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

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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* ¹⁹F and ³¹P 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.

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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 gold-catalyzed 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 powerful solvent widely used for stabilizing charged intermediates,⁸ but more recently used in organometallic chemistry, particularly in gold catalysis.⁹ 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 to heterocycles (Fig. 1C).⁹

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 atom-economical 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, which would be an asset and would hopefully contribute to high regio- and stereoselectivity in the resulting products.¹²

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

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Fig. 1 (A) Gold-catalyzed cyclizations of nitroalkynes 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.

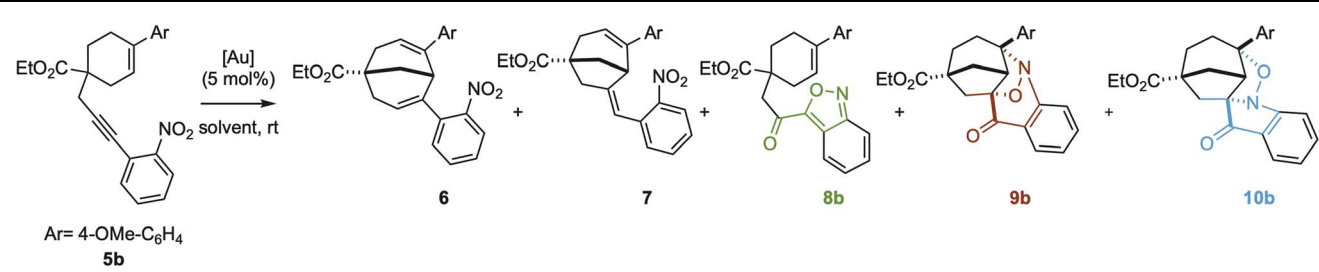
Results and discussion

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 **3j** 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.¹⁵ Derivatives **3a** to **3j** 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 **5a** to **5z** (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 (**5i**), a nitroquinoline (**5v**) and 2-nitrothiophenes (**5w**, **5x**). We then initiated our study with 1,6-enyne **5b** 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).



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 ₃ AuNTf 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 ₂ CO 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	^t 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.

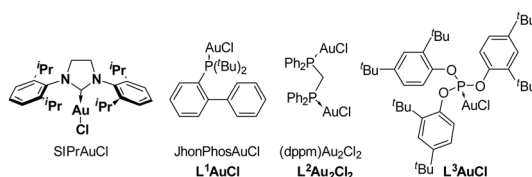
With selective conditions for each of the desired products in hand, we then started to evaluate the scope and the limitations of our reactions, by first targeting hexacycle **9b** bearing a bicyclo [3.2.1]octane and a benzoxazinone units (Scheme 2).

We began by the modification of the R¹ 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 R¹ 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 ₃ AuNTf 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	PPh ₃ AuCl	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 ² Au ₂ Cl ₂	HFIP	6	4	6	—	40	
13	L ³ Au ₂ Cl ₂	HFIP	3	—	9	8	28	84
14 ^c	PPh ₃ AuCl	HFIP	—	—	—	11	36	90
15 ^d	PPh ₃ AuCl	HFIP	—	—	—	—	50	
16	None	HFIP	—	—	—	—	—	0



^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 AgBF₄ and PPh₃AuCl with HFIP in ¹⁹F NMR (left) and ³¹P 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 R¹. 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 R¹, 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 fluorine in *meta* position led to hexacycle **9k** with a fair yield of 65%. The influence of electronic properties of the aromatic substituent (R²) was also evaluated: the presence of an electron-

donating group led to a loss of reactivity, as no conversion was observed for **5o**, **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 R² 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 by-products. 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 R¹ group (**9h**), we wondered if it was compatible with more decorated R² aromatic rings. Finally, compounds **9y** 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**).

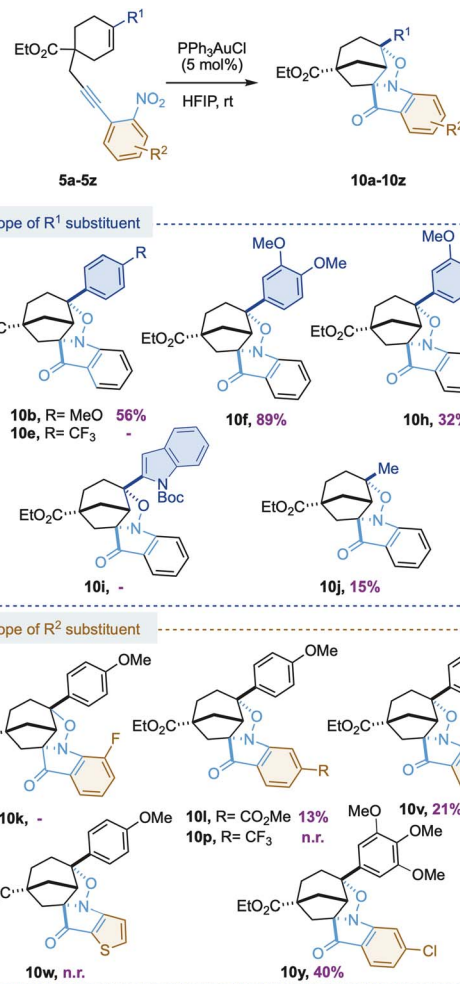
To investigate the scope of the formation of product **10**, we selected diverse substrates and explored their reactivity using triphenylphosphine gold chloride as catalyst. These conditions appeared unexpectedly to be more challenging compared to those optimized derivative **9** (Scheme 3). Indeed, 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.^{11a} Anthranile derivative **8** was obtained by cyclization of the nitroalkyne framework. Such reactivity has been well described in the



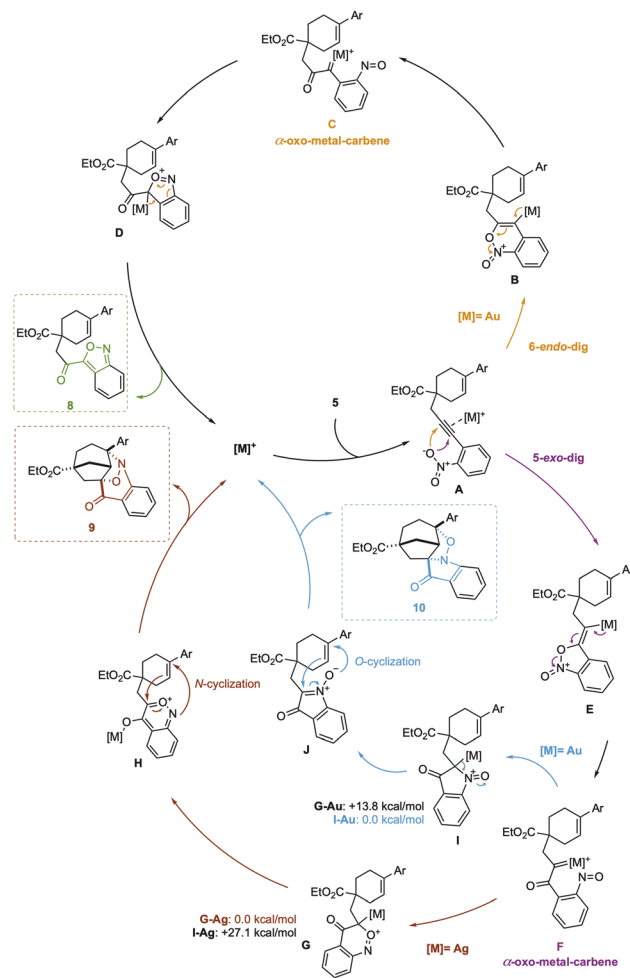


Scheme 4 Scope and limitations of the synthesis of derivatives 8.

literature,³ so we could easily assume that the addition of the nitro group onto the gold-activated alkyne occurred *via* a 6-*endo*-dig 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 **5j** (Scheme 6). Indeed, in presence of AgBF_4 , the cyclization of **5j** did not lead to the expected hexacyclic derivative **9j** but product **11** was isolated with a yield of 82%. In the presence of PPh_3AuCl , **10j** 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 -oxo-silver-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 **F**. Indeed, depending on the heteroatom of the nitroso group involved in the coordination, the α -oxo-metal-carbene **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

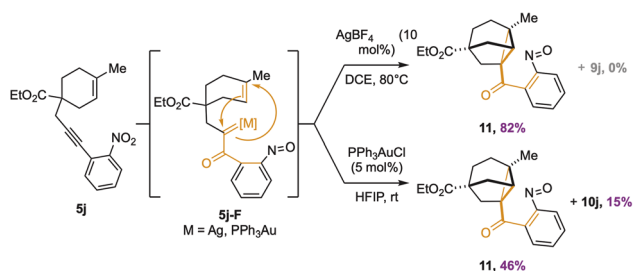


Scheme 5 Proposed mechanism of the reaction.

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 $27.1 \text{ kcal mol}^{-1}$ (Scheme 5, **G-Ag** vs. to **I-Ag**).¹⁹ Nevertheless, while using triphenylphosphine gold chloride as catalyst, the formation of the five-membered ring was favored by a difference of $13.8 \text{ kcal mol}^{-1}$.

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



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

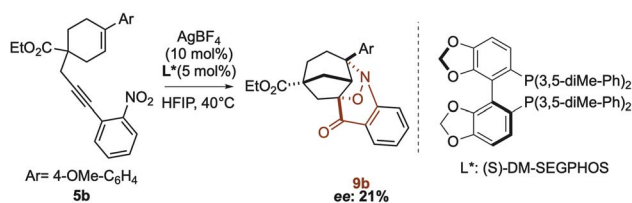
nitrene **J**. Finally, the intramolecular [3 + 2] cycloaddition could be performed *via* a *O*-cyclization leading to derivative **10**.

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 nitrene **J** (Scheme 5).

Under these conditions, a mixture of products **9b** and **10b** was obtained; chirality 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 LiAlH_4 , 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 high-yielding reactions, including two palladium-catalyzed cross-coupling 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 five-membered or a six-membered ring intermediate was favored, followed by a *N*- or *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>.

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