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Enantioselective Folding of Enynes by Gold(I) Catalysts with a Remote C_2-Chiral Element

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Supporting Information Placeholder

ABSTRACT: Chiral gold(I) catalysts have been designed based on a modified JohnPhos ligand with a distal C_2-2,5-diarylpyrrolidine that creates a tight binding cavity. The C_2-chiral element is close to where the C-C bond formation takes place in cyclizations of 1,6-enynes. These chiral mononuclear catalysts have been applied for the enantioselective 5-*exo*-dig and 6-*endo*-dig cyclization of different 1,6-enynes as well as in the first enantioselective total synthesis of three members of the carexane family of natural products. Opposite enantioselectivities have been achieved in seemingly analogous reactions of 1,6-enynes, which result from different chiral folding of the substrates based on attractive aryl-aryl interactions.

Gold(I) catalysts are highly selective for the activation of alkynes under very mild conditions by the addition of a wide variety of nucleophiles to intermediate (η^2-alkynes)gold(I) complexes.[1] However, in the context of asymmetric catalysis, the linear coordination adopted by gold(I) complexes, which places the substrate on the opposite side of the ancillary ligand the outer-sphere nature of the nucleophilic attack, limits the efficiency of the enantio-induction from chiral ligands (Figure 1a).[2] The main solutions have been based on the use of axially chiral digold complexes, monodentate phosphoramidite ligands or the synergistic use of non-chiral gold(I) complexes with chiral counter anions.[1b,2a] Recent progress relies on the development of ligands bearing chiral sulfinamides,[3] helically chiral phosphine ligands,[4] and the use of axially chiral monodentate phosphine ligands with a remote cooperative functionality.[5] Other approaches such as the encapsulation of gold(I) in capped cyclodextrin cavities[6] and the use of well-defined gold(III) complexes[7] are recently emerging.

Due to the ambiguous mode of action of chiral catalysts, to achieve high enantioselectivities in gold(I)-catalyzed transformations often requires the screening of many chiral ligands. Furthermore, the activation of alkynes, which are not prochiral, presents a special difficulty in enantioselective gold(I) catalysis. Thus, a system that allows for the accurate study of the reaction pathway as well as the specific enantioselective folding of enynes is highly desirable. To meet this challenge, we took inspiration from the ability of polyene cyclases to fold polyunsaturated molecules in an enantioselective fashion.[8] Hence, we propose a new conceptual design based on mononuclear gold(I) complexes with a new class of chiral JohnPhos-type ligands bearing a C_2-chiral *trans*-2,5-diaryl pyrrolidine at the para position of the biphenyl backbone (Figure 1a). This type of C_2-chiral pyrrolidine motif has been incorporated in organocatalysts,[9] chiral auxiliaries[10] and chiral ligands.[11] In our design, the rigid biphenyl scaffold serves as a holder to connect the chiral element and the phosphine, encompassing the gold(I) nucleus in a chiral envelope-type cavity. The bulky substituents on the phosphine prevent rotation around the C_{aryl}-P bond and force the P-Au-Cl axis to be parallel to the biphenyl axis, pointing towards the chiral environment.

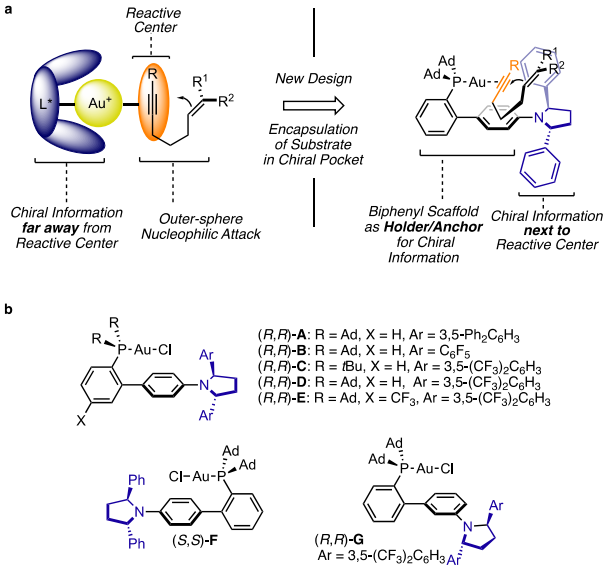


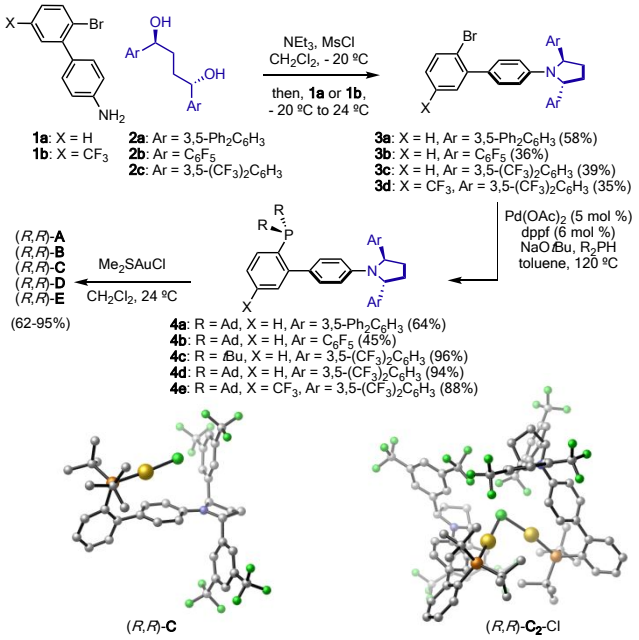
Figure 1. Traditional approach in asymmetric gold(I) catalysis and new catalyst design.

Here, we report the synthesis of new chiral catalysts **A**-**G** (Figure 1b) and their application in the enantioselective cyclization of 1,6-enynes. Remarkably, opposite enantioselectivities were observed in the cyclization of similar substrates. One of these cyclizations has been applied in the first enantioselective total synthesis of three members of the carexane family of natural products. The model for stereo-induction has been elucidated experimentally and

computationally as arising from attractive aryl-aryl interactions.

The new class of chiral ligands **4a-e** (Scheme 1) was prepared modularly from enantiopure benzylic diols **2a-c** and biphenylamines **1a**,**b**. Mesylation of diols **2a-c** and reaction with anilines **1a**,**b** afforded **3a-d**. Complexes **A-E** were obtained by palladium-catalyzed coupling reaction of **3a-d** with dialkyl phosphines R_2PH to give **4a-e**, followed by complexation with Me_2SAuCl. Complex **F** was synthesized from (*R*,*R*)-1,4-diphenylbutane-1,4-diol and complex **G** was prepared by a similar route from 2'-bromo-(1,1'-biphenyl)-3-amine. The structures of complexes **C**-**G** were confirmed by X-ray diffraction. Upon treatment of (*R*,*R*)-**C** with $NaBAr^F_4$, chloride-bridged digold complex (*R*,*R*)-$\mathbf{C}_2$-Cl was generated.[12] Prolonged heating of this solution at 50 °C led to the formation of a new species showing a singlet in the ^{31}P NMR spectrum at 67.5 ppm, characteristic of arene-gold(I) complexes.[13]

Scheme 1. Synthetic sequence for the preparation of complexes A-E



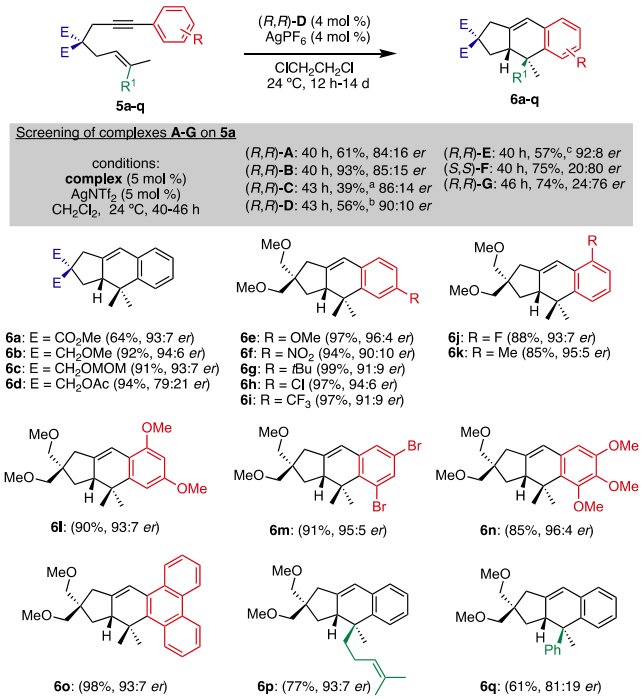
(*R*,*R*)-**C** (*R*,*R*)-$\mathbf{C}_2$-Cl

We studied the performance of the new catalysts on the formal [4+2] reaction previously reported by our group.[14] 1,6-Enyne **5a** was converted into cycloadduct **6a** with complexes **A-G** and $AgNTf_2$ (Table 1). The best enantioselectivities were obtained with complexes **D** and **E**, which led to **6a** with 90:10 *er* to 92:8 *er*, although the reaction with catalyst **D** was cleaner. Complex (*R*,*R*)-**G** afforded **6a** in good yield, but with moderate *er*. Interestingly, although the absolute configuration of **A-E** and **G** at the pyrrolidine is identical, catalyst (*R*,*R*)-**G** favors the formation of the opposite enantiomer *ent*-**6a**.

Upon further reaction optimization with (*R*,*R*)-**D** using $AgPF_6$ instead of $AgNTf_2$, compound **6a** was isolated in 64% of yield and 93:7 *er* (Table 1). Fused tricyclic compounds **6a-q** were obtained from the corresponding 1,6-enynes **5a-q**. Substrates with methyl- or MOM-protected alcohols at the enyne tether gave consistent good results (90:10 to 96:4 *er*), whereas the diacetate **6d** was obtained with lower enantioselectivity (79:21 *er*). The cyclizations leading to **6p** and **6q**, which were obtained as single diastereomers, required long reaction times (7 days and 14 days, respectively) and **6q** was obtained with 81:19 *er*. The absolute configuration of **6o** was assigned as *R* by single crystal X-ray diffraction[15] and those of the rest of the cycloadducts were correlated with that of **6o** by circular dichroism.

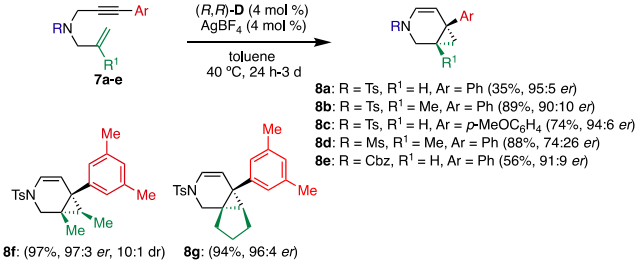
Similarly, the 6-*endo*-dig cyclization[16] reaction of *N*-tethered 1,6-enynes **7a-e** forms azabicyclo[4.1.0]hept-4-enes **8a-e** in moderate to good yields and good enantioselectivities (90:10 to 95:5 *er*), with the exception of mesyl-substituted **8d**, obtained with 74:26 *er* (Table. 2). Products **8f** and **8g** with different substitution patterns were also obtained in good yields and enantioselectivities. The absolute configuration of these compounds was assigned by comparison with those reported for **8b** and **8e**.[17]

Table 1. Enantioselective cyclization of 5a with catalysts A-G and scope of formal [4+2] cycloaddition



[a] 58% of conversion. [b] 68% of conversion. [c] 82% conversion, 6% of a side product. Yields determined by ^1H NMR using 1,3,5-tribromobenzene as internal standard.

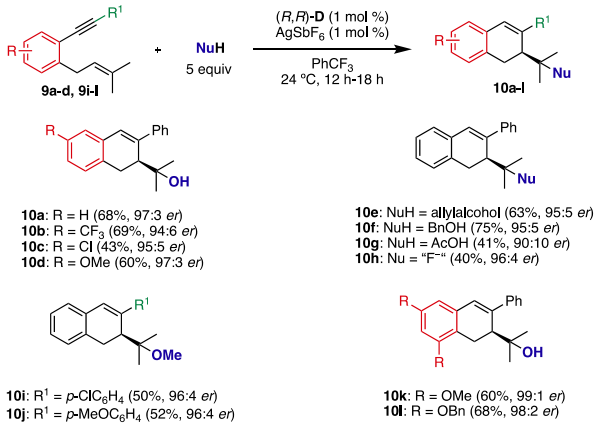
Table 2. Synthesis of azabicyclo[4.1.0]hept-4-enes 8a-g



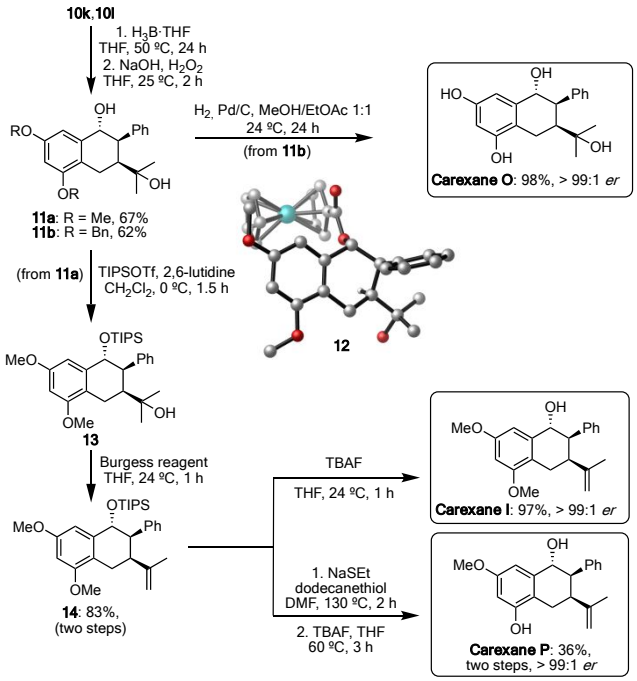
To study the generality of our system we tested the cyclization of 1,6-enynes **9a-d** and **9i-l** in the presence of water and other nucleophiles to give 2,3-disubstituted 1,2-dihydronaphthalenes **10a-l** by gold(I)-catalyzed 6-*endo*-dig cyclization, followed by nucleophilic addition (Table 3).[18] The reaction optimization was performed for the formation of **10k**, for which we tested *ca.* 80 chiral ligands from different families. Among them, only the JosiPhos family of ligands led

to significant enantioselectivities (up to 80:20 *er*).[19] Gratifyingly, complex (*R*,*R*)-**D** gave **10k** in 60% yield and excellent 99:1 *er*. Dihydronaphthalenes **10a-g** and **10i-l** were obtained in presence of water, alcohols, or acetic acid in 41-75% yield and 90:10 to 99:1 *er*. Remarkably, fluoride transfer was also achieved in the cyclization of **9a** with HF·pyridine to give **10h** (40%, 96:4 er).

Table 3. Synthesis of 1,2-dihydronaphthalenes 10a-l



Scheme 2. Asymmetric total synthesis of carexanes I, O, and P



We applied the preparation of 1,2-dihydronaphthalenes to the first enantioselective total synthesis of three members of the carexane family of natural products, which were isolated from the leaves of *Carex distachya*.[20] Chiral dihydronaphthalene **10k** (60% yield and 99:1 *er,* >99:1 *er* after recrystallization) was converted into diol **11a** in 67% yield by hydroboration–oxidation (Scheme 2). Reaction of **11a** with ferrocenoyl chloride gave crystalline ester **12** (73% yield), which allowed establishing its *S* absolute configuration by X-ray diffraction.[21] After selective protection of the benzylic alcohol with TIPSOTf to form **13**, dehydration with Burgess reagent gave **14** (83%, two steps). Desilylation of **14** afforded carexane I in 97% yield. Carexane P was prepared from **14** by selective deprotection of one methyl ether and desilylation (36% yield, two steps).[22] Carexane O was prepared from **11a** by demethylation[23] in low yield (18-39%) or more efficiently from **10l** (68% yield and 98:2 *er,* >99:1 *er* after recrystallization), by hydroboration-oxidation to give **11b** (62% yield) and subsequent hydrogenolysis of the benzyl ethers (98% yield). Thus, the concise total synthesis of carexanes I (8 steps), P (9 steps), and O (6-steps) has been achieved in 15%, 6% and 17% overall yield respectively, including the three steps required for the preparation of **9k-l**.

The simple design of our chiral mononuclear catalysts allows for the systematic investigation of their mode of action. The absolute configuration in **6**, **8** and **10** results from the different geometrical arrangement of 1,6-enynes **5**, **7**, and **9** inside the active chiral catalysts. The chiral folding favors reaction of the (η^2-alkyne)gold(I) complex with either the *Re* or the *Si*-prochiral face of the alkenes in the stereo-determining formation of the key cyclopropyl gold(I) intermediates (Scheme 3a). Remarkably, two different folding modes occur for this type of related substrates: 1,6-enynes **5** and **7** are disposed in a way that the alkene reacts with the (η^2-alkyne)gold(I) complex through the *Si* face, whereas 1,6-enynes **9** react at the alkene *Re* face. This suggests that, despite their similarity, 1,6-enynes **5** and **9** adopt distinct geometrical arrangements inside the chiral cavity.

We hypothesized that the aryl at C1 of the alkyne, which is a common element in enynes **5** and **7**, is the main responsible for the recognition by the chiral catalysts, whereas in the case of **9** the aryl tethering the alkynyl and the allyl chains directs the stereocontrol of the cyclization (Scheme 3a). To probe this assumption, we performed the cyclization of dienyne **15** in which the aryl at the alkyne is replaced by a smaller vinyl group, expected to have a weaker interaction with the catalyst. Indeed, cycloadduct **16** was obtained with poor enantioselectivity (Scheme. 3b). On the other hand, the hydroxycyclization of **17**, an analogue of **9a** with a cyclohexenyl ring instead of the phenyl at C1, gave dihydronaphthalene **18** with essentially the same enantioselectivity observed in the cyclization of **9a** to form **10a**.

Scheme 3. Stereo directing moieties in 1,6-enynes 5, 7a and 9 and control experiments with 15 and 17

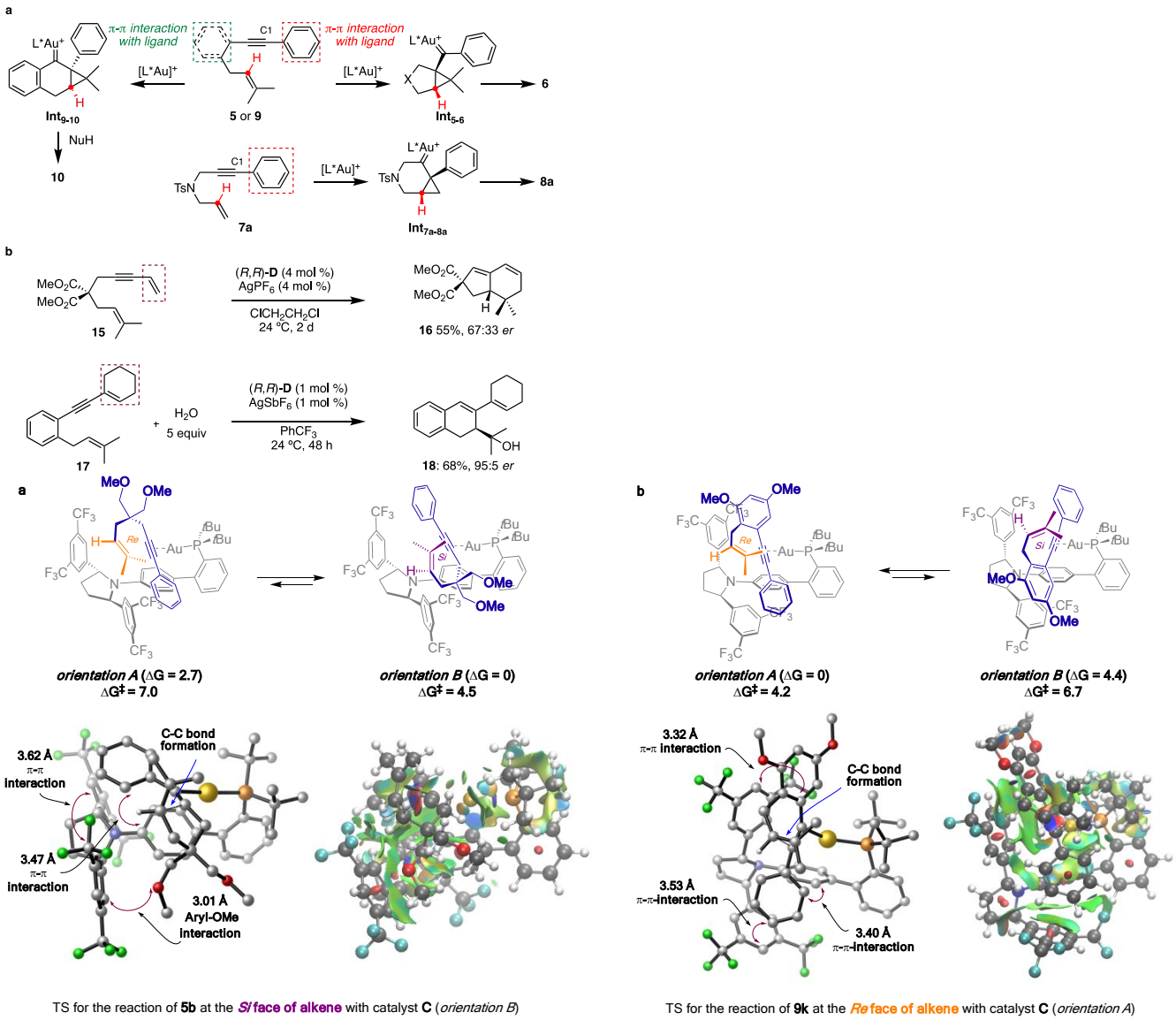


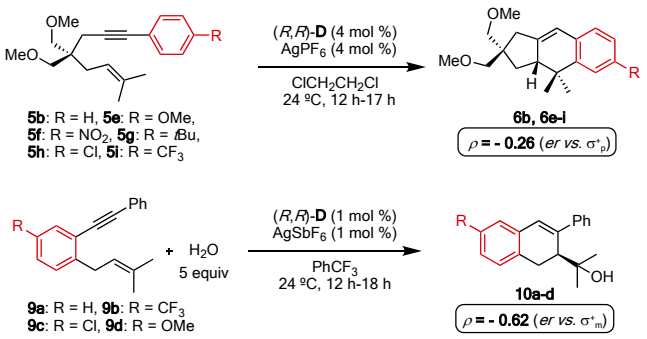
Figure 2. Two most relevant binding orientations (A and B) of enynes **5b** and **9k** coordinated to catalyst C and lowest energy transitions states (CYLview representations and NCI plots). Hydrogen atoms are omitted for clarity with the exception of the stereocenters. Strong attractive interactions are blue (C-C bond formation), weak attractive interactions are green (non-covalent interactions), and strong repulsive interactions are red. Color code: P: orange, Au: yellow, F: cyan, O: red, C: grey, and H: white. Energy values in Kcal/mol relative to the most stable orientation.

We computed the reaction coordinate for the cyclizations of enynes **5b** and **9k** using DFT calculations (BP86-D3/6-31G(d) (C, H, P, O, F, N) and SDD (Au), PCM = CH_2Cl_2) with complex **C**, which is similar to the best catalyst **D** (Figure 2a-b). In all cases, we found four minima resulting from two binding orientations *A* and *B* of the substrate coordinated to gold(I) through the alkyne and the reaction of the two enantiotopic faces of the alkene.[24] In the cyclization of **5b** (Figure 2a) with catalyst **C**, our computational work predicted preferential reaction through the *Si* face of the alkene, whereas for **9k** (Figure 2b) reaction through the *Re* face was favored, in agreement with the experimental results. In both cases, the lowest energy transitions states were achieved from the most stable orientations (*B* for **5b** and *A* for **9k**). As revealed by the NCI plots, attractive interactions between the aromatic moieties of the substrates and the aromatic substituents of the pyrrolidine of catalyst **C**, play the major role in the chiral folding of the substrate and in the stabilization of the corresponding transitions states. Additional stabilization is provided by interactions between the substrates and the biphenyl scaffold of the ligand. In the case of substrate **5b**, attractive aryl-OMe interactions are also stereo-controlling elements that favor reaction through the *Si* face of the alkene in orientation *B* (Figure 2a). This model is consistent with the lower enantioselectivity obtained with diacetate **5d**, in which a weaker stabilizing interaction probably occurs between the more electronegative OAc groups and the aryl substituent of the pyrrolidine. Hence, substrate recognition by the chiral catalysts induces one specific binding orientation via non-covalent interactions and leads to the distinct enantioselective folding in the enantioselective cyclization.[25]

A Hammett study of the reactions of substrates **5b**, **5e-i** (*er* vs. σ^+_p) and **9a-d** (*er* vs. σ^+_m) with catalyst **D**, showed negative slopes confirming the preferred binding of the most electron-

rich substrates by the catalyst bearing strongly electron-withdrawing CF_3-substituted aryl groups (Scheme 4).

Scheme 4. Hammett study of formal [4+2] cyclization of 5 and hydroxycyclization of 9



In summary, we have designed a new class of chiral gold(I) catalysts with monodentate pyrrolidinyl-biphenyl phosphine ligands that promotes the enantioselective cyclization of different types of 1,6-enynes. Non-covalent attractive π-π interactions with the chiral cavity of the catalysts induced by the distal C_2-chiral pyrrolidine have been shown to be key to achieve high enantioselectivities in cycloisomerization, hydroxycyclization, and other related gold(I)-catalyzed addition reactions, even in cases in which the alkyne is substituted by two aryl groups. The hydroxycyclization reaction has been applied for the first enantioselective total synthesis of three members of the carexane family of natural products. This work sets the basis for the design of similar modular catalysts to expand the scope of asymmetric gold(I)-catalyzed transformations and to mimic the action of polyene cyclases.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Crystallographic data for (*R*,*R*)-**C** (CIF)
Crystallographic data for (*R*,*R*)-**D** (CIF)
Crystallographic data for (*R*,*R*)-**E** (CIF)
Crystallographic data for (*S*,*S*)-**F** (CIF)
Crystallographic data for (*R*,*R*)-**G** (CIF)
Crystallographic data for (*R*,*R*)-$\mathbf{C_2}$-Cl (CIF)
Crystallographic data for **6o** (CIF)
Crystallographic data for **10k** (CIF)
Crystallographic data for **12** (CIF)
Crystallographic data for Carexanene I (CIF)
Crystallographic data for Carexanene P (CIF)
Crystallographic data for Carexanene O (CIF)

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Notes

The authors declare no competing financial interest.

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