(2019), Gold(I)–catalyzed enantioselective annulations between allenes and alkene-tethered oxime ethers: A straight entry to highly substituted piperidines and aza-bridged medium-sized carbocycles. J. Am. Chem. Soc., 140, 16821-16833 [doi: 10.1021/jacs.8b10388]. This article may be used for non-commercial purposes in accordance with ACS Terms and Conditions for self-archiving.

Gold(I)–catalyzed enantioselective annulations between allenes and alkene-tethered oxime ethers: A straight entry to highly substituted piperidines and *aza*-bridged medium-sized carbocycles

David C. Marcote,[†,‡] Iván Varela,[†,‡] Jaime Fernández-Casado,[†] José L. Mascareñas,*[,†] Fernando López*[,†,#]

[†]Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares (CiQUS) and Departamento de Química Orgánica. Universidad de Santiago de Compostela, 15782, Santiago de Compostela, Spain

[#] Instituto de Química Orgánica General CSIC, Juan de la Cierva 3, 28006, Madrid, Spain

Supporting Information Placeholders

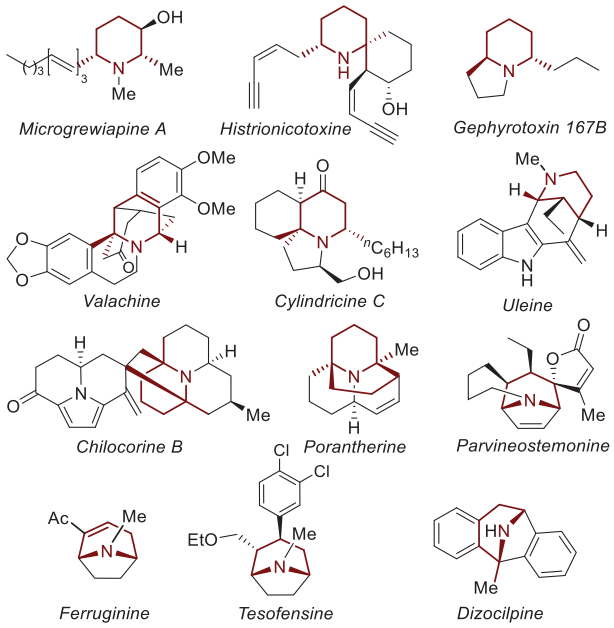
ABSTRACT: Piperidine scaffolds are present in a wide range of bioactive natural products, and are therefore considered as highly valuable, privileged synthetic targets. In this manuscript, we describe a gold-catalyzed annulation strategy that allows a straightforward assembly of piperidines and piperidine-containing *aza*-bridged products from readily available alkene-tethered oxime ethers (or esters) and *N*-allenamides. Importantly, we demonstrate the advantages of using oxime derivatives over imines, something pertinent to the whole area of gold catalysis, and provide relevant mechanistic experiments that shed light into the factors affecting the annulation processes. Moreover, we also describe preliminary experiments demonstrating the viability of enantioselective versions of the above reactions.

INTRODUCTION

Nitrogen-based heterocycles form the basic structural framework of many bioactive natural products, and are present in more than 50% of marketed drugs.[1] Especially abundant among these heterocycles are those featuring a piperidine skeleton, a privileged structure that forms the core of many alkaloids exhibiting potent biological activities, including antitumoral, antihypertensive, antibiotic or anesthetic profiles, among others (Figure 1).[2] Although numerous stereoselective approaches for assembling piperidines have been developed, most of them require several steps and/or the use of elaborated precursors;[3] and in many cases they do not comply with the principles of atom-economical synthesis.[4] Moreover, the number of enantioselective approaches that allow a one-step access to these scaffolds is rather limited.[5] These drawbacks are even more pronounced in the case of piperidines containing highly substituted carbon stereocenters adjacent to their nitrogen atom.[6]

The piperidine scaffold is also embedded in the skeleton of many polycyclic natural products exhibiting complex structures.[7] Especially relevant because of their biological and medical significance are those which feature tropane-like *aza*-bridged skeletons (Figure 1). Indeed, there are hundreds of alkaloids exhibiting azabicyclo[3.2.1]octane frameworks, with several of them being used in the clinic.[8] The prominence of these *aza*-bridged bicyclic products has stimulated important synthetic efforts in the area, however most of the approaches so far developed rely on stoichiometric rather than catalytic processes, and very few involve enantioselective catalysis.[9] Moreover, most of these methods are restricted to the building of *aza*-bridged products with a seven-membered carbocycle, so catalytic entries to challenging eight- and nine-membered counterparts, are very scarce.[10] In this context, the development of catalytic, versatile and enantioselective approaches to α-substituted piperidines and *aza*-bridged piperidine-containing products is of upmost interest.

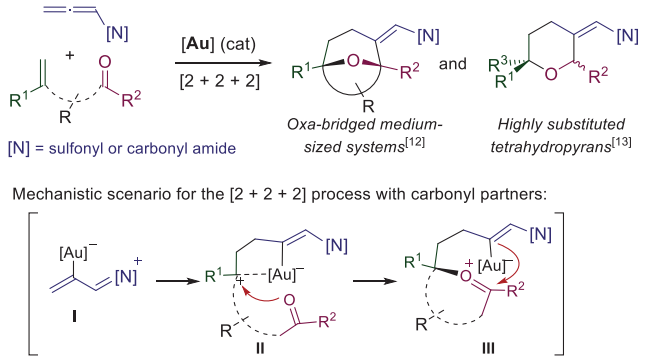
Figure 1. Some *aza*-heterocycles containing piperidine scaffolds, some of them with highly substituted α-carbons



As part of our ongoing work in gold catalysis,[11] we have recently reported a gold-catalyzed annulation between allenamides and alkene-tethered carbonyl derivatives that allows a straightforward assembly of *oxa*-bridged medium-sized carbocycles.[12] Additionally, we have developed a fully intermolecular annulation between allenamides, alkenes and carbonyl derivatives, which provides highly substituted tetrahydropyran systems in high yield and with moderate to good diastereo- and enantioselectivities (Scheme 1).[13] These

annulations have been proposed to proceed by an initial activation of the allene moiety by the gold(I) complex, which likely generates a zwitterionic intermediate of type **I**.[14] This species undergoes the addition of the alkene to its γ-position to provide a carbocationic intermediate **II**, in which an electrostatic interaction between the gold(I) atom and the carbocation has been proposed to account for the observed stereospecificity.[13a] Then, an inter- or intramolecular interception of this carbocation by the carbonyl moiety generates an oxonium (**III**), which undergoes a *Prins*-like cyclization to deliver the observed oxacycle.

Scheme 1. Previous Au^{I}-catalyzed formal [2 + 2 + 2] Cycloadditions Towards *Oxa*-heterocycles[12,13]



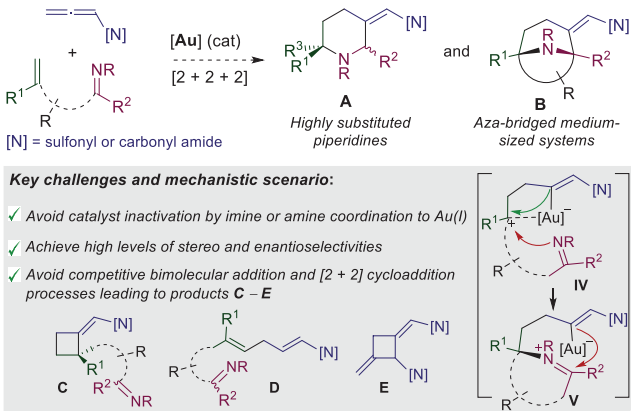
With this conceptual framework at hand, we questioned whether it would be possible to extend this methodology to imine instead of carbonyl partners, and therefore lever a direct, atom-economical entry to densely substituted piperidine-containing scaffolds, including *aza*-bridged medium sized carbocycles (Scheme 2, products **A** and **B**).

Although this extrapolation could appear trivial, finding a gold catalyst compatible with imine partners, and capable of triggering the desired annulation with allenes to produce azacyclic products, is far from obvious. Indeed, despite extraordinary advances in homogeneous gold catalysis during the last two decades, most annulation processes are still limited to the generation of carbocycles and oxygen-based heterocycles;[15] with progress on gold-catalyzed annulations using nitrogenated partners clearly lagging behind. The reasons behind this disparity might be rooted in the intrinsic properties of gold(I) complexes since, despite their acute carbophilicity, they also show affinity for soft Lewis bases such as amines and imines, which therefore interfere with the activity of the gold(I) reagents.[16-18] In fact, the use of gold(I) catalysis in intermolecular reactions involving tertiary amines other than anilines is very scarce, and limited to very particular cases.[19] Moreover, although several *aza*-reagents bearing less basic nitrogens (sp- and sp^2-nitrogens) can participate in gold(I) catalysis (e.g., nitriles, azides, pyridines or isoxazoles), intermolecular examples with simple imines are not abundant, usually require heating, and are typically limited to less basic aromatic or conjugated imines.[20]

In this context, discovering imine partners compatible with the carbophilic gold catalysts, but nucleophilic enough to intercept carbocationic intermediates of type **IV**, is critical for succeeding in the desired annulations (Scheme 2). Also importantly, the iminium species **V** should be electrophilic enough to undergo the *aza*-Prins-like cyclization that would eventually deliver the product.[21] Conversely, if the carbophilicity of the catalyst and the imine basicity are not properly matched, side products resulting from allenamide dimerizations and polymerizations, as well as bimolecular alkene-allenamide [2 + 2] cycloadditions and hydrofunctionalizations could predominate (Scheme 2, products **C**–**E**).[22] Additionally, the desired piperidine products (**A** and **B**) might also hamper the catalytic activity by coordinating the gold(I) complex.[18]

Herein, we demonstrate that these challenges can be efficiently approached by using oximes instead of imines as reactions partners. Specifically, we report a gold-catalyzed formal [2 + 2 + 2] cycloaddition between *N*-allenamides and *C*- or *O*-tethered alkenyl oxime ethers that allows a direct, catalytic and efficient entry to highly substituted piperidine-based heterocyclic systems, as well as to synthetically appealing *aza*-bridged medium-sized carbocycles. Moreover, by performing the reaction with chiral phosphoramidite-gold complexes, the products can be obtained in good to excellent enantiomeric ratios. Finally, we also detail relevant mechanistic experiments that shed light on the enantio- and turnover-determining steps of these processes, as well as on the reasons beyond the superior performance of oximes versus imines.

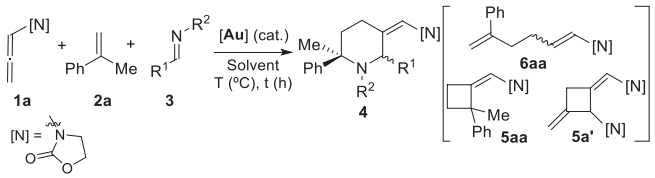
Scheme 2. Envisioned Au^{I}-Catalyzed [2 + 2 + 2] Cycloadditions Towards Relevant *Aza*-heterocycles; Key Challenges



RESULTS AND DISCUSSION

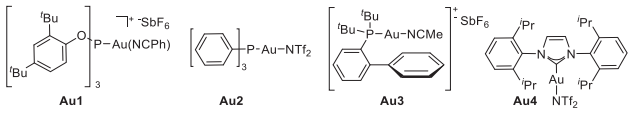
Feasibility of an Intermolecular [2 + 2 + 2] annulation between Allenes, Alkenes and Imines. We initially assessed the viability of a fully intermolecular formal cycloaddition by selecting as model substrates the allenamide **1a**, α-methyl styrene (**2a**) and a variety of imines (**3**) with diverse electronic and steric characteristics (Table 1 and Table S1).[23] Unfortunately, despite extensive screening, none of the gold catalysts and reaction conditions provided the desired piperidines **4**. However, we observed different reactivities depending on the type of imine employed. With the benzyl imine of benzaldehyde (**3a**), there was not reactivity at *rt*; while after prolonged heating at 85 ºC, we detected side products arising from self-polymerization of the allenamide (Table 1, entries 1 and 2). Considering that [2 + 2] adducts like **5aa** and **5a'**, as well as the addition product **6aa**, are known to be readily formed at temperatures below 0 ºC when the gold-catalyzed reaction is carried out in absence of the imines,[11d,12,13] these preliminary results suggest that the imine component is inactivating the gold(I) complex. Indeed, with less basic imines such as the *N*-*tert*-butylsulfinyl derivative **3b**, we observed partial formation of these bimolecular products at *rt*; however, the desired piperidine adducts were never detected in the crude mixtures (entry 3). Similarly, using aryl imines such as **3c**, we observed the formation of complex reaction mixtures (entry 4), whereas the more bulky mesityl imine (**3d**) did not provide significantly better results (entry 5). Therefore, although these less basic imines did not fully inhibit the activity of the gold complex, they do not participate in the desired annulation processes.

Table 1. Preliminary Screening of an Intermolecular [2 + 2 + 2] Cycloaddition[a]



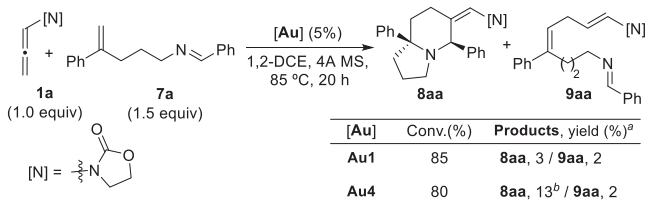
entry	R^1 / R^2	3	Conv. (%)	T (ºC)	**Products**, yield (%)
1	Ph / Bn	**3a**	0	rt	-[b]
2	Ph / Bn	**3a**	78	*rt* -> 85	-[b,c]
3	Ph / S(O)^{t}Bu	**3b**	100	rt	**5aa**, 42 / **6aa**, 3[c]
4	Ph / Ph	**3c**	100	rt	**5aa**, < 5[d]
5	Ph / Mesityl	**3d**	100	*rt* -> 85	**5aa**, 35 / **6aa**, 10[b]

[a] *Conditions*: Allenamide **1a** (1 equiv), **2a** (2 equiv) and the imine (2-5 equiv) were treated with **Au1** (5 mol%) in CH_2Cl_2 or 1,2-DCE at the indicated temperature for 2-20 h, unless otherwise noted.[23] [b] Results using **Au2**, **Au3** and **Au4** were not significantly different (see Table S1).[23] [c] Degradation and polymerization of **1a** is observed.[23] [d] Complex mixture of several unidentified products.



Overall, these results confirm not only the difficulties for accomplishing the designed heteroannulation, but also our initial suspects on the interference of imines with gold(I) catalysis. We next hypothesized that tethering the alkene and the imine might favor the interception of the carbocation in intermediates of type **IV** (Scheme 2), and hence drive the desired cascade annulation. Nevertheless, treatment of **1a** with **7a** (1.5 equiv), in the presence of **Au1** (5 mol%), at room temperature, led to complete recovery of starting materials. However, heating these mixtures up to 85 ºC for 24h led to traces of two new products (**8aa** and **9aa**), the former being compatible with a formal [2 + 2 + 2] adduct that holds the two phenyl substituents of the piperidine moiety in *cis* disposition (Scheme 3). From all other gold catalysts tested, only **Au4** slightly improved the performance of **Au1**, to afford a still very poor 13% yield of the indolizidine adduct **8aa** (Scheme 3 and Scheme S1).[23,24] Unfortunately, all attempts to increase the yield of the desired cycloadduct (**8aa**), by modifying the reaction conditions and/or the catalyst were unsuccessful.

Scheme 3. Preliminary Screening of a Au(I)-Catalyzed Cycloaddition using the *N*-tethered Alkenyl Imine 7a



[Au]	Conv.(%)	**Products**, yield (%)[a]
Au1	85	**8aa**, 3 / **9aa**, 2
Au4	80	**8aa**, 13[b] / **9aa**, 2

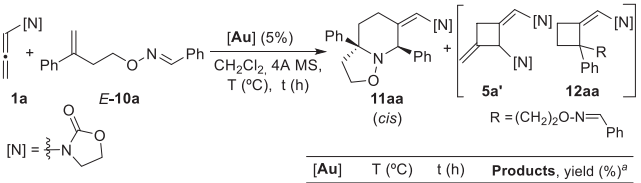
[a] Yields determined by ^{1}H-NMR with internal standard. [b] Isolated yield.

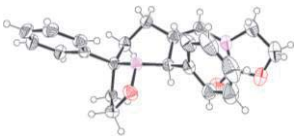
At this point, we decided to tackle this poor performance by testing the reactivity of precursors containing an alkyl oxime instead of the imine (Scheme 4). We anticipated that the lower Lewis basicity of the nitrogen atom of the oxime ether could lead to more labile N–Au bonds and therefore favor the catalytic activity of the gold complexes. Oxime ethers present additional advantages, such as a higher stability to hydrolysis, even in the case of those made from linear aliphatic aldehydes bearing α-hydrogens.[25] Moreover, both *cis* and *trans* oxime isomers are configurationally stable and potentially accessible.[26] Not less important, the N–O bond that is present in the products should provide for further elaboration into a variety of piperidine derivatives.[27]

Oxime ethers (as well as esters) have been unevenly employed in transition metal catalysis, and most of their reactions involve the excision of the oxime N–O bond (through oxidative additions or via homolytic cleavage).[28] In the particular case of gold catalysis, the use of oxime ethers has been limited to a handful of isolated examples.[29] On the other hand, it is striking that, despite imines have been exploited in several types of catalytic annulation reactions, oxime ethers (and esters) have been barely investigated in this type of transformations.[30,31]

Gratifyingly, in line with our hypothesis, treatment of a mixture of allenamide **1a** and the *E*-oxime ether **10a** (1.5 equiv) with the phosphite gold complex **Au1** (5 mol%), at -15 ºC, led to the desired azacycle **11aa** in an excellent 85% yield, and with complete diastereoselectivity and chemoselectivity (i.e. the [2 + 2] adducts **5a'** and **12aa** were not detected, Scheme 4). The configuration of the adduct **11aa**, which holds the two phenyl groups in *cis* disposition was unambiguously determined by 1D- and 2D-NMR studies, as well as by X-ray crystallography.[23] Gold complex $Ph_3PAuNTf_2$ (**Au2**) was also equally effective at this temperature (-15 ºC), whereas with less electrophilic gold complexes, such as JohnPhosAu(NCMe)SbF_6 (**Au3**) or IPrAuNTf$_2$ (**Au4**), obtaining full conversions required warming up to 0 ºC, and the reactions were both less efficient and chemoselective (Scheme 4). With the phosphite gold catalyst **Au1**, the adduct **11aa** could also be obtained in good yield using just equimolar amounts of allenamide **1a** and alkenyl oxime **10a**, (reaction time: 0.5h, 83% yield, Scheme 4).

Scheme 4. Preliminary Screening using the *O*-tethered Alkenyl Oxime 10a[a]





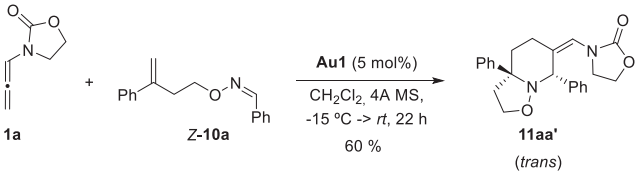
X-Ray of **11aa**

[Au]	T (ºC)	t (h)	**Products**, yield (%)[a]
Au1	-15	0.1	**11aa**, 85
Au2	-15	7	**11aa**, 87
Au3	-15 -> 0	22	**11aa**, 56 / **5a'**, 18[b]
Au4	-15 -> 0	22	**11aa**, 70 / **5a'**, 16[b]
Au1	-15	0.5	**11aa**, 83[c]

[a] *Conditions*: **1a** (1.0 equiv) and ***E*-10a** (1.5 equiv) treated with [**Au**] (5 mol%) in CH_2Cl_2. [b] Traces (< 5% yield) of **12aa** were also detected in the crude mixture. [c] Carried out with 1.0 equiv of ***E*-10a.**

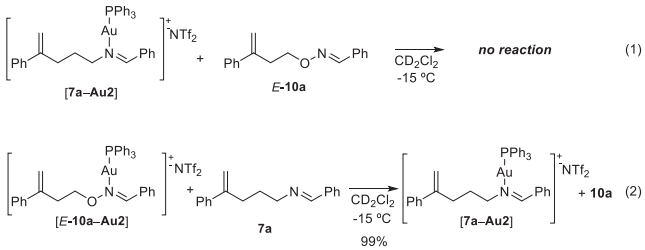
Interestingly, the reaction of **1a** with the corresponding *cis*-oxime ***Z*-10a**, under otherwise identical reaction conditions, proceeded at a much slower rate, providing full conversion only after 22 h (from -15 ºC to *rt*). Nonetheless, the reaction was completely chemoselective and stereospecific, providing a 60% yield of the adduct **11aa'**, which features the phenyl groups in *trans* disposition, as determined by NMR and X-ray diffraction analysis (Scheme 5).[23]

Scheme 5. Annulation of the *cis*-Oxime *Z*-10a



Interaction of Gold(I) Complexes with Imines and Oximes. To shed light into the striking differences in reactivity of imine **7a** and oxime **10a**, we monitored their interactions with a model gold complex such as $Ph_3PAuNTf_2$ (**Au2**) by NMR and ESI-MS (Figures S1-S17). Analysis of a mixture of **Au2** and **7a** by ESI-MS, showed the presence of a single molecular ion peak at *m/z* 708.19, which nicely fits with the complex [**7a**–**Au2**]. Further analysis by NMR, confirmed the formation of this new complex (^{31}P-NMR δ 29.30 ppm), which exhibits a downfield shift of the imine hydrogen signal in the ^{1}H-NMR, undoubtedly due to coordination of the gold(I) center to the imine nitrogen (Δδ = 0.08 ppm at 0 ºC; Figures S1–S5 and S11).[23,17] Likewise, mixing oxime *E*-**10a** and **Au2** allowed to detect the analog oxime-gold(I) complex [*E*-**10a–Au2**] by ESI-MS and NMR (*m/z* = 710.29; ^{31}P-NMR δ 28.75 ppm, Figures S6-S10 and S12). Interestingly, addition of the oxime derivative *E*-**10a** to the imine–gold complex [**7a**–**Au2**] at -15 ºC, did not induce any change in the mixture, as deduced by ^{31}P-NMR and ESI-MS analysis (Scheme 6, eq 1, Figure S16). However, addition of the imine **7a** to the oxime gold(I) complex [*E*-**10a–Au2**], induced the quantitative formation of the imine counterpart [**7a–Au2**] (Scheme 6, eq 2, Figure S17). Overall, these results confirm that the coordination of the imine to gold(I) is much stronger than that of the homologous oxime ether.

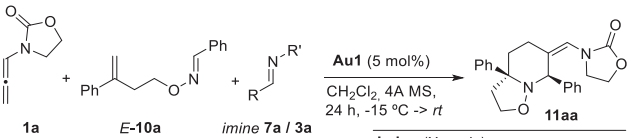
Scheme 6. Relative Stability of Imine- and Oxime-Gold Complexes [7a–Au2] and [*E*-10a–Au2]



The stronger coordination of the imines to the gold(I) complex might be behind their observed lack of reactivity in the proposed annulations. Indeed, addition of the imine **7a** (50 mol%) to a mixture of allenamide **1a** (1 equiv) and oxime ether **10a** (1.5 equiv), in presence of the gold catalyst **Au1** (5 mol%), led to a complete suppression of the reactivity (Scheme 7). Even the presence of 10 mol% of the imine **7a** completely inhibited the reaction, whereas the use of equimolar amounts of **Au1** and **7a** (5 mol%) led to a poor 17% yield of **11aa** after 24 h (50% conversion). Interestingly, in this case the reactivity could be mostly recovered by adding an additional 5 mol% of catalyst **Au1** to the reaction, which eventually provided a 55 % yield of **11aa**. A similar inhibition of the catalytic activity was observed using benzyl imine **3a** instead of **7a**, confirming the poisoning effect of alkyl imines in these gold(I)-promoted reactions (Scheme 7).

Noticeably, the higher affinity of imines to gold(I) complexes was also confirmed by DFT theoretical calculations. Thus, a theoretical characterization of the complexes of **Au2** with the imine **7a** and the oxime *E*-**10a** revealed that the imine derivative, [**7a–Au2**], is ~7 kcal·mol^{-1} more stable than its oxime-gold counterpart [*E*-**10a–Au2**] (Figure S18).[23]

Scheme 7. Inhibition of the Au(I)-Catalyzed Cycloaddition of 1a and *O*-Tethered Alkenyl Oxime 10a by Imines 7a and 3a



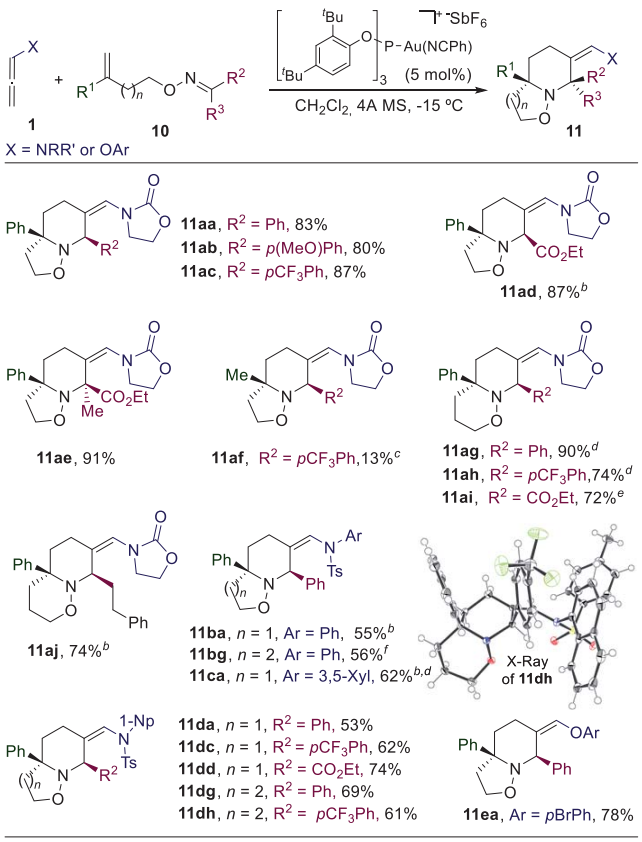
Imine (X equiv)		% yield (**11aa**)
7a	0.5	0
7a	0.1	0
7a	0.05	17
7a	0.05	55[a]
3a	0.05	30

[a] After 4 h at -15 ºC (0% yield of **11aa**), an additional 5 mol% of **Au1** was added (overall reaction time: 6 h at -15 ºC).

Scope of the Annulation between Allenes and *O*-Tethered Alkenyl Oximes. Having demonstrated the viability of engaging the alkenyl oxime ether **10a** in the desired cascade annulation with allenamide **1a**, we analyzed the scope of the process using other precursors (Table 2). Gratifyingly, electron-donating and electron-withdrawing groups at the aryl group of the oxime are well tolerated, and the products **11ab** and **11ac** could be obtained with comparable efficiency. Although yields were similar in the three cases (80 – 87% yield), the formation of **11c**, derived from the oxime with a more electron-deficient aryl group, proved to be faster (vide infra).[23] In consonance with this result, the reaction of a glyoxalate oxime also proceeded with a high reaction rate (< 0.1 h at -15 ºC) to provide the desired adduct **11ad** with complete stereoselectivity and an excellent 87% isolated yield. In general, complete stereoselectivities in favor of the *cis* isomer (**11**) were obtained in all cases, provided that the parent oxime precursor **10** is configurationally *E*-pure.[32] Importantly, the generation of cycloadducts fully substituted at the *N*-adjacent carbon is also possible, as it is exemplified with **11ae**, which was isolated with excellent yield and complete stereoselectivity. However, alkenes with a methyl, instead of a phenyl substituent, led to poorer reaction yields (**11af**, 13% yield). Likely, the alkyl substituent does not provide enough stabilization to the cationic intermediate that is presumably formed after addition of the alkene of **10** to the gold-activated allenamide species **I** (vide infra).

The reaction tolerates an increase in the length of the tether connecting the alkene and the oxime. Thus, cycloadducts **11ag-11ai** were obtained from the corresponding oximes with moderate to excellent yields and again complete stereoselectivity in favor of the *cis* isomer. On the other hand, oximes derived from aliphatic aldehydes also participated in the annulation, so that the desired product **11aj** was obtained in 74% yield. Finally, the behavior of different allene partners was also tested. Thus, the cycloaddition could also be carried out with *N*-tosyl aryl allenamides, to give the desired adducts with good yields (**11ba**, **11bg**, **11ca** and **11da-11dh**). The stereochemical outcome of these cycloadditions could also be confirmed by X-ray diffraction analysis of the product **11dh** (Table 2).[23] Finally, the scope of the annulation is not limited to *N*-allenamides; thus *O*-allenyl aryl ethers such as **1e** [OAr = O(*p*BrC$_6$H$_4$)][15c] also participated in the cascade cycloaddition to provide the corresponding adduct (i.e **11ea**) in very good yield and with complete diastereoselectivity.

Table 2. Scope of the Cycloaddition between Allenes (1) and *O*-Tethered Alkenyl Oximes (10)[a]



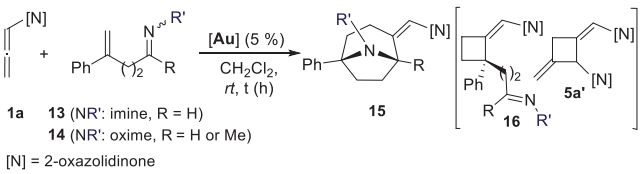
[a] *Conditions*: Allene **1** (1 equiv) and alkenyl oxime ether *E*-**10** (1.5 equiv) were treated with **Au1** (5 mol%) in CH_2Cl_2 at –15 ºC; Reaction times: 0.1 – 4 h. Products dr's are 1 : 0, unless otherwise noted. [b] The *E* / *Z* ratio of the oxime precursor (**10**) < 1 : 0. Thus, traces of the *trans* isomer of type **11'** were also detected.[23,32] [c] Carried out from -15 ºC to *rt*, for 26 h; Allene dimer **5a'** was the main product. [d] Small amounts (~5% yield) of the corresponding [2 + 2] adduct of type **12** was also obtained.[23] [e] Carried out at -78 ºC; the [2 + 2] adduct **12ai** (19% yield) was also obtained.[23] [f] Carried out at 0 ºC; the adduct **12bg** (20% yield) was also observed.[23] 1-Np = 1-Naphthyl.

Cycloaddition of Allenes and *C*-Tethered Alkenyl Oximes. Having demonstrated that *O*-tethered alkenyl oximes of type **10** are excellent partners in the cascade cycloadditions with allenes, we wondered whether tethering the alkene and the oxime moiety via the carbon, instead of the oxygen atom, could also lead to productive annulations. This would be especially relevant because the resulting products are *aza*-bridged medium sized carbocycles, highly appreciated, privileged scaffolds in biomedicine (Figure 1 and Scheme 2). Thus, *C*-tethered alkenyl oxime derivatives of type **14** (Table 3) were readily prepared from the corresponding carbonyl precursors in an easily scalable manner.[23] For comparison purposes, we also considered analogous imines of type **13** (Table 3); however, in contrast to the oxime ethers, which are perfectly stable and easily purified, most of the attempted imines suffered from low stability. This is probably associated to the presence of α-enolizable positions, which favor a rapid interconversion to the enamines. Indeed, only in the case of the sulfinyl imine derivative **13a**, we were able to obtain pure samples to test its reactivity. For related tosyl- and aryl-imines **13b** and **13c**, the reaction crudes had to be used without additional purification, to avoid decomposition of the imine.

As shown in Table 3 (entries 1-5), none of these imines (**13**) provided the azabicyclo[3.2.1]octane products (**15**). Using the imine **13a**, we detected the allenamide [2 + 2] dimer **5a'** (entries 1-3), whereas with imines **13b** and **13c**, the starting materials were recovered (entries 4-5). In contrast, we were pleased to observe that the *O*-methyl aldoxime *E*-**14a** reacts efficiently with **1a** to provide the desired 8-azabicyclo[3.2.1]octane derivative **15aa** in 68% yield, together with traces of the [2 + 2] cycloadduct **16aa** (entry 6).[33] Other catalysts such as **Au2** and **Au4** also provided the desired product, but with lower selectivities (entries 7-9). Interestingly, the *cis* aldoxime *Z*-**14a** did not provide the expected product; instead, we only observed decomposition of the allenamide after prolonged reaction times (entry 10). Using a 1:1 *E* / *Z* mixture of **14a**, the desired product **15aa** could be obtained, albeit in significantly lower yields (up to 45% yield with **Au4**, entries 11 and 12). The lack of the reactivity of the *Z*-oxime derivative is consistent with the topological requirements of the annulation process, in particular with the interception of the carbocationic intermediate of type **IV** by the nitrogen lone pair, which is geometrically difficult in the case of the *Z*-isomer of the oxime (Scheme 2).

The viability of the cycloaddition was also analyzed with the methyl ketoxime **14b** (entries 13 – 16). Gratifyingly, treatment of *E*-**14b** with several gold(I) catalysts also provided the desired *aza*-bridged medium sized carbocycle **15ab**. The phosphite gold catalyst **Au1** and the NHC-based catalyst **Au4** provided the best yields, of up to 89% (entry 13). As with the aldoxime **14a**, the use of the *cis* isomer (*Z*-**14b**) did not lead to the desired adduct. In this case, we could observe the formation of the [2 + 2] adduct **16ab'** (isolated in 75% yield), together with minor amounts of an acyclic hydrofunctionalization product (10% yield, entry 16).[23]

Table 3. Viability of the Annulation with *C*-Tethered Alkenyl Imines (13) and Oximes (14)[a]



entry	R'	R	**13** or **14**	[**Au**]	Conv. (%)	**Products**, yield (%)
1	S(O)^{t}Bu	H	**13a**	**Au1**	0	-
2	S(O)^{t}Bu	H	**13a**	**Au1**	100	**5a'**, 24[b]
3	S(O)^{t}Bu	H	**13a**	**Au4**	100	**5a'**, 45[c]
4[d]	SO_2tol	H	**13b**	**Au1**	0	-
5[d]	*p*(MeO)Ph	H	**13c**	**Au1**	0	-
6	OMe	H	*E*-**14a**	**Au1**	99	**15aa**, 68 / **16aa**, 5
7	OMe	H	*E*-**14a**	**Au2**	99	**15aa**, 55 / **16aa**, <5
8	OMe	H	*E*-**14a**	**Au3**	50	**15aa**, 5 / **16aa**, <5
9	OMe	H	*E*-**14a**	**Au4**	99	**15aa**, 60 / **16aa**, 40
10	OMe	H	*Z*-**14a**	**Au1**	99	-[e]
11	OMe	H	**14a** (*E*/*Z*:1:1)	**Au1**	92	**15aa**, 35
12	OMe	H	**14a** (*E*/*Z*:1:1)	**Au4**	99	**15aa**, 45 / **16aa**, 10
13	OMe,	Me	*E*-**14b**	**Au1**	99	**15ab**, 89 / **5a'**, 6
14	OMe	Me	*E*-**14b**	**Au4**	99	**15ab**, 60 / **16ab**, 5
15	OMe	Me	*E*-**14b**	**Au2**	99	**15ab**, 26 / **5a'**, 14
16	OMe	Me	*Z*-**14b**	**Au1**	99	**16ab'**, 75 / **17ab**, 10

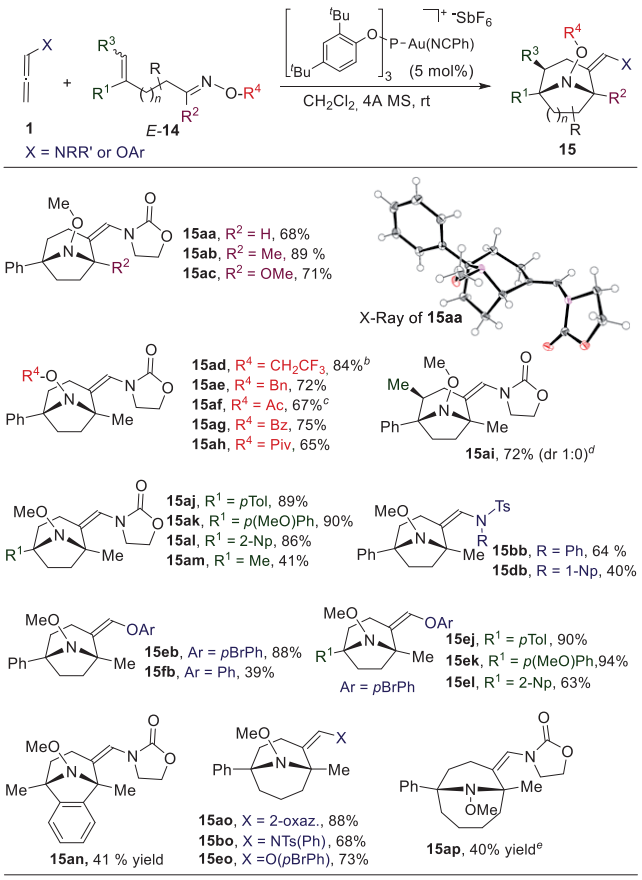
[a] *Conditions*: Allenamide **1a** (1 equiv) and **13** or **14** (1.5 equiv) were treated with the gold catalyst [**Au**] (5 mol%) in CH_2Cl_2 at *rt* for 1 h, unless otherwise noted. [b] Carried out in toluene from *rt* to 85 ºC for 1h. [c] Carried out in toluene at *rt* for 1h. [d] The crude mixture containing the imine **13** was used without purification. [e] After 24h, decomposition of **1a** was just observed.

Having demonstrated the viability of the tandem annulation process, we checked its scope (Table 4). Gratifyingly, the reaction was not limited to the aldoxime and ketoxime precursors **14a** and **14b**; a methyl oxamate also provided the desired product **15ac**, in a good 71% yield. Notably, the reaction works with oxime derivatives having substituents at the oxygen atom others than methyl (R^4). Therefore, the reaction worked well with substrates bearing trifluoroethyl, benzyl and acyl substituents such as acetyl, benzoyl or pivaloyl, to give the expected products in yields varying from 65 to 84% (**15ad-15ah**).

The annulation tolerates aryl substituents other than phenyl at the alkene moiety and, remarkably, it is also viable with an alkenyl-oxime substrate bearing a methyl at this internal position of the alkene. Therefore, azacyclic products **15aj** – **15am** were obtained in yields varying from 41 to 90%. We also investigated the influence of an additional methyl substituent at the terminal position of the phenyl alkene moiety (**14i**, alkene *E* / *Z* ratio = 1.1 : 1). In agreement with previous results for the [2 + 2] cycloadditions,[11d] we only observed the reaction of the *trans* isomer (*E*-**14i**), which efficiently afforded the azabicylic product **15ai** as a single diastereoisomer (72% yield).

Moreover, other *N*-allenyl amides or *O*-allenyl ethers can also participate as annulation partners to give the expected products **15bb** – **15fb**. Particularly efficient were the cycloadditions of the allenyl ether **1e**, which provided the corresponding tropane derivatives **15ej - 15el** with yields up to 94%. The cascade cycloaddition is also effective for the synthesis of benzotropane derivatives such as **15an**. Importantly, oximes bearing a one-carbon longer connecting tether also participated in the process, affording the corresponding *aza*-bridged cyclooctanes (**15ao**, **15bo** and **15eo**) in good yields, varying from 68 to 88%. Finally, the synthesis of the azabicyclo[4.3.1]decane **15ap**, featuring an *aza*-bridged nine-membered carbocycle was also possible (40% yield), albeit in this case the crude reaction mixture also contained substantial amounts of the competitive [2 + 2] adduct **16ap** and the acyclic addition product **17ap**.[23]

Table 4. Au(I)-Catalyzed Formal [2 + 2 + 2] Cycloaddition of Allenes (1) and *C*-Tethered Alkenyl Oximes (14)[a]



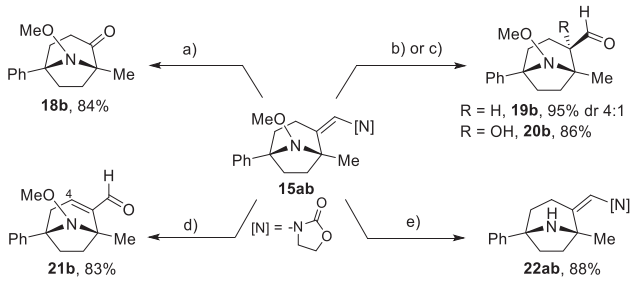
[a] *Conditions*: Allene **1** (1 equiv) and *E*-alkenyl oxime **14** (1.5 equiv) were treated with **Au1** (5 mol%) in CH_2Cl_2 at *rt* (reaction times: from 0.1 h to 6 h).[23] Products are mixtures of axial and equatorial *N*-invertomers, with ratios varying from 1.1 : 1 (**15ah**) to 1 : 0 (**15ae**) (see the Supp. Info. for each particular case). Isolated yields. [b] 3.0 equiv of oxime **14d** (*E* / *Z* = 2.1 : 1) were used. [c] Carried out at -30 ºC. [d] 3.0 equiv of oxime **14i** (alkene *E* / *Z* ratio = 1.1 : 1). [e] The [2 + 2] adduct **16ap** (30% yield) and an acyclic addition product **17ap** (18% yield, see the S.I.) were also obtained.[23] 2-Np = 2-Naphthyl.

Synthetic Elaboration of the Cycloadducts. The presence of the *exo*-enamide and the alkoxyamine moieties provides for further elaboration of the azabicyclic adducts (Scheme 8). For instance, treatment of **15ab** with $RuCl_3$ / $NaIO_4$ cleanly afforded the corresponding ketone, **18b**, in 84% yield. Alternatively, hydrolysis of the enamide with HCl (aq) efficiently provides the aldehyde **19b**, whereas a dihydroxylation reaction with OsO_4 leads to the α-hydroxy aldehyde **20b** as a single diastereoisomer, in excellent yield. On the other hand, treatment of **15ab** with SeO_2 provided the α,β-unsaturated aldehyde **21b** in 83% yield.[34] Noticeably, this efficient transformation paves the way for introducing further substituents at the key C4-position of the tropane skeleton by means of Michael additions of different nucleophiles. Finally, the N–OMe group can be readily cleaved by treatment with Zn / AcOH to give the corresponding secondary amine (**22ab**) in an excellent 88% yield.

With respect to the piperidine scaffolds, treatment of **11aa** with Zn / AcOH provided a 90% yield of the piperidine **23aa** (Scheme 9). Piperidines like **23ae**, featuring fully substituted centers at their nitrogen-adjacent positions, can also be readily obtained. Interestingly, piperidine **23ag** could be easily transformed into the indolizidine derivative **8aa** by treatment with MsCl and Et_3N. On the other hand, treatment **11aa** with $Pd(OH)_2$ under H_2 (1 atm) at *rt*, provided

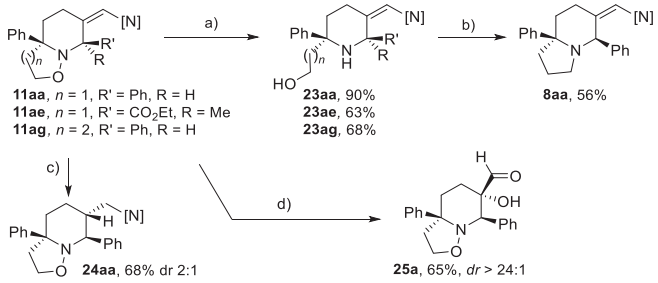
the hydrogenated product **24aa**. Finally, as in the case of the tropane derivatives, treatment of **11aa** with OsO_4 afforded the corresponding α-hydroxy aldehyde (**25a**) in good yield and with almost perfect diastereoselectivity (Scheme 9).

Scheme 8. Synthetic Elaboration of Azabicycles of Type 15[a]



[a] *Conditions*: a) $RuCl_3$, $NaIO_4$, MeCN / EtOAc / H_2O, *rt*, 84% yield; b) HCl (6 N), $CHCl_3$, reflux, 95% yield, dr 4:1; c) OsO_4 (6%), NMO, Acetone / MeCN, H_2O, *rt*, 86% yield; d) SeO_2, 1,4-dioxane, reflux, 83% yield; e) Zn, AcOH / H_2O (2:1), 100 ºC, 88% yield. [N] = 2-oxazolidinone.

Scheme 9. Synthetic elaboration of azabicycles of type 11[a]



[a] *Conditions*: a) Zn, AcOH / H_2O (2:1), 100 ºC, 63 – 90% yield; b) MsCl, Et_3N, CH_2Cl_2, -20 ºC -> 0 ºC, 56% yield; c) $Pd(OH)_2$, H_2 (1 atm), MeOH, *rt*, 68% yield, dr 2 : 1; d) OsO_4 (cat.), NMO, Acetone / MeCN, H_2O, *rt*, 65% yield, dr > 24:1; [N] = 2-oxazolidinone.

Preliminary studies on Enantioselective Variants. Overall, the above reaction manifolds highlight the great potential and versatility of alkenyl-containing oximes of type **10** and **14** for a straightforward and versatile synthesis of *aza*-bridged medium-sized carbocycles and piperidine scaffolds. An additional, major step forward in this research would consist of the development of enantioselective variants. In general, direct enantiocatalytic approaches to *aza*-bridged medium sized carbocycles are very scarce and limited to the synthesis of products with the tropane azabicyclic core.[9] Moreover, we are not aware of approaches that allow the preparation of optically active piperidines and *aza*-bridged medium-sized carbocycles heavily substituted at the α-positions of the N-atom.

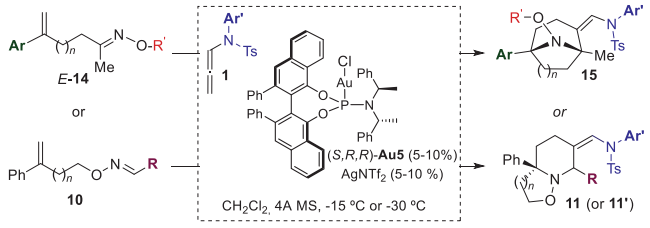
A preliminary screening of chiral gold(I) complexes led us to identify the phosphoramidite-gold complex (*S*,*R*,*R*)-**Au5**/$AgNTf_2$ as a suitable catalyst to achieve asymmetric cycloadditions between *C*-tethered alkenyl oximes of type *E*-**14** and *N*-tosyl allenamides (e.g. **1b**).[23] Thus, as shown in the Table 5, the cycloaddition of *N*-tosyl phenyl allenamide **1b** with alkenyl *O*-methyl oxime *E*-**14b** proceeded smoothly at 0 ºC to provide after 4 h, the desired *aza*-bridged carbocycle (**15bb**) in 65% yield and with an enantiomeric ratio (er) of 83:17. Decreasing the reaction temperature to -15 ºC brought only a marginal increase of the er, and compromised the yield. However, the use of the allenamide **1d**, bearing a 1-naphthyl ring at the tosyl amide, led to a better yield (**15db**, 61%) and a slightly better er. Likewise, other *O*-methyl oximes, featuring different substituents at the aryl moiety of the alkene, also provided their respective tropanic products (**15bj**-**15bl**) with good yields at -15 ºC (70 – 79%), and good er's, which varied from 86:14 (**15bj**) to 92:8 (**15bk**).

Fine tuning of the alkenyl oxime partner (**14**) allowed to further improve the enantioselectivity. In particular, the use of *O*-benzoyl oximes, instead of the *O*-methyl counterparts, provided for slightly but consistently higher enantiomeric ratios [e.g. **15dg** (90:10 er) *vs* **15db** (87:13 er)]. Along these lines, the cycloaddition of *N*-tosyl phenyl allenamide (**1b**) with several *O*-benzoyl oximes bearing electron donating substituents at the aryl moiety of their alkenes, afforded their respective *aza*-bridged carbocycles with excellent enantiomeric ratios, which varied from 94:6 (**15br** and **15bs**) to 95:5 (**15bq** and **15bt**). Importantly, the enantioselective variant is not limited to the synthesis of *aza*-bridged seven-membered rings; indeed, the eight-membered carbocycle **15bp** could also be obtained with moderate yield and with an enantiomeric ratio of 90:10.

We then checked whether the same catalytic system could also be successful in the tandem annulation between allenamides and *O*-tethered oximes of type **10**. Gratifyingly, the cycloaddition of **1b** and **10a** could be efficiently carried out at -30 ºC to exclusively afford the desired piperidine (**11ba**) in good yield and with a good enantiomeric ratio of 87:13 (Table 5). This could be further improved by using the *N*-tosyl-1-naphthyl allenamide **1d**, so that product **11da** was obtained in 83% yield and an excellent 93:7 er. Importantly, the complex (*S*,*R*,*R*)-**Au5**/$AgNTf_2$ also catalyzes the cycloaddition of allenamide **1d** with other alkenyl oximes such as **10c** and **10g**, to provide the corresponding azacycles (**11dc** and **11dg**) with good yields and er's of 92:8 and 91:9, respectively.

Finally, we also checked whether a *cis* oxime like *Z*-**10a** could also participate in an enantioselective annulation. Gratifyingly, its cycloaddition with **1b**, catalyzed by (*S*,*R*,*R*)-**Au5**/$AgNTf_2$, gave the expected *trans* piperidine bicyclic system **11ba'** in 81% yield and 87:13 er, identical to that obtained for **11ba**, from *E*-**10a**. Similarly, other *cis* oxime precursors of type *Z*-**10** also provided their corresponding adducts with the same er than their respective *E*-isomers.[23,35]

Table 5. Preliminary Enantioselective Au(I)-Catalyzed Cycloaddition of Allenamides and *C*- and *O*-Tethered Oximes[a]



15	Ar	Ar'	%yield	er
15bb	Ph	Ph	65	83:17[b]
15bb	Ph	Ph	41	86:14
15db	Ph	1-Np	61	87:13
15bj	*p*Tol	Ph	79	86:14
15bk	*p*(MeO)Ph	Ph	76	92:8
15bl	2-Np	Ph	70	87:13

15	Ar	Ar'	%yield	er
15bg	Ph	Ph	48	87:13
15dg	Ph	1-Np	60	90:10
15bq	*p*(MeO)Ph	Ph	51	95:5
15br	*3,4*-(OCH_2O)Ph	Ph	52	94:6
15bs	*p*(BnO)Ph	Ph	66	94:6
15bt	*p*(MeS)Ph	Ph	62	95:5

15bp
41%, 90:10 er

11	R	Ar'	%yield	er
11ba	Ph	Ph	67	87:13[c,d]
11da	Ph	1-Np	83	93:7[c,d]
11dc	*p*CF_3Ph	1-Np	72	92:8[c,e]

11	Ar'	%yield	er
11bg	Ph	59	85:15[c,f]
11dg	1-Np	65	91:9[c,d]

11ba'
81%, 87:13 er[c,d,g]

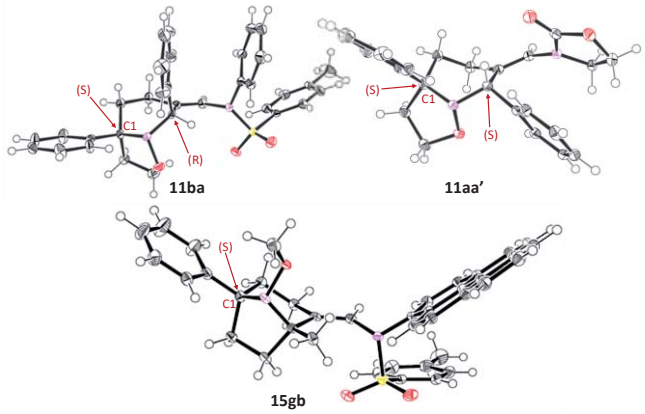
[a] *Conditions:* Allenamide **1** (1 equiv) and *E*-alkenyl oxime (**10** or **14**, 1.5 equiv) were treated with (*S,R,R*)-**Au5** (10 mol%) / $AgNTf_2$ (10 mol%) in CH_2Cl_2 at -15 ºC (reaction times: 0.5 - 6 h),[23] unless otherwise noted. [b] Carried out at 0 ºC with 5 mol% of catalyst for 4 h; [c] Carried out with 5 mol% of catalyst. [d] Carried out at -30 ºC for 17 h. [e] Carried out at -50 ºC for 5 h. [f] Carried out at 0 ºC for 0.5 h; A [2 + 2] adduct (**12bg**) was also obtained in 15% yield and 93 : 7 er. [g] Carried out with *Z*-**10a** instead of *E*-**10a**. Np = naphthyl.

Absolute Configuration and Mechanistic Interpretations. X-ray analysis of the absolute configuration of the *cis* and *trans* cycloadducts **11ba** and **11aa'** confirmed that both piperidine type of scaffolds share the same absolute configuration of the chiral center generated at the position labeled as C-1 (Figure 2). Moreover, the absolute configuration of the homologous stereocenter in the tropane derivative **15gb** is also the same. Therefore, both types of cascade annulations most likely share the same enantio-determining step, namely, the addition of the alkene moiety to the gold activated allenamide (zwitterionic intermediate **I**, Scheme 10) to afford intermediate species of type **IV** or **VI** (Scheme 10). These species should not be viewed as standard benzylic carbocations but rather as configurationally stable carbocations, in which the rotation around the C-1 – C-2 bond is restricted due to an electrostatic interaction between C-1 and the gold(I) atom.[14, 36] Then, an intramolecular stereospecific attack of the oxime nitrogen would produce the corresponding iminium species **V** and **VII**, respectively. A subsequent stereospecific *aza*-Prins cyclization in **VII** would provide the epimeric piperidines **11** (from the *trans* oxime *E*-**10**) and **11'** (from the *Z*-counterpart), both presenting the same enantiomeric excess (Scheme 10).[23] Likewise, a related *aza*-Prins cyclization in cyclic iminium **V** affords the tropane derivatives **15**, which are obtained with similar er values to piperidines **11** / **11'**, as well as with the same absolute configuration at C-1.

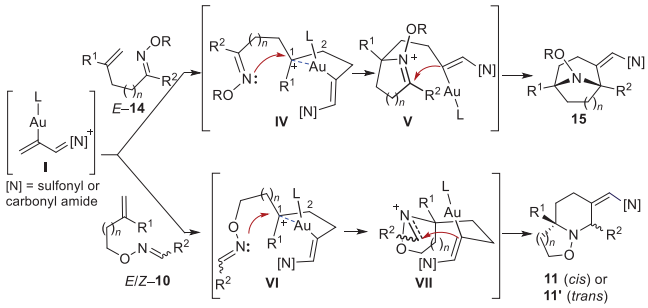
When the interception of the C-1 carbocation by the oximic nitrogen is not efficient, competitive [2 + 2] cycloadducts of type **12** (or **16**) can be obtained. Curiously, these cyclobutanes are regularly obtained with slightly higher er's than their respective [2 + 2 + 2] counterparts.[37, 23] Based on previous results on enantioselective [2 + 2] cycloadditions of *N*-sulfonyl allenamides,[38] we can additionally propose that these cyclobutane side-products are obtained with the opposite absolute configuration at their homologue stereocenter, when the same chiral catalyst is used to carry out the cycloaddition [(*S,R,R*)-**Au5** / $AgNTf_2$].

Overall, these results strongly suggest that the three pathways, towards piperidines (**11** / **11'**), tropanes **15** and cyclobutanes (**12** / **16**), share the same enantiodetermining step (formation of species **IV**/**VI**, Scheme 10); however, the asymmetric induction attained in these intermediates is slightly eroded during their transformation into species **V** or **VII**. This step must involve an attack *anti* with respect to the Au(I) atom,[13a] so that cyclobutanes (**12** and **16**) and the [2 + 2 + 2] adducts (**11** and **15**) are obtained with opposite absolute configurations at their shared stereocenter (C-1).

Figure 2. X-ray diffraction analysis of enantiorich 11ba, 11aa', 15gb, showing the absolute configuration[39]



Scheme 10. Mechanistic Hypothesis Accounting for the Observed Stereoselectivity



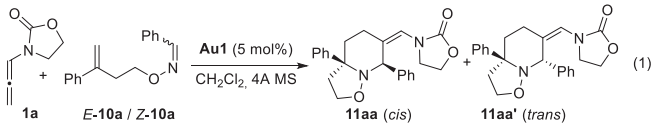
While the mechanistic profiles outlined in Scheme 10 seem appropriate to describe the annulations, there are several experimental observations that deserve further attention and interpretation. As shown in Scheme 11 (eq 1), there is a great difference in reaction rates for oxime ethers *Z*-**10a** and *E*-**10a** (full conversion of *E*-**10a** after 0.1 h at -15 ºC *vs* 22 h at *rt* for *Z*-**10a**). Remarkably, adding a small proportion of the *cis*-oxime *Z*-**10a** to *E*-**10a** (final *E* / *Z* ratio of 11:1) causes a drastic reduction of the reaction rate (from 0.1 h to 5 h for full conversion at -15 ºC). These results suggest that the *cis*-oxime *Z*-**10a** is inhibiting the reactivity, likely because of a stronger coordination to the Au(I) complex, which decreases the effective concentration of an active gold(I) catalyst in the reaction media. On the other hand, when a 1:1 mixture of *E*- and *Z*-**10a** is employed, the reaction required 20 h at *rt* for completion, and led to a 1.6 : 1 ratio of **11aa** and **11aa'** (75% global yield, Scheme 11, eq 1). Since the trapping of intermediate **I** by the alkene moiety of **10a**, or the interception of the carbocation in **VI** by the oximic nitrogen to generate **VII** should not be significantly influenced by the *E*/*Z* stereochemistry of the oxime moiety, it can be anticipated that this 1.6:1 ratio is essentially reflecting the different rates of the *aza*-Prins cyclizations of the *Z*- and *E*-oxime intermediates of type **VII**.[40]

As previously commented, the reaction of alkenyl oxime *E*-**10c**, which bears an electron withdrawing *p*CF_3 at the aryl substituent, is significantly faster than that of *E*-**10a** (Scheme 11, eq 2). This could potentially be explained either in terms of the weaker gold coordination ability of the oximic nitrogen of **10c** (due to the withdrawing effect of the *p*CF_3 substituent), or on the basis of a faster *aza*-Prins cyclization of the more electrophilic iminium intermediate (**VII**) derived from **10c**.[41] Notably, when a 1 : 1 mixture of *E*-**10a** and *E*-**10c** was treated under standard reaction conditions, a 1.3 : 1 mixture of the products in favor of **11aa** was obtained (90%

global yield, Scheme 11, eq 2). Therefore, when the effective concentration of the gold(I) catalyst is the same for both substrates, the oxime *E*-**10a**, equipped with the more basic nitrogen, reacts faster. This suggests that the nucleophilic interception of the carbocation of **VI** exerts a higher influence than the *aza*-Prins cyclization on the overall rate of the process,[42] so that the different rates of **10a** and **10c** are essentially due to their dissimilar coordination strengths to the gold(I) complex.

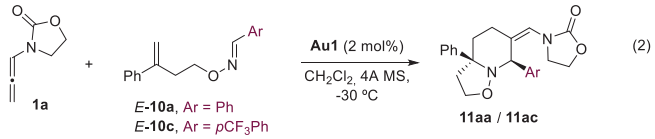
Related electronic effects of the oxime counterpart are observed in the assembly of the *aza*-bridged systems. Thus, in independent experiments, the reaction of the less coordinating *O*-benzoyl oxime **14g** was significantly faster than that of the *O*-methyl derivative **14b** (0.1 h *vs* 4 h, Scheme 11, eq 3). Additionally, when a 1:1 mixture of both oximes was used, a 1 *:* 1 mixture of the products, **15ab** and **15ag**, was obtained. These results confirm that the step from **IV** to **V** has also a higher influence than the *aza*-Prins cyclization on the rate of the process that leads to the tropanic scaffolds (**15**).

Scheme 11. Mechanistic experiments



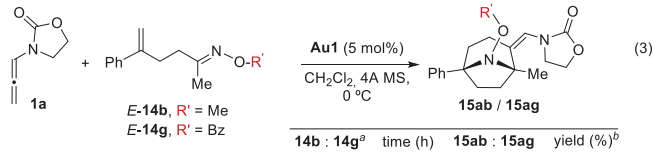
10a (*E* : *Z*)[a]	t (ºC)	time (h)	**11aa** : **11aa'**	yield (%)[b]
1 : 0	-15	0.1	0 : 1	85
0 : 1	-15 -> rt	22	1 : 0	60
11 : 1	-15	5	>18 : 1	75[d]
1 : 1[c]	-15	20	1.6 : 1	70[d]
3.5 : 1	-15	20	5.8 :1	78[d]

[a] 1.5 equiv of **10a** was used unless otherwise noted. [b] Combined isolated yield. [c] 2.0 equiv of this mixture was used. [d] Yield determined by ^{1}H-NMR in the crude mixture (with internal standard).



10a : **10c**[a]	time	**11aa** : **11ac**	yield (%)[b]
1 : 0	15 min	1 : 0	92
0 : 1	5 min	0 : 1	95
1 : 1[c]	15 min	1.3 : 1	90

[a] 1.5 equiv of oxime **10** was used unless otherwise noted. [b] Determined by ^{1}H-NMR in the crude mixture (with internal standard). [c] 2.0 equiv of this mixture were used.



14b : **14g**[a]	time (h)	**15ab** : **15ag**	yield (%)[b]
1 : 0	4	1 : 0	90
0 : 1	0.1	0 : 1	79
1 : 1[c]	2.5	1 : 1	92

[a] 1.5 equiv of oxime **14** was used unless otherwise noted. [b] Determined by ^{1}H-NMR in the crude mixture (with internal standard). [c] 2.0 equiv of this mixture were used.

CONCLUSION

To conclude, we have developed a new approach to the straightforward construction of piperidine scaffolds from readily available alkenyl-tethered oximes and *N*-allenamides, using a gold-catalyzed formal [2 + 2 + 2] annulation. Depending on the topology of the tethers connecting the oxime and the alkenyl moieties, the strategy provides either piperidine products or tropane-like azabicyclic systems. The annulations have a significant scope and versatility, and the resulting products are amenable of divergent elaboration in synthetically relevant manners. We also demonstrated the viability of achieving enantioselective versions, and provided mechanistically relevant experimental data that confirm the relevance of balancing the nucleophilic character and the gold coordinating ability of the sp^2-nitrogen atoms of the oxime units for obtaining successful results. Our discoveries bring new opportunities in the area of gold catalysis, especially for the development of methodologies that involve the use of reaction partners equipped with nitrogen atoms.

Supporting Information

Full experimental procedures, complementary mechanistic studies, optimization of the catalysts and characterization of all new compounds, including ^{1}H-, ^{13}C-NMR spectra, MS and HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

Prof. J. L. Mascareñas. joseluis.mascarenas@usc.es,
Dr. F. López.: fernando.lopez@csic.es

ORCID

José L. Mascareñas: 0000-0002-7789-700X
Fernando López: 0000-0002-0235-6858

Author Contributions

‡These authors contributed equally.

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

This work received financial support from the Spanish MINECO (SAF2016-76689-R, CTQ2017-84767-P, FPU fellowship to I.V. and J.F.C), the Xunta de Galicia (ED431C 2017/19, 2015-CP082, Centro Singular de Investigación de Galicia accreditation 2016-2019 ED431G/09 and predoctoral fellowship to D.C.M.), the ERDF, ERC (Adv. Grant No. 340055) and the Orfeo-Cinqa network (CTQ2016-81797-REDC). Dr. Rebeca García-Fandiño is acknowledged for her contribution to DFT studies.

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(31) Conversely, *O*-unsubstituted oximes (C=N–OH) have been frequently used in cycloaddition reactions, mostly as precursors of nitrile oxides and nitrones. See: Rai, K. M. L.: Heterocycles via Oxime Cycloadditions. In *Synthesis of Heterocycles Via Cycloadditions*; Hassner, A., Ed.; Topics in Heterocyclic Chemistry, 2008; Vol. 13; pp 1-69.

(32) In few cases, the parent oxime partner employed in the cycloaddition consisted of a *E* / *Z* mixture (from 6 : 1 to 15 : 1). Only in these cases, small amounts of the *trans* adducts of type **11'** were observed in the crude mixture (**11** / **11'** ratios >15 : 1). The isomeric ratio of the products (**11** / **11'**) was consistently higher than that of the parent oximes **10**, due to the higher reactivity of the *E*-isomers. See the Supp. Info. for each case.

(33) The 8-azabicyclo[3.2.1]octane derivative **15aa** was isolated as a 2.6 *:* 1 mixture of *N*-invertomers (equatorial and axial N–OMe disposition). This was confirmed by variable temperature NMR and derivatization experiments (see the Supporting Information). For selected precedents on this isomerism in tropane scaffolds, see: (a) Kashman, Y.; Cherkez, S. The Synthesis of Heterocyclic Systems from Cyclohepta-2,6-dienone. *Synthesis* **1974**; 1974, 885-887. (b) Cherkez, S.; Yellin, H.;

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(34) For related transformations, see: Reich, H. J.; Wollowitz, S, Preparation of α,β-Unsaturated Carbonyl Compounds and Nitriles by Selenoxide Elimination. *Org. React. (Hoboken, NJ, U. S.)* **1993**, *44*, pp 1-296.

(35) Generally, when cycloadditions were carried out with *E* / *Z* mixtures of oxime ethers of type **10**, mixtures of the corresponding piperidines **11** and **11'** were obtained, both of them with the same er values (see Table S7).[23]

(36) See also: González, A. Z.; Benitez, D.; Tkatchouk, E.; Goddard, W. A., 3rd; Toste, F. D., Phosphoramidite Gold(I)-Catalyzed Diastereo- and Enantioselective Synthesis of 3,4-Substituted Pyrrolidines. *J. Am. Chem. Soc.* **2011,** *133*, 5500-5507.

(37) As a representative case, whereas the [2 + 2 + 2] adduct **11bg** is obtained with 85:15 er (59% yield), its corresponding [2 + 2] side product **12bg** (15% yield) is isolated with an er of 93:7 (Table 5). See Table S8 for additional cases.

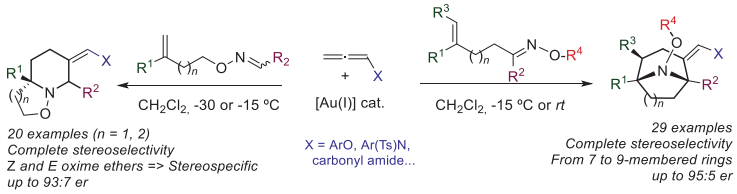
(38) Suárez-Pantiga, S.; Hernández-Diaz, C.; Rubio, E.; González, J. M., Intermolecular [2 + 2] Reaction of *N*-Allenylsulfonamides with Vinylarenes: Enantioselective Gold(I)-Catalyzed Synthesis of Cyclobutane Derivatives. *Angew. Chem. Int. Ed.* **2012**, *51*, 11552-11555.

(39) Adduct **15gb** (54% yield and 85 : 15 er) was obtained from *N*-pyrenyl tosyl allenamide **1g** and the alkenyl oxime *E*-**14b**.[23]

(40) In consonance with these results, when a different *E* / *Z* mixture of **10a** was used (e.g. *E* / *Z* = 3.5 : 1), the observed ratio between **11aa** and **11aa'** (**11aa** / **11aa'** = 5.8 : 1) again reflected a 1.6 fold isomeric enrichment in favor of the *cis* isomer **11aa**.

(41) The *aza*-Prins cyclization is expected to be faster with electron deficient groups at the *C*-oxime substituent.

(42) (a) In consonance with these results, *O*-alkenyl oximes of type **10** with longer tethers between the alkene and the oxime ether only provided the competitive [2 + 2] side-product (see the Supporting Information, Scheme S2). (b) Likewise, fully intermolecular reactions between allenamide **1a**, α-methyl styrene **2a** and different types of aldehyde oxime ethers only provided the bimolecular [2 + 2] cycloadduct **5aa**. Further studies to identify the appropriate type of oxime that could participate in this intermolecular [2 + 2 + 2] transformation are underway.


CH2Cl2, -30 or -15 °C
[Au(I)] cat.
X = ArO, Ar(Ts)N, carbonyl amide...
CH2Cl2, -15 °C or rt
20 examples (n = 1, 2)
Complete stereoselectivity
Z and E oxime ethers => Stereospecific
up to 93:7 er
29 examples
Complete stereoselectivity
From 7 to 9-membered rings
up to 95:5 er