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One-pot and Regioselective Gold-Catalyzed Synthesis of 2-Imidazolyl-1-pyrazolylbenzenes from 1-Propargyl-1*H*-benzotriazoles, Alkynes and Nitriles through α-Imino Gold(I) Carbene Complexes

Jairo González,[a] Javier Santamaría,[a] Ángel L. Suárez-Sobrino[a] and Alfredo Ballesteros[a]*

[a] Instituto Universitario de Química Organometálica "Enrique Moles" and Departamento de Química Orgánica e Inorgánica
Universidad de Oviedo
c/ Julián Clavería 8, 33006, Oviedo (Spain)
E-mail: abg@uniovi.es
Phone: +34 985103506

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Abstract. A three-components gold(I)-catalyzed synthesis of 2-imidazoyl-1-pyrazolylbenzenes from 1-propargyl-1*H*-benzotriazole is described here. Initially benzotriazole derivative suffers an intramolecular 5-*endo*-dig cyclization to form a triazapentalene. This dipolar compound is able to perform an intermolecular and regioselective attack to a gold-activated alkyne. After triazole breakage, pyrazole ring and α-imino gold carbene complex are formed. Finally, iminocarbene is captured by a nitrile to form an imidazole ring.

Keywords: gold catalysis; alkynes; iminocarbenes; imidazoles; pyrazoles

The synthesis of azoles, as pyrazoles[1] or imidazoles,[2] is a common target due to their appearance in the structure of natural products, biologically active compounds and also ligands in coordination chemistry. On the other hand, gold-catalyzed reactions involving π-carbophilic gold alkyne activation represent an important step forward in heterocyclic synthesis.[3] Although the use of methodologies involving α-oxo gold carbenes has been widely described,[4] their nitrogenated counterparts, the α-imino gold carbenes, have received less attention[5] (Figure 1). This type of intermediates was first proposed by Toste and co-workers in a gold-catalyzed intramolecular pyrrole synthesis from homopropargyl azides as nitrene equivalents.[6] Since that seminal contribution, the most extended procedure for the access to α-imino gold carbenes as intermediates is based on intramolecular transformations of azides with gold-activated alkynes.[7] In addition, a few intermolecular approaches have been carried out, although they require the use of heteroatom-polarized alkynes as ynamides.[8] The use of other nucleophilic nitrenoids as pyridine-*N*-aminides[9] or 2*H*-azirine derivatives,[10] has recently emerged as an elegant alternative to azides, however these methodologies present similar limitations in terms of intermolecular reactivity. Finally, isoxazoles[11] can also act as nitrene equivalents. In this field, the very recent work developed by Hashmi et al. involving benzo[*c*]isoxazoles,[11c] represents the sole example reported to date of intermolecular reactions with simple alkynes.

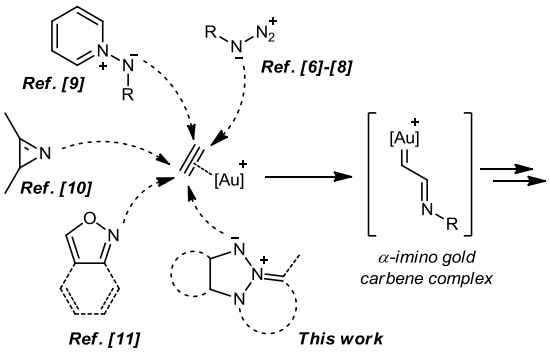
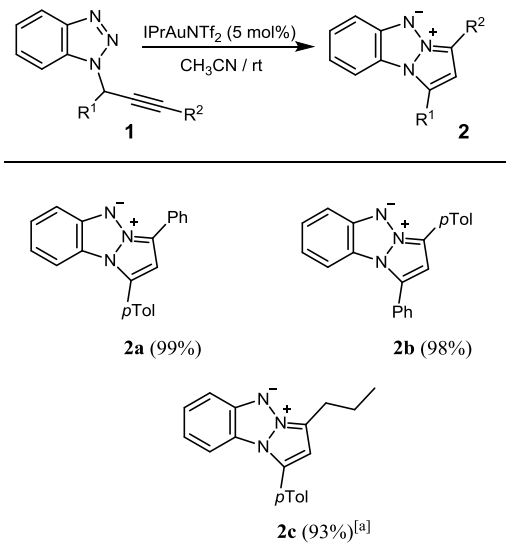


Figure 1. α-Imino gold carbene formation from nitrene equivalents and alkynes.

Herein we describe a catalytic methodology, involving three components, for the formation of 2-imidazolyl-1-pyrazolylbenzene derivatives. The synthesis is triggered by a 5-*endo*-dig cyclization of a 1-propargyl-1*H*-benzotriazole that generates a dipolar triazapentalene derivative (azomethine imine type).[12] The nucleophilicity of the dipole allows its

intermolecular attack to a gold-activated alkyne, to initiate a second catalytic cycle that involves the participation of a α-imino gold carbene intermediate.

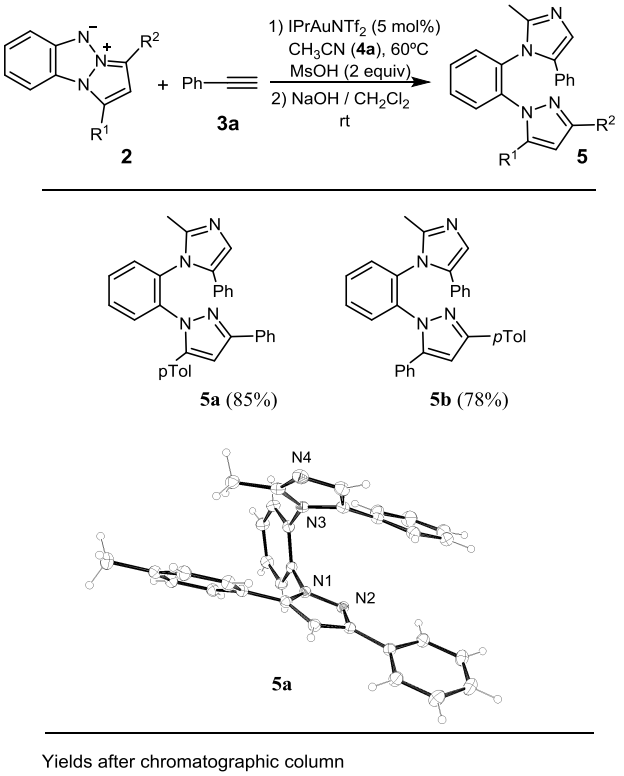
In the course of our work in gold catalysis with alkynyl compounds,[13] we observed that treatment of 1-propargyl-1*H*-benzotriazole[14] **1a** with 5 mol% of $IPrAuNTf_2$ in 1,2-dichloroethane at 70ºC for 4h, give rise to benzofusedtriazapentalene **2a** in 78% yield.[15] This result indicates a 5-*endo*-dig nucleophilic attack from the central nitrogen atom of the triazole[16] to the gold-activated triple bond. However, when this reaction was performed in acetonitrile at room temperature, we observed, after 30 minutes, the formation of a precipitate. Upon filtration, a yellow solid was isolated in an almost quantitative yield[17] and identified as triazapentalene **2a** (Scheme 1). This methodology can be extended to the use of other benzotriazoles **1** allowing the formation of a family of dipolar compounds **2** with different substitution patterns. It is worth to mention at this point that, although the use of acetonitrile dramatically increases the rate of the reaction, for the formation of **2c** no precipitate was observed and the corresponding triazapentalene **2c** was isolated after heating at 60ºC and chromatographic column.



Scheme 1: Gold-catalyzed synthesis of triazapentalene **2** from benzotriazole **1**.

The structure of compounds **2** could be unambiguously determined by an X-ray diffraction analysis performed on a monocristal of **2b**[18] obtained from a mixture of CH_2Cl_2-pentane.

Next, we focussed our interest into the similarities of the structure of dipolar triazapentalene **2** with alkyl or arylazides. Due to the high attention received by azides in their reaction with gold-activated alkynes,[6-8] we decided to explore the reactivity of triazapentalenes **2** with alkynes in the presence of a gold catalyst. However, the treatment of the dipolar compound **2a** with phenylacetylene **3a**, in acetonitrile at 60ºC, in the presence of a NHC gold(I) complex ($IPrAuNTf_2$ (5 mol%)), resulted in no positive reaction. The triazapentalene **2a** was recovered almost unchanged. Fortunately, the use of methanesulfonic acid as additive leaded to the formation of a salt. Basic treatment of the salt with a diluted sodium hydroxide solution, turned into compound **5a** in high overall yield and as a single regioisomer (Scheme 2). A similar result was accomplished starting from triazapentalene **2b**.

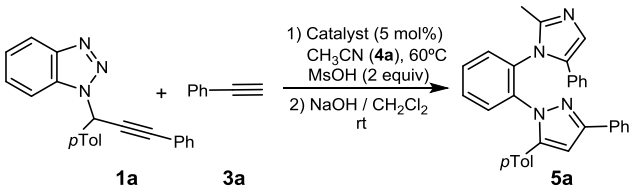


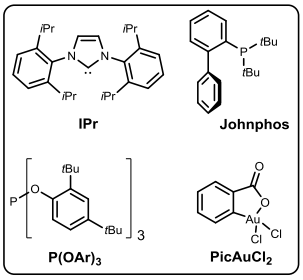
Scheme 2. Formation of *orto*-imidazolylpyrazolylbenzene derivatives **5** from triazapentalenes **2**. Solid-state molecular structure of compound **5a**. The ellipsoids in the ortep view are plotted with a 50% of probability.

The structure of compounds **5** was determined by mono and bidimensional NMR spectroscopic experiments and confirmed by an X-ray diffraction analysis of compound **5a**[18] (Scheme 2). From this structure can be deduced the incorporation of three components: triazapentalene **2**, phenylacetylene **3a** and one molecule of acetonitrile **4a**. On the other hand, the triazole heterocycle is broken up and two new heterocycles are simultaneously generated: a pyrazole and an imidazole.

These results encourage us to extend this procedure to a one-pot combination of both gold-catalyzed reactions. Initially, selecting propargylic benzotriazole **1a**, phenylacetylene **3a** and acetonitrile

4a as third component and solvent, we tested the activity of different gold catalysts in the formation of compound **5a** (Scheme 3). After a period of 30 min at room temperature, the reaction mixture was heated at 60ºC for three additional hours. The outcome of these assays shows that several gold complexes are able to accomplish the one-pot reaction. The best result is achieved using $IPrAuNTf_2$ complex as the gold catalyst, so we selected the *N*-heterocyclic carbene (IPr) as the appropriate ligand for gold. Finally, bis(trifluoromethanesulfonyl)imidate was selected as the counterion on a routine basis, avoiding the use of silver salts to generate the corresponding gold catalyst.[19]



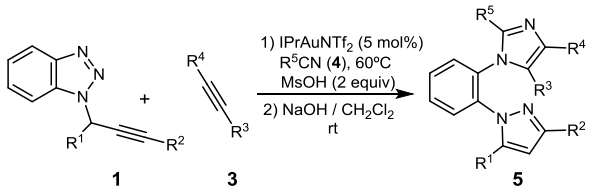


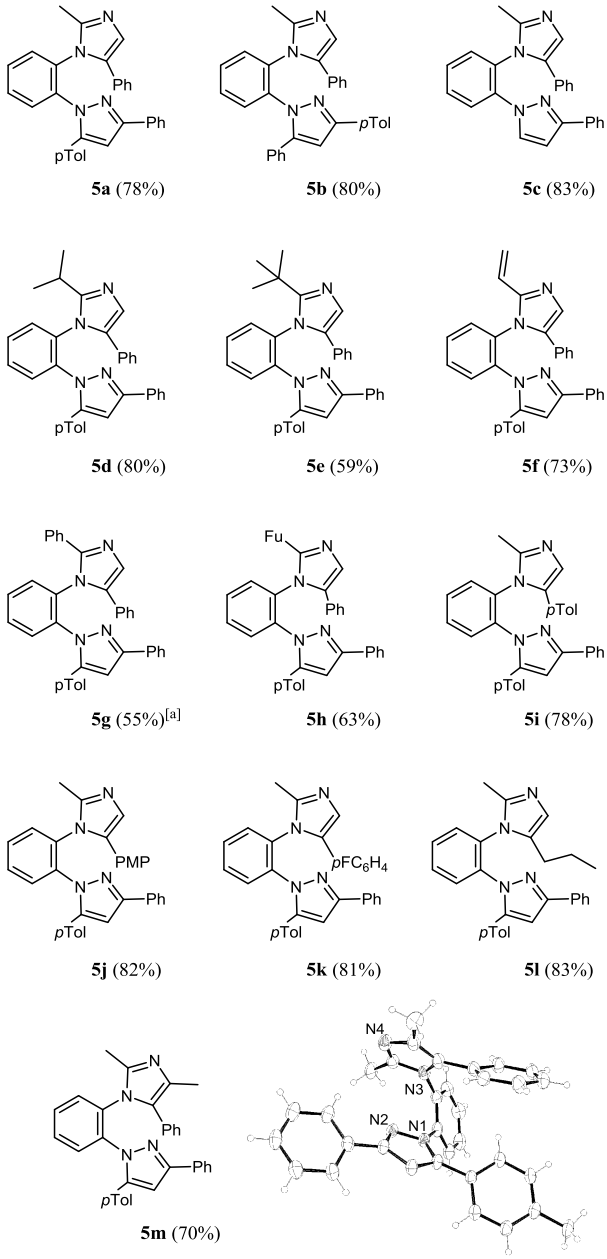
Catalyst	Yield[a]
$IPrAuNTf_2$:	80%[b]
$JohnPhosAuNTf_2$:	71%
$Ph_3PAuCl/AgNTf_2$:	48%
$(ArO)_3PAuNTf_2$:	46%
$PicAuCl_2$	63%
$AuCl_3$	73%
None:	0%

Scheme 3. Gold(I)-catalyzed one-pot formation of compound **5a**. [a]Yields were determined by ^{1}H-NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard. [b] Yields dropped to 49% and 58% for reactions performed in 1,2-dichloroethane using 3 and 10 equiv of acetonitrile, respectively.

Next, we explored the scope of this three-component one-pot reaction according to the substitution pattern of the different reagents. From Table 1 can be observed that the reaction proceeds in moderate to high yields. Thus, as it has been previously shown in the synthesis of the triazapentalene intermediate **2** (Scheme 1), modifications in the propargylic benzotriazole **1** are satisfactorily tolerated (compounds **5a-c**). On the other hand, a wide range of nitriles can be employed. Thus, in addition to the acetonitrile, the imidazole ring was also accessed using other alkylnitriles with different levels of substitution (compounds **5d-e**) and alkenylnitriles (compound **5f**). Aromatic (compound **5g**) or heteroaromatic nitriles (compound **5h**) can also be used. Finally, this reaction shows a high versatility in terms of the alkyne substitution as aliphatic (compound **5l**) and aromatic alkynes (compounds **5i-k**) can be employed. Among them, aromatic rings with electron-donating or electron-withdrawing groups are tolerated.

Table 1. One-pot formation of **5**. The ellipsoids in the ortep view are plotted with a 50% of probability for the solid-state molecular structure of compound **5m**.



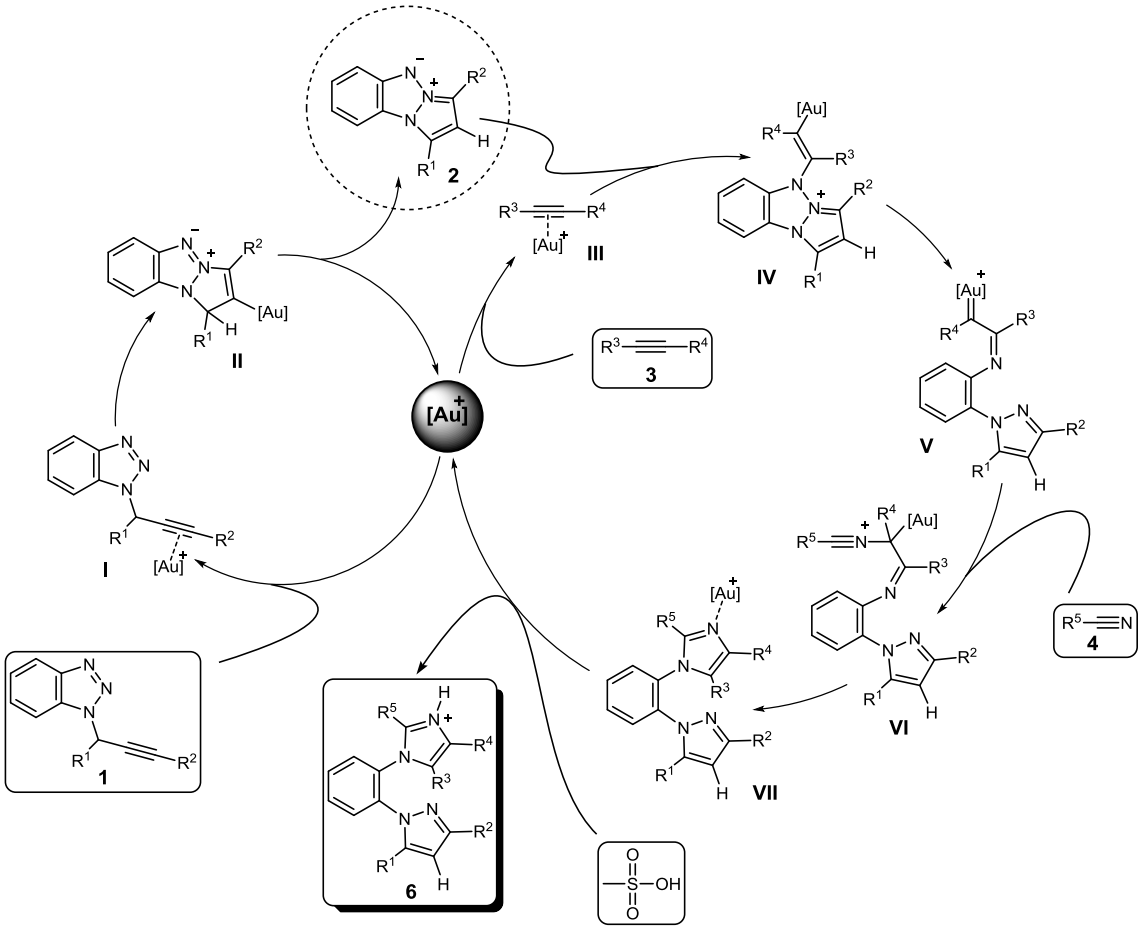


[a] Reaction performed at 60ºC for 15 hours.
PMP = *p*-MeO-C_6H_4; Fu = 2-furyl.

In addition to these results, the use of a disubstituted and non-symmetrical alkyne leaded to the formation of compound **5m** as a single regioisomer. The structure of **5m** was determined by an X-ray diffraction analysis[18] and indicates a nucleophilic attack from the dipole to the position of the activated alkyne bearing the aromatic ring.

A mechanistic proposal for the formation of the new heterocycles is shown in Scheme 4. Thus, formation of compound **5** involves two consecutive catalytic cycles. First, starting from propargylic benzotriazole **1**, the formation of the dipolar benzofusedtriazapentalene **2** is initiated by coordination of the gold(I) complex to the triple bond, which suffers a nucleophilic 5-*endo*-dig attack from the triazole ring. Next, corresponding protodeauration of intermediate **II** gives rise to the formation of triazapentalene **2**. As it has been previously shown, triazapentalene **2** can be isolated or be involved in a second catalytic cycle. Thus, gold catalyst liberated from intermediate **II** is able to activate alkyne **3**, to initiate a new catalytic cycle. At this point, intermediate **III** may suffer a nucleophilic attack by the triazapentalene **2** previously formed, to generate vinylgold intermediate **IV**. This intermediate **IV** could evolve through the formation of the α-imino gold carbene intermediate **V**. This evolution is facilitated by the triazole ring rupture. Finally, highly electrophilic iminocarbene **V** can be captured by the nitrile[20] **4** and an intramolecular ring closing occurs.[7h, 21] Finally, as the new heterocycles could inhibit the reaction by gold coordination,[7h] a final step of protodeauration is needed. Methanesulfonic acid is able to release the gold catalyst attached to the imidazole or pyrazole ring, leading to the formation of salt **6**.

As both, methanesulfonic acid and gold complex can activate carbon-carbon triple bonds, additional experimental support for this mechanistic proposal was performed. Thereby, when 1-propargyl-1*H*-benzotriazole **1a** was stirred under similar conditions, in presence of methanesulfonic acid and in absence of gold catalyst, triazapentalene **2a** was not obtained. This result indicates that the first catalytic cycle is initiated only after gold activation.



Scheme 4. Mechanistic proposal for the one-pot three-component gold-catalyzed formation of compound **6.**

In conclusion, we describe here a new, regioselective and atom-economical gold-catalyzed reaction involving three components: 1-propargyl-1*H*-benzotriazole, alkyne and nitrile, and two consecutive catalytic cycles. As the results of this, triazole ring is broken up and two new heterocycles: pyrazole and imidazole, are formed. In addition, this protocol represents a novel strategy to access to α-imino gold carbene complexes, valuable intermediates in organic synthesis. In this sense, this work, in addition to the very recent report by Hashmi et al.,[11c] are the only two strategies to access to these intermediates involving an intermolecular attack to non-heteroatom-polarized gold-activated alkynes. From this work, azomethine imines such as triazapentalenes, easily isolated in high yields, emerge as valuable compounds for intermolecular access to α-imino gold carbenes. New gold-catalyzed reactions involving triazapentalenes are under current work in our group.

Experimental Section

Synthesis of triazapentalenes 2:

To a solution of 0.2 mmol of 1-propargyl-1*H*-benzotriazole **1** in 1.5 ml of acetonitrile, 0.01 mmol (5 mol%) of $IPrAuNTf_2$ was added. The mixture was stirred for 45 minutes at room temperature (2 hours at 60ºC for **2c**). The yellow precipitate (**2a**,**b**) was filtered and washed with cold acetonitrile, to yield pure triazapentalenes **2a** and **2b**, respectively. For **2c**, the acetonitrile was removed under vacuum and the residue purified by chromatographic column through silica gel (hexane/ethyl acetate; (5:1)).

Synthesis of 2-imidazolyl-1-pyrazolylbenzenes 5

Method A. *(From triazapentalene* **2***)*: To a mixture of 0.2 mmol of pentalene **2** in 1.5 ml of the corresponding nitrile **4**, 1 mmol of alkyne **3**, 0.4 mmol of methanesulfonic acid and 0.01 mmol (5 mol%) of gold catalyst ($IPrAuNTf_2$) were added. The mixture was stirred for 3 hours at 60ºC. After removal of the solvent, the residue was dissolved in ethyl acetate and filtered through a short pad of deactivated silica gel (see Supporting Information), using ethyl acetate to wash the compound and methanol to recover it. Next, solvents were removed under vacuum, the residue dissolved in 5 ml of dichloromethane and 2 ml of a 3M solution of sodium hydroxide was added. After 15 minutes, the mixture was extracted with dichloromethane (2 x 10 ml) and washed with brine (2 x 10 ml). Finally, chromatographic purification through silica gel (dichloromethane/methanol/aqueous ammonia (28-30%); (100:5:1)) yields the corresponding 2-imidazolyl-1-pyrazolylbenzenes **5**.

Method B. *(From* 1-propargyl-1*H*-benzotriazole **1***)*: To a solution of 0.2 mmol of 1-propargyl-1*H*-benzotriazole **1** in 1.5 ml of the corresponding nitrile **4**, 0.01 mmol (5 mol%) of $IPrAuNTf_2$ was added and the mixture stirred for 30 minutes at room temperature. Next, 1 mmol of the alkyne **3** and 0.4 mmol of methanesulfonic acid was added and the mixture heated for 3h (15h for **5g**). From this point to the end, it was followed the experimental procedure described as Method A.

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COMMUNICATION

One-pot and Regioselective Gold-Catalyzed Synthesis of 2-Imidazolyl-1-pyrazolylbenzenes from 1-Propargyl-1*H*-benzotriazoles, Alkynes and Nitriles through α-Imino Gold(I) Carbene Complexes

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