How to cite: *Angew. Chem. Int. Ed.* **2023**, *62*, e202312874
doi.org/10.1002/anie.202312874

Gold Catalysis

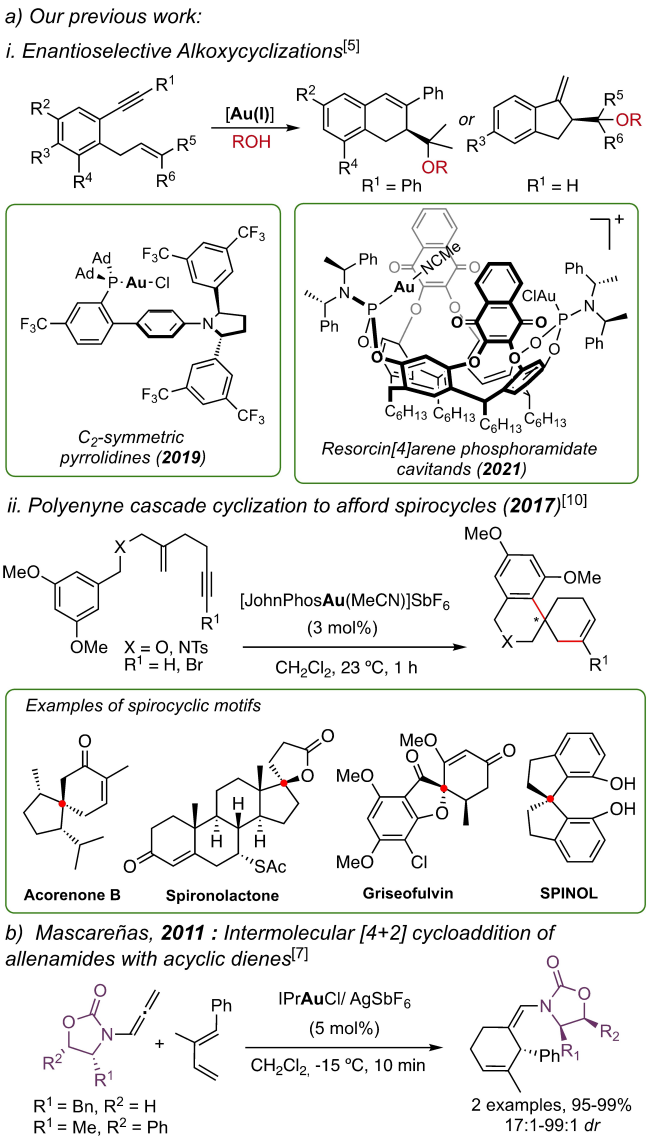
Chiral Auxiliary Approach for Gold(I)-Catalyzed Cyclizations

*Andrea Cataffo, Miguel Peña-López, Riccardo Pedrazzani, and Antonio M. Echavarren**

Abstract: Two different classes of stereoselective cyclizations have been developed using a chiral auxiliary approach with commercially available [JohnPhosAu(MeCN)SbF_6] as catalyst. First, a stereoselective cascade cyclization of 1,5-enynes was achieved using the Oppolzer camphorsultam as chiral auxiliary. In this case, a one-pot cyclization-hydrolysis sequence was developed to directly afford enantioenriched spirocyclic ketones. Then, the stereoselective alkoxycyclization of 1,6-enynes was mediated by an Evans-type oxazolidinone. A reduction-hydrolysis sequence was selected to remove the auxiliary to give enantioenriched β-tetralones. DFT studies confirmed that the steric clash between the chiral auxiliary and alkene accounts for the experimentally observed diastereoselective cyclization through the Si face.

Introduction

Gold(I) catalysis stands out for the fast and atom economical assembly of complex molecular structures.[1,2] However, in general, the linear dicoordination of gold(I) catalysis poses limitations to the developing of general enantioselective transformations since the ancillary chiral ligand is in the opposite site of the substrate.[3] Since 2005, with the first example of enantioselective gold(I)-catalyzed alkoxycyclizations,[4] our group has developed new chiral gold(I) catalysts that provide high enantioselectivities in selected transformations[5] (Scheme 1a-i). Nonetheless, the design of chiral ligands for gold(I) is often time-consuming practice and alternatives to obtain enantioenriched compounds would be of interest. Despite the broad application of chiral auxiliaries in asymmetric synthesis,[6] only one isolated example has been reported in gold(I) catalyzed cyclizations by the group of Mascareñas using a chiral oxazolidinone for the stereoselective [4+2] cycloaddition of two allenamide substrates with acyclic dienes (Scheme 1b).[7] Very recently, the group of Shi, has also reported the use of chiral oxazolidinones for performing asymmetric hydrative aldol reaction through a combined Au/Fe catalysis.[8] Given the wide number of transformations involving chiral ynamides[9] and, in parallel, of gold(I)-catalyzed cyclizations of ynamide containing enynes (enynamides) in literature,[1h]

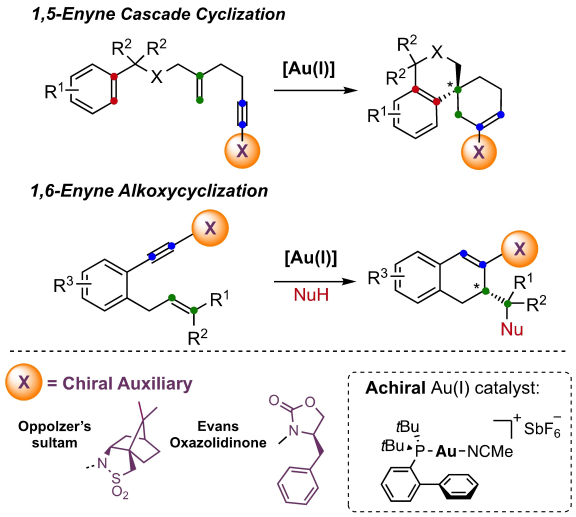


Scheme 1. Previous work on gold(I)-catalyzed cyclizations.

[*] A. Cataffo, Dr. M. Peña-López, R. Pedrazzani, A. M. Echavarren
Institute of Chemical Research of Catalonia (ICIQ), CERCA, Barcelona Institute of Science and Technology
Av. Països Catalans 16, 43007 Tarragona (Spain)
and
Departament de Química Analítica i Química Orgànica, Universitat Rovira i Virgili
C/Marcel·lí Domingo s/n, 43007 Tarragona (Spain)
E-mail: aechavarren@iciq.es

and their application to build complex cyclic structures,[10] the design of substrates bearing chiral auxiliaries at *N*-substituted alkynes seemed to constitute a logic approach for developing stereoselective reactions with alkenes under gold(I) catalysis. We have reported the gold(I)-catalyzed cyclization of 1,5- and 1,6-enynes in which the activation of terminal alkynes or bromoalkynes triggers a cascade cyclization to form spirocyclic compounds in racemic manner (Scheme 1a-ii).[11] The spiro motif is found in many biologically active natural,[12] synthetic[13] products, and chiral ligands.[14] Although underrepresented compared to flat aromatic scaffolds, spirocyclic compounds are increasingly becoming more important in modern drug discovery.[15] For the buildup of such a chiral spirofused molecular scaffold several transition metal-mediated and organocatalytic methods have emerged, which mainly rely on cycloadditions, inter- and intramolecular substitutions and radical strategies.[1,16]

Despite this progress, the synthesis of chiral spirocycles remains relatively underdeveloped. Furthermore, in contrast to 1,6-enynes, there are very few reports on enantioselective cyclizations involving 1,5-enynes so far[17] and none describing cascade cyclizations. Therefore, in the present work, we have designed a cascade cyclization of 1,5-enynes to yield spirofused ketones employing the Oppolzer camphorsultam[18] as a chiral auxiliary (Scheme 2). Additionally, using a commercially available Evans oxazolidinone[19] chiral auxiliary, the alkoxycyclization of 1,6-enynes was applied to a wide range of substrates with excellent stereoselectivities. Apart from alcohols as *O*-nucleophiles, electron-rich indoles could also be used as *C*-nucleophiles.[20] Finally, upon the cleavage of the chiral auxiliary it was possible to isolate a new class of highly enantioenriched β-tetralone derivatives, which are valuable frameworks in organic synthesis[21] and pharmacologically relevant intermediates such as antidepressants[22] or benzomorphan analgesics.[23]



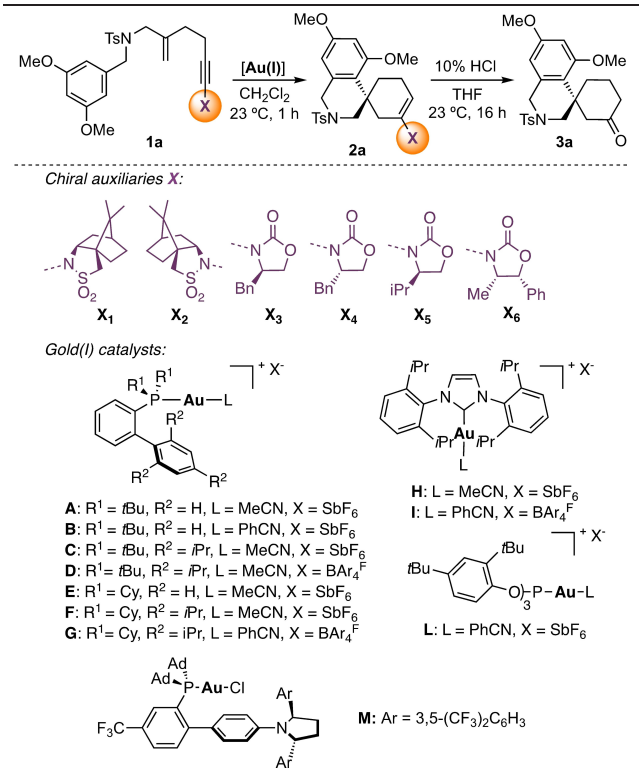
Scheme 2. Chiral auxiliary-based approach for stereoselective cyclizations.

Results and Discussion

1,5-Enyne Cascade Cyclization

We commenced our studies with 1,5-enynamide **1a** bearing Oppolzer's sultam $\mathbf{X_1}$ as the chiral auxiliary (Table 1). We

Table 1: Stereoselective gold(I)-catalyzed synthesis of spirocyclic ketone **3a** from 1,5-enyne **1a** using chiral auxiliaries.[a]



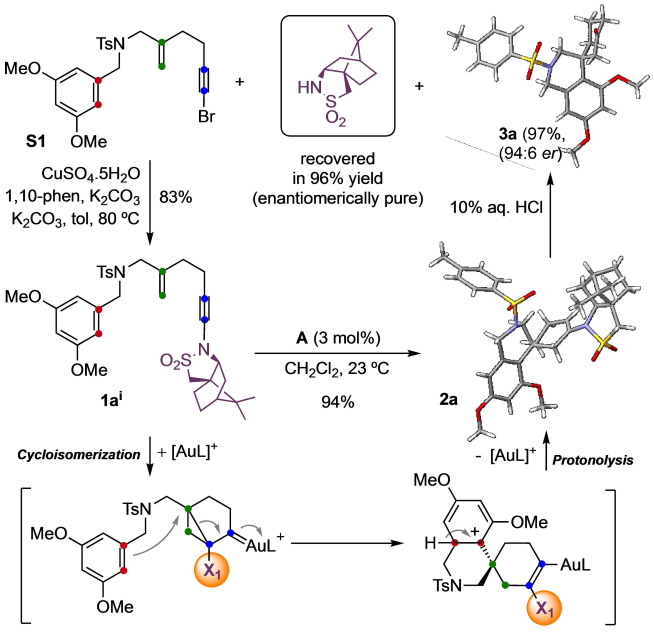
Entry	X	[Au(I)]	Yield **2a** [%][b]	Yield **3a** [%][d]	er **3a** [e]
1	$\mathbf{X_1}$	**A** (5 mol%)	91	98	93:7
2	$\mathbf{X_1}$	**B** (5 mol%)	88	96	93:7
3	$\mathbf{X_1}$	**C** (5 mol%)	81	95	90:10
4	$\mathbf{X_1}$	**D** (5 mol%)	82	88	92:8
5	$\mathbf{X_1}$	**E** (5 mol%)	29	98	88:12
6	$\mathbf{X_1}$	**F** (5 mol%)	81	91	89:11
7	$\mathbf{X_1}$	**H** (5 mol%)	85	93	93:7
8	$\mathbf{X_1}$	**I** (5 mol%)	73	93	93:7
9	$\mathbf{X_1}$	**L** (5 mol%)	19	89	77:23
10	$\mathbf{X_1}$	**A** (3 mol%)	**95(94)**[c]	**96**	**94:6**
11[f]	$\mathbf{X_1}$	**A** (3 mol%)	65	72	96:4
12	$\mathbf{X_2}$	**A** (3 mol%)	91	88	6:94
13	$\mathbf{X_3}$	**A** (3 mol%)	86	92	12:88
14	$\mathbf{X_6}$	**A** (3 mol%)	88	89	89:11
15	$\mathbf{X_7}$	**A** (3 mol%)	93	91	51:49
16[g]	$\mathbf{X_7}$	**M** (3 mol%)	85	64	51:49

[a] Reactions were carried out with **1a** (0.1 mmol) and **A**–**L** in CH_2Cl_2 (2 mL) at 23 °C for 1 h. The solvent was evaporated and the crude product was treated with 10% aq. HCl (1.5 mL) in THF (3 mL) at 23 °C for 16 h. [b] NMR yield using durene or 1,1,2,2-tetrachloroethane as internal standard. [c] In parenthesis, isolated yield. [d] Overall isolated yield for the two-step sequence starting from **1a**. [e] Chiral HPLC (ChiralPak® IA Column, 1.0 mL/min, 90:10 Hex/*i*PrOH). [f] Reaction at −20 °C for 24 h. [g] $AgSbF_6$ (3 mol%) was used to activate **M**.

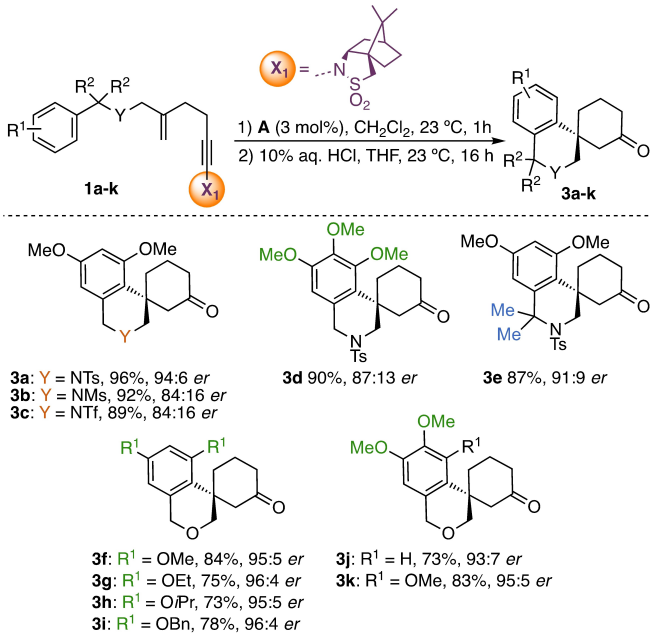
reasoned that a two-step sequence including gold(I)-catalyzed cyclization followed by acid-catalyzed hydrolysis would give access to enantioenriched chiral spirocyclic ketones **3a**. Cationic gold(I) complexes **A-L** presenting JohnPhos, XPhos, NHC, and phosphite type ligands, afforded spirocyclic ketone **3a** in good yield and enantiomeric ratios, whereby catalyst **A** performed best (98%, 93:7 *er*) (Table 1, entries 1 and 2–9). Lowering the catalyst loading to 3 mol% gave **3a** in 96% yield and slightly improved 94:6 *er* (Table 1, entry 10). Lowering the temperature to −20 °C for 24 h improved the *er* to 96:4 but resulted in a lower yield (Table 1, entry 11). The opposite enantiomer of **3a** was efficiently obtained (88%, 6:94 *er*) using the enantiomeric camphorsultam $\mathbf{X_2}$ (Table 1, entry 12). Other chiral auxiliaries such as Evans-type oxazolidinones $\mathbf{X_3}$ and $\mathbf{X_6}$ gave **3a** with lower enantioselectivity (Table 1, entries 13 and 14). As a control, achiral *N*-methyl methanesulfonamide $\mathbf{X_7}$ yielded racemic **3a** 91% yield (Table 1, entry 15).[24] The achiral substrate presenting $\mathbf{X_7}$ was also subjected to chiral catalyst **M**, which was previously optimized in our group for 1,6-enyne cyclizations,[5a] to compare the enantioselective approach with the chiral auxiliary one: in this case, essentially racemic **3a** was obtained in 64% yield (Table 1, entry 16). The absolute configurations of **2a** and **3a** were confirmed as *S* by single crystal X-ray diffraction (Scheme 3).[25] Satisfactorily, after the hydrolysis, the Oppolzer's sultam ($\mathbf{X_1}$) was recovered enantiomerically pure in an excellent 96% yield. This sequence presumably proceeds by the initial formation of a gold(I)-keteniminium intermediate,[26] which triggers a cascade process to form the polycyclic compound (Scheme 3). After the alkyne activation, a *6-endo-dig* cyclization with the terminal alkene occurs to furnish a distorted cyclopropyl gold(I)-carbene / gold(I)-stabilized carbocation.

Subsequent intramolecular attack of the aryl ring, followed by a rearomatization step, provides an alkenyl-gold(I) species. A second bond is here constructed giving place to the stereocenter under control of the chiral auxiliary present at the substrate. Finally, protodeauration affords **2a**.

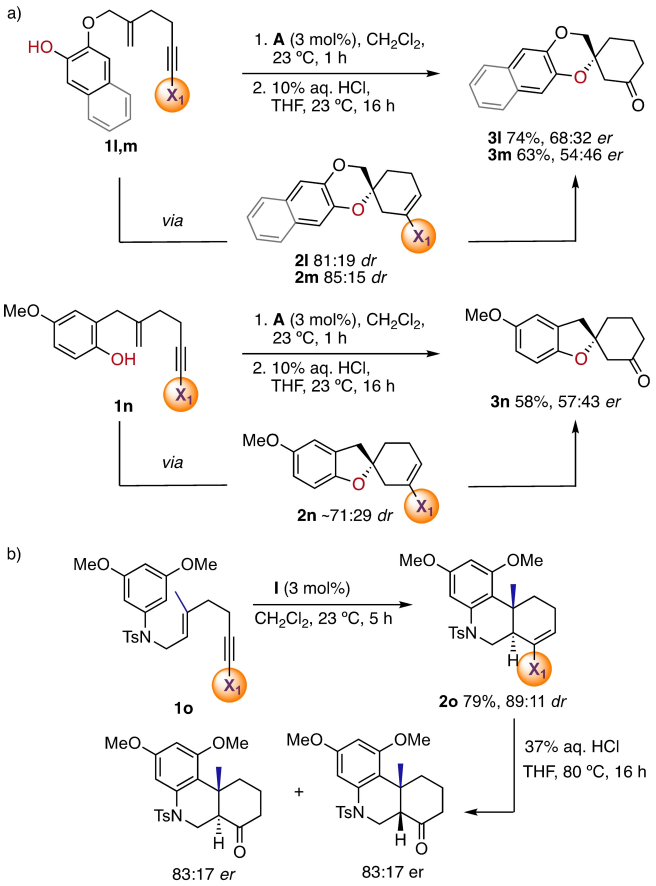
The reaction scope was investigated with the optimized reaction conditions (Scheme 4). Ketones **3b** and **3c** with other electron withdrawing substituents at the *N*-tether were obtained in good yields but with slightly lower enantiomeric ratios (89–92%, 84:16 *er*). Enynamides **1d** with 3,4,5-trimethoxybenzene and **1e** with benzylic *gem*-dimethyl substituents gave ketones **3d** and **3e** in good yields and enantiomeric ratios (87–90%, 87:13 to 91:9 *er*). We also examined the formation of the analogous oxo-spiro cyclic ketones. Different OR groups at positions 3 and 5 on the aromatic moiety provided ketones **3f–i** in good yields and excellent enantioselectivities (73–84%, 95:5 to 96:4 *er*). The reaction also proceeded smoothly with 3,4-dimethoxybenzene- and 3,4,5-trimethoxybenzene-containing 1,5-enynamides **1j** and **1k** giving ketones **3j** and **3k** in 73 and 83% yield and 93:7 and 95:5 *er*, respectively. Our protocol was also tested with substituted phenols (Scheme 5a). In this case, the hydroxy group acts as nucleophile in the attack to the intermediate cyclopropyl gold(I)-carbene species giving place to the formation of a new C–O bond.[11] Reasonable yields were obtained for the formation of heterocyclic structures **3l–m** and **3n** but the enantioselectivities were low (68:32 for **3l**, 54:46 for **3m**, and 57:43 for **3n**). The



Scheme 3. Introduction/recovery of the chiral auxiliary starting from bromoenyne **S1** and determination of absolute configuration for **2a** and **3a** by X-ray diffraction. Reaction pathway of stereoselective gold(I)-catalyzed cyclization of 1,5-enynes using Oppolzer's sultam as chiral auxiliary.



Scheme 4. Synthesis of spirocyclic ketones **3a–k**. Reactions were carried out with **1a–k** and **A** (3 mol%) in CH_2Cl_2 at 23 °C for 1 h. After solvent evaporation, the mixture was treated with 10% aq. HCl in THF at 23 °C for 16 h Isolated yields for the two-step sequence starting from **1a–k** and the *er* were measured by chiral HPLC (see SI).



Scheme 5. Cyclization of 1,5-enynes with a) substituted phenols and b) internal alkenes. The *dr* were calculated by ^{1}H NMR integration for **2l–n**, and by HPLC for **2o**.

intermediate enamine intermediates with the Oppolzer auxiliary showed higher *dr* values (81:19 for **2l**, 85:15 for **2m**, and 71:29 for **2n**), which indicates that partial racemization happens during the hydrolysis step.[24] We considered the application of the same conditions to the structurally different substrate **1o** which would give place to the formation of two new stereogenic carbons (Scheme 5b).

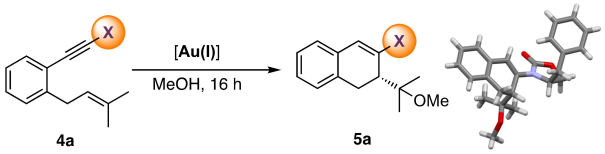
In this case, an additional optimization for the gold(I)-catalyzed reaction was required,[24] finding that the more electron rich gold(I)-carbene **I** (3 mol%) provided the polycyclic enamine **2o** in 79% yield after 5 h at 23 °C. Previous hydrolysis conditions showed no conversion, whereas the desired ketone **3o** could be obtained by application of a stronger acidic medium (37% aq. HCl, 80 °C). However, such conditions involved isomerization of the enamine **2o** with subsequent epimerization of one of the stereogenic centers formed during the polycyclization, which yielded a 1.9:1 ratio of diastereomers, each presenting a 83:17 *er*.

1,6-Enyne Alkoxycyclization

Given the promising results furnished by the Oppolzer's sultam $\mathbf{X_1}$ as a chiral auxiliary, we initially studied the alkoxycyclization of 1,6-enynamide **4a** bearing $\mathbf{X_1}$. The gold(I)-catalyzed cyclization in the presence of MeOH at 23 °C using catalyst **A** afforded the *6-endo-dig* product **5a** in 38% yield and 83:27 *dr* (Table 2, entry 1). No traces of the *5-exo-dig* adduct were detected. Before proceeding with the optimization of the reaction conditions, different attempts to hydrolyze the enamine under acidic conditions to obtain the resulting enantioenriched ketone were performed, with no success.[24] Evans-type auxiliaries were therefore taken in consideration (Table 2, entries 2–4).

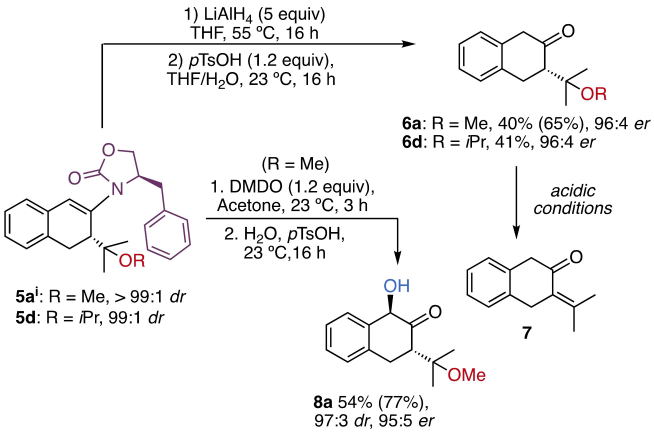
The protocol for their removal involved $LiAlH_4$ reduction,[27] followed by hydrolysis catalyzed by *p*TsOH (Scheme 6). Even though oxazolidinone $\mathbf{X_5}$ performed better in terms of stereoselectivity (96:4 *dr*, Table 2, entry 2) compared to $\mathbf{X_3}$ in the cyclization in step at 23 °C, the latter gave a better overall yield in the two-step one-pot reduction hydrolysis,[24] so it was chosen as auxiliary to move forward with the optimisation. Among the 10 screened gold(I) catalysts, **A** was again the best (Table 2, entries 4–13), affording **5a**$^{\mathbf{i}}$ in 97% yield and 93:7 *dr* (Table 2, entry 4). The configuration of the new stereocenter of **5a**$^{\mathbf{i}}$ was determined as *R* by X-ray diffraction (Table 2).[25] Increasing the amount of nucleophile had a positive effect on the *dr* (Table 2, compare entries 14 and 15). Finally, the temperature was lowered down to −20 °C, where full conversion and 99:1 *dr* was observed after 16 h (Table 2, entry 16). The

Table 2: Optimization study for the stereoselective gold(I)-catalyzed alkoxycyclization of 1,6-enyne **4a** with chiral auxiliaries.[a] Determination of absolute configuration for **5a**$^{\mathbf{i}}$ by X-ray diffraction.



Entry	X	[Au(I)]	n MeOH	Yield **5a** [%][b]	dr **5a**[c]
1	$\mathbf{X_1}$	**A** (5 mol%)	1:1 in DCE	38	83:27
2	$\mathbf{X_5}$	**A** (5 mol%)	1:1 with DCE	97	96:4
3	$\mathbf{X_6}$	**A** (5 mol%)	1:1 with DCE	99	88:22
4	$\mathbf{X_3}$	**A** (5 mol%)	1:1 with DCE	97	93:7
5	$\mathbf{X_3}$	**B** (5 mol%)	1:1 with DCE	96	93:7
6	$\mathbf{X_3}$	**C** (5 mol%)	1:1 with DCE	94	92:8
7	$\mathbf{X_3}$	**D** (5 mol%)	1:1 with DCE	97	91:9
8	$\mathbf{X_3}$	**E** (5 mol%)	1:1 with DCE	95	87:23
9	$\mathbf{X_3}$	**F** (5 mol%)	1:1 with DCE	92	92:8
10	$\mathbf{X_3}$	**G** (5 mol%)	1:1 with DCE	96	92:8
11	$\mathbf{X_3}$	**H** (5 mol%)	1:1 with DCE	99	90:10
12	$\mathbf{X_3}$	**I** (5 mol%)	1:1 with DCE	90	89:11
13	$\mathbf{X_3}$	**L** (5 mol%)	1:1 with DCE	88	91:9
14	$\mathbf{X_3}$	**A** (5 mol%)	10 equiv. in DCE	97	92:8
15	$\mathbf{X_3}$	**A** (5 mol%)	MeOH	99	94:6
16[d]	$\mathbf{X_3}$	**A** (5 mol%)	MeOH	99	>99:1
17[d]	$\mathbf{X_3}$	**A (3 mol%)**	**MeOH**	**99**	**99:1**
18	$\mathbf{X_4}$	**A** (3 mol%)	MeOH	99	1:99
19[e]	$\mathbf{X_8}$	**M** (3 mol%)	1:1 with CH_2Cl_2	88%	91:9 (*er*)

[a] All the reactions were performed at 0.1 M concentration and at 23 °C, unless otherwise stated. DCE = 1,2-dichloroethane. [b] NMR yield using trichloroethylene as internal standard. [c] *dr* measured at ^{1}H NMR and confirmed by LC–MS analysis. [d] Reactions performed at −20 °C. [e] $AgSbF_6$ (3 mol%) was used to activate **M**.



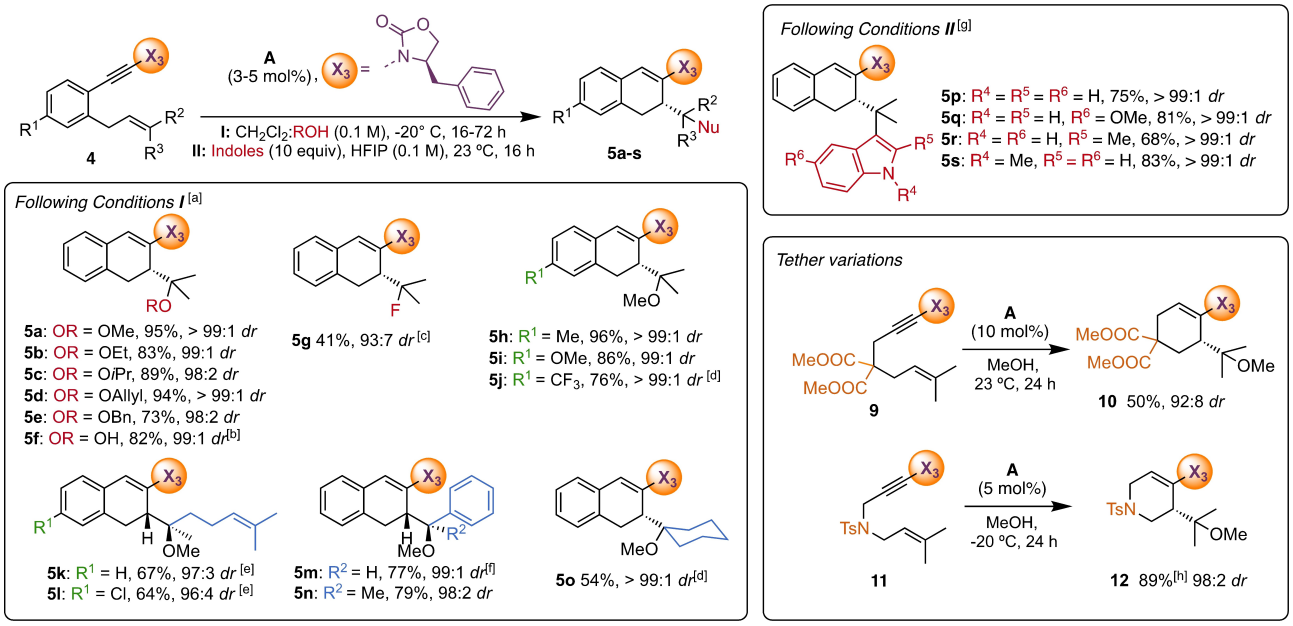
Scheme 6. Chiral auxiliary removal to generate enantioenriched β-tetralones and decomposition pathway in acidic conditions. In parenthesis are reported the NMR yields using trichloroethylene as internal standard.

catalyst loading could be lowered to 3 % with no loss in yield or *dr* (Table 2, entry 17). Using the optimised conditions, the reaction with the (*S*)-benzoxazolidinone auxiliary afforded the enantiomer of **5a**^{i} in 99 % and 1:99 *dr* (Table 2, entry 18). As in the case of 1,5-enynes, the reaction involving the achiral 2-oxazolidinone $\mathbf{X_8}$ was performed using chiral catalyst **M** to give product **5a**^{v} in 88 % yield and 91:9 *er*.[24]

As anticipated above, the auxiliary of **5a** and **5d** was cleaved to give **6a** and **6d**, respectively, by a carbamate reduction/hydrolysis sequence, which proceeded with very small racemization (from 99:1 *dr* to 96:4 *er*) (Scheme 6). Even though the NMR yield for **6a** was 65 % over two steps, part of the final product was lost in the purification step due to its instability in silica or alumina, resulting in 40 % isolated yield.[24] We have found that this class of 3-subsituted-2-tetralones, never synthesized before, is particularly sensitive to acidic conditions due to the loss of the alcohol functionality leading to the formation of the stable achiral product **7**. Epoxidation of **5a**^{i} with DMDO (dimethyl dioxirane),[28] followed by hydrolysis led to 1-hydroxy-2-tetralone **8a** in in 54 % yield and 95:5 *er*, whose configuration at C2 was assigned as *R* by NOESY[24] (Scheme 6).

The generality of the diastereoselective 6-*endo-dig* cyclization of 1,6-enynamides was explored in the presence of diverse alcohols and indoles as nucleophiles (Scheme 7). Substrate **4a**^{i} gave **5a–e** in good to excellent yields and diastereoselectivities. Water also acted as a nucleophile affording **5f** in 82 % yield and 99:1 *dr*. When using HF-pyridine as a source of F^-, product **5g** was obtained with 41 % yield with 93:7 *dr*.

Electron withdrawing and electron-donating substituents at the aryl led to the corresponding adducts **5h–j** without loss in diastereoselectivity. The alkene chain could also be changed to provide **5k–o** in satisfactory yields and high *dr*. When we tried addition indoles as carbon nucleophiles[20,29] with 1,6-enynamides **4** under the same conditions for the



Scheme 7. Nucleophilic addition of alcohols and indoles by 6-*endo-dig* cyclization of *N*-substituted 1,6-enynes. Yields of isolated products and the *dr* determined by both ^{1}H NMR integration and LC–MS analysis after column chromatography. The specific reaction times are reported in the SI. [a] Unless stated differently, 5 mol % of **A** was used and CH_2Cl_2:ROH = 1:3. [b] The reaction was conducted at 23 °C. [c] HF-pyridine (3 equiv) was used in this case as a F^- source.[22] [d] Reactions performed with 10 mol % of **A**. [e] The reported yields and *dr* are referred to two of the four possible diastereomers which formed during the reaction. [f] Three of the four possible diastereomers were isolated in 11:3:1 ratio and the reported yield refers to the major one, together with its *dr* with respect to the fourth diastereomer which was not isolated. [g] 3 mol % of **A** was used. [h] Yield was determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as internal standard.

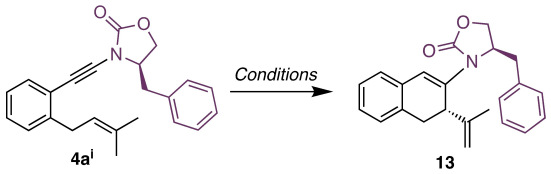
addition of alcohols (**Conditions I**), only the starting materials were recovered, even when increasing temperature, nucleophile equivalents, or catalyst loading. We envisioned that in absence of the alcohol, the reaction would not occur, since it is well known in fact, that proton sources facilitate the protodeauration step in gold(I) catalysis.[30] Therefore, after screening of different acidic species,[24] **4a** could be cyclized in the presence of electron rich indoles using hexafluoroisopropanol (HFIP) as a solvent (**Conditions II**) to afford **5p–s** in good yields and excellent diastereoselectivities. This solvent might not only kinetically favor the reaction by stabilizing the cationic species involved,[31] but it also serves as a proton shuttle for the protodeauration step, as elaborated more in detail below. Product **5p** could finally also be isolated in 70% yield using JohnphosAuCl as a catalyst,[24] confirming that HFIP can additionally activate gold(I)-chloride precursors, as recently reported by Nolan and Vougioukalakis.[32] Different tethers were then tested, and while the malonate substrate **9** afforded **10** only in moderate yield and 92:8 *dr* using 10 mol% of gold(I) catalyst at 23°C (very slow conversion was observed at −20°C), the *N*-tosyl tethered enynamide **11** afforded **12** under the optimized conditions in good NMR yield and 98:2 *dr*.

To gain deeper insight on the reaction mechanism, control experiments were performed (Table 3) and the origin of the stereoselectivity was modelled by means of DFT calculations (Scheme 8). Full recovery of the starting material was observed in the absence of nucleophile (Table 3, entry 1).

To rationalize why the substrate does not afford **13** in the absence of nucleophile, the reaction was run again in the presence of a stoichiometric amount of anhydrous PPTS (pyridinium *p*-toluenesulfonate) to verify whether under the standard conditions the alcohol was serving as a proton shuttle for the protodeauration step[33] (Table 3, entry 2). Under these conditions, conversion of **4a^{i}** into the cyclization-elimination product **13** (91:9 *dr*) was observed, and when lowering the amount of PPTS to 5 mol%, the same result was obtained (Table 3, entry 3).

To discard the possibility that the process could be proton-catalyzed, the reaction was performed in the sole presence of a stoichiometric amount of PPTS, but starting material was recovered (Table 3, entry 4). The reaction was also run in the presence of NaOTs, to verify whether the tosylate anion, which might be responsible for the deprotonation of one of the two terminal methyls, would itself serve as a shuttle for the protodeauration. When running the reaction under anhydrous conditions (Table 3, entry 6) no product was observed. Therefore, the presence of the pyridinium as a Brønsted acid still seems to be fundamental to operate the protodeauration step. These results indicate that the transformation is gold(I)-catalyzed, but the presence of a proton shuttle is necessary to facilitate the protodemetalation leading to the *6-endo-dig* product. The reaction was also run in the presence of the Lewis acid $CeCl_3$ to discard the possibility of competition, in the gold coordination step, between the alkyne and the carbonyl group of the carbamate (Table 3, entry 7). Again, no reactivity was observed (Table 3, entry 7). Our original hypothesis that the catalyst turnover determining step is the protodeauration, as observed previously in some cases for gold catalysis,[29b,34] was therefore confirmed.

Table 3: Control experiments in the cyclization of **4a^{i}** to form **13**.[a]

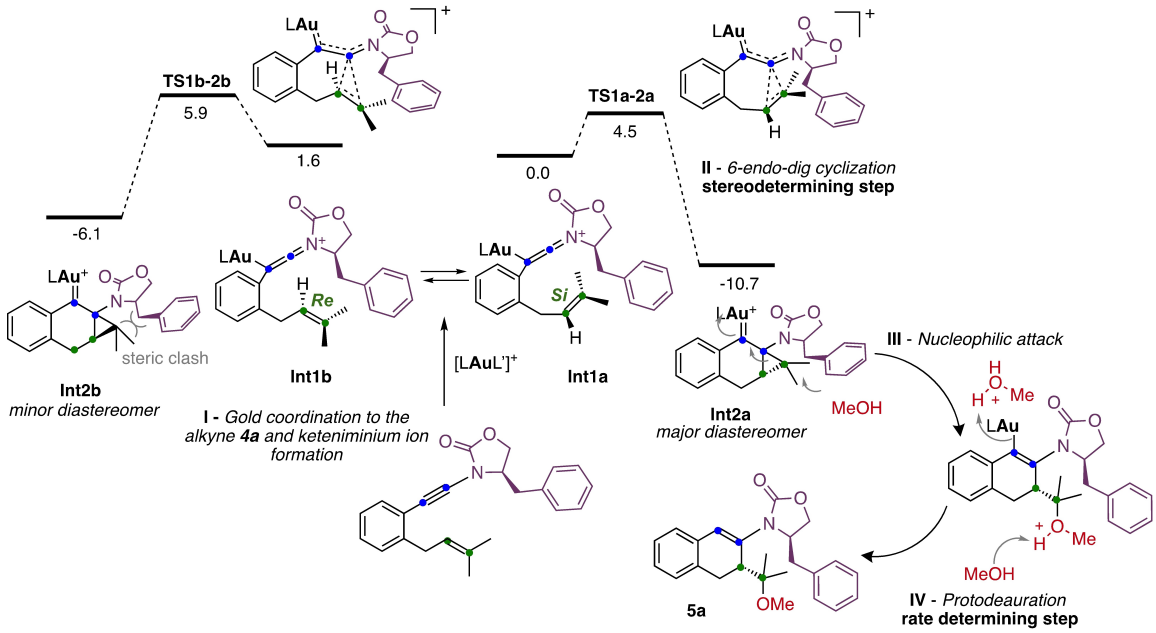


Entry	[Au(I)]	Additive	Product
1	**A** (5 mol%)	/	/
2	**A** (5 mol%)	PPTS (1 equiv)	**13** (65%)[b]
3	**A** (5 mol%)	PPTS (5 mol%)	**13** (62%)[b]
4	/	PPTS (1 equiv)	/
5	**A** (5 mol%)	NaOTs (1 equiv), 15-crown-5 (1 equiv)[c]	**13** (42%)[d] + **5f** (21%)[d]
6	**A** (5 mol%)	NaOTs (1 equiv), 15-crown-5 (1 equiv)[c], molecular sieves (4 Å)	/
7	**A** (5 mol%)	$CeCl_3$ (5 mol%)	/

[a] Reactions were performed in the at 23°C during 24 h using dry CH_2Cl_2 (0.1 M). [b] Isolated yields. [c] The crown ether was used to dissolve NaOTs in CH_2Cl_2. Since the first trial performed with wet 15-crown-5 afforded the elimination product **13** together with the hydroxycyclization one (**5f**), we repeated the experiment in the presence of molecular sieves to operate in the total absence of water that would serve itself as a proton shuttle. [d] NMR yield using 1,1,2,2-tetrachloroethane as internal standard.

Conclusion

We have developed the stereoselective gold(I)-catalyzed cascade cyclization of 1,5-enynes to afford spirocyclic ketones using the Oppolzer's sultam as chiral auxiliary. This strategy allows for the simultaneous formation of two C–C bonds and a chiral spiro center in very good yields and enantioselectivities. The use of a commercially available gold(I) catalyst and the recovery of the chiral auxiliary make this process efficient and straightforward. Furthermore, the highly diastereoselective gold(I)-catalyzed alkoxycyclization of 1,6-enynes was achieved using in this case Evans-type oxazolidinones. Through this transformation, access to a new class of enantiomerically enriched *β*-tetralones was obtained and full understanding of the chiral auxiliaries mode of action under gold(I)-catalysis was achieved. The methodology brought on in the context of this work represents a valid alternative to the usually more expensive



Scheme 8. Proposed mechanism of the stereoselective gold(I)-catalyzed alkoxycyclization of 1,6-enynes using an Evans-type oxazolidinone as chiral auxiliary. For the stereodetermining step, DFT calculations were performed with B3LYP/6-31G(d) (C, H, P, O), LANL2DZ (Br) and SDD (Au) in CH_2Cl_2 (PCM). Free energies in Kcal/mol. L = JohnPhos.

and time-consuming enantioselective approach based on ligand optimization.

Supporting Information

The authors have cited additional references within the Supporting Information.[35–62]

Acknowledgements

We thank the MCIN/AEI/10.13039/501100011033 (PID2022-136623NB-I00, and CEX2019-000925-S), the European Research Council (Advanced Grant 835080), the AGAUR (2021 SGR 01256), and CERCA Program/Generalitat de Catalunya for financial support. We thank Zhouting Rong for his results on enantioselective polyenyne cyclizations, which were the basis to develop the current work. We also thank ICIQ X-ray diffraction, NMR, and mass spectrometry units.

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: Alkoxycyclization · Chiral Auxiliaries · Enynes · Gold Catalysis · Spirocyclic Ketones

[1] a) A. Fürstner, *Chem. Soc. Rev.* **2009**, *38*, 3208–3221; b) N. D. Shapiro, F. D. Toste, *Synlett* **2010**, 675–691; c) C. Obradors, A. M. Echavarren, *Acc. Chem. Res.* **2014**, *47*, 902–912; d) L. Fensterbank, M. Malacria, *Acc. Chem. Res.* **2014**, *47*, 953–965; e) R. Dorel, A. M. Echavarren, *Chem. Rev.* **2015**, *115*, 9028–9072; f) D. Pflästerer, A. S. K. Hashmi, *Chem. Soc. Rev.* **2016**, *45*, 1331–1367; g) A. S. K. Hashmi, *Chem. Rev.* **2021**, *121*, 8309–8310; h) D. Campeau, D. F. L. Rayo, A. Mansour, K. Muratov, F. Gagosz, *Chem. Rev.* **2021**, *121*, 8756–8867.

[2] a) L. Zhang, S. A. Kozmin, *J. Am. Chem. Soc.* **2005**, *127*, 6962–6963; b) K. Tsuchikama, Y. Kuwata, T. Shibata, *J. Am. Chem. Soc.* **2006**, *128*, 13686–13687; c) S. G. Sethofer, S. T. Staben, O. Y. Hung, F. D. Toste, *Org. Lett.* **2008**, *10*, 4315–4318; d) G. Lemière, V. Gandon, K. Cariou, A. Hours, T. Fukuyama, A. L. Dhimane, L. Fensterbank, M. Malacria, *J. Am. Chem. Soc.* **2009**, *131*, 2993–3006; e) Y. Horino, T. Yamamoto, K. Ueda, S. Kuroda, F. D. Toste, *J. Am. Chem. Soc.* **2009**, *131*, 2809–2811; f) D. Qian, J. Zhang, *Chem. Eur. J.* **2013**, *19*, 6984–6988; g) J. F. Briones, H. M. L. Davies, *J. Am. Chem. Soc.* **2013**, *135*, 13314–13317.

[3] a) R. A. Widenhoefer, *Chem. Eur. J.* **2008**, *14*, 5382–5391; b) S. Sengupta, X. Shi, *ChemCatChem* **2010**, *2*, 609–619; c) A. Pradal, P. Y. Toullec, V. Michelet, *Synthesis* **2011**, *10*, 1501–1514; d) N. T. Patil, *Chem. Asian J.* **2012**, *7*, 2186–2194; e) Y. M. Wang, A. D. Lackner, F. D. Toste, *Acc. Chem. Res.* **2014**, *47*, 889–901; f) W. Zi, F. D. Toste, *Chem. Soc. Rev.* **2016**, *45*, 4567–4589; g) Y. Li, W. Li, J. Zhang, *Chem. Eur. J.* **2017**, *23*, 467–512; h) J. J. Jiang, M. K. Wong, *Chem. Asian J.* **2021**, *16*, 364–377; i) G. Zuccarello, I. Escofet, U. Caniparoli, A. M. Echavarren, *ChemPlusChem* **2021**, *86*, 1283–1296; j) A. Das, N. T. Patil, *Chem. Eur. J.* **2022**, *28*, e202104371; k) C. C. Chintawar, N. T. Patil, *Gold Bull.* **2022**, *55*, 161–168; l) S.

Mishra, Urvashi, N. T. Patil, *Isr. J. Chem.* **2022**, *62*, e202200039.
[4] M. P. Muñoz, J. Adrio, J. C. Carretero, A. M. Echavarren, *Organometallics* **2005**, *24*, 1293–1300.
[5] a) G. Zuccarello, J. G. Mayans, I. Escofet, D. Scharnagel, M. S. Kirilova, A. H. Pérez-Jimeno, P. Calleja, J. R. Boothe, A. M. Echavarren, *J. Am. Chem. Soc.* **2019**, *141*, 11858–11863; b) I. Martín-Torres, G. Ogalla, Y.-M. Yang, A. Rinaldi, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2021**, *60*, 9339–9344; *Angew. Chem.* **2021**, *133*, 9425–9430; c) A. Franchino, À. Martí, A. M. Echavarren, *J. Am. Chem. Soc.* **2022**, *144*, 3497–3509.
[6] D. C. de Rezende, M. Alves Nogueira Diaz, *Chirality* **2019**, *31*, 776–812.
[7] H. Faustino, F. López, L. Castedo, J. L. Mascareñas, *Chem. Sci.* **2011**, *2*, 633–637.
[8] T. Yuan, K. Radefeld, C. Shan, C. Wegner, E. Nichols, X. Ye, Q. Tang, L. Wojtas, X. Shi, *Angew. Chem. Int. Ed.* **2023**, *62*, e202305810.
[9] a) H. Li, J. E. Antoline, J. H. Yang, Z. F. Al-Rashid, R. P. Hsung, *New J. Chem.* **2010**, *34*, 1309–1316; b) L. Li, X.-Q. Zhu, Y.-Q. Zhang, H.-Z. Bu, P. Yuan, J. Chen, J. Su, X. Deng, L.-W. Ye, *Chem. Sci.* **2019**, *10*, 3123–3129; c) C. C. Lynch, A. Sripada, C. Wolf, *Chem. Soc. Rev.* **2020**, *49*, 8543–8583.
[10] a) X. Wang, H. Yeom, L. Fang, S. He, Z. Ma, B. Kedrowski, R. P. Hsung, *Acc. Chem. Res.* **2014**, *47*, 560–578.
[11] Z. Rong, A. M. Echavarren, *Org. Biomol. Chem.* **2017**, *15*, 2163–2167.
[12] L. K. Smith, I. R. Baxendale, *Org. Biomol. Chem.* **2015**, *13*, 9907–9933.
[13] V. A. D'Yakonov, O. A. Trapeznikova, A. de Meijere, U. M. Dzhemilev, *Chem. Rev.* **2014**, *114*, 5775–5814.
[14] K. Ding, Z. Han, Z. Wang, *Chem. Asian J.* **2009**, *4*, 32–41.
[15] Y. Zheng, C. M. Tice, S. B. Singh, *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3673–3682.
[16] a) N. D. Shapiro, F. D. Toste, *Synlett* **2010**, 675–691; b) D. P. Day, P. W. H. Chan, *Adv. Synth. Catal.* **2016**, *358*, 1368–1384.
[17] a) H. Zheng, R. J. Felix, M. R. Gagné, *Org. Lett.* **2014**, *16*, 2272–2275; b) Z. Wu, P. Retailleau, V. Gandon, A. Voituriez, A. Marinetti, *Eur. J. Org. Chem.* **2016**, 70–75; c) X. Han, P. Retailleau, V. Gandon, A. Voituriez, *Chem. Commun.* **2020**, *56*, 9457–9460.
[18] M. M. Heravi, V. Zadsirjan, *Tetrahedron: Asymmetry* **2014**, *25*, 1061–1090.
[19] M. M. Heravi, V. Zadsirjan, B. Farajpour, *RSC Adv.* **2016**, *6*, 30498–30551.
[20] C. H. M. Amijs, V. López-Carrillo, M. Raducan, P. Pérez-Galán, C. Ferrer, A. M. Echavarren, *J. Org. Chem.* **2008**, *73*, 7721–7730.
[21] V. F. Shner, N. M. Przhiyaglovskaya, *Russ. Chem. Rev.* **1966**, *35*, 523–531.
[22] M. P. Wentland, D. M. Bailey, E. J. Alexander, M. J. Castaldi, R. A. Ferrari, D. R. Haubrich, D. A. Luttinger, M. H. Perrone, *J. Med. Chem.* **1987**, *30*, 1482–1489.
[23] a) J. A. Barltrop, *J. Chem. Soc.* **1947**, 399–401; b) J. A. Barltrop, *J. Chem. Soc.* **1952**, 1038–1041.
[24] See Supporting Information for additional details.
[25] CCDC Deposition numbers **2a**: 2271455, **3a**: 2271454, **5a**^{i}: 2271456. The deposition numbers contain 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 www.ccdc.cam.ac.uk/structures.
[26] a) G. Evano, M. Lecomte, P. Thilmany, C. Theunissen, *Synthesis* **2017**, *49*, 3183–3214; b) Y. Chen, P. Qian, L Ye, *Chem. Soc. Rev.* **2020**, *49*, 8897–8909.
[27] H.-H. Huo, H.-K. Zhang, X.-E. Xia, P.-Q. Huang, *Org. Lett.* **2012**, *14*, 4834–4837.
[28] W. Adam, E.-M. Peters, K. Peters, H. G. Von Schnering, V. Voerckel, *Chem. Ber.* **1992**, *125*, 1263–1266.
[29] a) P. Y. Toullec, E. Genin, L. Leseurre, J.-P. Genêt, V. Michelet, *Angew. Chem. Int. Ed.* **2006**, *45*, 7427–7430; b) H. M. Amijs, C. Ferrer, A. M. Echavarren, *Chem. Commun.* **2007**, 698–700.
[30] The effect of acids on protodeauration has been demonstrated by the isolation and protonation of the vinylgold intermediate: a) L–P. Liu, B. Xu, M. S. Mashuta, G. B. Hammond, *J. Am. Chem. Soc.* **2008** *130*, 17642–17643; see also: b) Y. Zhu, B. Yu, *Angew. Chem. Int. Ed.* **2011**, *50*, 8329–8332; c) Z. Lu, T. Li, S. R. Mudshinge, B. Xu, G. B. Hammond, *Chem. Rev.* **2021**, *121*, 8452–8477.
[31] a) J.-P. Bégué, D. Bonnet-Delpon, B. Crousse, *Synlett* **2004**, *18–29*; b) V. Pozhydaiev, M. Power, V. Gandon, J. Moran, D. Lebœuf, *Chem. Commun.* **2020**, *56*, 11548–11564.
[32] a) N. V. Tzouras, A. Gobbo, N. B. Pozsoni, S. G. Chalkidis, S. Bhandary, K. Van Hecke, G. C. Vougioukalakis, S. P. Nolan, *Chem. Commun.* **2022**, *58*, 8516; b) N. V. Tzouras, L. P. Zorba, E. Kaplanai, N. Tsoureas, D. J. Nelson, S. P. Nolan, G. C. Vougioukalakis, *ACS Catal.* **2023**, *13*, 8845–8860.
[33] M. Navarro, M. G. Alférez, M. de Sousa, J. Miranda-Pizarro, J. Campos, *ACS Catal.* **2022**, *12*, 4227–4241.
[34] a) I. Stylianakis, O. Nieto Faza, C. Silva López, A. Kolocouris, *Org. Chem. Front.* **2020**, *7*, 997–1005; b) J. Gubler, M. Radić, Y. Stöferle, P. Chen, *Chem. Eur. J.* **2022**, *28*, e202200332.
[35] D. Fujino, H. Yorimitsu, A. Osaka, *J. Am. Chem. Soc.* **2014**, *136*, 6255–6258.
[36] S. O'Sullivan, E. Doni, T. Tuttle, J. A. Murphy, *Angew. Chem. Int. Ed.* **2014**, *53*, 474–478; *Angew. Chem.* **2014**,*126*, 484–488.
[37] R. Ma, M. C. White, *J. Am. Chem. Soc.* **2018**, *140*, 3202–3205.
[38] R. Plamont, L. V. Graux, H. Clavier, *Eur. J. Org. Chem.* **2018**, 1372–1376.
[39] C. Schneider, E. Broda, V. Snieckus, *Org. Lett.* **2011**, *13*, 3588–3591.
[40] C. Yu, X. Zhang, J. Zhang, *Tetrahedron* **2016**, *72*, 4337–4345.
[41] S. E. St. John, K. C. Jensen, S. Kang, Y. Chen, B. Calamini, A. D. Mesecar, M. A. Lipton, *Bioorg. Med. Chem.* **2013**, *21*, 6022–6037.
[42] X. Wan, X.-B. Wang, M.-H. Yang, J.-S. Wang, L.-Y. Kong, *Bioorg. Med. Chem.* **2011**, *19*, 5085–5092.
[43] A. S. Mitchell, R. A. Russell, *Tetrahedron* **1997**, *53*, 4387–4410.
[44] D. Mal, P. Pahari, B. K. Senapati, *Tetrahedron Lett.* **2005**, *46*, 2097–2100.
[45] a) M. C. Burla, R. Caliandro, B. Carrozzini, G. L. Cascarano, C. Cuocci, C. Giacovazzo, M. Mallamo, A. Mazzone, G. Polidori, *J. Appl. Crystallogr.* **2015**, *48*, 306–309; b) G. M. Sheldrick, *Acta Crystallogr. Sect. C* **2015**, *71*, 3–8.
[46] H. Hou, Y. Xu, H. Yang, X. Chen, C. Yan, Y. Shi, S. Zhu, *Org. Lett.* **2020**, *22*, 748–1753.
[47] T. Nishikawa, S. Shibuya, S. Hosokawa, M. Isobe, *Synlett* **1994**, 485–486.
[48] T. Nguyen, N. O. Thiel, F. Pape, J. F. Teichert, *Org. Lett.* **2016**, *18*, 2455–2458.
[49] S. E. Denmark, D. J. P. Kornflit, *J. Org. Chem.* **2017**, *82*, 3192–3222.
[50] D. R. White, E. M. Hinds, E. C. Bornowski, J. P. Wolfe, *Org. Lett.* **2019**, *21*, 3813–3816.
[51] Q. Chen, Z. Yang, *Tetrahedron Lett.* **1986**, *27*, 1171–1174.
[52] a) C. Nieto-Oberhuber, M. P. Muñoz, S. López, E. Jiménez-Núñez, C. Nevado, E. Herrero-Gómez, M. Raducan, A. M. Echavarren, *Chem. Eur. J.* **2006**, *12*, 1677–1693; b) E. Jiménez-Núñez, C. K. Claverie, C. Bour, D. J. Cárdenas, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2008**, *47*, 7892–7895, *Angew. Chem.* **2008**, *120*, 8010–8013.

[53] H. Xiong, R. P. Hsung, L. Shen, J. M. Hahn, *Tetrahedron Lett.* **2002**, *43*, 4449–4453.
[54] D. F. Taber, P. W. DeMatteo, R. A. Hassan, *Org. Synth.* **2013**, *90*, 350–357.
[55] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, *Gaussian 09, Revision B.1*, Gaussian, Inc., Wallingford CT **2009**.
[56] a) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648–5652; b) C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785; c) P. J. Stephens, F. J. Devlin, C. F. Chabalowsky, M. J. Frisch, *J. Phys. Chem.* **1994**, *98*, 11623–11627.
[57] a) C. Nieto-Oberhuber, P. Pérez-Galán, E. Herrero-Gómez, T. Lauterbach, C. Rodríguez, S. López, C. Bour, A. Rosellón, D. J. Cárdenas, A. M. Echavarren, *J. Am. Chem. Soc.* **2008**, *130*, 269–279:; b) C. García-Morales, X. Pei, J. M. Sarria Toro, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2019**, *58*, 3957–3961.
[58] D. Andrae, U. Haussermann, M. Dolg, H. Stoll, H. Preuss, *Theor. Chim. Acta* **1990**, *77*, 123–141.
[59] W. J. Hehre, R. Ditchfield, J. A. Pople, *J. Chem. Phys.* **1972**, *56*, 2257–2261.
[60] M. T. Cancès, B. B. Mennucci, J. Tomasi, *J. Chem. Phys.* **1997**, *107*, 3032–3041.
[61] A dataset collection of computational results is available in the ioChem-BD repository and can be accessed https://doi.org/10.19061/iochem-bd-1-281. M. Álvarez-Moreno, C. de Graaf, N. Lopez, F. Maseras, J. M. Poblet, C. Bo, *J. Chem. Inf. Model.* **2015**, *55*, 95–103.
[62] a) M. E. De Orbe, A. M. Echavarren, *Org. Synth.* **2016**, *93*, 115–126; b) V. López-Carrillo, A. M. Echavarren, *J. Am. Chem. Soc.* **2010**, *132*, 9292–9294; c) J. S. Johnson, E. Chong, K. N. Tu, S. A. Blum, *Organometallics* **2016**, *35*, 655–662; d) N. Huguet, D. Leboeuf, A. M. Echavarren, *Chem. Eur. J.* **2013**, *19*, 6581–6585.

Manuscript received: August 31, 2023
Accepted manuscript online: October 23, 2023
Version of record online: November 6, 2023