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# Enantioselective Au(I)-Catalyzed Multicomponent Annulation *via* Tethered Counterion-Directed Catalysis

Zhenhao Zhang,<sup>a,b</sup> Nazarii Sabat,<sup>a</sup> Gilles Frison,<sup>b,c</sup> Angela Marinetti,<sup>a,\*</sup> Xavier Guinchard<sup>a,\*</sup>

a Dr Zhenhao Zhang, Dr Nazarii Sabat, Dr Angela Marinetti, Dr Xavier Guinchard  
Université Paris-Saclay, CNRS, Institut de Chimie des Substances Naturelles, UPR 2301, 91198, Gif-sur-Yvette, France.  
E-mail: [angela.marinetti@cnrs.fr](mailto:angela.marinetti@cnrs.fr) ; [xavier.guinchard@cnrs.fr](mailto:xavier.guinchard@cnrs.fr)

b Dr Zhenhao Zhang, Dr Gilles Frison  
LCM, CNRS, Ecole Polytechnique, Institut Polytechnique de Paris, 91128 Palaiseau, France.

c Dr Gilles Frison  
Sorbonne Université, CNRS, Laboratoire de Chimie Théorique, 75005 Paris, France

*Gold(I) complexes of a new chiral phosphoric acid functionalized phosphine of the CPA-Phos series enable the enantioselective multicomponent reactions between aldehydes, hydroxylamines and cyclic yne-enones, leading to 3,4-dihydro-1H-furo[3,4-d][1,2]oxazines. This represents the first example of highly enantioselective multicomponent reaction in gold(I) catalysis. The reactions proceed at low catalyst loading, provide high yields, total diastereoselectivity and enantiomeric excesses up to 99%. Silver-free conditions can be applied. The method has a very broad scope, as it applies to both aliphatic and aromatic aldehydes and hydroxylamines, to a variety of cyclic yne-enones, as well as to yne-enone derived oximes. DFT calculations are reported that enlighten the enantiocontrol pathway.*

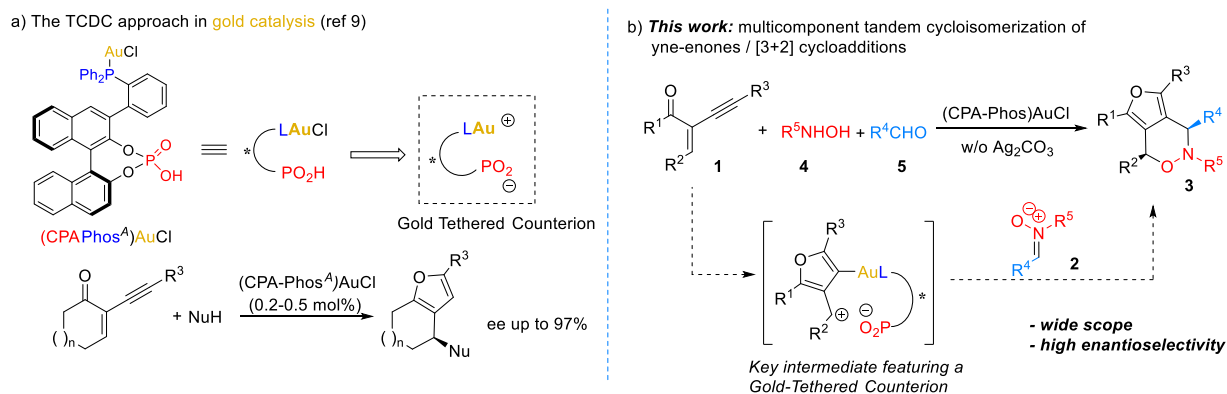
## Introduction

Multi-component reactions are defined as reactions involving at least three different substrates in a multistep sequence by which most atoms of the substrates are incorporated in the final product. Such an approach has witnessed a tremendous interest in the last decades,<sup>[1]</sup> because of its operational simplicity ('pot, atom and step-economy': PASE<sup>[2]</sup>) and because of the huge structural diversity that can be attained in a restricted timespan. The field of gold catalysis also bloomed in the last decades,<sup>[3]</sup> notably thanks to the design of new chiral ligands, leading to novel ways of thinking disconnections between C-C and/or C-heteroatom bonds.<sup>[4],[5]</sup> Multicomponent gold-promoted reactions have however been largely neglected so far. One of the rare examples is the coupling of aldehydes, amines and alkynes, known as the A<sup>3</sup> coupling,<sup>[6]</sup> while, as far as we know, no successful enantioselective Au(I)-catalyzed multicomponent reactions have been disclosed, despite sporadic attempts.<sup>[7],[8]</sup>

Therefore, setting of gold(I) promoted multicomponent reactions represents today a synthetically relevant objective that we have tackled by leveraging on our original catalytic strategy called TCDC (Tethered Counterion Directed Catalysis).<sup>[9]</sup>

Indeed, as a complement to the Asymmetric Counterion-Directed Catalysis (ACDC) approach,<sup>[10]</sup> introduced in gold catalysis by Toste in 2007<sup>[11]</sup> and applied then to a handful of catalytic reactions,<sup>[12]</sup> we have proposed recently a strategy based on gold catalysts where the gold atom and its counterion are tethered together. The tether should create additional conformational and steric constraints, and ultimately enable better stereochemical control. To this end, we have introduced a novel class of chiral Au(I) pre-catalysts featuring a bifunctional phosphine-phosphoric acid ligand called CPA-Phos<sup>A</sup> that would generate a gold-tethered phosphate counterion (Scheme 1a). We have demonstrated then that these catalysts give high enantioselectivity in selected catalytic reactions, namely in the tandem cycloisomerization/

nucleophilic additions on 2-alkynyl enones<sup>[13], [9a]</sup> (Scheme 1a), and in the dearomatization of naphthols with allenamides.<sup>[9b]</sup>



**Scheme 1.** Purpose of this study: multicomponent gold promoted annulation reaction *via* the asymmetric TCDC approach

Hereafter we show that the TCDC approach applies successfully to the enantioselective tandem reactions of the 2-alkynyl enones **1** with nitrones **2**, in which nitrones behave as nucleophilic 1,3-dipoles giving the formal [3+3] cycloaddition products **3** (Scheme 1b).<sup>[14]</sup> Moreover, we demonstrate that these tandem cyclization/[3+3] cycloadditions can be carried out as multicomponent reactions, *via in situ* formation of the nitrones from hydroxylamines **4** and aldehydes **5**. The method applies to a wide range of aryl and alkyl substituted substrates and overcomes some of the current limitations of enantioselective reactions of this class.<sup>[14]</sup> The method relies on a new CPA-Phos type ligand, and operates both in the presence and in the absence of activating silver salts. DFT calculations provide insights in the behavior of the new Au(I) complex in this reaction.

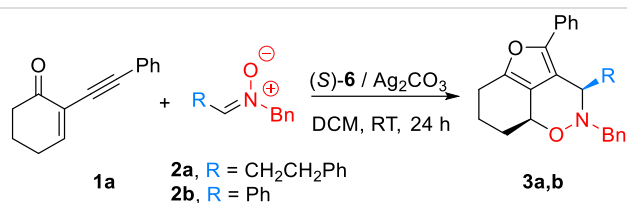
## Results and Discussion

In preliminary experiments, we have considered the reactions of 2-alkynyl cyclohexenone **1a** with *N*-benzyl-nitrones **2a** (R = CH<sub>2</sub>CH<sub>2</sub>Ph) and **2b** (R = Ph) in the presence of the gold complex (CPA-Phos<sup>A</sup>)AuCl **6a**.<sup>[9a]</sup> Ag<sub>2</sub>CO<sub>3</sub> has been used to generate *in situ* the catalytically active gold phosphate. After a few optimization experiments (see SI), both reactions could be carried out in good yields and high enantioselectivity (93% and 98% ee respectively), at a 1 mol% catalyst loading (Table 1, entries 1 and 2). The furo-oxazines **3a,b** have been obtained as single *syn* diastereomers with (3*R*,8*aS*) absolute configurations of the stereogenic centres.<sup>[14c]</sup> Gratifyingly, with nitron **2b**, the catalyst loading could be decreased to 0.2 mol%, while retaining a good isolated yield and the same ee (entry 3). Overall, these results validate the TCDC approach and the efficiency of catalyst **6a** in a new set of reactions. Especially noteworthy is the efficiency attained with nitron **6a** featuring two aliphatic groups (Bn and CH<sub>2</sub>CH<sub>2</sub>Ph), when considering that these nitrones have never been used before in these reactions.<sup>[14]</sup>

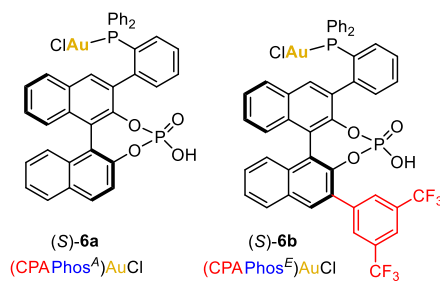
The preliminary catalytic screening of the reaction in Table 1 has been extended then to the newly prepared (CPA-Phos<sup>B</sup>)AuCl complex **6b**. In catalyst **6b** the phosphoric acid-tethered phosphine CPA-Phos<sup>B</sup> features a 3,5-bis(trifluoromethyl)phenyl substituent on the 3' position of the BINOL unit (See the SI for the synthesis of this complex). We were pleased to see that complex (*S*)-**6b** promotes the tandem cycloisomerization/1,3-dipolar cycloaddition sequences

in Table 1 giving excellent ees and high yields even at a catalyst loading of only 0.2 mol% (entries 4 and 5). Both **3a** and **3b** were obtained with almost perfect enantioselectivity.

**Table 1.** Tandem cycloisomerization/nitrone annulation reactions on 2-(phenylethynyl)cyclohex-2-en-1-one **1a**.<sup>a</sup>



entry	<b>14</b>	(S)- <b>6</b> (mol %)	yield (%)	ee (%)
1	<b>2a</b>	<b>6a</b> (1)	91 <sup>a</sup>	93
2	<b>2b</b>	<b>6a</b> (1)	80	98
3	<b>2b</b>	<b>6a</b> (0.2)	74	98
4	<b>2a</b>	<b>6b</b> (1)	87 <sup>a</sup>	99
5	<b>2b</b>	<b>6b</b> (0.2)	89	98



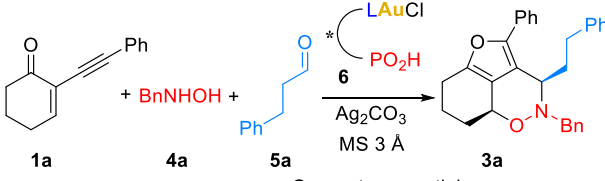
[a] Conditions: **2**:**1** ratio = 1:1.5; Ag<sub>2</sub>CO<sub>3</sub>: **6** ratio = 0.5:1. The absolute configuration of **3b** has been assigned from  $\alpha_D$  values and chiral HPLC data, by comparison with the literature.<sup>[14c]</sup>

Next, to make this promising method even more efficient, fast and cost-effective, we have envisioned avoiding the upstream synthesis and isolation of the nitrones. A convenient alternative is indeed to generate nitrones *in situ* by reacting the aldehyde and *N*-hydroxylamine precursors in the presence of a dehydrating agent, such as molecular sieve. With this in mind, we have investigated both sequential and *in-situ* gold-catalyzed multicomponent reactions between the  $\alpha$ -alkynyl-enone **1a**, hydroxylamines and aldehydes.

In the initial experiments, aldehyde **5a**, *N*-benzyl hydroxylamine **4a**, and the yne-enone **1a** were reacted in the presence of the (CPAPhos)AuCl complexes **6a,b**, silver carbonate and MS 3 Å in DCM, by following the two protocols in Table 2.

In the sequential one-pot protocol, dihydrocinnamaldehyde, *N*-benzylhydroxylamine and MS 3 Å were combined in DCM for 3 h, before addition of the catalyst. Using pre-catalyst **6a** (1 mol%) and silver carbonate (0.5 mol%), the expected product **3a** was obtained in 72% yield after 16 h (entry 1). Thus, under these conditions, the yield was lower than in the reaction on preformed nitrones (Table 1, entry 1), but the ee proved extremely high (96% ee).

We then performed the same reaction by combining all reactants at once in a multicomponent procedure. Using pre-catalyst **6a**, these conditions led to an excellent 95% isolated yield, with a 98% ee (entry 2). The excellent chemoselectivity is especially remarkable, since the multicomponent reaction might be hampered by numerous side reactions, such as Michael additions to **1a** or competitive trapping of the key carbocationic intermediate (see Scheme 1) by either water or hydroxylamine **4a**.

**Table 2.** First experiments toward multicomponent reaction


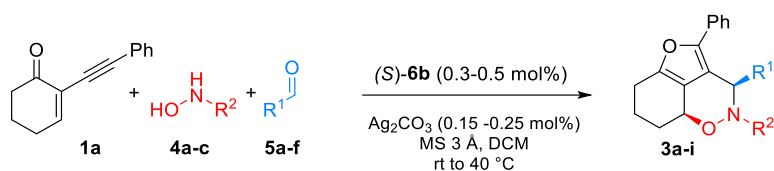
	<b>6</b> (mol %)	Protocol <sup>[a]</sup>	yield (%) <sup>[b]</sup>	ee (%) <sup>[c]</sup>
1	<b>6a</b> (1)	<i>One-pot sequential</i>	72	96
2	<b>6a</b> (1)	<i>Multicomponent</i>	95	98
3	<b>6a</b> (0.3)	<i>Multicomponent</i> <sup>[d]</sup>	31	89
4	<b>6b</b> (0.3)	<i>Multicomponent</i>	96	99

[a] One-pot sequential protocol: 1) **5a** + **4a** (1:1 ratio), MS 3 Å, DCM, RT, 3 h. 2) **1a** (1.5 equiv), **6a** (1 mol%), Ag<sub>2</sub>CO<sub>3</sub> (0.5 mol%), RT, 16 h. Multicomponent protocol: **5a** + **4a** (1:1 ratio) + **1a** (1.5 equiv), **6a** or **6b** (0.3-1 mol%), Ag<sub>2</sub>CO<sub>3</sub>, MS 3 Å, DCM, RT, 24 h. [b] Isolated yields. [c] Determined by chiral HPLC. [d] Reaction time 89 h.

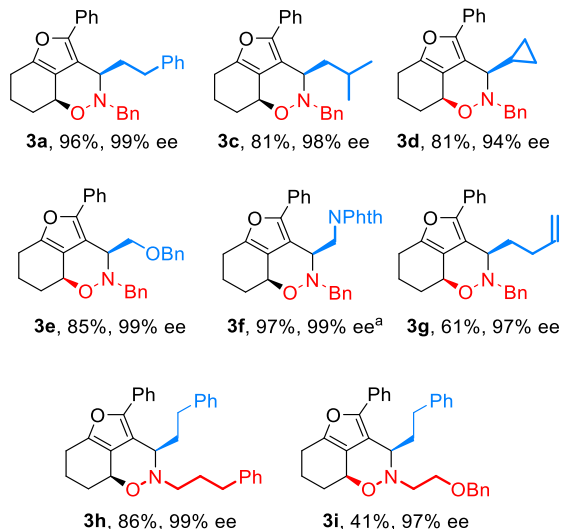
Unfortunately, when the catalyst loading was decreased to 0.3 mol%, both the enantiomeric excess and yield dropped significantly, even after a prolonged reaction time of 89 h (31% yield after 89h, 89% ee, Table 2, entry 3).

However, we were pleased to find that the CPA-Phos<sup>B</sup> gold(I) complex **6b** retains excellent catalytic activity even at such low catalytic loading (0.3 mol%), leading to the dihydrooxazine **3a** with both excellent yield (96%) and ee (99%) after 24 h at RT (entry 4). Catalyst **6b** clearly overcomes catalyst **6a** in these reactions, as a result of the electron-poor nature and/or increased steric hindrance of the aryl substituted phosphoric acid unit.

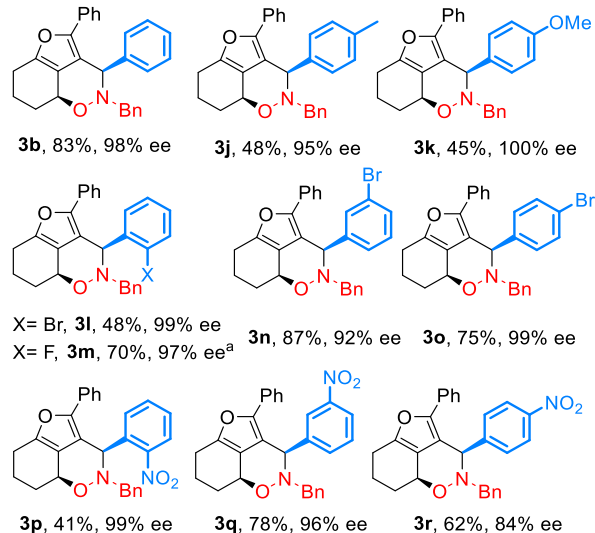
In order to validate the exciting perspectives offered by this novel multicomponent approach for the fast enantioselective synthesis of chiral dihydrooxazines, we undertook a systematic study of the scope of this process. We first focused on aldehydes **5** and hydroxylamines **4** with aliphatic R<sup>1</sup> and R<sup>2</sup> substituents, given that these substrates have been never (for R<sup>1</sup> = alkyl) or scarcely (for R<sup>2</sup> = alkyl) used in these reactions (Scheme 3, Part 1). The benzylhydroxylamine **4a** (R<sup>2</sup>= Bn) was screened against a series of aliphatic aldehydes in the reaction with ketone **1a** (0.3 mmol scale), using 0.3 mol% precatalyst **6b**. In addition to the previously mentioned dihydrocinnamaldehyde, the reaction was carried out with simple aldehydes such as isovaleraldehyde (**3c**, 81% yield) or cyclopropylcarboxaldehyde (**3d**, 81% yield), giving remarkably high ees (>94% ee) in both cases. Excellent results were obtained also with aldehydes featuring benzyloxy and phthalimide functionalities (**3e** and **3f**, >98% ee), granting routes towards alcohol and amine functions. In the case of 2-phthalimidoacetaldehyde, the sequential procedure (nitron pre-generated *in situ*) ensured higher yields. Gratifyingly, the reaction also tolerated an olefinic bond, despite the affinity of gold(I) complexes towards such functions, that could have hampered the reaction (**3g**, 61% yield, 97% ee). Finally, the aliphatic hydroxylamines **4b** and **4c** featuring 3-phenylpropyl and 2-benzyloxyethyl chains have been engaged in the reaction, leading to **3h** and **3i** with excellent enantioselectivities (97-99% ee).



Part 1: aliphatic aldehydes



Part 2: aromatic aldehydes

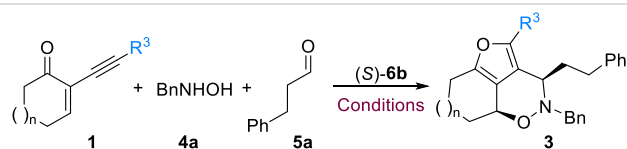


**Scheme 3** Scope of the enantioselective multicomponent reaction. Part 1: screening of aliphatic aldehydes and *N*-alkylhydroxylamines (Conditions: 0.3 mol% **6b**, rt.) Part 2: screening of aromatic aldehydes with *N*-benzylhydroxylamine (Conditions: 0.5 mol% **6b**, 40°C.). <sup>a</sup> Sequential procedure

Next, aromatic aldehydes have been considered in the reaction with benzylhydroxylamine **4a** and ketone **1a** (Scheme 3, Part 2). These reactions required slight modifications of the conditions to be effective, i.e. a catalyst loading of 0.5 mol% and a reaction temperature of 40 °C. Starting from benzaldehyde, the reaction led to **3b** in 83% yield and 98% ee. Electron-donating groups (Me and MeO) were introduced at the *para* position of the aromatic aldehyde, leading to the corresponding cyclization products **3j** and **3k** in excellent ees, while the yield dropped to 45-48%, despite prolonged reaction times.<sup>[15]</sup> Further experiments demonstrated that both halogens and highly electrodeficient nitro-groups are tolerated at the *ortho*, *meta* and *para*-positions of the aryl group, leading to excellent enantioselectivity levels (**3l-r**, 84-99% ee). All compounds were obtained in moderate to good yields under these conditions (48-87% yield).

In a second series of experiments, we screened various cyclic enones **1**, by either replacing the phenyl group on the alkyne moiety by a range of R<sup>3</sup> alkyl groups (**3s-v**) or by changing the ring size (**3w**, n=2) (Table 3). Under the usual conditions, enones with *n*Pr, cyclopentyl and cyclopropyl R<sup>3</sup> substituents led to high enantioselectivities (**3s-u**, 89-92% ee, entries 1-3), unlocking the use of aliphatic R<sup>1</sup> substituent in this reaction, reputed to lead to low enantioselectivities.<sup>[14]</sup> When R<sup>3</sup> was an aliphatic chain decorated with a benzyloxy group, the cyclization product **3v** was obtained in a high 91% ee (entry 4). We also found out that ketone **1f** featuring a 7-membered ring is a suitable substrate, leading to **3w** with 97% ee (entry 5). In these reactions, yields are overall moderate but they increase slightly by increasing the catalyst loading to 0.6 mol% (see SI).

**Table 3:** a) Scope of the enantioselective multicomponent reaction. Part 3: screening of enones. b) Silver-free reactions.



**Conditions A:** **6b** (0.3 mol%), Ag<sub>2</sub>CO<sub>3</sub> (0.15 mol%), MS 3 Å, DCM, RT

**Silver-free conditions:** **6b** (0.3 mol%), MS 3 Å, DCM, RT

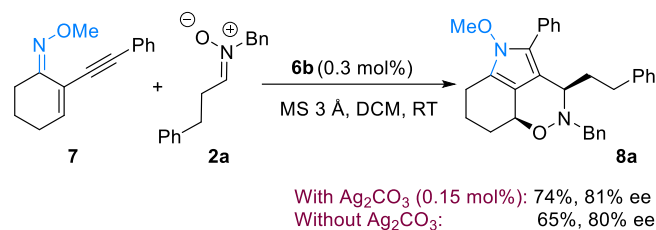
Product <b>3</b>	Cond. A ee (yield) <sup>a</sup>	Silver-free cond. ee (yield)
1  <b>3s</b>	89 (44)	88 (44)
2  <b>3t</b>	90 (63)	92 (53)
3  <b>3u</b>	92 (58)	93 (57)
4  <b>3v</b>	91 (37)	92 (54)
5  <b>3w</b>	97 (39)	95 (15)
6  <b>3a</b>	99 (96)	98 (91)

[a] ee determined by chiral HPLC. Isolated yields.

In our previous study on catalyst **6a**<sup>[9a]</sup> we have established that, in some instances, silver-free conditions can be used, thanks to the self-activation of the gold-chloride complex. Therefore, being aware of the huge practical interest of silver-free conditions in Au(I) catalysis,<sup>[3c, 16],[17]</sup> we have investigated also the possibility of using such conditions in the multicomponent reaction above. Selected results are displayed in Table 3 (see the 'silver-free conditions' column). They demonstrate that the silver-free protocol can be applied successfully to several enones, leading to ees in the same range as for the classical silver-based protocol and mostly comparable yields.

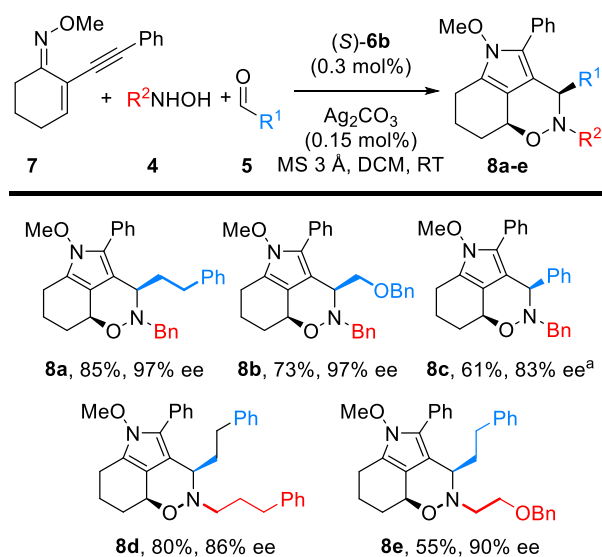
In the last part of this study, to further support the efficiency of the asymmetric TCDC approach based on catalysts **6**, we have demonstrated that these catalysts enable highly enantioselective cyclisations between nitrones and the oximes derived from some of the 2-alkynyl-enones above. These reactions, leading to tricyclic *N*-alkoxyppyroles, are known to take place under gold(I) catalysis. Previous enantioselective variants were investigated only with nitrones bearing aryl substituents.<sup>[18]</sup>

We have considered first the reaction of oxime **7** with nitron **2a** using 0.3 mol% of catalyst **6b** (Scheme 4). The expected *N*-alkoxyppyrole **8a** was obtained in 74% yield and 81% ee. Importantly, the same reaction could be performed without silver carbonate, leading to comparable results (65% yield, 80% ee).



**Scheme 4:** Enantioselective tandem cycloisomerization/addition reactions between oximes and nitrones.

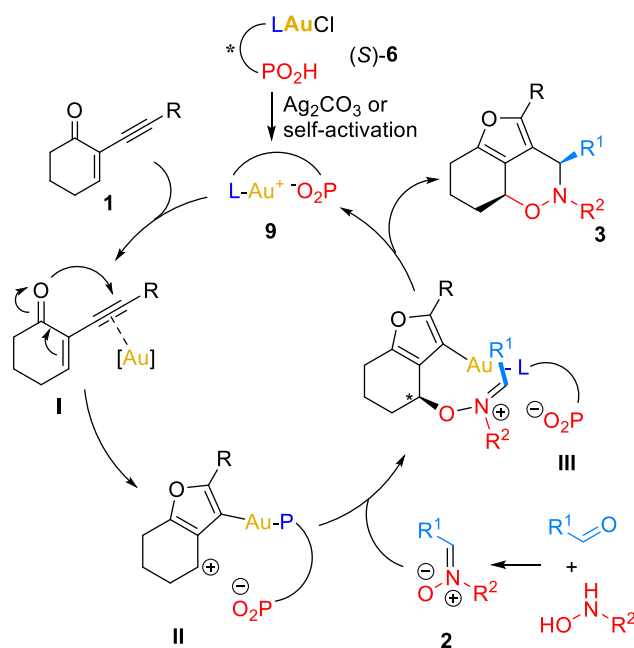
Gratifyingly, the same reaction could be carried out as a multicomponent process (Scheme 6). The reaction of oxime **7** with dihydrocinnamaldehyde and *N*-benzylhydroxylamine **4a** in the presence of 0.3 mol% of catalyst **6b** and silver carbonate led to **8a** in 85% yield and 97% ee. This method proved to be quite general: the reaction could be extended successfully to benzyloxyacetaldehyde and benzaldehyde, as well as to other alkyl-hydroxylamine components leading to the corresponding pyrroles **8b-e** with ees in the range 83-97%. Thus, this study provides unprecedented, highly enantioselective tandem reactions between oximes **7** and *N*-alkyl substituted nitrones, via both two- and three-component procedures.



**Scheme 6:** Scope of the enantioselective multicomponent reactions of *N*-oxime **7**. <sup>a</sup> Reaction performed at 40°C.

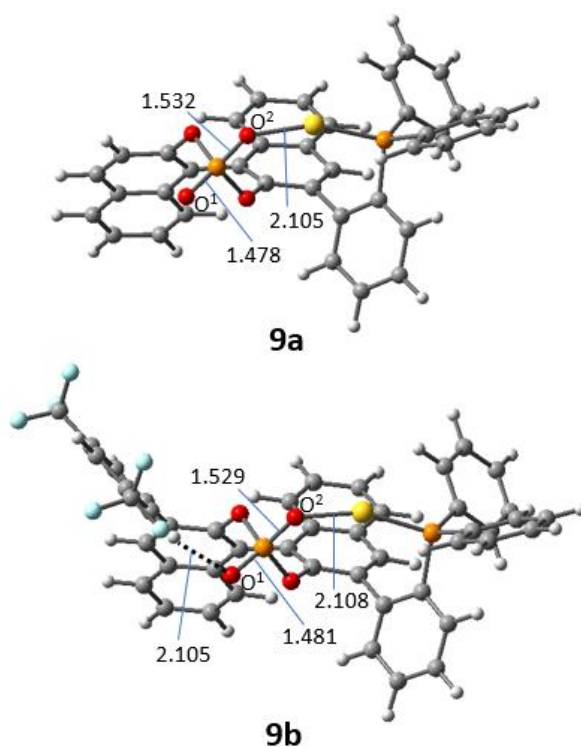


To get a better insight on how such high enantioselectivities are reached, as well as on the effects of the aryl-substituent in catalyst **6b**, we performed DFT calculations based on the generally assumed mechanistic hypothesis<sup>[14c],[9a]</sup> that is displayed in Scheme 7. The reaction starts with the coordination of ketone **1** to the active catalyst **9**, which results from either silver activation or self-activation of the precatalyst (*S*)-**6**. The gold-induced cycloisomerization then generates carbocation **II**. The enantiodetermining step should be the addition of the nitron **2** to this intermediate. Thus, the chiral environment created by the hybrid phosphine-phosphate ligand in intermediate **II**, should induce a facial-selective approach of the nitron to the carbocation. The stereochemical assignment of the final products has shown that this step generates an *S*-configured carbon centre. On the other hand, the diastereomeric ratios in the final products **3** should be controlled at the final deauration step *via* a face selective reaction on the electrophilic iminium ion **III**. As said before, a *syn* stereochemistry is observed experimentally.



**Scheme 7.** Postulated mechanism for the cycloisomerization/nitron addition reactions.

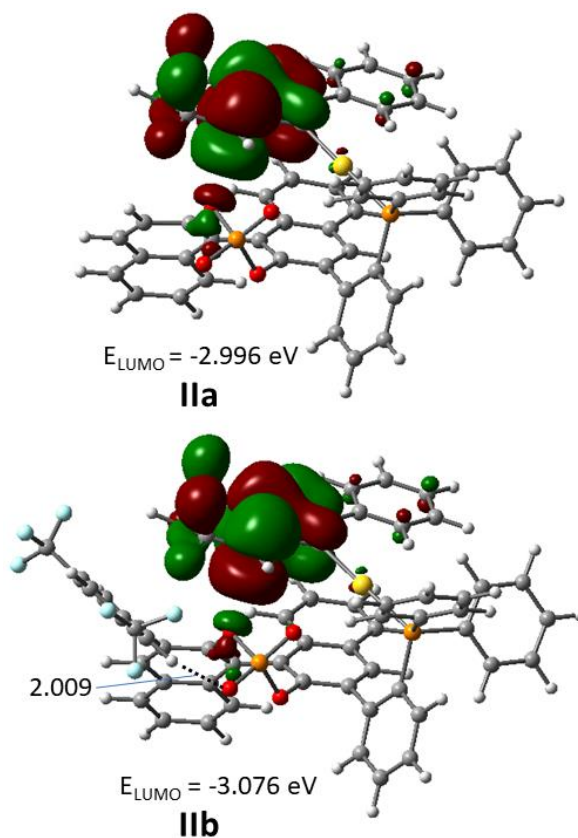
We performed DFT calculations to determine the three-dimensional structure of the active catalyst **17** and intermediate **II**. In particular we compared the structures of the intermediates obtained from pre-catalyst **6a**<sup>[9a]</sup> (active catalyst **9a** and intermediate **IIa**) with those obtained from pre-catalyst **6b** (active catalyst **9b** and intermediate **IIb**). The most stable conformation of **9b**, optimized at the M06/def2-SVP level including solvent (DCM) effect, is close to that of **9a** (Figure 1). The 3,5-bis(trifluoromethyl)phenyl group is oriented so as to establish an intramolecular C-H $\cdots$ O hydrogen bond with the O<sup>1</sup> oxygen atom of the phosphate group which is not bound to the metal center. The C $\cdots$ O<sup>1</sup> (3.158 Å) and H $\cdots$ O<sup>1</sup> (2.105 Å) distances, as well as the C-H $\cdots$ O<sup>1</sup> bond angle of 160.2° suggest an effective interaction.<sup>[19]</sup> Rotation of the aryl group leads to a second isomer **9b'**, slightly higher in energy than **9b** (+1.0 kJ/mol), in which this H-bond is lacking. Due to the presence of the metal centre, the phosphate group in **9a** is polarized towards the mesomeric form O<sup>1</sup>=P-O<sup>2(-)</sup> $\cdots$ Au. The 3,5-bis(trifluoromethyl)phenyl group changes this polarization as **9b** shows slightly longer P-O<sup>1</sup> (1.481 vs 1.478 Å) and shorter P-O<sup>2</sup> (1.529 vs 1.532 Å) bonds compared to **9a**. This suggests that the CF<sub>3</sub>-substituted aryl group might give increased ionic character to the phosphate-gold bond



**Figure 1:** Structure and relative energy (in kJ/mol) of active catalysts **9a** and **9b**.

The coordination of ketone **1** to **9b** and its cycloisomerization leads to **IIb** which has a DFT optimized structure close to that of **IIa**, with an intramolecular ion pairing in both cases (Figure 2). However, in **IIb** the hydrogen bond between the 3,5-bis(trifluoromethyl)phenyl group and the O<sup>1</sup> oxygen of the phosphate group weakens to some extent the ion pairing between the phosphate and the carbocation. The latter is therefore less stabilized than in **IIa**. This statement is supported also by the calculation of the lowest unoccupied molecular orbital (LUMO) of intermediates **IIa** and **IIb** (Figure 2), which display similar shapes, localized on the cationic site, but that of **IIb** is lower in energy ( $E = -2.996$  eV and  $-3.076$  eV for **IIa** and **IIb** respectively).

This effect might explain the higher reactivity of **6b** toward the nucleophilic nitron, compared to **6a**.



**Figure 2:** LUMO of intermediates **IIa** and **IIb**

## Conclusion

As a conclusion, we have shown that CPAPhos are excellent chiral ligands in the Au(I)-catalyzed reactions of 2-alkynyl enones and derived oximes with nitrones, delivering furoxazines and *N*-alkoxy pyrroles in high yields and excellent enantioselectivities. Remarkably, (CPAPhos)AuCl complexes also enable these annulations to be carried out as multicomponent reactions. Most of these annulations proceed efficiently under silver-free conditions. Beyond avoiding the synthesis of nitrones, this procedure is operationally simple, efficient and proceeds at a very low, 0.3 mol% catalyst loading. To the best of our knowledge, these are the first examples of enantioselective gold-catalyzed multicomponent reactions.

## Acknowledgements

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