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Divergent synthesis of two polycyclic frameworks containing tricyclic bridgehead carbon centers by gold-catalyzed cycloisomerization of *o*-cyclopropylidenemethyl-*o*′-alkynylbiaryls

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Compounds containing tricyclic bridgehead carbon centers are privileged structures in drug discovery. In this work, two different polycyclic scaffolds containing this substructure have been accessed by divergent gold-catalyzed cycloisomerizations of *o*-cyclopropylidenemethyl-*o*′-alkynylbiaryls. Selectivity towards one or the other scaffold is mainly controlled by temperature. The electronic nature of the arene group at the alkyne also plays a significant role, which is explained based on the proposed mechanism.

Introduction

The beneficial effect of incorporating sp^3 carbon atoms in molecules intended for drug discovery has been recognized in the past few years.[1] This design allows for the exploration of novel chemical space and increases the likelihood of finding new clinical candidates with high potency and selectivity.[2] Spirocyclic compounds in which two or more rings are connected by a single quaternary carbon constitute a specific motif that is frequently found in bioactive natural and synthetic products.[3] Derivatives in which the quaternary center is embedded within three fused rings (TBCCs, Fig. 1a) are particularly appealing, but synthetically challenging.[4] Therefore, the development of efficient synthetic procedures for constructing these types of frameworks is a major goal in organic synthesis.

Gold catalysis is currently a well-stablished and powerful tool for organic synthesis,[5] and has found significant applications in different fields such as total synthesis[6] and materials science.[7] Specifically, gold catalysts are highly useful for assembling cyclic frameworks of different sizes and complexity.[8] Among all the possible transformations enabled by the unique ability of gold complexes to activate π-systems under mild conditions, the cycloisomerizations of enynes are particularly valuable for the construction of carbocyclic compounds.[9] Moreover, the use of methylenecyclopropane-containing molecules as precursors for gold-catalyzed reactions has also provided useful methods for organic synthesis.[10,11] Methylenecyclopropanes (MCPs, Fig. 1b) are a class of readily accessible but highly reactive molecules, which are involved in numerous valuable transformations driven by the release of their high strain,[12] enabling the synthesis of diverse cyclic compounds.[13]

With this background, our group recently focused on the gold-catalyzed cyclization of *o*-alkenyl-*o*′-alkynylbiaryls, developing efficient methods for the selective synthesis of phenanthrenes,[14] dihydrophenanthrenes[14,15] and benzo[*b*]triphenylenes.[15] The utility of the former methodology was evidenced through its application as a key step in the total synthesis of Laetevirenol A,[16] a natural product with antioxidant activity. The gold-catalyzed reactions of *o*-alkenyl-*o*′-alkynylbiaryls mentioned above are proposed to proceed *via* initial 6-*exo*-*dig* cyclizations, but we anticipated that the use of precursors having an MCP as alkene moiety could alter the preferred cyclization mode, opening the door to novel polycyclic frameworks (Fig. 1c). Thus, a 6-*exo*-*dig* cyclization would give rise to a carbocation within a cyclopropane ring, which would be disfavored, whereas a 7-*exo*-*dig* cyclization would generate an α-cyclopropylcarbocation, which would be particularly stabilized. Herein, we report the selective synthesis of two different frameworks incorporating tricyclic bridgehead carbon centers, based on the gold-catalyzed 7-*exo*-*dig* cyclization of alkynylbiaryls bearing a methylenecyclopropane unit, which are easily accessible from commercially available reagents *via* well stablished Sonogashira, Suzuki and Wittig reactions (Fig. 1d).

Results and discussion

For our initial experiments, we selected 2-(cyclopropylidenemethyl)-2′-(phenylethynyl)-1,1′-biphenyl **1a** as the model

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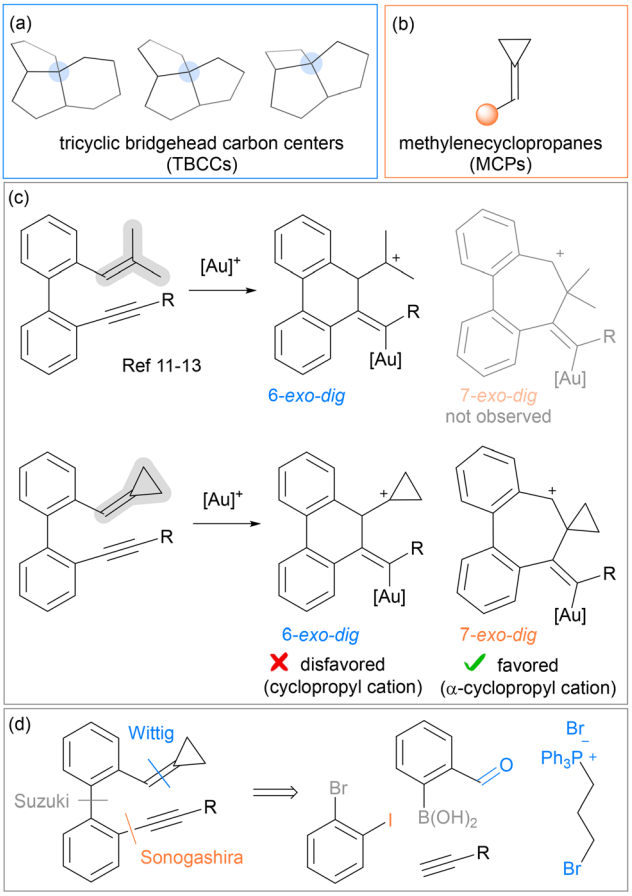
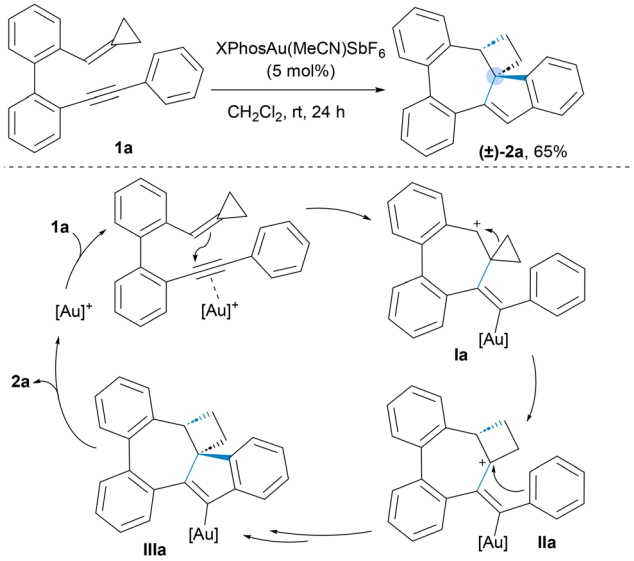


Fig. 1 (a) General structure of TBCCs targeted in this work. (b) General structure of MCPs used as starting materials. (c) Possible cyclization modes for *o*-alkenyl-*o*′-alkynylbiaryls. (d) Synthesis of *o*-alkenyl-*o*′-alkynylbiaryls.

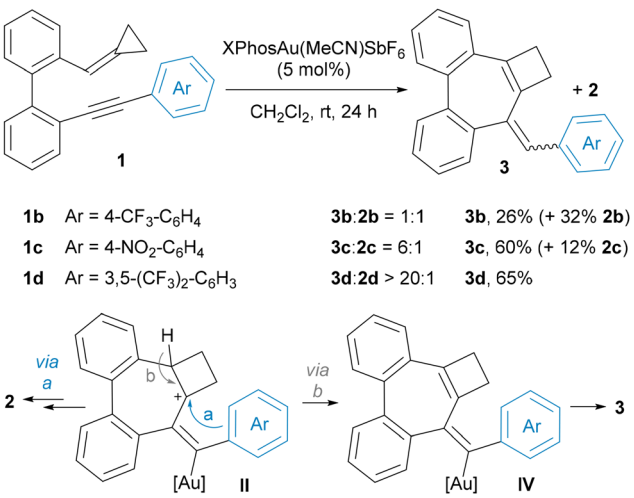
substrate and tested its reactivity in the presence of different gold catalysts under diverse reaction conditions (see Table S1 in the SI for details). Under optimized conditions, consisting in the use of 5 mol% of XPhosAu(MeCN)SbF_6 in CH_2Cl_2 at room temperature, we selectively obtained the polycyclic compound **2a**, which could be isolated in good yield (Scheme 1). **2a** was formed as a single diastereomer, resulting from the expected *cis* fusion of the cyclobutane ring.

The transformation of **1a** to **2a** implies the formation of two new cycles and the expansion of the original cyclopropane to a cyclobutane, generating a compound that contains a four-, a five-, and a seven-membered ring, which share a quaternary carbon. The proposed mechanism for the formation of product **2a** is shown in Scheme 1. The reaction would be initiated by the coordination of the gold complex to the triple bond of **1a**, followed by intramolecular nucleophilic attack of the alkene, leading to a 7-*exo-dig* cyclization, which generates the carbocationic intermediate **Ia**, as expected. Ring expansion would give rise to the carbocationic intermediate **IIa**, which would suffer an intramolecular nucleophilic attack by the phenyl group initially bonded to the alkyne. Finally, a protodemetallation would afford the polycyclic compound **2a** and regenerate the catalytic gold species.



Scheme 1 Initial result and proposed mechanism.

It is noteworthy that a preliminary substrate scope study under the initially optimized conditions revealed that the electronic nature of the alkyne substituent had a huge impact on the outcome of the reaction. Thus, for substrate **1b** having a *p*-CF_3-phenyl group, an equimolecular mixture of **2b** and dibenzoheptafulvene **3b** was obtained (Scheme 2). The formation of **3b** can be explained by an alternative mechanistic pathway from the initially formed carbocation **II**, which would take place *via* proton elimination (*via* path *b*) instead of the nucleophilic attack proposed for the formation of **2** (*via* path *a*). This change in the selectivity of the reaction of **1b** compared to **1a** can be rationalized by the lower nucleophilicity of

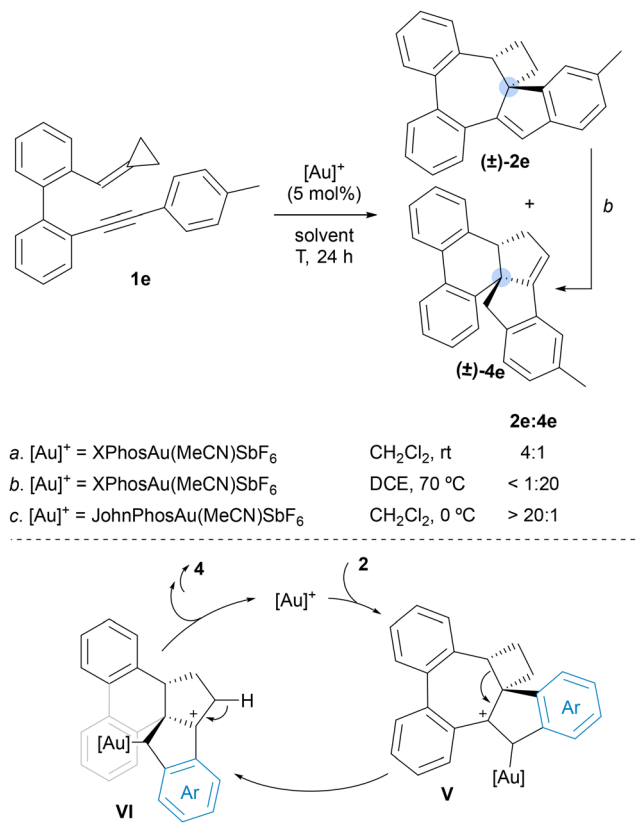


Scheme 2 Gold-catalyzed cyclization of enynes with electron-withdrawing substituents at the alkyne.

the aryl ring in **1b**, disfavoring path *a*. Accordingly, the reaction of the starting materials **1c** and **1d**, having even less nucleophilic arenes, provided compounds **3c** and **3d** with high selectivity and good yields.

On the other hand, in the cyclization of substrates having electron-donating substituents at the alkyne, we observed the formation of a secondary product **4** (Scheme 3), whose amount increased with the electron-rich character of the alkyne substituent (see Scheme S1 in the SI for details). Compounds **4** are polycycles which, similar to products **2**, contain a tricyclic bridgehead carbon center, but in this case embedded within two five- and one six-membered rings. Given our interest toward both structures, we decided to carry out an optimization to try and direct the cyclization towards either compounds **2** or **4**. Therefore, a screening of conditions was performed for **1e**, having a 4-methylphenyl substituent at the alkyne, which yielded a 4 : 1 mixture of **2e** and **4e** under the initial conditions (Scheme 3, conditions *a*).

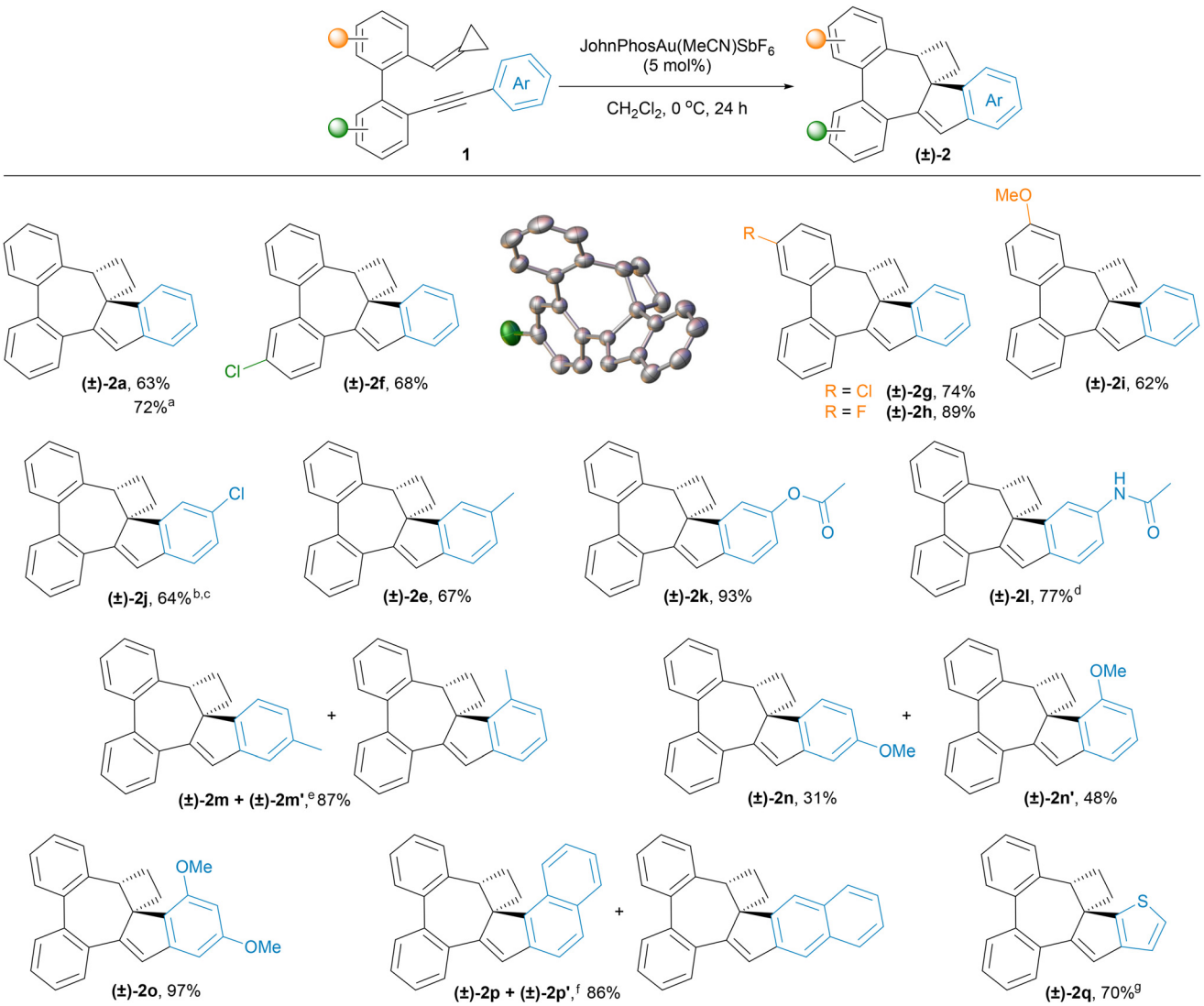
Thus, we found that it is possible to selectively obtain **4e** by heating to 70 °C in 1,2-dichloroethane (DCE) (conditions *b*), whereas lowering the temperature to 0 °C and using JohnPhosAu(MeCN)SbF_6 as the catalyst (conditions *c*) led to the selective formation of **2e**. Moreover, we proved that the isolated compound **2e** can be transformed into product **4e** with full conversion by heating in the presence of the gold catalyst under conditions *b*, indicating that **2e** is an intermediate in the formation of **4e**. Based on these observations, the formation of **4** can be explained by an independent catalytic cycle, in which the gold complex would coordinate with the double bond present in **2**, leading to the carbocationic intermediate **V**. This intermediate could experience a bond migration generating intermediate **VI**, in which the four-membered ring has expanded to a five-membered ring, and the seven-membered ring has contracted to a six-membered ring. In accordance with the experimental results, the proposed skeletal rearrangement appears to involve a relatively high energy barrier, requiring heating to proceed efficiently. However, this evolution of intermediate **V** would be favored when the aryl group is electron-donating and therefore able to stabilize the new carbocation present in **VI**, which would explain the higher amount of **4** observed in the cyclization at room temperature of substrates bearing alkynes with higher electron-rich character.



Scheme 3 Preliminary results of the gold-catalyzed cyclization of enynes with electron-donating substituents at the alkyne.

After establishing the appropriate conditions for the selective synthesis of both types of polycyclic compounds (**2** and **4**), with a tricyclic bridgehead carbon center, we next explored the scope of these transformations. First, we tested the cyclization of various *o*-cyclopropylidenemethyl-*o*′-alkynylbiaryls **1** using 5 mol% of JohnPhosAu(MeCN)SbF_6 at 0 °C in CH_2Cl_2 (Scheme 4). The model substrate **1a** selectively cyclized under these conditions providing **2a** in good yields, which was further improved when the reaction was carried out at the 1 mmol scale. In addition, the method allowed the synthesis of derivatives **2** with varied substitution patterns and diverse functional groups. The reaction is compatible with the presence of substituents in any of the arene rings of the biphenyl moiety, including halogens such as chlorine or fluorine, or a methoxy group, yielding in any case the corresponding polycyclic compounds **2f–i** in good yields. It also tolerates diverse substituents at the aryl group of the alkyne, including an electron-withdrawing halogen atom (**2j**) and electron-donating substituents, such as methyl or methoxy groups (**2e** and **2m–o**), and functional groups like an ester (**2k**) or an amide (**2l**).[17,18] When the substituent is located at the *meta* position, mixtures of the two possible regioisomers, arising from the attack of the two non-equivalent nucleophilic positions of the arene, are observed (**2m**/**2m**′ and **2n**/**2n**′). Conversely, *ortho* substitution in the alkyne ring was not well tolerated. For substrates having either a chlorine atom or a methyl group in this position, mixtures of products were obtained, among which compounds **2** and **3** were detected but could not be isolated. Finally, the reaction is compatible with substrates bearing fused arenes (**2p**) or heteroaromatic substituents (**2q**). For the synthesis of **2q**, the temperature had to be lowered to −20 °C, as significant amounts of rearranged compound **4q** formed even at 0 °C. The structure of polycyclic compounds **2** was unambiguously confirmed by X-ray diffraction analysis of **2f**.

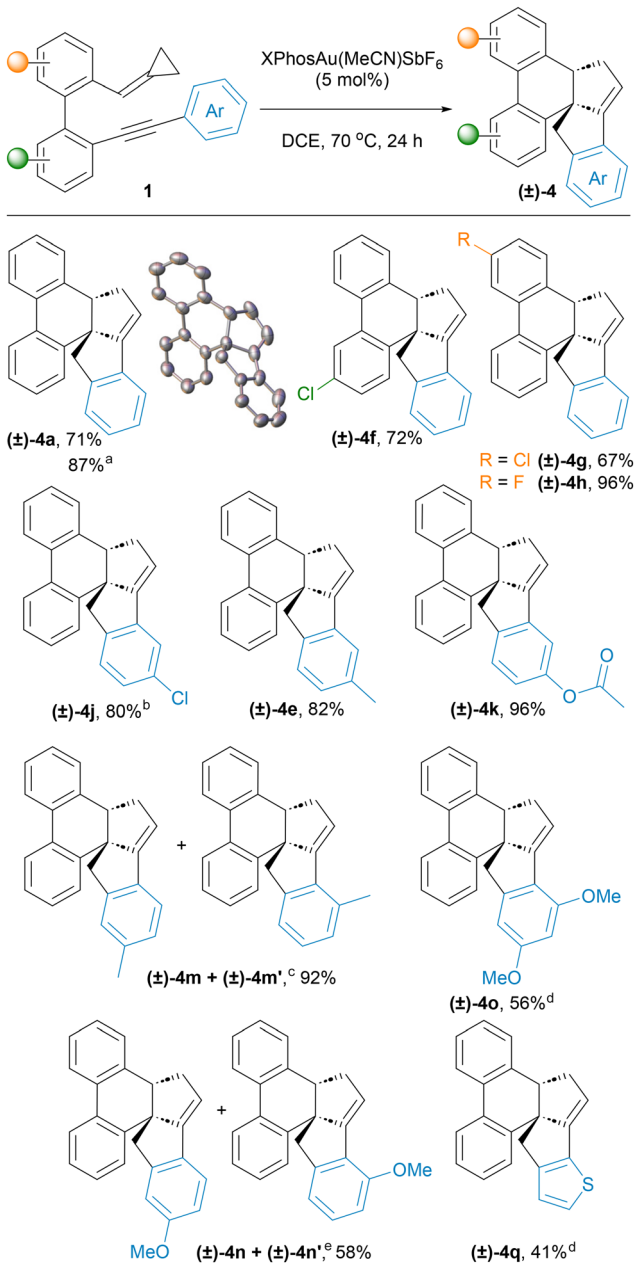
On the other hand, the cyclization of *o*-cyclopropylidenemethyl-*o*′-alkynylbiaryls **1** using XPhosAu(MeCN)SbF_6 as the catalyst at high temperature provided a method for the syn-



Scheme 4 Synthesis of polycyclic derivatives **2** (thermal ellipsoids are displayed at 50% probability level), conducted using 0.3 mmol of **1** in CH_2Cl_2 (0.05 M). [a] Using 1 mmol of **1a**. [b] Performed at rt. [c] 10% of **3j** was also isolated. [d] Using XPhosAu(MeCN)SbF_6 at 40° C. [e] 1.2 : 1 ratio observed in the crude reaction mixture. [f] 1.6 : 1 ratio observed in the crude reaction mixture. [g] Performed at −20 °C.

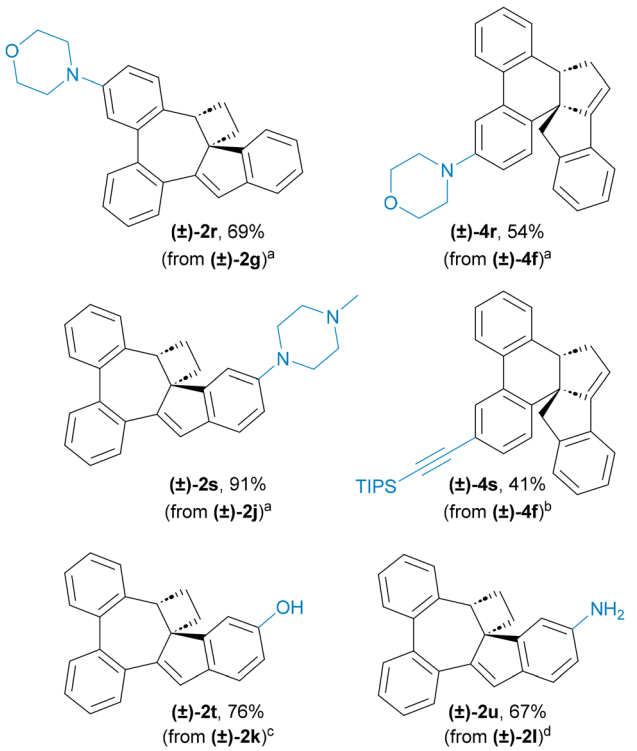
thesis of polycyclic compounds **4** (Scheme 5). This transformation is also scalable to the 1 mmol scale and is compatible with different groups, both in the biaryl moiety (**4f–h**) and in the alkyne substituent (**4j–q**). The structure of polycycles **4** was confirmed by X-ray diffraction analysis of **4a**.

As mentioned in the synthesis of polycycles **2**, substrates having *meta*-substituted arene rings at the alkyne led to mixtures of isomers (**4m**/**4m′** and **4n**/**4n′**), each of which could be explained by the rearrangement of one of the regioisomers (**2m**/**2m′** and **2n**/**2n′**) shown in Scheme 4. Complete selectivity towards the formation of polycycles **4** was observed in all cases under the optimal conditions, except for the cyclization of **1j**, with an electron-deficient arene at the alkyne, in which case **4j** was obtained together with minor amounts of the non-rearranged compound **2j** (**4j** : **2j** = 3 : 1).[19] Nevertheless, increasing the reaction temperature to 90 °C led to the selective formation of **4j**, which could be isolated in high yield. In contrast, for starting materials having particularly electron-rich arenes at the alkyne, such as **1o** and **1q**, heating to 40 °C was enough to promote full rearrangement towards the formation of **4o** and **4q**. Therefore, the stability of intermediate **VI** with respect to **V** (see Scheme 3) seems to be essential in enabling this transformation. In this regard, the cyclization of **1p**, with a naphthyl group, led to an inseparable mixture of **2p′** and **4p**, that is, the initially formed regioisomer **2p** was completely rearranged whereas **2p′** remained unchanged, which can be attributed to the difference in the stability of **VIp** and **VIp′**.[20] On the other hand, **1l**, containing an amide group, led mainly to **2l** under the optimal conditions for the synthesis of polycycles **4**. Heating to 90 °C promoted the expansion, but only a 1 : 1 inseparable mixture of **2l** and **4l** could be achieved.



Scheme 5 Synthesis of rearranged polycycles **4** (thermal ellipsoids are displayed at 50% probability level), conducted using 0.3 mmol of **1** in DCE (0.05 M). [a] Using 1 mmol of **1a**. [b] Performed at 90 °C. [c] 1.1 : 1 ratio observed in the crude reaction mixture. [d] Performed at 40 °C. [e] 1.3 : 1 ratio observed in the crude reaction mixture.

In addition, both novel TBCC-containing polycyclic cores exhibit good stability, allowing for further functionalization at their periphery under a variety of conditions (Scheme 6). For instance, amine groups can be introduced from chloro-substituted derivatives of compounds **2** and **4** *via* Buchwald–Hartwig reaction. Similarly, alkynes can be incorporated through Sonogashira cross-coupling. Moreover, free alcohols and amines can be accessed by hydrolysis of the corresponding ester- or amide-containing derivatives.



Scheme 6 Synthetic transformations of TBCC-containing polycycles **2** and **4**. [a] Morpholine or *N*-methylpiperazine (2 equiv.), $Pd_2(dba)_3$ (10 mol%), XPhos (20 mol%), NaO*t*Bu (2 equiv.), toluene, 110 °C, 4 h. [b] (Triisopropylsilyl)acetylene (2 equiv.), $Pd_2(dba)_3$ (1 mol%), XPhos (4 mol%), K_2CO_3 (3 equiv.), DMF, 120 °C, 16 h. [c] NaOH (10 M in MeOH), MeOH, rt, 1 h. [d] NaOH (4 M in MeOH), 1,4-dioxane, 80 °C, 16 h.

Conclusions

In conclusion, two different kinds of polycyclic structures containing tricyclic bridgehead carbon centers can be selectively synthesized from *o*-cyclopropylidenemethyl-*o'*-alkynylbiaryls *via* divergent gold-catalyzed cycloisomerizations. The presence of the cyclopropylidenemethyl unit promotes an initial selective 7-*exo-dig* cyclization, in contrast to the 6-*endo-dig* cyclizations observed for similar substrates having the alkene in a linear chain. The final outcome of the reaction is mainly controlled by temperature. Thus, compounds **2**, having seven-, five- and four-membered rings that share a bridgehead quaternary center, are selectively obtained and isolated in good yields using 5 mol% of JohnPhosAu(MeCN)SbF_6 as catalyst at 0 °C. On the other hand, the use of XPhosAu(MeCN)SbF_6 at increased temperatures (40–90 °C) leads to the selective formation of polycycles **4**, which contain a tricyclic bridgehead carbon center shared by two five- and one six-membered rings. Compounds **4** are proposed to be formed by a gold-catalyzed rearrangement of polycycles **2**. This transformation proceeds smoothly for substrates having electron-rich groups at the alkyne and requires higher temperatures as the electron-donating character decreases, which is attributed to the relative stability of the carbocations involved in the rearrangement.

The methodologies reported herein are expected to be useful in drug discovery programs for the exploration of novel chemical spaces.

Author contributions

M. A. F.-R. and P. G.-G. conceived and supervised the investigation. L. S.-J. optimized the reaction conditions. L. S.-J. and A. G. conducted all experiments and characterized the novel compounds. P. G.-G. prepared the original draft of the manuscript. All the authors reviewed and edited the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the SI.

Experimental details, NMR spectra for all new compounds, and X-ray crystallographic data for **2f** and **4a**. See DOI: https://doi.org/10.1039/d5qo00816f.

CCDC 2351880 and 2351888 contains the supplementary crystallographic data for this paper.[21]

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17 For substrate **1l**, a significant amount of decomposition was observed under the optimized conditions, leading to a low yield of **2l**. However, **2l** could be isolated in good yield by using XPhosAu(MeCN)SbF_6 as the catalyst and heating to 40 °C.

18 Substrates **1b–d**, bearing electron-withdrawing substituents on the alkyne, did not provide synthetically useful amounts of polycycles **2** under these conditions. Dibenzoheptafulvenes **3** remained the major products, although they were isolated in lower yields than those shown in Scheme 2.

19 According to the mechanism shown in Scheme 3, this could be explained by the lower stability of carbocation **VIi** compared to those having electron-rich arenes.

20 In **VIp**, the positive charge would be localized in a carbon bonded to the α position of the naphthalene, whereas in **VIp′**, it would be bonded to the β-position.

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