calcd for $[C_{29}H_{35}NO]^+$ m/z 413.2719, found: 413.2719. **d.r.** (NMR): 89:11.

*2-((S)-3-((R)-6-(3-Methoxypropyl)-6-methylcyclohex-1-en-1-yl)-1-phenylprop-2-yn-1-yl)-1,2,3,4-tetrahydro-3,4-dihydroisoquinoline (**1i**).* $(PPh_3)PdCl_2$ (4.4 mg, 0.00627 mmol) and CuI (2.4 mg, 0.0126 mmol) were dissolved in 4 mL of degassed THF:DEA (1:1). **9** (39.5 mg, 0.125 mmol) was added in 2 mL of THF, followed by propargylic amine (39 mg, 0.158 mmol) in 2 mL of THF after 5 min. The temperature was brought to 50 °C. After 15 h, the solvent was evaporated. Purification of the crude by column chromatography (SiO_2) using *n*-hexane and ethyl acetate as eluent (10:1) afforded 41.1 mg (0.0938 mmol, 79%) of the desired product. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.68−7.63 (m, 2H), 7.38−7.24 (m, 3H), 7.11−7.05 (m, 2H), 7.01−6.95 (m, 1H), 6.17 (t, J = 4.1 Hz, 1H), 4.97 (s, 1H), 3.77 (s, 2H), 3.33−3.25 (m, 1H), 3.23 (s, 3H), 2.93−2.74 (m, 2H), 2.11−1.95 (m, 1H), 1.70−1.33 (m, 8H), 1.14 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 139.0, 135.8, 135.6, 134.6, 129.3, 128.8, 128.6, 128.2, 127.6, 126.9, 126.0, 125.6, 88.5, 83.6, 73.7, 61.7, 58.6, 52.4, 47.4, 37.5, 36.6, 33.6, 29.9, 27.5, 26.2, 24.73, 18.8. **IR** (cm^{-1}, neat): 2930, 2866, 2826, 1263, 1493, 1117, 739, 700. **HRMS** (EI^+) calcd for $[C_{29}H_{35}NO]^+$ m/z 413.2719, found: 413.2722. **d.r.** (NMR): 88:12.

*1-Phenylprop-2-yn-1-yl-1,2,3,4-tetrahydro-3,4-dihydroisoquinoline Betulonic Acid Methyl Ester (**1j**).* $(PPh_3)PdCl_2$ (27.3 mg, 0.0389 mmol) and CuI (16.6 mg, 0.0871 mmol) were dissolved in 5 mL of DMF, after which propargylic amine (164 mg, 0.663 mmol) and TEA (101.7 mg) were added in 5 mL of DMF. This mixture was added to **3j** (400 mg, 0.666 mmol) in 27 mL of DMF and stirred for 10 min, after which the temperature was brought to 80 °C. After $1^1/_2$ h, 30 mL of water was added to the mixture, which was extracted with 3 × 30 mL of diethyl ether. The combined ethers were washed with 15 mL of water and 15 mL of brine and dried over Na_2SO_4. Purification of the crude by column chromatography (SiO_2) using *n*-hexane and ethyl acetate as eluent (20:1) afforded 336 mg (0.477 mmol, 72%) of the desired product. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.66 (d, J = 7.1 Hz), 7.38−7.25 (m), 7.13−7.04 (m), 7.02−6.95 (m), 6.00 (dd, J = 6.4, 2.1 Hz), 4.98 (s), 4.74 (d, J = 2.1 Hz), 4.60 (dd, J = 2.2, 1.4 Hz), 3.78 (s), 3.67 (s), 3.06−2.76 (m), 2.24 (qd, J = 8.1, 3.6 Hz), 2.08 (dd, J = 17.9, 6.6 Hz), 1.96−1.81 (m), 1.77−1.72 (m), 1.68 (s), 1.60 (dd, J = 15.4, 7.2 Hz), 1.53−1.29 (m), 1.21−1.18 (m), 1.17 (s), 1.14−1.08 (m), 1.06 (s), 1.05−1.00 (m), 0.97 (s), 0.95 (s), 0.86 (s). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 176.8, 150.7, 139.1, 135.7, 134.7, 132.3, 129.9, 128.8, 128.6, 128.2, 127.6, 126.9, 126.0, 125.6, 109.7, 89.0, 83.0, 61.7, 56.7, 52.4, 51.4, 49.6, 49.4, 47.4, 47.1, 42.5, 42.1, 40.7, 38.5, 37.1, 37.0, 36.3, 33.6, 32.3, 31.7, 30.8, 30.6, 29.8, 25.7, 22.8, 21.7, 21.4, 20.0, 19.5, 16.6, 15.7, 14.9, 14.3. **IR** (cm^{-1}, neat): 2944, 1726, 1445, 1377, 1143, 883, 739, 699. **HRMS** (EI^+) calcd for $[C_{49}H_{63}NO_2]^+$ m/z 697.4859, found: 697.4874.

*2-(1-(4-Methoxyphenyl)prop-2-yn-1-yl)-1,2,3,4-tetrahydro-3,4-dihydroisoquinoline (**4c**).* $Cu(OTf)\cdot(benzene)_{0.5}$ (24 mg, 0.954 mmol) and *R*(+)-BINAP (118 mg, 0.190 mmol) were dissolved in 7 mL of anhydrous methanol under an argon atmosphere and stirred for $2^1/_2$ h at 60 °C. The temperature was lowered to 0−5 °C (ice bath), and a solution of **5c** (388 mg, 1.90 mmol), DIPEA (288 mg, 2.23 mmol), and 1,2,3,4-tetrahydroisoquinoline (285 mg, 2.14 mmol) in anhydrous methanol (7 mL) was added to the mixture. The mixture was stirred for 20 h at 0−5 °C, after which the solution was filtered and washed with MeOH. The filtrate was removed under reduced pressure. Purification of the crude by column chromatography (SiO_2) using *n*-hexane and ethyl acetate as eluent (10:1) afforded 163 mg (0.589 mmol, 31%) of the desired product. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.55 (d, J = 8.2 Hz, 2H), 7.12−7.05 (m, 3H), 6.97 (d, J = 6.7 Hz, 1H), 6.88 (d, J = 8.2 Hz, 2H), 4.78 (s, 1H), 3.79 (s, 2H), 3.73 (s, 1H), 2.95−2.70 (m, 2H), 2.55−2.53 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.3, 135.3, 134.5, 129.9, 129.5, 128.8, 126.8, 126.0, 125.6, 113.7, 79.6, 75.9, 60.4, 55.4, 52.1, 47.0, 29.7. **IR** (cm^{-1}, neat): 3285, 2908, 2834, 1609, 1508, 1245, 1171, 1033, 839, 734, 689. **HRMS** (EI^+) calcd for $[C_{19}H_{19}NO]^+$ m/z 277.1467, found: 277.1476.

*2-(1-(4-Bromophenyl)prop-2-yn-1-yl)-1,2,3,4-tetrahydro-3,4-dihydroisoquinoline (**4b**).* $Cu(OTf)\cdot(benzene)_{0.5}$ (17.6 mg, 0.0700 mmol) and *R*(+)-BINAP (87 mg, 0.140 mmol) were dissolved in 7 mL of anhydrous methanol under an argon atmosphere and stirred for 2 h at 60 °C. The temperature was lowered to 0−5 °C (ice bath), and a solution of **5b** (354 mg, 1.40 mmol), DIPEA (212 mg, 1.64 mmol), and 1,2,3,4-tetrahydroisoquinoline (373 mg, 2.80 mmol) in anhydrous methanol (7 mL) was added to the mixture. The mixture was stirred for 63 h, and during this time, the temperature was let to rise to room temperature. The solution was filtered and washed with MeOH. The filtrate was removed under reduced pressure. Purification of the crude by column chromatography (SiO_2) using *n*-hexane and ethyl acetate as

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eluent (10:1) afforded 142.6 mg (0.434 mmol, 31%) of the desired product. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.54 (d, J = 8.1 Hz, 2H), 7.47 (d, J = 8.1 Hz, 2H), 7.13−7.06 (m, 3H), 6.97 (d, J = 6.4 Hz, 1H), 4.78 (s, 1H), 3.74, 3.71 (ABq, 2H, J_{AB} = 14.7 Hz), 2.96−2.68 (m, 4H), 2.60−2.54 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 137.0, 135.0, 134.4, 131.5, 130.1, 128.8, 126.8, 126.2, 125.7, 121.9, 78.6, 76.7, 60.4, 52.1, 47.1, 29.7. **IR** (cm^{-1}, neat): 3294, 2921, 1485, 1071, 1012, 951, 783, 740. **HRMS** (EI^+) calcd for $[C_{18}H_{16}BrN]^+$ m/z 325.0466, found: 325.0473.

*(R)-Methyl 3-(6-Methyl-1,4-dioxaspiro[4.5]decan-6-yl)propanoate (**7**).* Ketone (**6**) (199 mg, 1.00 mmol), *p*-TsOH (19.1 mg, 0.100 mmol), and ethylene glycol (624 mg, 10.1 mmol) were dissolved to 20 mL of toluene, and the mixture was refluxed in a Dean−Stark setup fitted with a drying tube ($CaCl_2$) for $2^1/_2$ h. The reaction was quenched with 5 mL of 2 N NaOH and diluted with 50 mL of EtOAc. The organic fraction was washed with 30 mL of water and 30 mL of brine and dried over Na_2SO_4. Purification of the crude by column chromatography (SiO_2) using *n*-hexane and ethyl acetate (10:1) as eluent afforded 176 mg (0.730 mmol, 73%) of the desired product. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.00−3.85 (m, 4H), 3.66 (s, 3H), 2.39−2.25 (m, 2H), 1.91−1.65 (m, 2H), 1.67−1.47 (m, 4H), 1.44−1.35 (m, 4H), 0.92 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 175.2, 112.8, 65.1, 64.8, 51.6, 40.9, 34.8, 30.6, 30.3, 29.4, 23.6, 20.9, 19.41. **IR** (cm^{-1}, neat): 2933, 2866, 1736, 1436, 1172, 1088, 948, 878. **HRMS** (EI^+) calcd for $[C_{13}H_{22}O_4]^+$ m/z 242.1518, found: 242.1513.

*(R)-3-(6-Methyl-1,4-dioxaspiro[4.5]decan-6-yl)propan-1-ol (**8**).* To stirred solution of $LiAlH_4$ (58 mg, 1.53 mmol) in 10 mL THF was added protected ester (**7**) (167 mg, 0.689 mmol) in 10 mL of THF, and the mixture was stirred at room temperature for 2 h 15 min. The reaction mixture was quenched with Rochelle's Salt, and the organic fraction was separated. The water phase was extracted with Et_2O (3 × 50 mL) and washed with 50 mL of H_2O and 50 mL brine and dried over Na_2SO_4. Purification of the crude by column chromatography (SiO_2) using *n*-hexane and ethyl acetate (1:1) as eluent afforded 121 mg (0.565 mmol, 82%) of the desired product. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.00−3.85 (m, 4H), 3.66−3.58 (m, 2H), 1.67−1.34 (m, 12H), 0.92 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 113.1, 65.1, 64.9, 64.2, 41.1, 34.4, 30.6, 30.5, 27.2, 23.8, 21.0, 19.6. **IR** (cm^{-1}, neat): 3360, 2931, 2865, 1467, 1448, 1174, 1126, 1089, 1054, 1026, 951, 879. **HRMS** (EI^+) calcd for $[C_{12}H_{22}O_3]^+$ m/z 214.1569, found: 214.1579.

*(R)-2-(3-Methoxypropyl)-2-methylcyclohexanone (**9**).* Protected alcohol (**8**) (105 mg, 0.490 mmol) in 10 mL of THF was added to a 55% NaH suspension (78 mg, 1.96 mmol) in 10 mL of THF at 0 °C. The reaction mixture was stirred for $2^1/_2$ h, after which MeI (556 mg, 3.92 mmol) was added and the mixture was stirred overnight. The next day, the reaction was quenched with water. THF was evaporated, and to the residue was added 10 mL of water, which was extracted with 3 × 20 mL of DCM. DCM was washed with 10 mL of H_2O and evaporated. The mixture was dissolved in 30 mL of 2:1 (THF:H_2O), and a catalytic quantity of *p*-TsOH was added. The mixture was heated to 70 °C, and after the disappearance of starting material (TLC), THF was evaporated. The residue was extracted with 3 × 20 mL of DCM. DCM was washed with 15 mL of sat. $NaHCO_3$ and 15 mL of brine and dried over Na_2SO_4. Purification of the crude by column chromatography (SiO_2) using *n*-hexane and ethyl acetate (3:1) as eluent afforded 78 mg (0.421 mmol, 86%) of the desired product. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.35 (t, J = 6.2 Hz, 2H), 3.32 (s, 2H), 2.46−2.30 (m, 2H), 1.93−1.64 (m, 6H), 1.62−1.43 (m, 4H), 1.40−1.31 (m, 1H), 1.06 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 215.9, 73.1, 58.6, 48.4, 39.5, 38.8, 34.1, 27.6, 24.2, 22.6, 21.1. **IR** (cm^{-1}, neat): 2932, 2863, 2827, 1703, 1452, 1116. **HRMS** (EI^+) calcd for $[C_{11}H_{20}O_2]^+$ m/z 184.1463, found:184.1469.

*(R)-6-(3-Methoxypropyl)-6-methylcyclohex-1-en-1-yl Trifluoromethanesulfonate (**10**).* To a stirred solution of ketone (**9**) (240 mg, 1.30 mmol) in 6 mL of THF was added LiHMDS (350 mg, 2.10 mmol) in 6 mL of THF at −84 °C. After 30 min, *N*,*N*-bis(trifluoromethylsulfonyl)-5-chloro-2-pyridylamine (561 mg, 1.43 mmol) was added in 9 mL of THF. The reaction mixture was brought to room temperature and left overnight. The next day, the reaction was quenched with water. THF was evaporated, and the residue was dissolved in 40 mL of DCM. DCM was washed with 20 mL of water and 20 mL of brine and dried with Na_2SO_4. Purification of the crude by column chromatography (SiO_2) using *n*-hexane and ethyl acetate (10:1) as eluent afforded 225 mg (0.715 mmol, 55%) of the desired product. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.72 (t, J = 4.1 Hz, 1H), 3.41−3.34 (m, 2H), 3.33 (s, 3H), 2.20−2.11 (m, 2H), 1.80−1.43 (m, 8H), 1.14 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 155.4, 118.6 (d, J = 318 Hz), 117.1, 73.2, 58.7, 38.1, 35.4, 35.1, 24.9, 24.8, 24.3, 18.5. **IR** (cm^{-1}, neat) 2942, 2868, 1408, 1141, 1016, 894, 866, 603.

*6-(tert-Butyl)cyclohex-1-en-1-yl Trifluoromethanesulfonate (**3g**).* To 2-(*t*-butyl)cyclohexanone (154 mg, 1 mmol) in 3 mL of THF was added LiHMDS (167 mg, 1 mmol) as a 1 M solution in THF at −78 °C. The mixture was stirred for 30 min, after which $PhNTf_2$ (357 mg, 1 mmol) was added as a 1 M solution in THF. The mixture was then stirred overnight, and the temperature was let to rise to room temperature during the stirring. The next day, the reaction was quenched with H_2O and THF was evaporated. The residue was dissolved in DCM, and the DCM was washed with H_2O and brine and dried over Na_2SO_4. Purification of the crude by column chromatography using pentane as eluent afforded 159 mg (0.560 mmol, 56%) of the desired product. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.92−5.86 (m, 1H), 2.37−2.29 (m, 1H), 2.25−2.03 (m, 2H), 1.91−1.79 (m, 1H), 1.79−1.60 (m, 2H), 1.57−1.41 (m, 1H), 1.01 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 152.2, 121.8, 118.7 (q, J = 320.3 Hz), 47.4, 34.2, 29.1, 26.8, 24.5, 20.4. **IR** (cm^{-1}, neat): 2962, 2874, 1671, 1414, 1244, 1200, 1140, 1014. **HRMS** (EI^+) calcd for $[C_{11}H_{17}F_3O_3S]^+$ m/z 286.0850, found: 286.0830.

*((2S)-1-(1-Phenylprop-2-yn-1-yl)pyrrolidin-2-yl)methanol (**4d**).* Cu(OTf)·(benzene)$_{0.5}$ (16 mg, 0.064 mmol) and *S*-(−)-Cl-MeO-BIPHEP (84 mg, 0.13 mmol) were dissolved in 3 mL of anhydrous methanol under an argon atmosphere and stirred for 1 h at 60 °C. The temperature was lowered to 0−5 °C (ice bath), and a solution of L-prolinol (131 mg, 1.3 mmol), DIPEA (335 mg, 2.6 mmol), and 1-phenylprop-2-yn-1-yl acetate (226 mg, 1.3 mmol) in anhydrous methanol (3 mL) was added to the mixture. The mixture was stirred for 22 h at 0−5 °C, after which the solution was filtered and washed with MeOH. The filtrate was removed under reduced pressure. Purification of the crude by column chromatography (SiO_2) using *n*-hexane and ethyl acetate as eluent (5:1) afforded 53 mg (0.589 mmol, 19%) of the desired product. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.57−7.51 (m, 2H), 7.38−7.24 (m, 3H), 4.92 (d, J = 1.9 Hz, 1H), 3.77 (dd, J = 11.0, 3.6 Hz, 1H), 3.51 (dd, J = 11.0, 2.4 Hz, 1H), 3.17 (dd, J = 6.0, 2.8 Hz, 1H), 2.75−2.64 (m, 1H), 2.62−2.49 (m, 3H), 2.03−1.55 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 138.6, 128.4, 128.0, 127.7, 79.70, 75.5, 62.0, 61.7, 55.7, 47.8, 28.0, 23.5. **IR** (cm^{-1}, neat): 3410, 3291, 3030, 2963, 2872, 1493, 1117, 1029, 701, 640. **HRMS** (EI^+) calcd for $[C_{14}H_{17}NO - CH_3O]^+$ m/z 184.1126, found: 184.1129.

*((2S)-1-(3-(6,6-Dimethylcyclohex-1-en-1-yl)-1-phenylprop-2-yn-1-yl)pyrrolidin-2-yl)methanol (**1k**).* $(PPh_3)PdCl_2$ (8.8 mg, 0.0125 mmol), CuI (4.8 mg, 0.025 mmol), and 6,6-dimethylcyclohex-1-en-1-yl trifluoromethanesulfonate (64.5 mg, 0.25 mmol) were dissolved in 2 mL of degassed THF:DEA (1:1). After 5 min, **4d** (53 mg, 0.25 mmol) in 2 mL of THF:DEA (1:1) was added and temperature was brought to 40 °C. After 22 h, the solvent was evaporated. Purification of the crude by column chromatography (SiO_2) using *n*-hexane and ethyl acetate as eluent (5:1) afforded 37.6 mg (0.117 mmol, 47%) of the desired product. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.60−7.51 (m, 2H), 7.39−7.21 (m, 3H), 6.10 (t, J = 4.1 Hz, 1H), 5.03 (s, 1H), 3.80 (dd, J = 10.9, 3.5 Hz, 1H), 3.51 (dd, J = 10.9, 2.2 Hz, 1H), 3.27−3.17 (m, 1H), 2.80−2.69 (m, J = 9.2, 7.3 Hz, 1H), 2.62−2.51 (m, 2H), 2.11−2.01 (m, 2H), 2.00−1.57 (m, 6H), 1.58−1.49 (m, 2H), 1.17 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 139.8, 134.6, 130.1, 128.3, 128.2, 127.5, 87.8, 83.9, 61.9, 61.8, 56.4, 47.9, 37.8, 33.8, 29.0, 28.2, 26.3, 23.7, 19.0. **IR** (cm^{-1}, neat): 3421, 2961, 2930, 2929, 2866, 2829, 1451, 1360, 1075, 1030, 703. **HRMS** (EI^+) calcd for $[C_{22}H_{29}NO - CH_3O]^+$ m/z 292.2065, found: 292.2075.

*(S)-7-Nitro-2-(1-phenylprop-2-yn-1-yl)-1,2,3,4-tetrahydroisoquinoline (**4e**).* Cu(OTf)·(benzene)$_{0.5}$ (2 mg, 0.008 mmol) and *R*-(+)-Cl-MeO-BIPHEP (11 mg, 0.016 mmol) were dissolved in 3 mL of

anhydrous methanol under an argon atmosphere, and the mixture was stirred for 1 h at 60 °C. The temperature was lowered to 0−5 °C (ice bath), and a solution of 7-nitro-1,2,3,4-tetrahydroisoquinoline (61 mg, 0.34 mmol), DIPEA (88 mg, 0.68 mmol), and 1-phenylprop-2-yn-1-yl acetate (30 mg, 0.17 mmol) in 3 mL of anhydrous methanol was added to the mixture. The mixture was stirred overnight, after which the solution was filtered and washed with MeOH. The filtrate was removed under reduced pressure. Purification of the crude by column chromatography (SiO_2) using *n*-hexane and ethyl acetate as eluent (10:1) afforded 37 mg (0.126 mmol, 74%) of the desired product. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.95 (dd, J = 8.4, 2.4 Hz, 1H), 7.87 (d, J = 2.2 Hz, 1H), 7.66−7.60 (m, 2H), 7.42−7.30 (m, 3H), 7.22 (d, J = 8.4 Hz, 1H), 4.88 (d, J = 2.2 Hz, 1H), 3.82 3.78 (ABq, J = 15.4 Hz, 2H), 3.06−2.77 (m, 4H), 2.61 (d, J = 2.3 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 146.2, 142.6, 137.2, 136.9, 129.7, 128.5, 128.4, 128.2, 122.0, 121.1, 78.7, 77.2, 76.6, 60.8, 51.7, 46.5, 30.0. **IR** (cm^{-1}, neat): 3290, 1592, 1346, 1101, 752, 697. **HRMS** (EI$^+$) calcd for $[C_{18}H_{16}N_2O_2]^+$ m/z 292.1212, found: 292.1211.

*(R)-2-(3-(6,6-Dimethylcyclohex-1-en-1-yl)-1-phenylprop-2-yn-1-yl)-7-nitro-1,2,3,4-tetrahydroisoquinoline (**1l**).* $(PPh_3)PdCl_2$ (5.3 mg, 0.0075 mmol) and CuI (3,2 mg, 0.017 mmol) were dissolved in 6 mL of degassed THF:DEA (1:1). After 5 min, 6,6-dimethylcyclohex-1-en-1-yl trifluoromethanesulfonate (78 mg, 0.275 mmol) in 3 mL of THF was added to the mixture, followed by (after 5 min stirring) **4e** (61 mg, 0.25 mmol) dissolved in 3 mL of THF. After stirring overnight at 40 °C, the solvent was evaporated. Purification of the crude by column chromatography (SiO_2) using *n*-hexane and ethyl acetate as eluent (20:1) afforded 64 mg (0.16 mmol, 64%) of the desired product. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.95 (dd, J = 8.4, 2.4 Hz, 1H), 7.88 (d, J = 2.2 Hz, 1H), 7.74−7.55 (m, 2H), 7.42−7.27 (m, 3H), 7.23 (d, J = 8.4 Hz, 1H), 6.12 (t, J = 4.1 Hz, 1H), 5.02 (s, 1H), 3.85 3.80 (ABq, J = 15.4 Hz, 2H), 3.06−2.75 (m, 4H), 2.18−2.00 (m, 2H), 1.73−1.42 (m, 4H), 1.17 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 146.1, 142.7, 138.4, 137.2, 134.9, 130.0, 129.7, 128.5, 128.4, 127.9, 122.1, 121.1, 89.0, 82.9, 61.5, 52.0, 46.8, 37.7, 33.8, 30.1, 29.06, 29.05, 26.3, 19.0. **IR** (cm^{-1}, neat): 2959, 2928, 2851, 1523, 1346, 1100, 750, 712, 696. **HRMS** (EI$^+$) calcd for $[C_{26}H_{28}N_2O_2]^+$ m/z 400.2151, found: 400.2154.

*(S)-N,N-Dimethyl-2-(1-phenylprop-2-yn-1-yl)-1,2,3,4-tetrahydroisoquinolin-7-amine (**4f**).* $Cu(OTf)\cdot(benzene)_{0.5}$ (6.9 mg, 0.0275 mmol) and *R*-(+)-Cl-MeO-BIPHEP (35.8 mg, 0.055 mmol) were dissolved in 5 mL of anhydrous methanol under an argon atmosphere and stirred for 1 h at 60 °C. The temperature was lowered to 0−5 °C (ice bath), and a solution of 7-dimethylamino-1,2,3,4-tetrahydroisoquinoline (98 mg, 0.55 mmol), DIPEA (284 mg, 2.22 mmol), and 1-phenylprop-2-yn-1-yl acetate (96 mg, 0.55 mmol) in 5 mL of anhydrous methanol was added to the mixture. The mixture was stirred overnight, after which the solution was filtered and washed with MeOH. The filtrate was removed under reduced pressure. Purification of the crude by column chromatography (SiO_2) using *n*-hexane and ethyl acetate as eluent (20:1) afforded 84.7 mg (0.292 mmol, 53%) of the desired product. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.74−7.66 (m, 2H), 7.44−7.29 (m, 3H), 7.00 (d, J = 8.4 Hz, 1H), 6.63 (dd, J = 8.4, 2.7 Hz, 1H), 6.41 (d, J = 2.5 Hz, 1H), 4.87 (d, J = 2.0 Hz, 1H), 3.76 3.73 (ABq, J = 14.7 Hz, 2H), 2.89 (s, 6H), 2.83 (d, J = 5.8 Hz, 4H), 2.61−2.58 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 149.2, 138.1, 135.7, 129.3, 128.4, 128.3, 127.8, 123.0, 112.0, 111.0, 79.5, 76.1, 61.1, 52.4, 47.8, 41.1, 28.8. **IR** (cm^{-1}, neat): 3285, 2912, 2798, 1616, 1514, 1339, 1088, 721, 698, 649. **HRMS** (EI$^+$) calcd for $[C_{20}H_{22}N_2]^+$ m/z 290.1783, found: 290.1780.

*(R)-2-(3-(6,6-Dimethylcyclohex-1-en-1-yl)-1-phenylprop-2-yn-1-yl)-N,N-dimethyl-1,2,3,4-tetrahydroisoquinolin-7-amine (**1m**).* $(PPh_3)PdCl_2$ (10 mg, 0.00145 mmol) and CuI (3.2 mg, 0.017 mmol) were dissolved in 10 mL of degassed THF:DEA (1:1). After 5 min, 6,6-dimethylcyclohex-1-en-1-yl trifluoromethanesulfonate (83 mg, 0.29 mmol) in 5 mL of THF was added to the mixture, followed by (after 5 min stirring) **4f** (75 mg, 0.25 mmol) dissolved in 5 mL of THF. After stirring overnight at 40 °C, the solvent was evaporated. Purification of the crude by column chromatography (SiO_2) using *n*-hexane and ethyl acetate as eluent (10:1) afforded 86 mg (0.215 mmol, 74%) of the desired product. **^{1}H NMR** (500 MHz, CD_3CN) δ 7.63 (d, J = 7.6 Hz, 2H), 7.37 (t, J = 7.5 Hz, 2H), 7.30 (t, J = 7.3 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 6.56 (dd, J = 8.4, 2.5 Hz, 1H), 6.37 (d, J = 2.3 Hz, 1H), 6.08 (t, J = 4.1 Hz, 1H), 4.95 (s, 1H), 3.70 3.62 (ABq, J = 14.7 Hz, 2H), 2.81 (s, 6H), 2.77−2.65 (m, 4H), 2.08−2.01 (m, 2H), 1.65−1.59 (m, 2H), 1.54−1.49 (m, 2H), 1.16 (s, 6H). **^{13}C NMR** (126 MHz, CD_3CN) δ 150.3, 140.4, 136.7, 135.5, 131.1, 130.1, 129.4, 129.3, 128.6, 123.6, 118.3, 112.7, 111.7, 89.3, 85.1, 62.4, 53.6, 49.0, 41.2, 38.5, 34.5, 29.5, 29.5, 27.0, 19.7. **IR** (cm^{-1}, neat): 2963, 2928, 2851, 1617, 1515, 1338, 796, 749, 698. **HRMS** (EI$^+$) calcd for $[C_{28}H_{34}N_2]^+$ m/z 398.2722, found: 398.2723.

*tert-Butyl 7-(Dimethylamino)-3,4-dihydroisoquinoline-2(1H)-carboxylate (**11**).* *tert*-Butyl 7-nitro-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (140 mg) and 5% Pd/C (14.8 mg) in 5 mL of MeOH were stirred at room temperature under a balloon of H_2. After 2 h, formalin (1 mL) and 0.1 mL of 3 N HCl was added to the mixture and the stirring was continued for 2 h. The reaction was quenched with saturated $NaHCO_3$ and filtered through a pad of Celite, which was washed with acetone. After evaporation of organic solvents, water was added to the residue. The water phase was extracted with 3 × 20 mL of DCM, and the organic phase was washed with brine. After drying the organic phase over Na_2SO_4, the solvent was evaporated. Purification of the crude by column chromatography (SiO_2) using *n*-hexane and ethyl acetate as eluent (3:1) afforded 82.9 mg (0.3 mmol, 60%) of the desired product. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.02 (d, J = 8.4 Hz, 1H), 6.63 (d, J = 7.2 Hz, 1H), 6.48 (s, 1H), 4.55 (s, 2H), 3.64 (s, 2H), 2.92 (s, 6H), 2.77 (d, J = 18.5 Hz, 2H), 1.51 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 155.0, 149.5, 129.3, 123.1, 111.8, 110.2, 79.6, 40.9, 28.6, 28.0. **IR** (cm^{-1}, neat): 2974, 2800, 1689, 1617, 1513, 1414, 1363, 1290, 1237, 1163, 1120, 730. **HRMS** (EI$^+$) calcd for $[C_{16}H_{24}N_2O_2]^+$ m/z 276.1838, found: 276.1840.

*N,N-Dimethyl-1,2,3,4-tetrahydroisoquinolin-7-amine (**12**).* **11** (150 mg, 0.54 mmol) was stirred in 6 mL of TFA:DCM overnight. The next day, solvents were evaporated and 20 mL of 2 N NaOH was added to the residue, which was extracted with 3 × 20 mL of Et_2O and washed with brine. After drying the organic phase with Na_2SO_4, the solvent was evaporated. Purification of the crude by column chromatography (SiO_2) using DCM and MeOH as eluent (1:1 → 1:3 → 0:1) afforded 97.7 mg (0.55 mmol, >99%) of the desired product. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.95 (d, J = 8.4 Hz, 1H), 6.60 (dd, J = 8.4, 2.7 Hz, 1H), 6.38 (d, J = 2.7 Hz, 1H), 3.96 (s, 2H), 3.10 (t, J = 6.0 Hz, 2H), 2.88 (s, 6H), 2.68 (t, J = 6.0 Hz, 2H), 2.22 (s, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 149.2, 136.3, 129.9, 123.1, 111.8, 110.3, 48.7, 44.3, 41.0, 28.2. **IR** (cm^{-1}, neat): 2924, 2798, 1676, 1513, 1345, 801. **HRMS** (EI$^+$) calcd for $[C_{11}H_{16}N_2]^+$ m/z 176.1313, found: 176.1310.

Computational Methods. All computations at the DFT level were performed using the Turbomole 6.4 program package.[57] Solvation effects were taken into account using the COSMO solvation model in all DFT computations with a dielectric constant of 1,1,2,2-tetrachloroethane (ε = 8.42) unless otherwise noted.[58] The TPSS-D3[37,38] functional was chosen with the triple ζ quality basis set, def2-TZVP.[39] Grid m4 was used in all computations. The MARI-J approximation was used in all computations with a suitable auxiliary basis set.[59−62] The scalar relativistic effects for gold were taken into account using the def2-ecp from the Stuttgart group.[63] Vibrational frequencies were calculated numerically for all complexes to obtain the chemical potential at 298.15 K (chem. pot.) and to confirm the nature of the stationary point (minima or TS). The Gibbs free energies were then calculated: $G = E(0)$ + chem. pot. All multireference calculations (CASSCF and NEVPT2) were performed using the ORCA 2.9.1 program package.[64]

The enantioselectivity determining cyclization step was also computed using various different DFT methods, namely, PBE-D3,[65] PBE0-D3,[65,66] TPSSh-D3,[37,67] B3LYP-D3,[68−70] and a double-hybrid functional B2PLYP-D3.[71] The D3 empirical dispersion corrections were used with zero damping. Pictures were generated with CYLview,[72] Gabedit,[73] and VMD.[74] Density differences were calculated using DGrid.[75]

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■ ASSOCIATED CONTENT

Supporting Information

NMR spectra, HPLC chromatograms, computational data, and *xyz* parameters. 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 interest.

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