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Asymmetric Synthesis

Enantioselective Alkoxycyclization of 1,6-Enynes with Gold(I)-Cavitands: Total Synthesis of Mafaicheenamine C

*Inmaculada Martín-Torres, Gala Ogalla, Jin-Ming Yang, Antonia Rinaldi, and Antonio M. Echavarren**

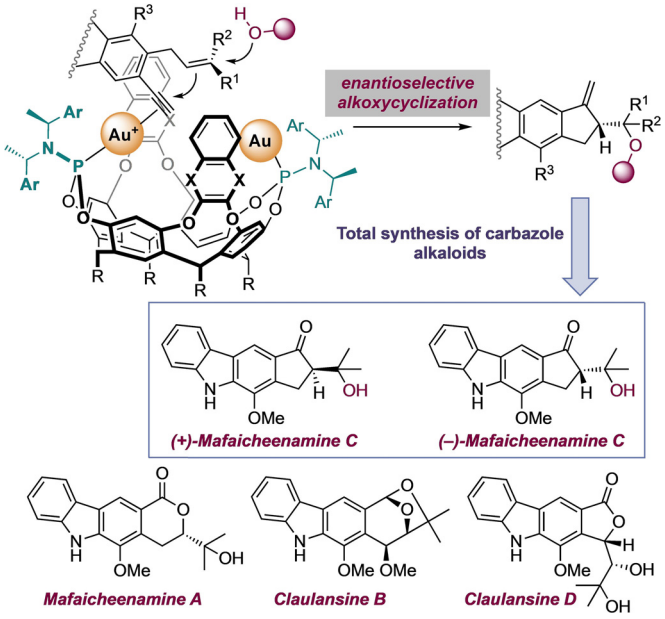
Abstract: *Chiral gold(I)-cavitand complexes have been developed for the enantioselective alkoxycyclization of 1,6-enynes. This enantioselective cyclization has been applied for the first total synthesis of carbazole alkaloid (+)-mafaicheenamine C and its enantiomer, establishing its configuration as R. The cavity effect was also evaluated in the cycloisomerization of dienynes. A combination of experiments and theoretical studies demonstrates that the cavity of the gold(I) complexes forces the enynes to adopt constrained conformations, which results in the high observed regio- and stereoselectivities.*

The design of supramolecular entities that mimic the activity of enzymes is an attractive approach for enhancing the selectivity of metal catalysts.[1] In this regard, gold(I) cavitands based on resorcin[4]arene skeletons have been applied for cross-dimerization[2] and hydration of alkynes,[3] cyclization of alkynyl carboxylic acids,[4] and intramolecular arene–alkyne reactions.[5] However, gold(I) cavitands have not yet been applied in the context of more challenging asymmetric transformations.[6]

Our group reported the use of non-C_2-symmetrical chiral digold(I)[7] and pyrrolidinyl–biphenyl phosphine gold(I) complexes[8] in enantioselective [2+2] and [4+2] cycloadditions and cycloisomerization reactions. Other approaches in asymmetric gold(I) catalysis are based on the use of monodentate chiral phosphoramidites,[9] chiral cationic phosphonites,[10] axially chiral monodentate phosphine ligands with a remote cooperative functionality,[11] catalysts with chiral sulfinamides,[12] helically chiral phosphine ligands,[13] cyclodextrin-NHC-gold(I) complexes,[14] chiral counteranions,[15] and chiral rotaxanes.[16]

From the outset, achieving satisfactory levels in the enantioselective gold(I)-catalyzed alkoxycyclization of 1,6-enynes proved to be difficult. Thus, using [Tol-BINAP-$(AuCl)_2$] as precatalyst we only achived good results with one substrate with a phenyl-substituted alkyne.[17] Since then, other groups achieved moderate enantioselectivities with chiral gold(I) catalysts,[18,19] the exception being the recent elegant work of Sollogoub, Fensterbank, and Mouriès-Mansuy using NHC-capped β-cyclodextrin gold(I) catalysts, which led to up to 94–98% *ee* in the hydroxy- and methoxycyclization of 1,6-enynes.[14d,e] However, being based on cyclodextrins, these catalysts only provide one of the two possible enantiomeric forms of the final cyclized products.

We explored the prospect of achieving enantioselectivity in gold(I) catalysis by employing gold(I) complexes with chiral resorcin[4]arene phosphoramidite as ligands (Scheme 1). Specifically, our aim was to enantioselectively activate 1,6-enynes with terminal alkynes in reactions with alcohols (alkoxycyclization) to form 1-methylene-2,3-dihydro-1*H*-indenes, whose oxidative cleavage would furnish synthetically useful chiral indanones. Herein, we report an enantioselective alkoxycyclization of 1,6-enynes by using



Scheme 1. Gold(I)-cavitand catalysts for the enantioselective alkoxycyclization of 1,6-enynes and application to the total synthesis of (+)- and (−)-mafaicheenamine C.

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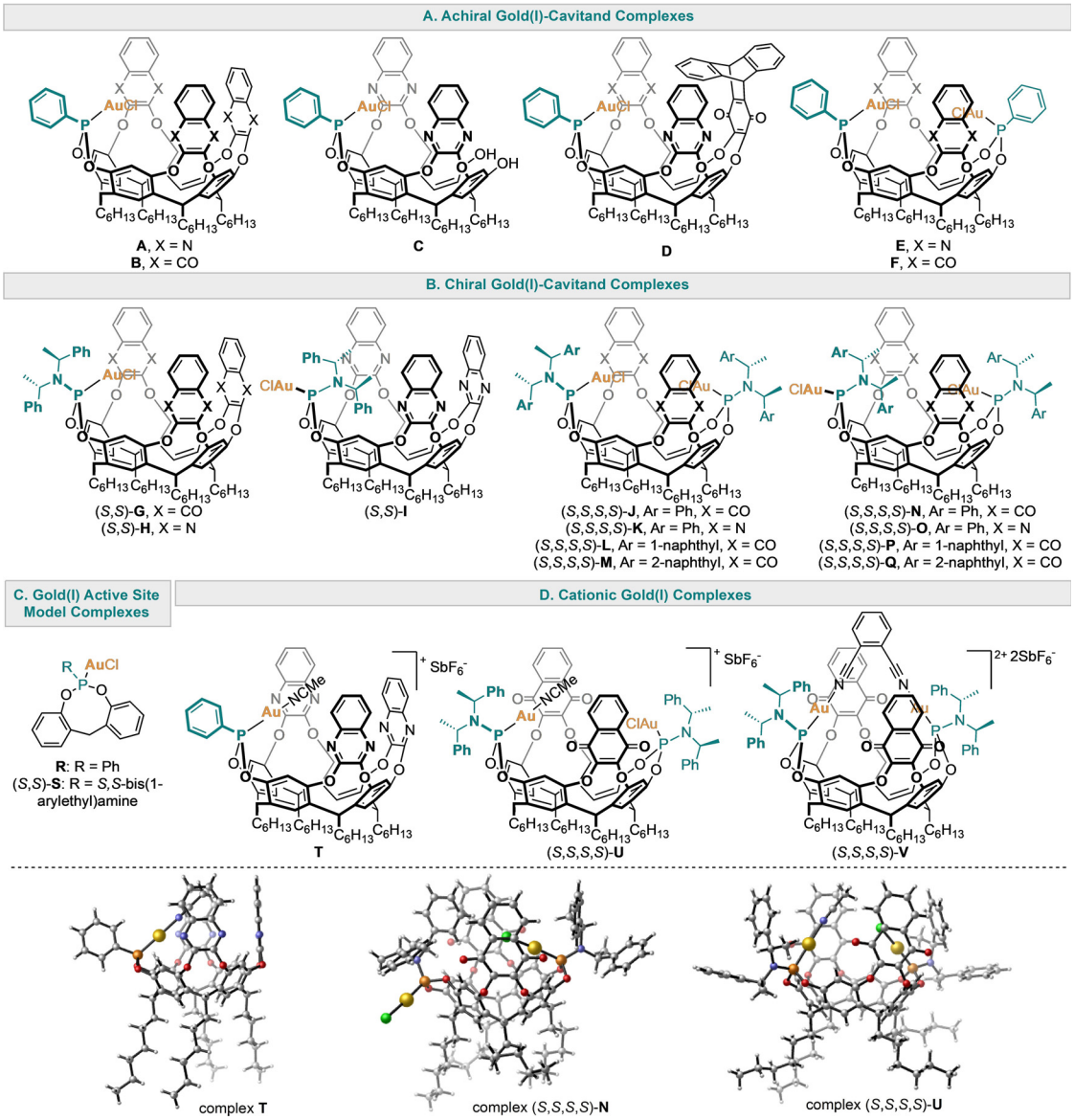


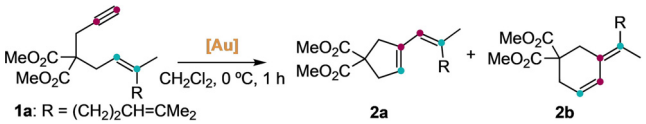
Figure 1. Structures of gold(I) complexes and selected X-ray diffraction structures of complexes **T**, **N**, and **U**.

chiral mono-cationic gold(I) resorcin[4]arene phosphoramidite complexes as catalysts. To demonstrate their potential, we have completed the first total synthesis of (+)-mafaicheenamine C as well as its non-natural enantiomer, establishing the absolute configuration of the natural product. (+)-Mafaicheenamine C belongs to a family of bioactive carbazole alkaloids isolated from the plant *Clausena lansium*,[20] which also produces compounds such as mafaicheenamine A and claulansines B and D.[21,22]

Mono- and dinuclear achiral complexes **A**–**F** (Figure 1 A) and chiral gold(I)-cavitand complexes **G**–**Q** (Figure 1 B) were prepared by the methods developed by the group of Iwasawa.[23] In addition to those with quinoxaline walls, we also prepared gold(I)-cavitand complexes with naphthoquinone walls **B**, **F**, **G**, **J**, **L**, **M**, **N**, **P**, and **Q**. Chirality in **G**–**Q** was introduced via the phosphoramidites derived from either *R*,*R*- or *S*,*S*-bis(1-arylethyl)amines. For the chiral mononuclear gold(I) complexes, we prepared complexes **G** and **H**, with the metal inside the cavity, and **I** with the metal outside. In the case of dinuclear gold(I) complexes, we also synthesized *in–in* **J**–**M** and *in–out* complexes **N**–**Q**. To determine the effect of the cavity, we prepared achiral **R** and chiral **S** complexes with electronically similar active sites (Figure 1 C). Cationic gold(I) cavitands **T** and **U** were obtained by treatment of the neutral digold complexes with $AgSbF_6$ in acetonitrile. Dicationic gold(I) complex **V** with a bridged phthalonitrile ligand (Figure 1 D) and the enantiomers of **J**, **N**, and **U** were also synthesized. The structure of **A**, **D**, **E**, **F**, **H**, **I**, **J**, **N**, **O**, **R**, **S**, **T**, and **U** was confirmed by X-ray diffraction.[24]

We first tested the activity of the gold(I) cavitands in the cyclization of (*Z*)-1,6-dienyne **1a** (Table 1). Reaction of **1a** with $[Au(PPh_3)Cl]$, $[Au(P(OMe)_3)Cl]$, or **R** and $AgSbF_6$ selectively gave **2a** as the product of exocyclic single-cleavage skeletal rearrangement[25] (Table 1, entries 1–3). However, gold(I) cavitand **A** led to the preferred formation of endocyclic single-cleavage skeletal rearrangement product

Table 1: *Exo/endo* Selectivity in the cyclization of (*Z*)-1,6-dienyne **1a**.



1a: R = $(CH_2)_2CH{=}CMe_2$ **2a** **2b**

Entry	[Au] (2 mol%)	$AgSbF_6$ [mol%]	Yield [%][a] (**2a**/**2b**)
1	$[Au(PPh_3)Cl]$	2	65 (11:1)
2	$[Au(P(OMe)_3)Cl]$	2	56 (>20:1)[b]
3	**R**	2	77 (>20:1)
4	**A**	2	95 (1:5)
5	**B**	2	89 (8:1)
6	**C**	2	79 (1:2)
7	**D**	2	83 (1:1)
8	**E**	4	92 (1:1)
9	**F**	4	87 (3:1)
10	**T**	–	97 (1:5)[c]

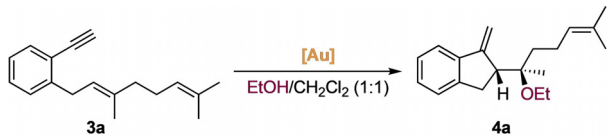
[a] Yields determined by ^1H NMR with Ph_2CH_2 as internal standard. [b] 67% conversion. [c] Isolated yield.

2b[26] (Table 1, entry 4). Significant ammounts of **2a** were also obtained with mono- or dinuclear complexes **B**–**F** (Table 1, entries 5–9). The fact that complex **R**, with an electronically very similar ligand to those of gold(I)-cavitand complexes, gives **2a** exclusively (Table 1, entry 3) shows that the cavity of the cavitands plays a major role in the change of the *exo*- to *endo*-selectivity. As expected, complex **T** (the cationic derivative of **A**) showed the same selectivity as cavitand **A**, leading to **2a**/**2b** in excellent yield (Table 1, entry 10).

Chiral gold(I)-cavitand complexes were investigated in the enantioselective alkoxycyclization of 1,6-enyne **3a** using ethanol as nucleophile (Table 2).[24] Mononuclear cavitand complexes (*S*,*S*)-**G** and (*S*,*S*)-**H** with AuCl inside the cavity gave **4a** in good yield but with low enantioselectivity (Table 2, entries 1 and 2). With complex (*S*,*S*)-**I**, in which gold is outside the cavity, low yield and enantioselectivity were obtained (36%, 45:55 *er*) (Table 2, entry 3). The best results were achieved with dinuclear complexes with both AuCl located inside the cavity. Precatalyst (*S*,*S*,*S*,*S*)-**J** afforded **4a** with 89:11 *er* in 90% yield (Table 2, entry 4). The effect of the cavitand walls was studied by replacing the naphthoquinone units for quinoxalines (complex (*S*,*S*,*S*,*S*)-**K**), obtaining **4a** with 86:14 *er* in 80% yield (Table 2, entry 5). Replacing the phenyl groups for naphthyl groups in (*S*,*S*,*S*,*S*)-**L** and **M** afforded **4a** in 74:26 *er* and 88:12 *er*, respectively (Table 2, entries 6 and 7). Dinuclear cavitands with one AuCl moiety inside the pocket and the other one outside led to lower enantioselectivities (Table 2, entries 8–11). Simple chiral complex (*S*,*S*)-**S** with an electronically similar active site led to **4a** with very low enantioselectivity (48%, 57:43 *er*; Table 2, entry 12), confirming the cavity effect in these reactions. Using lower amounts of $AgSbF_6$ led to very similar results (Table 2, entry 13). Cationic gold(I) cavitand (*S*,*S*,*S*,*S*)-**U** showed the same activity as the one formed in situ from (*S*,*S*,*S*,*S*)-**J**. However, with dicationic gold(I) complex (*S*,*S*,*S*,*S*)-**V** both yield and enantioselectivity slightly decreased (74%, 81:19 *er*; Table 2, entry 15). Lowering the temperature to −50 °C with complex (*S*,*S*,*S*,*S*)-**U** further improved the enantioselectivity, leading to **4a** in 90% yield and 96:4 *er* (Table 2, entry 16).

The reaction of different enynes and nucleophiles was performed using (*S*,*S*,*S*,*S*)-**U** (Scheme 2). We observed a slight decrease in enantioselectivity using nucleophiles less bulky than ethanol. Thus, reaction a (*E*)-1,6-dienyne **3a** with

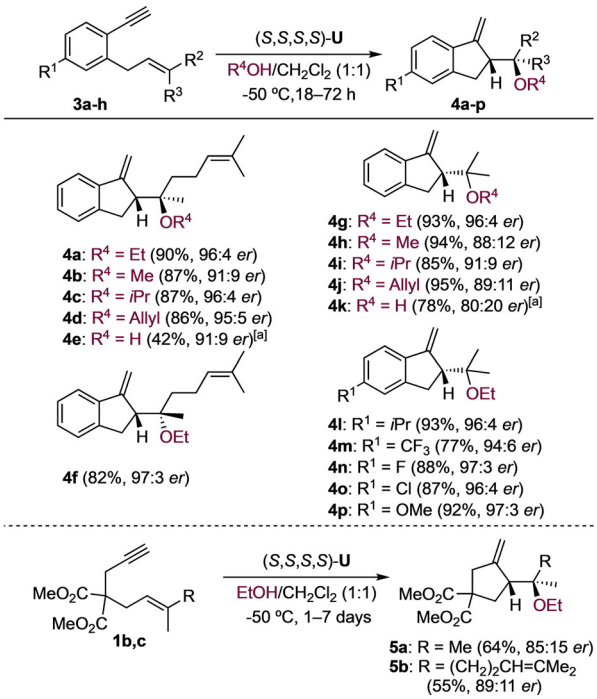
Table 2: Enantioselective alkoxycyclization of *E*-1,6-dienyne **3a**.



3a **4a**

Entry	[Au] (3 mol%)	$AgSbF_6$ [mol%]	*T* [°C]	*t* [h]	Yield [%][a]	*er*[b]
1	(*S*,*S*)-**G**	3	23	1	83	51:49
2	(*S*,*S*)-**H**	3	23	1	74	59:41
3	(*S*,*S*)-**I**	3	23	1	36	45:55
4	(*S*,*S*,*S*,*S*)-**J**	6	23	1	90	89:11
5	(*S*,*S*,*S*,*S*)-**K**	6	23	1	80	86:14
6	(*S*,*S*,*S*,*S*)-**L**	6	23	1	84	74:26
7	(*S*,*S*,*S*,*S*)-**M**	6	23	1	83	88:12
8	(*S*,*S*,*S*,*S*)-**N**	6	23	1	86	55:45
9	(*S*,*S*,*S*,*S*)-**O**	6	23	1	69	57:43
10	(*S*,*S*,*S*,*S*)-**P**	6	23	1	67	68:32
11	(*S*,*S*,*S*,*S*)-**Q**	6	23	1	91	53:47
12	(*S*,*S*)-**S**	3	23	1	48	57:43
13	(*S*,*S*,*S*,*S*)-**J**	3	23	1	88	89:11
14	(*S*,*S*,*S*,*S*)-**U**	–	23	1	89	89:11
15	(*S*,*S*,*S*,*S*)-**V**	–	23	3	74	81:19
16	(*S*,*S*,*S*,*S*)-**U**	–	−50	18	90[c]	96:4

[a] Yields determined by ^1H NMR using Ph_2CH_2 as internal standard. [b] Enantiomeric ratios determined by HPLC. [c] **3a** (0.4 mmol scale), isolated yield.

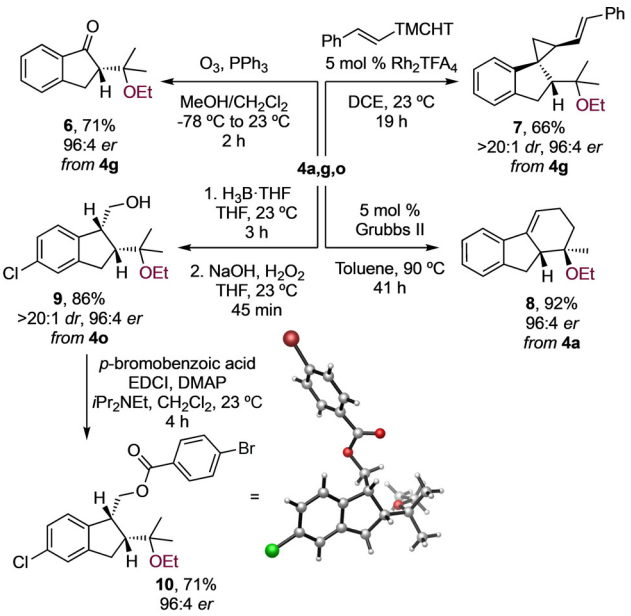


Scheme 2. Reaction scope of the enantioselective alkoxycyclization. [a] Solvent/nucleophile: acetone/H_2O 1:1 at −20 °C.

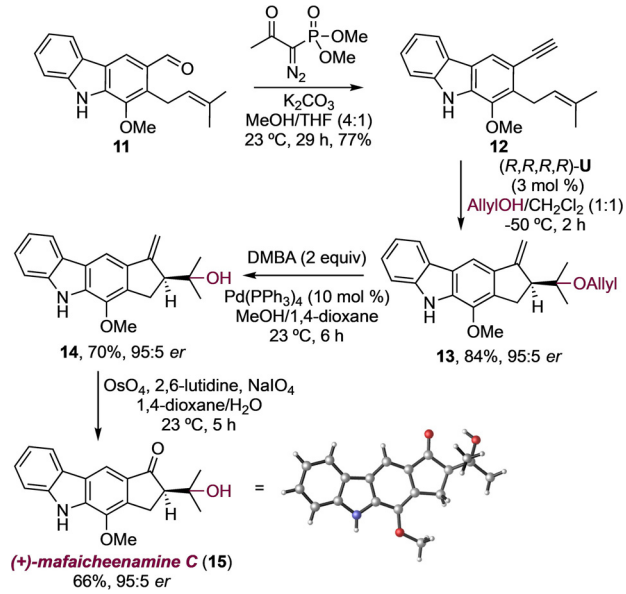
methanol or water led to **4b** and **4e** in 91:9 *er*, whereas reaction with 2-propanol and allyl alcohol gave **4c**,**d** with essentially the same *er* to that of **4a**. We also tested dienyne **3b**, the *Z* diastereomer of **3a**, which led stereospecifically to **4f** in 97:3 *er*. Similar results were observed in the formation of compounds **4g**–**p**, with the exception of products of methoxy- (**4h**) and hydroxycyclization (**4k**), which were obtained with lower enantioselectivities. Enynes **1b**,**c** led to **5a**,**b** in 85:15 to 89:11 *er*.

The products of alkoxycyclization were converted into a variety of enantioenriched structures (Scheme 3). Thus, ozonolysis of **4g** cleanly afforded indanone **6**, whereas cyclopropanation of **4g** via retro-Buchner reaction[27] provided **7** with excellent diastereoselectivity (>20:1). Tetrahydro-1*H*-fluorene **8** was obtained by ring closing metathesis of **4a** using 2nd generation Grubbs catalyst. On the other hand, hydroboration-oxidation of **4o** led diastereoselectively to alcohol **9**, whose crystalline *p*-bromobenzoate **10** allowed assigning its absolute configuration by X-ray diffraction.

To demonstrate the application of this enantioselective alkoxycyclization, we completed the first total synthesis of (+)-mafaicheenamine C (**15**) in an enantioselective manner (Scheme 4). We started from known carbazole aldehyde **11**.[22c] Reaction of **11** with the Bestmann–Ohira reagent provided **12** (77% yield), whose reaction with allyl alcohol in the presence of (*R*,*R*,*R*,*R*)-**U** at −50 °C led to ether **13** in 84% yield and 95:5 *er*. Pd-catalyzed deallylation led to alcohol **14**. Final oxidative cleavage of the exocyclic alkene gave (+)-mafaicheenamine C (**15**), whose absolute configuration was assigned as *R* by X-ray diffraction.[20] We also obtained the non-natural antipode (−)-mafaicheenamine C in 96:4 *er* using chiral gold(I) catalyst (*S*,*S*,*S*,*S*)-**U** in the alkoxycyclization reaction.[24]

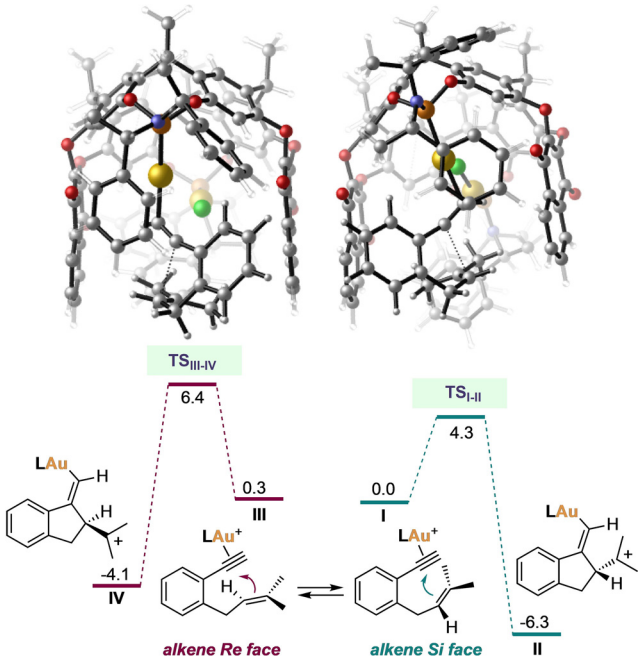


Scheme 3. Transformation of products **4a**,**g**,**o** into **6**–**9** and assignment of the absolute configuration by X-ray diffraction via ester **10**. TMCHT = 1,3,5-trimethylcyclohepta-1,3,5-triene, DCE = 1,2-dichloroethane, EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, DMPA = 4-dimethylaminopyridine.



Scheme 4. Total synthesis of (+)-mafaicheenamine C. DMBA = dimethylbarbituric acid.

Finally, we studied the origin of enantioselectivity by DFT calculations at the B3LYP/6-31G(d,p) (C, H, P, O, Cl, N), SDD (Au) (SMD = ethanol) level of theory using enyne **3c** and simplified gold(I) cavitand (*S*,*S*,*S*,*S*)-**U** without aliphatic chains.[24] The enantiodetermining step of the process is the initial cyclization leading to carbocationic gold(I) intermediates **II** or **IV**[28] from the two most favorable orientations of the coordinated enyne, with the aryl ring outside the cavity. $\mathbf{TS_{I–II}}$ was found to be 2.1 kcal mol^{-1} lower in energy than $\mathbf{TS_{III–IV}}$, which is consistent with the selective formation of the enantiomer observed experimentally (Scheme 5). NCI plot



Scheme 5. Free-energy profile for the Au^{I}-catalyzed alkoxycyclization reaction of **3c** (kcal mol^{-1} at 25 °C). Transition state representations by CYLview.

studies of the two possible transition states show attractive interactions between the cavitand and the aromatic ring of the enyne and non-covalent interactions within the complex itself in $\mathbf{TS_{I–II}}$, which are weaker in $\mathbf{TS_{III–IV}}$.[29]

To sum up, we have designed a new family of achiral and chiral gold(I)-cavitand complexes, easily synthesized in either enantiomeric form in a modular manner from resorcin-[4]arenes and commercially available chiral secondary amines. While new selectivity was uncovered in the cyclization of dienynes with achiral gold(I)-cavitand complexes, the chiral catalysts allowed to develop an enantioselective alkoxycyclization of 1,6-enynes, which has been applied for the first total synthesis of (+)- and (−)-mafaicheenamine C, assigning the absolute configuration of the natural compound. The stereochemical outcome of the transformation is supported by a theoretical model which suggests that the high enantioselectivity results from stabilizing non-covalent interactions.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkoxycyclization · asymmetric synthesis · gold(I) cavitands · natural product synthesis

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