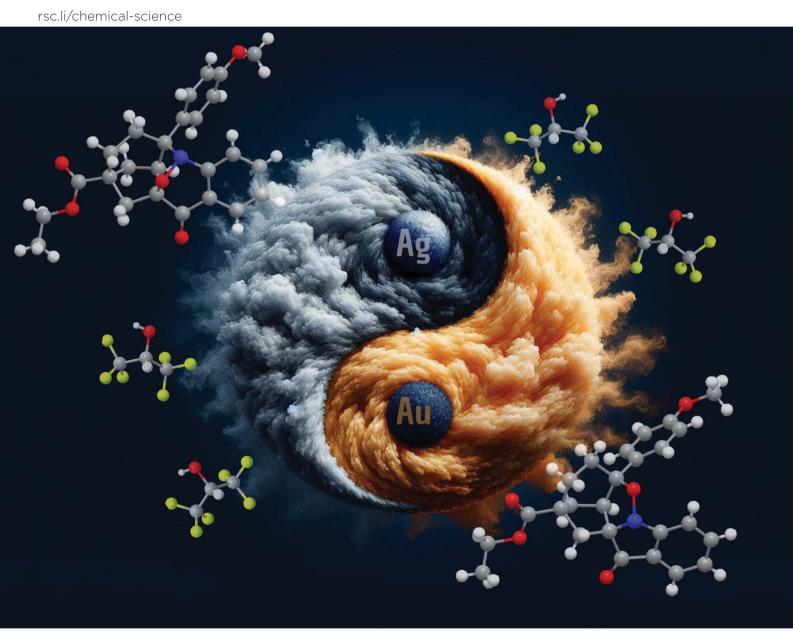
Chemical Science

Volume 16 Number 38 14 October 2025 Pages 17509-17972



ISSN 2041-6539



EDGE ARTICLE

Véronique Michelet *et al.*Silver- and gold-catalyzed divergent cascade cycloisomerization/[3 + 2] *versus* [2 + 2 + 1] cycloaddition towards a stereoselective access to heterohexacyclic derivatives



Chemical Science



EDGE ARTICLE

View Article Online
View Journal | View Issue



Cite this: Chem. Sci., 2025, 16, 17611

dll publication charges for this article have been paid for by the Royal Society of Chemistry

Received 17th July 2025 Accepted 9th September 2025

DOI: 10.1039/d5sc05338b

rsc.li/chemical-science

Silver- and gold-catalyzed divergent cascade cycloisomerization/[3 + 2] versus [2 + 2 + 1] cycloaddition towards a stereoselective access to heterohexacyclic derivatives

Emilie Gentilini,^a Anaïs Bouschon,^a Vincent Davenel,^b Fabien Fontaine-Vive,^a Jean-Marie Fourquez^b and Véronique Michelet ^b*

A divergent cascade cycloisomerization/[3 + 2] vs. [2 + 2 + 1]-cycloaddition via gold or silver catalysis has been reported in 1,1,1,3,3,3-hexafluoroisopropan-2-ol (HFIP). The reaction was independently optimized for both metals leading to two hexacyclic derivatives comprising a bicyclo[3.2.1]octane unit and respectively a benzoxazinone or a N-oxo-indolinone pattern. The unique influence of HFIP was demonstrated via 19 F and 31 P NMR analyses. This process, involving the formation of C-C, C-O, and C-N bonds and of three stereogenic centers led to privileged scaffolds in a context of the search for increased molecular diversity of drug-candidate libraries. The versatility of this methodology was demonstrated by the synthesis of 25 different hexacyclic scaffolds (yields up to 98%). Gram-scale synthesis as well as post-functionalization reactions illustrated the versatility and interest of these catalytic transformations. DFT calculations were performed to rationalize the proposed mechanism of this cascade reaction.

to heterocycles (Fig. 1C).9

Introduction

Regarding the relevance of complex heterocycles in biologically active molecules but also the recent concept of "Escape from Flatland",1 designing new and sustainable methods for access to poly-heterocyclic derivatives appears to be still very challenging. In this context, catalytic cascade cycloisomerization processes offer an access to diverse and complex scaffolds, while maintaining atom economy and mild reaction conditions. Among these cascade reactions, the cycloisomerization of o-(alkynyl)nitrobenzene derivatives drew our attention, as in recent years, in addition to the classic reactivity leading to the anthranil or isatogen units,2 different intra-3 or intermolecular4 metal-catalyzed cascade reactions have been reported (Fig. 1). In 2011, Liu and co-workers reported a gold-catalyzed intermolecular nitroalkyne redox cyclization/[2 + 2 + 1]-cycloaddition leading to an azacyclic compound in a stereoselective manner (Fig. 1A).5 In comparison with the literature on these goldcatalyzed transformations, studies on the catalytic activity of silver compounds are relatively scarce.6 For example, a sequential silver-catalyzed oxidative cyclization of 2-alkynylanilines has been reported by Arcadi and our group leading to anthranil

derivatives (Fig. 1B).7 Hexafluoroisopropanol (HFIP) is a power-

ful solvent widely used for stabilizing charged intermediates,8

but more recently used in organometallic chemistry, particularly in gold catalysis. Its strong hydrogen-bonding ability and

high polarity was a key feature for accelerating reaction rates and improving selectivity. The combination of 1,1,1,3,3,3-

hexafluoroisopropanol (HFIP) with gold complexes has proven

highly effective in catalytic cycloisomerization reactions leading

On the other hand, designing methods for selectively synthesizing different products from the same starting material, only by modifying the reaction conditions and/or the catalysts, is challenging but represents also a valuable tool for divergent synthesis.¹³ In this context, starting from a 1,6-cyclohexenylalkyne scaffold, we envisaged to explore the reactivity of

which would be an asset and would hopefully contribute to high

regio- and stereoselectivity in the resulting products.12

While combination of HFIP with silver catalysts in cycloisomerization reactions is limited, 10 the synergistic effects observed in gold catalysis suggest that exploring HFIP's role in silver-catalyzed processes could be a promising area for future research. Following our interest in organometallic atomeconomical transformations, 11 we therefore embarked in this study and anticipated that this synergy would facilitate the activation of alkynes in the case of silver complexes as for gold catalysts. Additionally, HFIP is known to improve the solubility of substrates and to create a network closed to water network,

[&]quot;Université Côte d'Azur, Institut de Chimie de Nice, Valrose Park, 06108, Nice Cedex 2, France. E-mail: veronique.michelet@univ-cotedazur.fr

^bInstitut Servier d'Innovation Thérapeutique Paris-Saclay, 22 Route 128 – Rue Francis Perrin, 91190 Gif sur Yvette, France

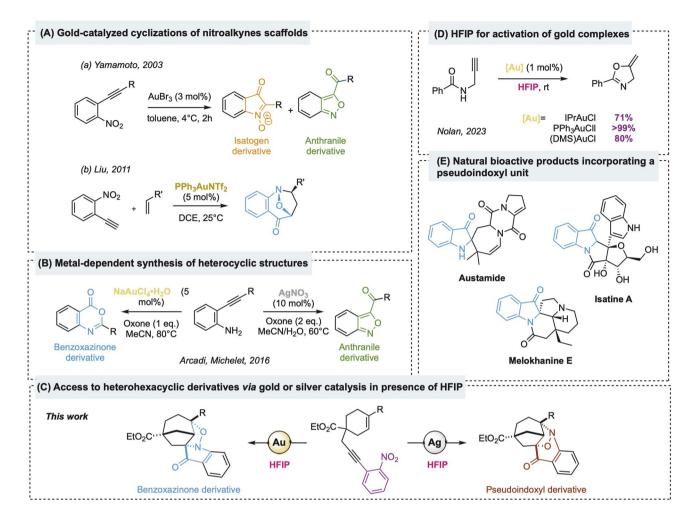


Fig. 1 (A) Gold-catalyzed cyclizations of nitroalkyne scaffolds. (B) Metal-dependent synthesis of heterocyclic structures. (C) Access to heterohexacyclic derivatives via gold or silver catalysis in the presence of HFIP. (D) HFIP for activation of gold complexes. (E) Natural bioactive products incorporating a pseudoindoxyl unit.

such substrates while adding an o-nitrophenyl on the alkyne (Fig. 1D). Considering the potent reactivity of nitroalkynes derivatives but also of 1,6-enynes, we expected an intramolecular cascade reaction involving these three functions. We wish therefore to report therein a divergent synthesis of two hexacyclic derivatives via a silver or gold-catalyzed cycloisomerization and [3 + 2] or [2 + 2 + 1] cycloaddition cascade reaction (Fig. 1D).

Starting from the same compound, and by switching from gold to silver catalysts, we designed two unprecedented selective methods leading to complex scaffolds bearing respectively a benzoxazinone and a *N*-oxo-indolinone units. These structures represent privileged scaffolds in a search for increased molecular diversity of drug-candidate libraries.

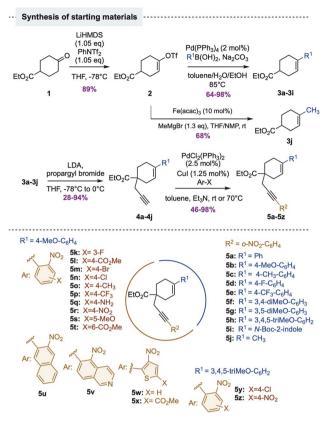
Results and discussion

The 1,6-enyne derivatives were prepared through a four-step sequence starting from ethyl 4-oxocyclohexane carboxylate 1.^{11a,14} After triflation, a Suzuki-Miyaura coupling was performed (yields from 64% to 98%) to reach derivatives 3a to 3i

(Scheme 1). The substrate $3\mathbf{j}$ was obtained via an iron-coupling using MeMgBr and 10 mol% of Fe(acac)₃ in a THF/NMP mixture, according to a procedure described by Fürstner's group. Derivatives $3\mathbf{a}$ to $3\mathbf{j}$ were then engaged in a propargylation reaction with yields from 28% to 94% and subsequently in a Sonogashira cross-coupling, leading to the desired starting 1,6-enynes $5\mathbf{a}$ to $5\mathbf{z}$ (26 derivatives) with yields ranging from 46% to 98% (Scheme 1). The substitution on the aromatic ring R^2 was highly diversified with electron-withdrawing and electron-donating groups. Similar modifications were designed for group R^1 (see SI for details). We also introduced relevant heterocycles such as an indole ($5\mathbf{i}$), a nitroquinoline ($5\mathbf{v}$) and 2-nitrothiophenes ($5\mathbf{w}$, $5\mathbf{x}$). We then initiated our study with 1,6-enyne $5\mathbf{b}$ bearing a para-methoxyphenyl as model substrate.

Regarding the different functions, five products were initially observed, bicyclic derivatives **6** and 7 coming from respectively the 6-*endo* and 5-*exo* cycloisomerization of the enyne moiety, product **8b** obtained after the classical nitroalkyne cyclization^{15,16} and hexacycles **9b** and **10b** resulting from the cycloisomerization/[3 + 2] or [2 + 2 + 1]-cycloaddition cascade reaction (Table 1).

Edge Article



Scheme 1 Synthesis of starting materials.

Regarding the complexity and the similarity of these two products **9b** and **10b**, their structures were unambiguously confirmed by X-ray diffraction of derivatives **9b** and **10b**, bearing a *para*-methoxyphenyl as aromatic ring (Fig. 2).¹⁷

Due to the similarities between each product, we evaluated ratios between the five products by ¹H NMR using 3,4,5-trichloropyridine as an internal standard. We evaluated the efficiency of our previous conditions, eg 5 mol% of IPrAuNTf2 in toluene at 80 °C. We obtained a selectivity of 37% for the anthranile derivative 8b. We therefore started our investigations by testing different solvents and observed that the use of DCE at room temperature gave a better yield for 8b (49%) and 10b (26%) (Table 1, entry 2). We then explored the impact of the ligand. Switching from NHC ligand to PPh₃ provided a major selectivity (56%) for hexacycle 10b. Keeping in mind the existing literature cited before on the difference of selectivity between the use of silver and gold catalysts on similar transformations,⁷ we wondered if silver catalysts were suitable in our reaction. We first employed AgNO3 but unfortunately, no conversion was observed (Table 1, entry 4). Rewardingly, using 5 mol% of AgNTf2 in DCE at room temperature led to the formation of product 9b as major product despite a modest yield and a partial conversion (Table 1, entry 5). Increasing the temperature to 80 °C allowed a total conversion with a better yield of 55% for 9b (Table 1, entry 6). Different silver salts had been tested such as AgSbF₆, AgOTf, Ag₂CO₃ (Table 1, entries 7 to 9), but none of them gave satisfying results. Interestingly, the use

of AgBF4 led to a total selectivity for hexacycle 9b with a yield of 56% (Table 1, entry 10). Further optimizations in different solvents did not give satisfactory results, as no reaction occurred in toluene or acetonitrile (Table 1, entries 11-12) and a mixture of 8b and 9b was observed in nitromethane (Table 1, entry 13). We performed the cyclization in HFIP and observed a better yield of 67% (Table 1, entry 14). To determine if this result was solely due to the protic nature of HFIP or to its properties,8 we also conducted the reaction in MeOH, PrOH, ^tBuOH and TFE, but no reactivity was detected (Table 1, entries 15-18). Considering the unstable aspect of silver salts, we envisaged to use a ligand to increase the efficiency of the reaction, unfortunately the addition of 20 mol% PPh3 resulted in a total loss of reactivity (Table 1, entry 19).18 Finally, increasing the catalytic charge from 5 to 10 mol% (Table 1, entry 20) allowed to reach a yield of 78%, giving us our final conditions for the formation of **9b**: 10 mol% of AgBF₄ in HFIP at 40 °C.

With these successful conditions for 9b in hands, we then came back to some optimization that would allow the formation of hexacycle 10b. The best result obtained so far was 43% yield using 5 mol% of PPh₃AuNTf₂ in DCE at room temperature (Table 2, entry 1). We started the optimization by performing the reaction in different solvents, but once again, no better results were obtained in nitromethane, acetonitrile, chloroform or methanol (Table 2, entries 2 to 6). We mentioned earlier the growing interest on the use of HFIP for transition-metal catalysis and this applies particularly to reactions involving gold complexes. HFIP demonstrated indeed an ability to activate gold chloride species. It has been shown that the acidic properties of HFIP weaken the Au-Cl bond by creating a network of hydrogen bonds, enabling the generation of the active cationic gold form.9 Regarding the drawbacks of the use of additives such as silver salts but also the great solubility of [AuCl(L)] complexes in this solvent, HFIP appeared to be very suitable for methodologies involving gold catalysis. In this context, we performed the reaction in HFIP, using first the active species PPh₃AuNTf₂ which led to a yield of 48% for 10b (Table 2, entry 7). Switching to the usually unreactive chloride form, PPh₃AuCl, gladly provided a full selectivity for 10b with a yield of 56% (Table 2, entry 8). We already observed at the beginning of the optimization that NHC ligands favored the formation of 8b, so the chloride forms of such complexes (IPrAuCl and SIPrAuCl) were also engaged in HFIP (Table 2, entries 8 and 9). A slight difference was observed and a yield of 50% was obtained for 8b using SIPrAuCl in HFIP at rt (entry 10). Considering the higher ease of use of this catalyst, these conditions were kept as final ones in order to target the anthranile scaffold of product 8.

Concerning the access to hexacyclic scaffold **10b**, we then explored the effect of other phosphine ligands. We selected two phosphine-based ligands and one phosphite. JohnPhos and the phosphite-ligand based complex (Table 2, entries 11 and 13) gave similar results, a mixture of all the five products with a slight selectivity around 30% for **10b** (with a conversion of 84% for the phosphite) while dppm (Table 2, entry 12) provided a selectivity of 40% for the desired hexacycle. With the best result with triphenylphosphine gold(I) chloride in hand, we finally investigated the effect of the temperature (Table 2,

Table 1 Optimization of reaction targeting hexacycle 9b

Entry	[M]	T (°C)	Solvent	6 ^a (%)	7 ^a (%)	8b ^a (%)	9b ^a (%)	10b ^a (%)
1	$IPrAuNTf_2$	80	Toluene	4	5	37	Traces	13
2	$IPrAuNTf_2$	rt	DCE	_	_	49	3	26
3	PPh_3AuNTf_2	rt	DCE	3	3	6	21	43
4^b	$AgNO_3$	rt	DCE	_	_	_	_	_
5 ^c	$AgNTf_2$	rt	DCE	_	_	6	31	12
6	$AgNTf_2$	80	DCE	_	_	8	55	_
7	AgSbF ₆	80	DCE	_	_	_	37	_
8^d	AgOTf	80	DCE	_	_	_	43	_
9^b	Ag_2CO_3	80	DCE	_	_	_	_	_
10	AgBF_4	80	DCE	_	_	_	56	_
11	$AgBF_4$	80	Toluene	_	_	_	_	_
12^b	AgBF_4	80	MeCN	_	_	_	_	_
13 ^b	$AgBF_4$	80	$MeNO_2$	_	_	19	27	_
14	AgBF_4	40	HFIP	_	_	_	67	_
15^b	AgBF_4	40	MeOH	_	_	_	_	_
16^b	AgBF_4	40	ⁱ PrOH	_	_	_	_	_
17 ^b	AgBF_4	40	t BuOH	_	_	_	_	_
18^b	AgBF_4	40	TFE	_	_	_	_	_
$19^{b,e}$	AgBF_4	40	HFIP	_	_	_	_	_
20 ^f	$AgBF_4$	40	HFIP	_	_	_	78	_
21^f	AgBF_4	80	DCE	_	_	_	65	_
22^g	_	80	DCE	_	_	_	_	_

^a Determined by ¹H NMR. ^b 0% conversion. ^c 66% conversion. ^d 62% conversion. ^e Addition of 20% of PPh₃. ^f 10 mol% of [Ag]. ^g Addition of 10 mol% of HNTf₂, only degradation of starting material was observed.

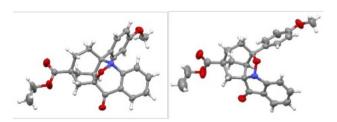


Fig. 2 X-ray diffractions of 9b (left) and 10b (right).

entries 14 and 15) but we observed lower activity at lower or higher temperature. A control experiment without gold species was performed and no reaction was observed (Table 2, entry 16). Thus, we finally chose as final conditions for **10b** the use of 5 mol% of PPh₃AuCl in HFIP at room temperature.

Interactions between metal complexes and HFIP had also been investigated *via* NMR studies: with ¹⁹F NMR for AgBF₄ (Fig. 3, left) and ³¹P NMR for PPh₃AuCl (Fig. 3, right).

Both signals (in green) showed an upfield signal in presence of HFIP compared to the one of the complexes alone (in red). This result supports the existence of an interaction between the complex used — either gold or silver — and HFIP, potentially leading to the formation of a network between these species. This could also explain the particular selectivity observed when HFIP is used as the solvent.

With selective conditions for each of the desired products in hand, we then started to evaluate the scope and the limitations of our reactions, by first targeting hexacycle **9b** bearing a bicyclo [3.2.1]octane and a benzoxazinone units (Scheme 2).

We began by the modification of the R^1 group. Our model substrate was with a p-methoxy-phenyl, so we first ran the reaction with a phenyl substituent that led to the exact same yield of 78% (**9a**, **9b**). Switching to p-tolyl (**9c**) or 3,4-dimethoxyphenyl (**9f**) aromatic rings provided the desired compound in modest yields. Unfortunately, we could not isolate product **9d**, where R^1 was a p-fluorophenyl group. The synthesis of starting materials bearing electron-withdrawing groups on R-position was somewhat complicated, however, the silver-

Table 2 Optimization of reaction targeting hexacycle 10b

Entry	[M]	Solvent	6 ^a (%)	7 ^a (%)	8b ^a (%)	9b ^a (%)	10b ^a (%)	Conv ^b (%)
1	PPh_3AuNTf_2	DCE	2	4	6	21	43	
2	PPh ₃ AuNTf ₂	Toluene	6	6	_	18	41	
3	PPh ₃ AuNTf ₂	$MeNO_2$	2	_	_	16	18	76
4	PPh ₃ AuNTf ₂	MeCN	1	_	5	11	10	69
5	PPh ₃ AuNTf ₂	$CHCl_3$	4	_	_	18	20	90
6	PPh ₃ AuNTf ₂	MeOH	_	_	_	_	_	0
7	PPh ₃ AuNTf ₂	HFIP	_	_	_	4	48	
8	PPh₃AuCl	HFIP	_	_	_	_	56	
9	IPrAuCl	HFIP	_	_	47	7	17	
10	SIPrAuCl	HFIP	_	_	50	6	20	
11	L ¹ AuCl	HFIP	8	4	14	8	30	
12	$L^2Au_2Cl_2$	HFIP	6	4	6	_	40	
13	$L^3Au_2Cl_2$	HFIP	3	_	9	8	28	84
14^c	PPh₃AuCl	HFIP	_	_	_	11	36	90
15^d	PPh ₃ AuCl	HFIP	_	_	_	_	50	
16	None	HFIP	_	_	_	_	_	0
				AuCl	'Bu Q Q Q AuCl	/Bu 〉 ` [†] Bu		

^a Determined by ¹H NMR. ^b Conversion when not full. ^c Reaction performed at 0 °C. ^d Reaction performed at 40 °C.

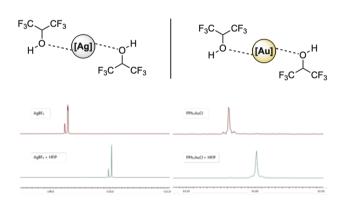


Fig. 3 Interactions of AgBF $_4$ and PPh $_3$ AuCl with HFIP in 19 F NMR (left) and 31 P NMR (right).

catalyzed cyclization step provided compound 9e in a good yield of 65%. The *para* position for substitution seemed to be crucial, with no reaction occurring for example with 9g, while an excellent yield of 98% was obtained for 9h bearing 3,4,5-trimethoxyphenyl as R^1 . We started to perceive the limitation of our catalytic system with N-Boc-indole instead of the phenyl group (9i). With a methyl group in position R^1 , the desired compound 9j was also not observed, but another product was isolated (Scheme 6, *vide infra*). We continued our investigations by modifying the aromatic ring bearing the nitro group. Adding a fluor in *meta* position led to hexacycle 9k with a fair yield of 65%. The influence of electronic properties of the aromatic substituent (R^2) was also evaluated: the presence of an electron-

donating group led to a loss of reactivity, as no conversion was observed for 50, 5q and 5s. In contrast, the introduction of electron-withdrawing groups proved to be effective, with yields ranging from 48% to 76%. The steric hindrance was also studied, using methylester in ortho (9t) and para (9l) positions as substituents on the R^2 aromatic ring. We obtained the corresponding products with respectively 74% and 76% yields, indicating that the ortho position is as well tolerated as the para. We were pleased to observe that the reaction conditions were also suitable with halogen substituents (9m, 9n), allowing to envisage cross-couplings as further post-functionalization. The use of larger aromatic systems such as naphthalene provided product 9u, which could not be cleanly isolated from several byproducts. Replacing the phenyl ring by a quinoline one also proved successful, with 50% yield for the compound 9v while the introduction of a thiophene unit didn't allow the synthesis of hexacyclic compounds 9w and 9x. Regarding the excellent yield obtained using 3,4,5-trimethoxyphenyl as R^1 group (9h), we wondered if it was compatible with more decorated R^2 aromatic rings. Finally, compounds 9v and 9z were isolated with slightly better yields than their respective p-methoxyphenyl substituted analogs (72% yield for 9y compared to 65% for 9n and 50% yield for 9z compared to 48% for 9r).

To investigate the scope of the formation of product **10**, we selected diverse substrates and explored their reactivity using triphenylphosphine gold chloride as catalyst. These conditions appeared unexpectedly to be more challenging compared to those optimized derivative **9** (Scheme 3). Indeed, only seven out of the twelve derivatives led to the desired corresponding

Scheme 2 Scope and limitations of the synthesis of derivatives 9.

compounds. In the case of **10e** and **10i**, a mixture of starting material and the anthranile derivatives **8**, resulting solely from the cyclization of the nitro moiety with the alkyne, was observed. Rewardingly, we were pleased to observe that switching p-methoxyphenyl to 3,4-dimethoxyphenyl as R^1 led to the formation of hexacycle **10f** with 89% yield, and 3,4,5-trimethoxyphenyl provided **10h** with 32% yield. Remarkably, substitution with a methyl group was also suitable with these conditions and led to compound **10j** with a yield of 15%. Concerning R^2 substituent, adding an ester moiety in para position decreased the yield to 13% (**10l**) while adding a Cl atom led to a 40% yield (**10y**). Replacing the phenyl by a quinoline ring (**10v**) provided a modest yield of 21%. Example **10k** was, for its part,

Scheme 3 Scope and limitations of the synthesis of derivatives 10

observed on the crude ¹H NMR spectra but unfortunately could not be isolated from several by-products.

To fully complete our study and get a vast array of products, the formation of anthranile scaffold **8** was also investigated, using the conditions described in Table 2, entry 10. Six 1,6-enynes were engaged in presence of 5 mol% of SIPrAuCl in HFIP at room temperature (Scheme 4). Switching from p-methoxyphenyl (**8b**, 50% yield) to a phenyl (**8a**) or a 3,5-dimethoxyphenyl (**8c**) allowed the formation of desired compounds with a similar yield of 51%. Concerning R^2 , three different positions (C3, C4, C5) and substituents were investigated. The introduction of a fluor atom provided compound **8k** with a yield of 56% while a methoxy in C5-position led to **8s** with a slightly lower yield of 44%. For its part, bromo-substituted anthranile derivative **8m** was obtained with a satisfying yield of 69% (Scheme 4).

Concerning the mechanism of the reaction, different pathways could be envisaged (Schemes 5 and 6). Bicyclo[3.2.1]nonene 6 and bicyclo[3.2.1]octene 7 resulted respectively from the cycloisomerization of the 1,6-enyne moiety under a 6-endo or a 5-exo pathway, as already described by our group. 114 Anthranile derivative 8 was obtained by cyclization of the nitroalkyne framework. Such reactivity has been well described in the

Edge Article Chemical Science

Scheme 4 Scope and limitations of the synthesis of derivatives 8.

literature,³ so we could easily assume that the addition of the nitro group onto the gold-activated alkyne occurred via a 6-endodig process leading to compound 8 via the α -oxo-gold-carbene intermediate C (Scheme 5). Regarding hexacyclic derivatives 9 and 10, based on the literature,^{3,5} we envisaged that the nitro function could be added via a 5-exo-dig route allowing the formation of α -oxo-metal-carbene intermediate **F**. The passage through such intermediate had been proven thanks to an intramolecular trapping on substrate 5**j** (Scheme 6). Indeed, in presence of AgBF₄, the cyclization of 5**j** did not lead to the expected hexacyclic derivative 9**j** but product 11 was isolated with a yield of 82%. In the presence of PPh₃AuCl, 10**j** was synthesized with a yield of 15% but 11 was also obtained as a major product (46% yield).

This product resulted from the intramolecular trapping of intermediate 5j-F by the alkene of the cyclohexene scaffold (Scheme 6). These results demonstrated the existence of α -oxosilver-carbene and α -oxo-gold-carbene as intermediates for the synthesis of hexacyclic derivatives 9 and 10.

Then, two different routes could be proposed for the subsequent intramolecular cyclization of metal carbenoid ${\bf F}$. Indeed, depending on the heteroatom of the nitroso group involved in the coordination, the α -oxo-metal-carbene ${\bf F}$ could cyclize to form either a five-membered ring with a coordination of the nitrogen, or a six-membered ring with a coordination of the oxygen atom. We investigated via DFT calculations the different free energies of these intermediates in the presence of gold and silver complexes in order to rationalize the selectivity between the two metals. Interestingly, in the case of a silver catalyst, the

Scheme 5 Proposed mechanism of the reaction.

coordination of oxygen, leading to the six-membered ring intermediate **G-Ag** appeared to be the most stable species. Intermediate **I-Ag**, corresponding to nitrogen-coordination had a higher free enthalpy of 27.1 kcal mol⁻¹ (Scheme 5, **G-Ag** vs. to **I-Ag**). Nevertheless, while using triphenylphosphine gold chloride as catalyst, the formation of the five-membered ring was favored by a difference of 13.8 kcal mol⁻¹.

These results and some data from the literature provide strong support to propose the following mechanism. In the presence of a silver catalyst, the second cyclization occurring is a [2+2+1] cycloaddition between the alkene, the nitroso moieties and the carbon bearing the gold complex as depicted in Scheme 7.²⁰ This [2+2+1] cycloaddition proceeded first by the coordination of the oxygen atom, leading to the six-membered ring **G**. After a keto–enol tautomerism generating enol **H**, a [3+2] cycloaddition step would allow the *N*-cyclization to furnish benzoxazinone derivative **9**. In the case of triphenylphosphine gold chloride as catalyst, the coordination of the nitrogen atom of the nitroso would be preferred, leading to pseudoindoxyl scaffold **I** (Scheme 5). We assumed that the demetallation would then occur, leading to the metal-free

AgBF₄ (10 mol%) EtO₂C·····Me

+ 9j, 0%

DCE, 80°C

11, 82%

PPh₃AuCl (5 mol%)

HFIP, rt

EtO₂C······Me

N=0

+ 10j, 15%

Scheme 6 Intramolecular trapping of α -oxo-metal-carbenes.

nitrone **J**. Finally, the intramolecular [3 + 2] cycloaddition could be performed *via* a *O*-cyclization leading to derivative **10**.

In order to unveil the existence of the potential enol intermediate **H** (Scheme 5), we added a chiral ligand to perform the reaction. The use of (S)-DM-SEGPHOS led to an induction of chirality (21% of enantiomeric excess), confirming the presence of the metal during the [3+2] cycloaddition step (Scheme 8). In another hand, the use of gold complexes bearing chiral ligands didn't show any chirality induction, suggesting the formation of metal-free nitrone **J** (Scheme 5).

Under these conditions, a mixture of products **9b** and **10b** was obtained; chiral induction was only observed for compound **9b**, suggesting that only its formation was influenced by the metal. The conversion was full, indicating that the reaction did not involve kinetic resolution.

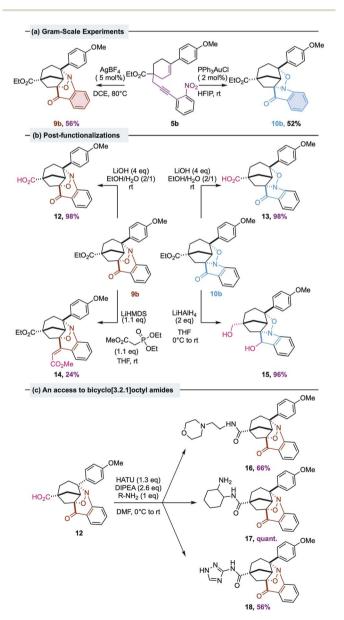
Then, the value of this divergent process catalyzed by either gold or silver could also be established by performing a scale-up and some post-functionalization experiments (Scheme 9). The gram-scale transformation of **5b** was performed on 3 mmol and led to **9b** in 56% and **10b** in 52% yield respectively (Scheme 9, (a)). Rewardingly, compounds **9b** and **10b** were subjected to several post-functionalization reactions to access new and original structures (Scheme 9, (b)). Carboxylic acids compounds **12** and **13** were obtained from respectively **9b** and **10b** using LiOH with both 98% of yields.

The reduction of the ester and the ketone of compound **10b**, using LiAlH₄, led to compound **15** in 96% yield. These two modifications greatly enhanced the substrate's capacity to form hydrogen bonds, a characteristic commonly observed in

Scheme 7 Formation of 9 via a [2 + 2 + 1] cycloaddition.

Scheme 8 Formation of 9 via a [2 + 2 + 1] cycloaddition.

biologically active molecules.²¹ Compound **9b** was also subjected to a non-optimized HWE reaction, leading to the corresponding (E)-alkene **14** in 24% yield. Finally, a wide range of bicyclo[3.2.1]octyl amides have shown biological activities, as drugs for central nervous system diseases or anxiety disorders,²²



Scheme 9 Gram-scale experiments and post-functionalization reactions.

but also as adenosine receptor antagonists²³ and thus have been patented in the last decade. In this context, we demonstrated that peptidic couplings were efficiently possible starting from compound 12, to reach three bicyclo[3.2.1]octyl amides in good to quantitative yields (Scheme 9(c), 16, 17, 18).

By using different kind of amines, we can provide an access to a huge number of molecules with potential biological activity. The reaction is completely diastereoselective and occurred under mild conditions.

Conclusion

In summary, we have developed a divergent synthesis of heterohexacyclic derivatives via a silver or gold-catalyzed cascade cycloisomerization/[3 + 2] or [2 + 2 + 1] cycloaddition in HFIP. We designed and optimized selective conditions for the formation of two different families of complexes scaffolds, bearing both a bicyclo[3.2.1]octane unit and respectively a benzoxazinone or a pseudoindoxyl moiety. We showed that interactions of HFIP with silver and gold were relevant making HFIP a key player in this study. The starting 1,6-enyne derivatives were conveniently synthesized through efficient, and highyielding reactions, including two palladium-catalyzed crosscoupling reactions. The core framework of these products was assembled via a [3 + 2] or [2 + 2 + 1] cycloaddition involving α carbonyl carbenoids, nitroso intermediates, and internal alkenes. We showed that depending on the metal, a fivemembered or a six-membered ring intermediate was favored, followed by a N- or a O-cyclization leading to two different hexacyclic derivatives. DFT calculations and control experiments were also carried out to support the proposed mechanism. Finally, we significantly increased the molecular complexity of our scaffolds, by the creation in a single step of 3 stereogenic centers and 3 cycles via the formation of C-C, C-O and C-N bonds. These building blocks contain key units commonly found in various biologically active natural products and could also be valued by several post-functionalizations. In a context of enhancing molecular diversity and complexity in chemical libraries, the tridimensional character of our compounds is currently investigated via PMI (principal moment of inertia) analysis and will be described in due course.

Author contributions

E. G. and A. B. carried out synthesis, optimization, substrate scope, and mechanistic studies. F. F.-V. performed the DFT calculations. E. G. wrote the first version of the manuscript and SI, all authors then contributed to the full preparation and participated in discussions. V. D., J.-M. F. and V. M. supervised the PhD student E. G. V. M. directed the project. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

Catalysis in HFIP: Silver- and gold-catalyzed divergent cascade cycloisomerization/[3 + 2] *versus* [2 + 2 + 1] cycloaddition towards a stereoselective access to heterohexacyclic derivatives.

CCDC 2362171 and 2362169 contain the supplementary crystallographic data for this paper.²⁴

Supplementary information is available. See DOI: https://doi.org/10.1039/d5sc05338b.

Acknowledgements

This work was supported by the Centre National de la Recherche Scientifique (CNRS) and the Université Côte d'Azur. Financial support from the Centre National de la Recherche Scientifique and the Université Côte d'Azur is gratefully acknowledged. We also gratefully acknowledge Institut Servier d'Innovation Thérapeutique for a PhD grant to E.G and for some HRMS and NMR analyses. We are grateful to MS3U-FR2769 platform (Sorbonne Université) for HRMS analyses and to Dr M. Giorgi (Aix-Marseille University) for X-ray analyses of 9b and 10b. The authors are grateful to the Université Côte d'Azur's Center for High-Performance Computing (OPAL infrastructure) for providing resources and support.

Notes and references

- 1 (a) F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem.*, 2009, 52, 6752–6756; (b) F. Lovering, *Med. Chem. Commun.*, 2013, 4, 515; (c) J. Meyers, M. Carter, N. Y. Mok and N. Brown, *Future Med. Chem.*, 2016, 8, 1753–1767.
- 2 (a) N. Asao, K. Sato and Y. Yamamoto, *Tetrahedron Lett.*, 2003, **44**, 5675–5677; (b) X. Li, T. Vogel, C. D. Incarvito and R. H. Crabtree, *Organometallics*, 2005, **24**, 62–76.
- 3 (a) P. Patel and C. V. Ramana, Org. Biomol. Chem., 2011, 9, 7327; (b) L. W. Chen, J. L. Xie, H. J. Song, Y. X. Liu, Y. C. Gu and Q. M. Wang, Org. Chem. Front., 2017, 4, 1731–1735.
- 4 (*a*) S. Zhou, Q. Liu, M. Bao, J. Huang, J. Wang, W. Hu and X. Xu, *Org. Chem. Front.*, 2021, **8**, 1808–1816; (*b*) G. Chen, Y. Wang, J. Zhao, X. Zhang and X. Fan, *J. Org. Chem.*, 2021, **86**, 14652–14662; (*c*) P. S. Dhote and C. V. Ramana, *Org. Lett.*, 2019, **21**, 6221–6224.
- 5 A. M. Jadhav, S. Bhunia, H.-Y. Liao and R.-S. Liu, *J. Am. Chem. Soc.*, 2011, 133, 1769–1771.
- 6 Silver in Organic Chemistry, ed. M. Harmata, Wiley, New Jersey, 2010.
- 7 (a) A. Arcadi, M. Chiarini, L. Del Vecchio, F. Marinelli and V. Michelet, Eur. J. Org Chem., 2017, 2017, 2214–2222; (b)
 A. Arcadi, M. Chiarini, L. Del Vecchio, F. Marinelli and V. Michelet, Chem. Commun., 2016, 52, 1458–1461.
- 8 Selected reviews:(a) I. Colomer, A. E. R. Chamberlain, M. B. Haughey and T. J. Donohoe, *Nat. Rev. Chem.*, 2017, 1, 0088; (b) H. F. Motiwala, A. M. Armaly, J. G. Cacioppo, T. C. Coombs, K. R. K. Koehn, V. M. Norwood and J. Aubé, *Chem. Rev.*, 2022, 122, 12544–12747; (c) M. Piejko, J. Moran and D. Lebœuf, *ACS Org. Inorg. Au*, 2024, 4, 287–300; (d)

- X.-D. An and J. Xiao, *Chem. Rec.*, 2020, 20, 142–161; Selected use of HFIP in total synthesis and for its Lewis acid properties:; (e) Y.-N. Ma, Y. Gao, Y. Ma, Y. Wang, H. Ren and X. Chen, *J. Am. Chem. Soc.*, 2022, 144, 8371–8378; (f) V. Pozhydaiev, M. Power, V. Gandon, J. Moran and D. Lebœuf, *Chem. Commun.*, 2020, 56, 11548–11564; (g) M. Van Hoof, R. J. Mayer, J. Moran and D. Lebœuf, *Angew. Chem., Int. Ed.*, 2024, e202417089; (h) S. Deswal, R. Chandra Das, D. Sarkar and A. T. Biju, *Angew. Chem., Int. Ed.*, 2025, e202501655.
- 9 Au:(a) N. V. Tzouras, L. P. Zorba, E. Kaplanai, N. Tsoureas, D. J. Nelson, S. P. Nolan and G. C. Vougioukalakis, ACS Catal., 2023, 13, 8845–8860; (b) N. V Tzouras, A. Gobbo, N. B. Pozsoni, S. G. Chalkidis, S. Bhandary, K. Van Hecke, G. C. Vougioukalakis and S. P. Nolan, Chem. Commun., 2022, 58, 8516–8519; (c) A. Truchon, A. Dupeux, S. Olivero and V. Michelet, Adv. Synth. Catal., 2023, 365, 2006–2012; Fe:; (d) V. Pozhydaiev, A. Paparesta, J. Moran and D. Lebœuf, Angew. Chem., Int. Ed., 2024, e202411992; Au/Ru:; (e) C. Xu, Y. Feng, F. Li, J. Han, Y.-M. He and Q.-H. Fan, Organometallics, 2019, 38, 3979–3990; Pd.; (f) T. Bhattacharya, A. Ghosh and D. Maiti, Chem. Sci., 2021, 12, 3857–3870.
- 10 (a) E. Kaplanai, N. V. Tzouras, N. Tsoureas, N. B. Pozsoni,
 S. Bhandary, K. Van Hecke, S. P. Nolan and
 G. C. Vougioukalakis, *Dalton Trans.*, 2024, 53, 11001–11008; (b) W. Wang, X. Cao, W. Xiao, X. Shi, X. Zuo, L. Liu,
 W. Chang and J. Li, *J. Org. Chem.*, 2020, 85, 7045–7059.
- 11 (a) V. Davenel, C. Nisole, F. Fontaine-Vive, J.-M. Fourquez, A.-M. Chollet and V. Michelet, J. Org. Chem., 2020, 85, 12657–12669; (b) V. Davenel, C. Puteaux, C. Nisole, F. Fontaine-Vive, J.-M. Fourquez and V. Michelet, Catalysts, 2021, 11, 546–550; (c) A. Truchon, A. Dupeux, S. Olivero and V. Michelet, Org. Chem. Front., 2024, 11, 4070–4076; (d) Y. Tang, I. Benaissa, M. Huynh, L. Vendier, N. Lugan, S. Bastin, P. Belmont, V. César and V. Michelet, Angew. Chem., Int. Ed., 2019, 58, 7977–7981; (e) A. Truchon, M. Gorodnichy, S. Olivero and V. Michelet, Org. Lett., 2024, 26, 6698–6702.
- 12 M. Barp, F. Kreuter, H. Buttkus, J. Jin, M. Kretzschmar, R. Tonner-Zech, K. Asmis and T. Gulder, *Angew. Chem., Int. Ed.*, 2025, **64**, e202417889.

- Selected reviews: (a) L. Li, Z. Chen, X. Zhang and Y. Jia, Chem. Rev., 2018, 118, 3752–3832; (b) Y. Wang, J. Feng, E.-Q. Li, Z. Jia and T.-P. Loh, Org. Biomol. Chem., 2024, 22, 37–54; (c) C. C. Chintawar, A. K. Yadav, A. Kumar, S. P. Sancheti and N. T. Patil, Chem. Rev., 2021, 121, 8478–8558.
- 14 A. Carrër, C. Péan, F. Perron-Sierra, O. Mirguet and V. Michelet, *Adv. Synth. Catal.*, 2016, 358, 1540–1545.
- 15 B. Scheiper, M. Bonnekessel, H. Krause and A. Fürstner, *J. Org. Chem.*, 2004, **69**, 3943–3949.
- 16 P. S. Dhote, S. V. Halnor and C. V. Ramana, *Chem. Rec.*, 2021, 21, 3546–3558.
- 17 CCDC2362171 (9b) and CCDC2362169 (10b) contains the supplementary crystallographic data for this paper. For details, see the SI.
- 18 Following referee inquiries, we conducted the reactions in the presence of ditertbutylpyridine and triphenylphosphine oxide instead of triphenylphosphine, as well as in the presence of 5 equivalents of water in HFIP but no conversion was observed.
- 19 Relative free energies of intermediates I and G in presence of AgBF₄ or PPh₃AuCl as catalysts with respect to the most stable. Values are in kcal/mol. For details, see the SI.
- 20 The reaction of **11** in the presence of gold or silver catalyst led to no conversion. Considering its formation, we therefore cannot exclude that the reaction could proceed *via* a three-membered ring intermediate.
- 21 C. Bissantz, M. Kuhn and M. Stahl, J. Med. Chem., 2010, 53, 5061–5084.
- 22 W. F. Kiesman, J. E. Dowling, C. L. Ensinger, G. Kumaravel, R. C. Petter, K. C. Lin and H. X. Chang, Biogen Inc., EP1230243, 2002.
- 23 G. Li, H. Zhou, J. Weiss, D. Doller and J. H. Ford, Lundbeck, WO2012088365A1, 2012.
- 24 E. Gentilini, A. Bouschon, V. Davenel, F. Fontaine-Vive, J.-M. Fourquez and V. Michelet, CCDC 2362171: Experimental Crystal Structure Determination, 2025, DOI: 10.5517/ccdc.csd.cc2k9120; E. Gentilini, A. Bouschon, V. Davenel, F. Fontaine-Vive, J.-M. Fourquez and V. Michelet, CCDC 2362169: Experimental Crystal Structure Determination, 2025, DOI: 10.5517/ccdc.csd.cc2k910y.