Gold(I)-catalyzed [8+2]–Cycloaddition of 8–Aryl–8–azaheptafulvenes with Allenamides and Ynamides: Regioselective Synthesis of Dihydrocycloheptapyrrole Derivatives

Tatiana Suárez–Rodríguez, Ángel L. Suárez–Sobrino and Alfredo Ballesteros*[a]

[a] Dr. T. Suárez-Rodríguez, Prof. Dr. A. L. Suárez-Sobrino, Prof. Dr. A. Ballesteros
Departamento de Química Orgánica e Inorgánica; Instituto de Química Organometálica "Enrique Moles"
Universidad de Oviedo
Julián Clavería, 8, 33006-Oviedo (Spain)
abg@uniovi.es

Supporting information for this article is given via a link at the end of the document.

Abstract: Gold(I)-catalyzed higher-order [8+2] cycloadditions of 8-aryl-8-azaheptafulvenes **1** with allenamides **2** and ynamides **3** were studied. 1,8–Dihydrocycloheptapyrroles **4** were achieved by a regioselective [8+2] cycloaddition of azaheptafulvenes **1** and allenamides **2** in the presence of $(2,4\text{–di}t\text{BuC}_6H_3O)_3PAuNTf_2$ as catalyst. Besides, ynamides **3** and 8–aryl-8–azaheptafulvenes **1**, undergo a regioselective [8+2] cycloaddition, to give 2-amido-1,4-dihydrocycloheptapyrroles **7** in the presence of $JohnPhosAuNTf_2$ as catalyst. Both reactions take place with good yields and with a variety of substituents. A plausible mechanism hypothesis suggests a nucleophilic attack of the 8-azaheptafulvene to the gold activated electron rich allene or alkyne moieties of the allenamide and ynamide respectively.

Introduction

Higher order cycloaddition reactions represent a useful tool for the preparation of medium size ring systems.[1] In this context, heptafulvenes[2] and their heteroanalogues, such as tropone,[3] and tropothione[4] are appropriate substrates for this kind of reactions; however, they present several problems, such as the low stability of some of these fulvenoid compounds or the low periselectivity in some reactions.

On the other hand, 8-azaheptafulvenes appear as the most reliable 8π partner to undergo [8+n] cycloadditions;[5] specifically the [8+2] reaction of azaheptafulvenes **1** is one of the most abundant higher-order reaction found in the literature, and represents an efficient access to the cycloheptapyrrole framework present in natural and bioactive products.[6] The first studies on this transformation involved the use of electron-deficient unsaturated systems as 2π partners; for instance, double-activated styrenes[7] and cumulenes[8] (Figure 1, section a). Later, it was described that the highly-electrophilic alkenyl[5a] and alkynyl[9] Fisher carbene metal complexes can react as 2π component with high efficiency and selectivity (Figure 1, section a).

Recently, the [8+2] cycloaddition reaction of 8-azaheptafulvenes **1** has gained more attention with the use of a catalyst, either to achieve good enantioselectivity[10] or to obtain *in situ* reactive intermediate species such as ammonium[10b] and *N*-heterocyclic carbene enolates,[11] or sulfonyl ketinimines.[12]

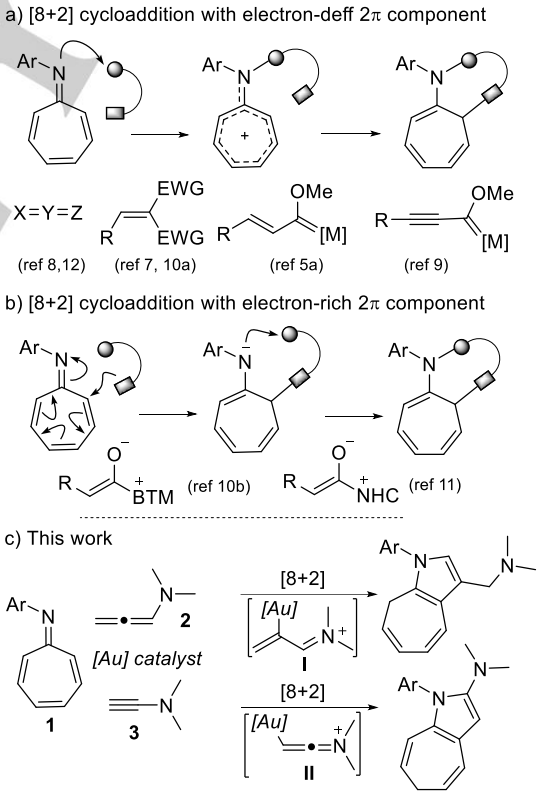


Figure 1. [8+2] Cycloaddition reactions of 8–aryl–8–azaheptafulvenes **1**.

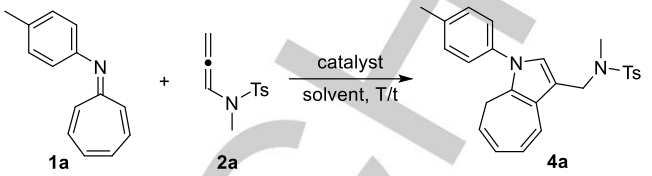
Except for the [8+2] cycloadditions with ammonium and *N*-heterocyclic carbene enolates (Figure 1, section b),[13] the general pattern for this reaction involves a step-way process initiated by a nucleophilic attack of the 8-azaheptafulvene

nitrogen to an electrophilic substrate and further cyclization of the resulting cycloheptadienyl cation (Figure 1, section a).[14]
Apart from the well-known electron-deficient unsaturated reagents, we found interesting to expand the number of unsaturated systems that can act as 2π component in these [8+2] cyclizations, employing electron-rich substrates such as allenamides[15] and ynamides[16]. Both systems are susceptible to be transformed into electrophilic intermediates in the presence of a catalytic carbophilic species. In the past years, it has been well demonstrated that gold catalysis allowed a number of different cycloadditions with both substrates,[17,18] through processes involving cationic intermediates such as vinylimidinium **I** or ketinimonium **II** (Figure 1, section c). However, higher-order cyclization reactions have not yet been described for these compounds. Herein we describe new higher order [8+2] cycloaddition reactions of allenamides and ynamides with azaheptafulvenes catalyzed by gold.

Results and Discussion

Gold-catalyzed [8+2] cycloaddition of allenamides and 8-azaheptafulvenes: Our study started with an initial experiment involving the reaction of 8-azaheptafulvene **1a** with tosylallenamide **2a** in the presence of 5 mol% of (2,4–di*t*Bu$C_6H_3O)_3$P$AuNTf_2$ as catalyst in dichloromethane (0.1 M). The mixture was maintained at room temperature for 18 h until total conversion of the allenamide **2a**. To our delight, a new product **4a** was isolated after purification by column chromatography (AlO_3/hexanes: ethyl acetate, 5:1) with a 40 % yield (Table 1, entry 1). Monodimensional and nuclear Overhauser effect (NOE) NMR experiments confirmed the structure of 1,8–dihydrocicloheptа[*b*]pyrrole for **4a**. With the aim of optimizing the reaction conditions, we heated the reagents at reflux of 1,2–dichloroethane for 15 min to the completion of the reaction, to get an improved yield of 72% (Table 1, entry 2). Temperature and reaction time were then modulated to 60ºC and 1 h respectively to obtain an 82% isolated yield of **4a** (Table 1, entry 3). Then, 1,2–dichloroethane was confirmed as the most effective medium for this reaction after a solvent screening; thus, under the same reaction conditions, the conversion and yield were significantly lower for non-polar solvents such as toluene, hexane, or more polar solvents such as THF or acetonitrile (Table 1, entries 4-7). Then, the evaluation of other gold catalysts confirmed that the change of the ligand resulted ineffective to improve the transformation (Table 1, entries 8,9). Furthermore, the use of gold (III) complex did not improve the results achieved with the phosphite ligand (Table 1, entry 10). The role of the Au catalyst was confirmed later by performing an experiment under catalyst-free conditions (Table 1, entry 11) without any conversion of the starting products. On the other hand, other metal salts, such $AgNTf_2$, $ZnCl_2$ or $In(OTf)_3$ (Table 1, entries 12-14) as well as HBF_4 Et_2O (Table 1, entry 15) did not afford any product, resulting in 8-azaheptafulvene decomposition. The final optimization included an increase from 1.1 to 1.3 equiv of 8-azaheptafulvene **1a** and a lower concentration (0.05 M instead of 0.1 M) that allowed to obtain **4a**, almost quantitatively (95% isolated yield), after completion of the reaction in 1.5 h (Table 1, entry 16). Finally, the reaction was scaled-up to 1 mmol with a catalyst charge of 2.5 mol% and 0.1 M concentration to get the final product with a 96% isolated yield in 4 hours (Table 1, entry 17).

Table 1. Optimization experiments for the reaction between 8–phenyl–8–azaheptafulvene **1a** and allenamide **2a**.



Entry[a]	catalyst	Solvent	T/t	conv[b]	Yield[c]
1	$(ArO)_3$P$AuNTf_2$[d]	DCM	rt/18h	100	40
2	$(ArO)_3$P$AuNTf_2$[d]	DCE	84ºC/15m	100	72
3	$(ArO)_3$P$AuNTf_2$[d]	DCE	60ºC/1h	100	82[e]
4	$(ArO)_3$P$AuNTf_2$[d]	Toluene	60ºC/1h	60	49
5	$(ArO)_3$P$AuNTf_2$[d]	Hexane	60ºC/1h	80	36
6	$(ArO)_3$P$AuNTf_2$[d]	THF	60ºC/1h	60	46
7	$(ArO)_3$P$AuNTf_2$[d]	CH_3CN	60ºC/1h	64	51
8	JohnPhosAuNTf_2[f]	DCE	60ºC/1h	11	7
9	IPrAuNTf_2[g]	DCE	60ºC/1h	0	0
10	Pic$AuCl_2$[h]	DCE	60ºC/1h	37	40
11	–	DCE	60ºC/1h	0	0
12	$AgNTf_2$	DCE	60ºC/1h	0	0
13	$ZnCl_2$[i]	DCE	60ºC/1h	0	0
14	$In(OTf)_3$[i]	DCE	60ºC/1h	0	0
15	HBF_4 Et_2O[i]	DCE	60ºC/1h	0	0
16[j]	$(ArO)_3$P$AuNTf_2$[d]	DCE	60ºC/1.5h	100	95[e]
17[k]	$(ArO)_3$P$AuNTf_2$[d]	DCE	60ºC/4h	100	96[e]

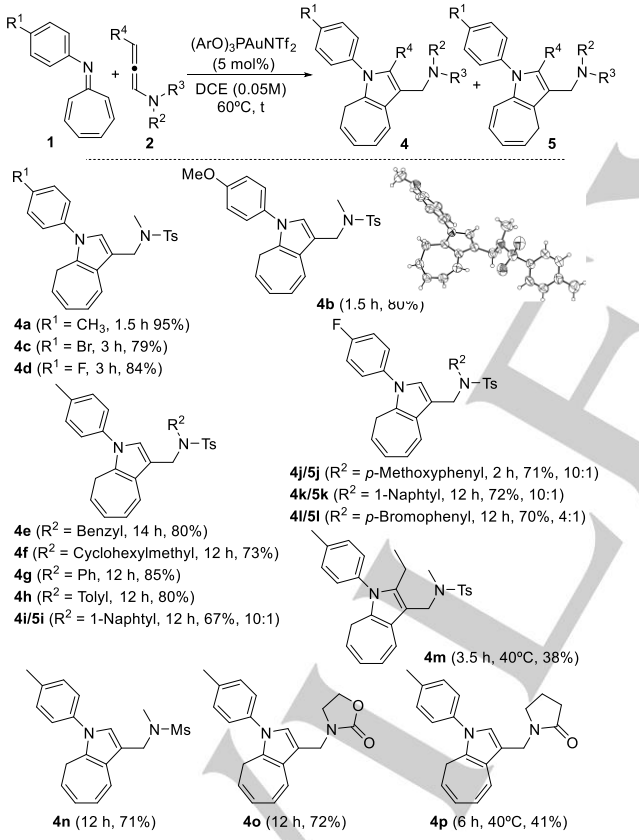
[a] Reaction conditions unless otherwise noted: **1a** (0.2 mmol, 1.1 equiv), **2a** (1 equiv), catalyst (5 mol%), solvent (0.1 M). [b] Conversion of **2a**, determined by NMR with 4–bromobenzaldehyde as internal standard. [c] Determined by NMR. [d] Ar= 2,4–di*t*BuC_6H_3. [e] Isolated yield. [f] JohnPhos: (2–biphenyl)–di–*t*Butylphosphine. [g] IPr: 1,3-bis(2,6–diisopropylphenyl) imidazol–2–ylidene. [h] Pic$AuCl_2$: dichloro(2–pyridinecarboxylate) gold. [i] Catalyst loading 10 mol%. [j] 1.3 equiv of **1a**, DCE (0.05 M). [k] **1a** (1 mmol, 1.3 equiv), **2a** (1 equiv), catalyst (2.5 mol%), DCE (0.1 M).

To evaluate the scope of the reaction (Scheme 1), we used the above-mentioned optimized reaction conditions; then, a 0.05M solution in 1,2–dichloromethane of 8–azaheptafulvenes **1** (1.3 equiv) and allenamides **2** in the presence of (2,4-di*t*Bu$C_6H_3O)_3$P$AuNTf_2$ (5 mol%) was heated at 60ºC. First, we checked different 8-azaheptafulvenes **1** to get products **4a-d** with good yields in all cases; moreover, we ascertained that the reaction tolerates well, either electron-rich (e.g. **4b**, *p*–OMe)[19] or electron-poor (*p*–Br, *p*–F) substituents at the phenyl moiety in the 8–aryl–8–azaheptafulvene (Scheme 1, products **4a–d**).

Interestingly, the reaction decelerates when the nucleophicity of the 8–azaheptafulvene nitrogen decreases (Scheme 1, **4c,d**).

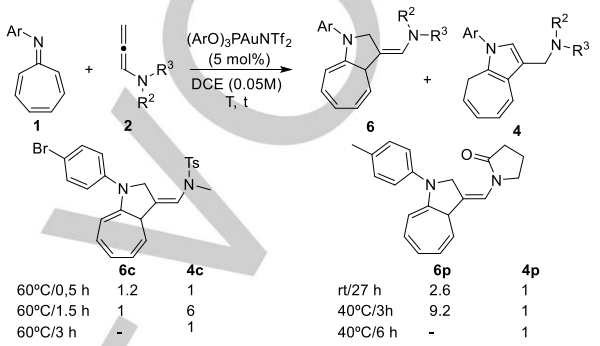
Then, we checked different tosyl allenamides (Scheme 1, products **4e–l**). Thus, we found that allenamides with highest steric demand significantly increased the reaction times (12–14 h), except for the allenamide containing the electron-donor *p*-methoxyphenyl group (Scheme 1, product **4j**). Regardless of this, all products were obtained with good yields. It is also remarkable that products **4i–l** were isolated along with the respective minor 1,4-dyhydro isomers **5i–l** formed after a hydrogen 1,5–sigmatropic rearrangement. On the other hand, 1,2–disubstituted–1,8–dihydrocyclohepta[*b*]pirrole **4m** was obtained, with poorer yield (38%) from the reaction of a γ-ethyl substituted allenamide; furthermore, in this case, softer conditions should be used.

Finally, we used other allenamides instead tosylallenamides. Thus, in the case of the mesyl and the oxazole–2–one derived allenamides (Scheme 1, products **4n,o**) the reaction is more sluggish (12 h *vs* 1.5 h for **4a**) under the same reaction conditions. In the other hand, pyrrolidin–3–one derived allenamide gave poorer yields (**4p**, 41% at 40ºC).



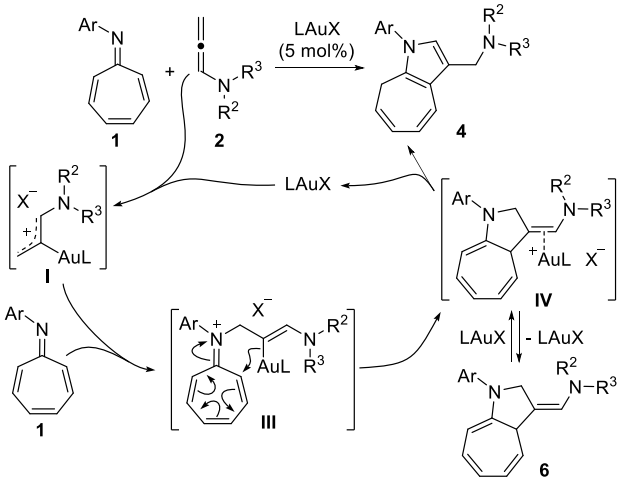
Scheme 1. Cycloaddition reaction of 8-aryl-8-azaheptafulvenes **1** and allenamides **2**.

To get insight into the reaction mechanism, we have monitored some reactions at shorter reaction times and lower temperatures (Scheme 2) Thus, the reaction between *p*-Br substituted 8-aryl-8-azafulvene **1c** and tosyl allenamide **2a** at 60ºC for 0.5 h gave an approximately equimolecular mixture of adduct **4c** and its isomer **6c**[20] in accordance with the ^{1}H-NMR of the crude reaction mixture; moreover, we observed the increase of **4c** ratio at longer reaction time until complete transformation of **6c** in 3 h (Scheme 2). On the other hand, when pyrrolidin–3–one allenamide **2p** reacts with 8-tolyl-8-azaheptafulvene **1a** at rt, [8+2] cycloadduct **6p** and **4p** were formed after 27 h in a 2.6:1 ratio, respectively. Additionally, **6p** was the mayor isomer (9.2:1) observed after 3 h at 40 ºC;[21] subsequently, if the reaction is allowed to progress to 6 h. it was completely transformed into **4p.** Alternatively, a longer heating period (15 h) was required for the quantitative transformation of isolated **6p** at 40ºC in DCE without gold catalyst.



Scheme 2. Formation and transformation of intermediate cycloadducts **6**. Isomer ratios determined by^{1}H NMR of the reaction crudes.

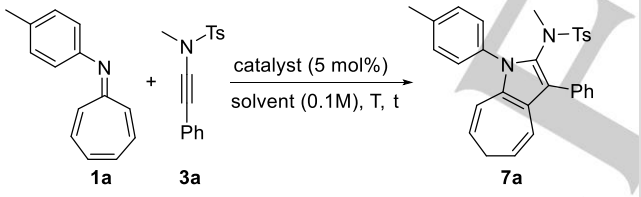
Scheme 3 shows our hypothesis on the mechanism of the reaction, according to our results and observations as well as to the precedents in allenamide gold catalysis.[22] The reaction would start from the complexation of gold catalyst to allenamide **2** to form allylic cationic intermediate **I**, that undergoes nucleophilic attack of the nitrogen of the azaheptafulvene to form intermediate **III**. This intermediate would cyclize to **6**. Under the reaction conditions, the final rearrangement to deliver 1,8–dyhydrocyclohepta[*b*]pyrrole derivatives **4**, is likely to be catalyzed by the gold complex. The rearrangement can also take place in the absence of catalyst, although longer reaction times are needed.



Scheme 3. Proposed mechanism for the cycloaddition reaction of 8-aryl-8-azaheptafulvenes **1** and allenames **2**.

Gold-catalyzed [8+2] cycloaddition of ynamides and 8-azaheptafulvenes: as we said in the introduction, ynamides are potential 2π components in [8+2] cycloadditions of 8-azaheptafulvene through the formation of electrophilic ketinimonium intermediates **II** by coordination to a gold catalyst (Figure 1, section c). In this way, our first experiment was carried out with 8–azaheptafulvene **1a** and tosylynamide **3a** in the reaction optimized conditions for allenamides (Table 2); accordingly, a solution of these compounds in DCE (0.1 M) was heated at 60ºC (Table 2, entry 1) in the presence of (2,4-di*t*Bu$C_6H_3O)_3PAuNTf_2$ (5 mol%) as catalyst. The reaction finished after 21 h, and a new product **7a** was isolated in a 79% yield for a 90% conversion after chromatographic purification (AlO_3, hexanes:ethyl acetate, 20:1). This new product was identified by NMR experiments as the 1-amido-1,4-dihydrocyclopenten[*b*]pyrrole **7a**, resulting from a regioselective [8+2] cycloaddition of **1a** and **3a.** Optimization studies of the reaction conditions allowed us to conclude that longer reaction times did not lead to better conversion of tosylynamide **3a**. Thus, when we tried other catalyst system such as JohnPhosAuNTf_2, in the same reaction conditions (Table 2, entry 2), **7a** was obtained only in a 52% yield (determined by NMR); however, the reaction ran with better conversion/yield ratio (56/52 *vs* 90/79). Considering this result, we raised the temperature to 110 ºC, in toluene as solvent and JohnPhosAuNTf_2 as catalyst to obtain **7a** with a 90% isolated yield for a 100% conversion (Table 2, entry 3). Once again, catalyst–free conditions (Table 2, entry 4) did not get any reaction, as well of other catalytic systems such as $HBF_4.Et_2O$ or $In(TfO)_3$ (Table 2, entries 5–6).

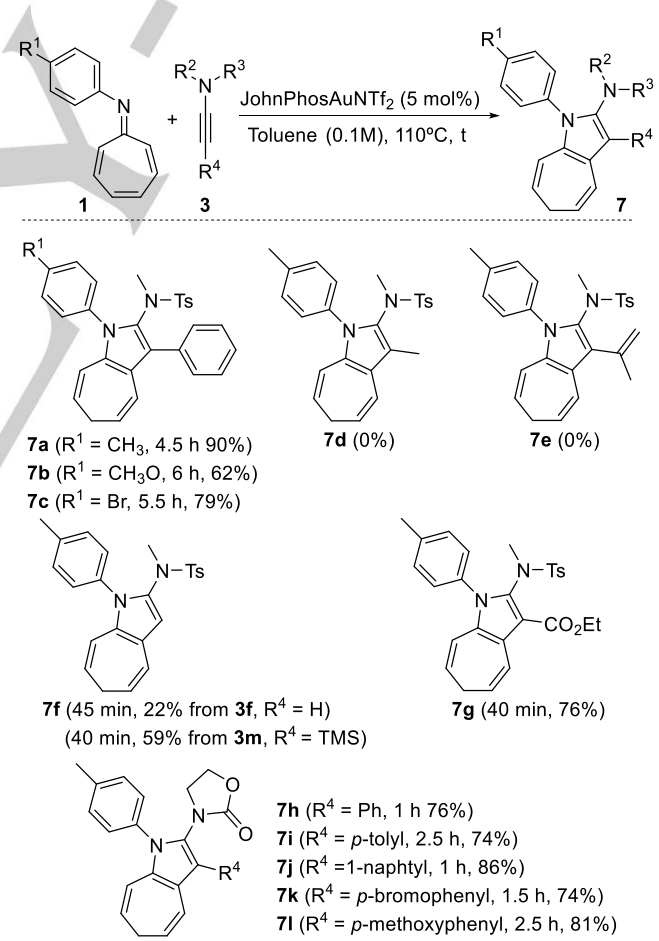
Table 2. Optimization experiments for the cycloaddition reaction between 8–phenyl–8–azaheptafulvene **1a** and ynamide **3a**.



Entry[a]	catalyst	Solvent	T(ºC)/t(h)	Yield %[b]
1	$(ArO)_3PAuNTf_2$[c]	DCE	60/21	79[d]
2	JohnPhosAuNTf_2[e]	DCE	60/21	52[f,g]
3	JohnPhosAuNTf_2	Toluene	110/4.5	90[h]
4	-	Toluene	110/4.5	0
5	$HBF_4.Et_2O$	Toluene	110/4.5	0
6	$In(OTf)_3$	Toluene	110/4.5	0

[a] **1a** (0.2 mmol, 1.5 eq,) **3a** (1 equiv), catalyst (5 mol%), solvent (0.1 M). [b] Isolated yield. [c] Ar = 2,4–di*t*BuC_6H_3. [d] Conversion of **3a** 90%. [e] JohnPhos: (2–biphenyl)di–*t*Buphosphine. [f] Conversion of **3a** 56%. [g] Determined by NMR using 4–bromobenzaldehide as internal standard. [h] Conversion of **3a** 100%.

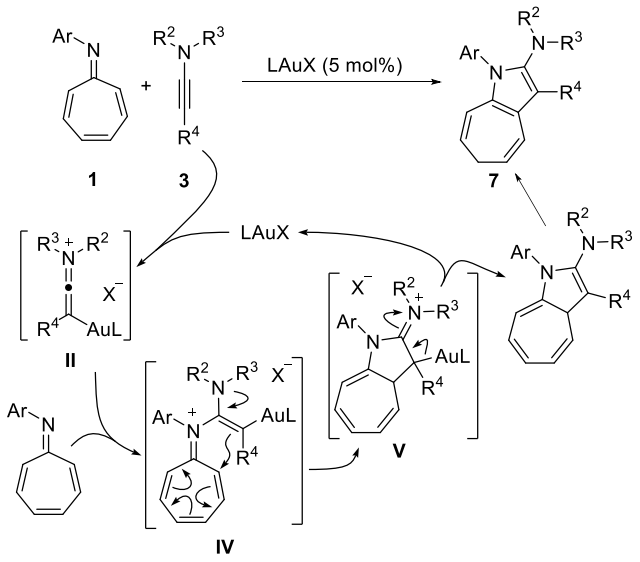
Next, we studied the scope of the reaction with these optimized reaction conditions using different 8-azaheptafulvenes **1** and ynamides **3** (Scheme 4). First, we proved that the [8+2] cycloaddition reaction of tosylynamide **3a** also works well, with good to moderated yields, for different substitution at the aryl moiety of the 8-azaheptafulvene, such as electron donating (*p*–OMe, **7b**) or electron withdrawing groups (*p*–Br, **7c**). Other substitution at the β-carbon of the ynamide (R^4) was also checked; in this case, alkyl (R^4 = methyl) or alkenyl (R^4 = methylethenyl) substituted ynamides gave complex mixtures; on the other hand, 3–unsubstituted [8+2] cycloadduct **7f** was obtained with low yield (22%) from the corresponding terminal ynamide, after completion of the reaction in a short time (45 min). Moreover, product **7f** could also be obtained with best yield (59%) after a desilylation process of the unstable 3–trimethylsilyl derived adduct obtained from the corresponding trimethylsilyl ynamide **3m** (R^4 = trimethylsilyl). On the other hand, adduct **7g** was obtained in a 76% yield after only 40 min, from the corresponding carboxylate substituted ynamide. Finally, ynamides derived from oxazolidinone were also tested, these compounds, which were also useful in different gold catalyzed transformation, were subjected to the same reaction conditions as tosyl ynamides to give the corresponding adducts **7h–l** with different aryl groups at the β–position, in good yields and shorter reaction times (Scheme 4).



Scheme 4. Cycloadducts obtained from of 8–aryl–8–azaheptafulvenes **1** and ynamides **3**.

According to these results and previous gold-catalyzed ynamide cycloadditions, our proposed mechanism would start from the

nucleophilic attack of the azaheptafulvene nitrogen to the α-carbon of the gold keteneinimium intermediate **II**[23] followed by intramolecular cyclization of **IV** to intermediate **V** and regeneration of the gold catalyst, to give **7** after hydrogen 1,5–shift (Scheme **5**).



Scheme 5. Proposed mechanism for the cycloaddition reaction of 8–aryl–8–azaheptafulvenes **1** and ynamides **3**.

Conclusions

In conclusion, we have described here new gold(I)-catalyzed higher–order [8+2] cyclizations of 8–azaheptafulvenes and electron-rich unsaturated systems as 2π components. The [8+2] cycloaddition of 8–azaheptafulvenes and allenamides takes place in the presence of Au(I) catalyst to give regioselectively 1,8–dihydrocyclohepta[*b*]pyrroles with good yields and a broad scope. On the other hand, ynamides undergo a similar regioselective [8+2] gold(I) catalyzed cycloaddition to give 1–amido–1,4–dihydrocyclohepta[*b*]pyrroles, also with good yields. Both reactions involve step-way processes initiated by the formation of electrophilic intermediates after coordination of cationic gold either to the allene or triple bond moieties, followed by nucleophilic attack of the heptafulvene nitrogen and subsequent cyclization. This is the first higher–order reaction that implies the use of a metal catalyst with allenamides and ynamides.

Experimental Section

Typical procedure. Preparation of 1,8–dihydrocyclohepta[*b*]pyrrole 4a. A solution of 8–phenyl–8-azaheptafulvene **1a** (47.1 mg, 0.26 mmol, 1.3 equiv.), allenamide **2a** (44,7 mg, 0.2 mmol, 1 equiv) and (2,4–di*t*BuC$_6$H$_3$O)$_3$PAuNTf$_2$ (11.0 mg, 5 mol%) in 1,2–dichloroethane (4 mL, 0.05M) was heated at 60 ºC. The reaction was monitored by TLC until the complete disappearance of the allenamide **2a** (1.5 h). Then, triphenylphosphine (5 mg, 10 mol%) was added, and the solvent was removed. The resulting crude was purified by neutral alumina column chromatography (Hexane/EtAcO, 5:1). The product was obtained in 95% yield (79.5 mg) as a yellow solid. R_f = 0.30 (hexane/EtAcO 5:1); m.p. 51–52ºC (decomp); ^{1}H NMR (300 MHz, CDCl$_3$): δ= 7.75 (m, 2H), 7.36 (m, 2H), 7.27–7.18 (m, 2H), 7.16 (m, 2H), 7.02 (d, ^3J= 11.2 Hz, 1H), 6.67 (s, 1H), 6.24 (dd, ^3J= 11.2, 5.7Hz, 1H), 6.12 (dd, ^3J= 10.2, 5.7Hz, 1H), 5.40 (dt, ^3J= 10.2, 6.3 Hz, 1H), 4.13 (s, 2H), 3.06 (d, ^3J= 6.3 Hz, 2H), 2.67 (s, 3H), 2.47 (s, 3H), 2.44 ppm (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$): δ= 143.2 (C), 137.2 (C), 136.5 (C), 134.1 (C), 129.9 (CH), 129.6 (CH), 128.3 (CH), 127.7 (CH), 126.2 (C), 125.3 (CH), 124.9 (CH), 123.4 (CH), 122.3 (CH), 120.5 (C), 120.2 (CH), 115.1 (C), 45.7 (CH$_2$), 34.1 (CH$_3$), 24.8 (CH$_2$), 21.5 (CH$_3$), 21.1 ppm (CH$_3$); HRMS (EI): *m/z* calcd for C$_{25}$H$_{26}$N$_2$O$_2$S: 418.1715 [*M*]$^+$; found: 418.1714.

Typical procedure. Preparation of 2-amido-1,6-dihydrocyclohepta[*b*] pyrrole 7a. A solution of 8–phenyl–8–azaheptafulvene **1** (54.3 mg, 0.3 mmol, 1.5 equiv.), ynamide **3a** (57.0 mg, 0.2 mmol, 1 equiv) and JohnPhosAuNTf$_2$ (8.0 mg, 5 mol%) in toluene (2 mL, 0.1 M) was heated at 100 ºC. The reaction was monitored by TLC until the complete disappearance of the ynamide **3** (4.5 h). Then triphenylphosphine (5 mg, 10%) was added and the solvent was removed. The resulting crude was purified by silica column chromatography (hexane/EtAcO, 20:1). The product was obtained in 90% yield (86.4 mg) as a yellow solid; R_f = 0.33 (hexane/EtAcO 9:1); m.p. 84–86ºC (decomp); ^{1}H NMR (300 MHz, CDCl$_3$): δ= 7.75–7.16 (m, 9H), 7.16–7.02 (m, 2H), 6.95–6.80 (m, 2H), 6.46 (d, ^3J= 9.5 Hz, 1H), 6.18 (d, ^3J= 9.8 Hz, 1H), 5.47–5.27 (m, 2H), 3.14 (s, 3H), 2.84–2.68 (m, 1H), 2.50–2.35 (m, 1H), 2.48 (s, 3H), 2.32 ppm (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$): δ= 142.6 (C), 138.5 (C), 136.3 (C), 134.3 (C), 133.8 (C), 132.3 (C), 129.8 (CH), 129.0 (CH), 128.1 (CH), 127.3 (CH), 126.8 (C), 126.3 (CH), 123.3 (CH), 121.9 (C), 121.1 (C), 119.6 (CH), 119.3 (CH), 116.3 (CH), 40.4 (CH$_3$), 27.1 (CH$_2$), 21.4 (CH$_3$), 21.3 ppm (CH$_3$); HRMS (ESI): *m/z* calcd for C$_{30}$H$_{25}$O$_2$S+Na$^+$: 503.1769 [*M* +Na]$^+$; found: 503.1764

Acknowledgements

This research was supported by grants from MINECO, AEI/FEDER–UE (CTQ2016–76840–R) and AEI (PID2019–107469RB–I00/AEI/10.13039/501100011033). T. S. –R. thanks Principado de Asturias for predoctoral scholarship. Authors also thank the reviewers for their comments and recommendations, and Prof. J. M. González for helpful discussions and suggestions.

Conflict of interest

The authors declare no conflict of interest

Keywords: 8–Azaheptafulvenes • Cycloaddition • Gold • Higher–Order Cyclization• Homogeneous Catalysis.

[1] a) J. H. Rigby, *Acc. Chem. Res*., **1993**, *26*, 579–585. b) J. H. Rigby, *Org. React*. **1997**, *49*, 331–435. b) M. Harmata, *Acc. Chem. Res.* **2001**, *34*, 595-605. c) M. Harmata, *Adv. Synth. Catal.* **2006**, *348*, 2297–2306. d) V. Nair, K. G. Abhilash, *Top Heterocycl. Chem*. **2008**, *13*, 173–200. e) V. Nair, K. G. Abhilash, *Synlett* **2008**, 301–312. f) A. G. Lohse, R. P. Hsung, *Chem Eur. J.* **2011**, *17*, 3812–3822. g) H. Pellissier, *Adv. Synth. Catal.* **2011**, *353*, 180–218. h) K. E. O. Ylijoki, J. M. Stryker, *Chem. Rev.* **2013**, *113*, 2244–2266. i) P. A. Inglesby, P. A. Evans in *Comprehensive Organic Synthesis II*, Vol. 5 (Eds.: P. Knochel, G. A. Molander) Elsevier, Amsterdam **2014**, pp. 656–702. j) T. A. Palazzo, R. Mose, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2017**, *56*, 10033–10038; *Angew. Chem.* **2017**, *129*, 10165–10171. k) D. McLeod, M. K. Thørgensen, N. I. Jessen, K. A. Jørgensen, C.S. Jamieson, X. –S. Xue, K. N. Houk, F. Liu, R. Hoffmann, *Acc. Chem. Rev*. **2019**, *52*, 3488–3501. l) S. Frankowski, M. Romaniszyn, A. Skrzyńska, Ł. Albrecht, *Chem. Eur. J.* **2020**, *26*, 2120–2132.

[2] H. Prinzbach, H. -J. Herr, W. Regel, *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 131–133; *Angew. Chem.* **1972**, *84*, 113–115. b) K. Komatsu, M. Fujimori, K. Okamoto, *Tetrahedron* **1977**, *33*, 2791–2797. c) C. –Y. Liu, J. Mareda, K. N. Houk, F. R. Fronczek, *J. Am. Chem. Soc.* **1983**, 105, 6714–6715. d) C. –Y. Liu, D. A. Smith, K. N. Houk, *Tetrahedon Lett.* **1986**, *27*, 4881–4884. e) V. Nair, K. G. Abhilash, A. T. Biju, E. Suresh, *Synthesis*, **2007**, 1833–1936. f) J. G. García–Rodríguez, J. González, J. Santamaría, A. L. Suárez–Sobrino, M. A. Rodríguez. *Dalton Trans*. **2016**, *45*, 11353–11361. g) Z. Gao, C. Wang, L. Zhou, C. Yuan, Y. Xiao, H. Gao. *Org. Lett.* **2018**, *20*, 4302–4305.

[3] a) J. Ciabattoni, H. W. Anderson, *Tetrahedron Lett.* **1967**, *8*, 3377–3381. b) W. E. Truce, C. –I. M. Lin, *J. Am. Chem. Soc.* **1973**, *95*, 4426–4428. c) M. Julino, U. Bergstraesser, M. Regitz, *J. Org. Chem*., **1995**, *60*, 5884–5890. d) K. Kumar, A. Kapur, M.P.S. Ishar, *Org. Lett.* **2000**, *2*, 787–789. e) A. R. Rivero, I. Fernández, M. A. Sierra, *Org. Lett*. **2013**, *15*, 4928–4931. f) N. Liu,, W. Song, C. M. Schienebeck, M. Zhang, W. Tang, *Tetrahedron* **2014**, *70*, 9281–9305. g) F. Esteban, R. Alfaro, F. Yuste, A. Parra, J. L. García–Ruano, J. Alemán, *Eur. J. Org. Chem.* **2014**, 1395–1400. h) S. Wang, C. Rodríguez–Escrich, M. Fianchini, F. Maseras, M. A. Pericás, *Org. Lett*. **2019**, *21*, 3187–3192. i) T. Roy; A. Jacob; S. Bhattarcharjee; A. T. Biju, *Chem. Asian J.,* **2019**, *14*, 4748–4753. j) F. Xia, Z. –H. Gao, C. –L. Zhang, S. Ye, *Adv. Synth. Catal.* **2019**, *361*, 2291–2294. k) S. Zhang, R. Xie, A. Tang, P. Chen, Z. Zhao, M. Miao, *Org. Lett*. **2020**, *22*, 3056–3061.

[4] a) T. Machiguchi, M. Hoshino, S. Ebine, Y. Kitahara, *J. Chem. Soc. Chem. Commun.* **1973**, 196–196. b) T. Machiguchi, H. Otani, Y. Ishii, T. Hasegawa, *Tetrahedron Lett.*, **1987**, *28*, 203–206. c) T. Machiguchi, T. Hasegawa, S. Itoh, H. Mizuno, *J. Am. Chem. Soc.* **1989**, *111*, 1920–1921. d) T. Machiguchi, T. Hasegawa, Y. Ishii, S. Yamabe, T. Minato, *J. Am. Chem. Soc*. **1993**, *113*, 11536–11541. e) T. Machiguchi, T. Hasegawa, H. Otami, S. Yamabe, H. Hizuno, *J. Am. Chem. Soc*. **1994**, *116*, 407–408. f) S. Yamabe, T. Minato, A. Ishiwata, O. Irinamihira, T. Machiguchi, *J. Org. Chem.* **2007**, *72*, 2832–2841. g) A. R. Rivero, I. Fernández, M. A. Sierra, *J. Org. Chem.* **2012**, *77*, 6648–6652. h) S. Frankowski, A. Skrzyńska, L. Albrecht, *Chem. Commun.* **2019**, *55*, 11675–11678.

[5] For instance, [8+3] cycloadditions: a) J. Barluenga, J. García–Rodríguez, S. Martínez, A. l. Suárez–Sobrino, M. Tomás, *Chem. Asian J.* **2008**, *3*, 767–775. b) W. Chen, Y. –L. Bai, Y. –C. Luo, P. –F. Xu, *Org. Lett.* **2017**, *19*, 364–367. c) W.B. Zhang, W. Xiao, H. Hu, L. Lin, X. Liu, X. Feng, *Chem. Eur. J.* **2018**, *24*, 13428–13431. [8+2]/Aryl–ene tandem reaction: d) Z. Wang, Y. Addepalli, Y. He, *Org. Lett.* **2018**, *20*, 644–647.

[6] a) N. Abe, T. Gunji, *Heterocycles* **2010**, *82*, 201–248. b) X. Zhou, T. Xiao, Y. Iwama, Y. Qin, *Angew. Chem. Int. Ed.* **2012**, *51*. 4909–4912. *Angew. Chem*. **2012**, *124*, 4993–4996. c) M. Nakatami, H. Fujii, T. Murafuji, T. Gunji, R. Ikeda, T. Konakahara, N. Abe, *Heterocycles* **2012**, *84*, 461–472.

[7] V. Nair, K. G. Abhilash, *Tetrahedron Lett.* **2006**, *47*, 8707–8709.

[8] Allenes: a) K. Hayakawa, H. Nishiyama, K. Kanematsu, *J. Org. Chem.* **1985**, *50* 512–517. Ketenes: b) K. Yamamoto, S. Kajigaeshi, S. Kanemasa, *Chem. Lett.* **1977**, *6*, 91–94. c) K. Takaoka, T. Aoyama, T. Shioiri, *Heterocycles*, **2001**, *54*, 209–215. Isocyanate and isothiocyanate: d) K. Yamamoto, S. Kajigaeshi, S. Kanemasa, *Chem. Lett.* **1977**, *6*, 85–90. Sulfenes: e) W. E. Truce, J. P. Shepherd, *J. Am. Chem. Soc.*, **1977**, *99*, 6453–6454.

[9] J. Barluenga, J. García–Rodríguez, A. L. Suárez–Sobrino, M. Tomás. *Chem. Eur. J.* **2009**, *15*, 8800–8806.

[10] a) M. Xie, X. Liu, X. Wu, Y. Cai, L. Lin, X. Feng, *Angewandte Chem. Int. Ed.* **2013**, *52*, 5604–5607; *Angew. Chem.* **2013**, *125*, 5714–5717. b) S. Wang, C. Rodríguez–Escrich, M. A. Pericás, *Angewandte Chem. Int. Ed.* **2017**, *56*, 15068–15072; *Angew. Chem*. **2017**, *129*, 15264–15268. c) R. Manzano, A. Romaniega, L. Prieto, E. Díaz, E. Reyes, U. Uría, L. Carrillo, J. L Vicario, *Org. Lett*. **2020**, *22*, 4721–4725.

[11] C. He, Z. Li, H. Zhou, J. Xu, *Org. Lett.* **2019**, *21*, 8022–8026.

[12] T.-L. Liu, Q.-H. Li, L. Wei, Y. Xiong, C.-J. Wang, *Adv. Synth. Catal.,* **2017**, *359*, 1854–1859.

[13] The authors in this case suggests an initial 1,8–nucleophilic addition onto the azaheptafulvene ring followed by cyclization. See references 10b and 11.

[14] For a mechanistic study with ketenes suggesting a step-way mechanism initiated by a nucleophilic attack to a ketene see: I. Fernández, M. A. Sierra, M. R. Torres, *Org. Lett.* **2011**, *13*, 2892–2895.

[15] Reviews on allenamides: a) L. –L. Wei, H. Xiong, R. P. Hsung, *Acc. Chem. Res.,* **2003**, *36*, 773–782. b) T. Lu, Z. Lu, Z. –X. Ma, Y. Zhang, R. P. Hsung, *Chem. Rev*. **2013**, *113*, 4862–4904. c) E. Manoni, M. Bandini, *Eur. J. Org. Chem*. **2016**, 3135–3142. d) J. L. Mascareñas, I. Varela, F. López, *Acc. Chem. Res*., **2019**, 52, 465–479.

[16] Reviews on ynamides: a) G. Evano, A. Coste, K. Jouvin, *Angew. Chem. Int. Ed.,* **2010**, *49*, 2840–2859; *Angew. Chem.* **2010**, *122*, 2902–2921. b) K. A. DeKorver, H. Li, A. G. Lohse, R. Hayashi, Z. Lu, Y. Zhang, R. P. Hsung, *Chem Rev*. **2010**, *110*, 5064–6106. c) X. –N. Wang, H. –S. Yeom, L. –C. Fang, S. He, Z. –X. Ma, B. L. Kedrowski, R. P. Hsung, *Acc. Chem. Res.* **2014**, *47*, 560–578. d) G. Evano, C. Theunissen, M. Lecomte, *Aldrichimica Acta*, **2015**, *48*, 75–86. e) F. Pan, C. Shu, L. –W. Ye, *Org. Biomol. Chem.* **2016**, *14*, 9456–9465. f) F. –L. Hong, L. –W, Ye, *Acc. Chem. Res.* **2020**, *53*, 2003–2019.

[17] Selected gold catalyzed allenamide cycloadditions, [2+2]: a) S. Suárez–Pantiga, C. Hernández–Díaz, E. Rubio, J. M. González *Angew. Chem. Int. Ed.* **2012**, *51*, 11552–11555; *Angew. Chem.* **2012**, *124*, 1170–11723. b) P. Bernal–Albert, H. Faustino, A. Gimeno, G. Asensio, J. L. Mascareñas, F. López, *Org. Lett.* **2014**, *16*, 6196–6199. c) M. Jia, M. Monari, Q. –Q. Yang, M. Bandini, *Chem. Commun.* **2015**, *51*, 2320–2323. [4 + 2]: d) J. Francos, F. Grande–Carmona, H. Faustino, J. Iglesias–Sigüenza, E. Díez, I. Alonso, R. Fernández, J. L. Lasaletta, F. López, J. L. Mascareñas. *J. Am. Chem. Soc.* **2012**, *13*, 14322–14325. f) V. Pirovano, M. Borri, G. Abbiati, S. Rizzato, E. Rossi. *Adv. Synth. Catal.* **2017**, *359*, 1912–1918. [3+2]: g) W. Zhou, X. –X. Li, G. –H. Li, Y. Wu, Z. Chen, *Chem. Commun.* **2013**, *49*, 3552-3554. h) G. –H. Li, W. Zhou, X. –X. Li, Q.-W. Bi, Z. Wang, Z. –G. Zhao, W. –X. Hu, Z. Chen, *Chem. Commun.* **2013**, *49*, 4770–4772. i) Y. Wang, P. Zhang, D. Qian, J. Zhang, *Angew. Chem. Int. Ed.* **2015**, *54*, 14849–14852; *Angew. Chem.* **2015**, *127*, 15062–15065. [5+2]: j) N. De, C. E. Song, D. H. Ryu, E. J. Yoo, *Chem. Commun*. **2018**, *54*, 6911–6914. [2 + 2 + 2]: k) H. Faustino, I. Alonso, J. L. Mascareñas, F. López, *Angew. Chem. Int. Ed.* **2013**, *52*, 6526–6530. *Angew. Chem.* **2013**, *125*, 6654–6658. l) D. C. Marcote, I. Varela, J. Fernández–Casado, J. L. Mascareñas, F. López, *J. Am. Chem. Soc.* **2018**, *140*, 16821–16833. m) C. Hernández–Díaz, E. Rubio, J. M. González *Eur. J. Org. Chem.* **2016**, 265–269. [4 + 2 + 2]: n) C. Wang, G. Xu, Y.Shao, S. Tang, J. Sun, *Org. Lett.* **2020**, *22*, 5990–5994

[18] Selected gold catalyzed ynamides cycloadditions, [4+2]: a) Z. Xin, S. Kramer, J. Overgaard, T. Skrydstrup, *Chem. Eur. J*. **2014**, *20*, 7926–7930. b) R. B. Dateer, B. S. Shaibu, R. –S. Liu *Angew. Chem. Int. Ed.* **2012**, *51*, 113–117; *Angew. Chem.* **2012**, *124*, 117–121. [4 + 3]: c) S. N. Karad, S. Bhumia, R. –S. Liu, *Angew. Chem. Int. Ed.* **2012**, *51*, 8722–8726; *Angew. Chem*. **2012**, *124*, 8852–8856. [3 + 2]: d) P. W. Davies, A. Cremonesi, L. Dimitrescu, *Angew. Chem. Int. Ed.* **2011**, *50*, 8931–8935; *Angew. Chem.,* **2011**, *123*, 9093–9097. e) Y. Yu, G. Chen, L. Zhu, Y. Liao, Y. Wu, X. Huang, *J. Org. Chem.* **2016**, *81*, 8142–8154 f) X. Tian, L. Song, C. Han, C. Zhang, Y. Wu, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Org. Lett.* **2019**, *21*, 2937–2940. g) E. M. Arce, S. G. Lamont, P. W. Davies, *Adv. Synth. Catal.* **2020**, *362*, 2503–2509. [2 + 2 + 2]: h) S. N. Karad, R. –S. Liu, *Angew. Chem. Int. Ed.* **2014**, *53*, 9072–9076; *Angew. Chem*. **2014**, *126*, 9218–9222. i) A. Y. Dubovtsev, N. V. Shcherbakov, D. V. Dar'in, V. Y. Kukushkin, *Adv. Synth. Catal.* **2020**, *362*, 2672–2682.

[19] Deposition Number CCDC–2047295 contains the supplementary crystallographic data for compound **4b**. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

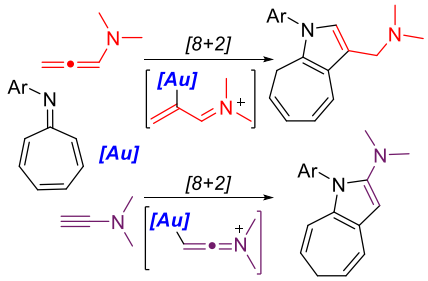
[20] Isomer **6c** could not be isolated since it is unstable in the isolation conditions.

[21] Cycloadduct **6p** was stable enough to be isolated (52% yield, 40ºC 3h) and characterized. See Supporting Information

[22] For examples in mechanism studies on gold catalysis in allenamides, see: a) S. Montserrat, H. Faustino, A. Lledós, J. L. Mascareñas, F. López, G. Ujaque. *Chem. Eur. J.* **2013**, *19*, 15248–15260. b) J. Sabbatini, X. Huang, L. F. Veiros, N. Maulide. *Chem. Eur. J*. **2014**, *20*, 10635–10639. c) Y. Wang, P. Zhang, Y. Liu, F. Xia, J. Zhang. *Chem. Sci.* **2015**, *6*, 5564–5570.

[23] For a mechanistic study implying gold-generated ketiniminium species see: R. Vanjari, S. Dutta, M. P. Gogoi, V. Gandon, A.K. Sahoo, *Org. Lett.* **2018**, *20*, 8077–8081

Entry for the Table of Contents



Gold (I)-catalyzed higher-order cycloaddition. 8–Aryl–8–azafulvenes undergo a regioselective gold catalyzed [8+2] cycloaddition with electron–rich allenamines and ynamides to give dihydrocyclohepta[*b*]pyrrole derivatives. The cyclization takes place after the nucleophilic attack of the heptafulvene to the electrophilic intermediates formed by the coordination of cationic gold to either allene or triple bond moieties of the unsaturated systems.