Platinum and Gold Catalysis: *à la Carte* Hydroamination of Terminal Activated Allenes with Azoles
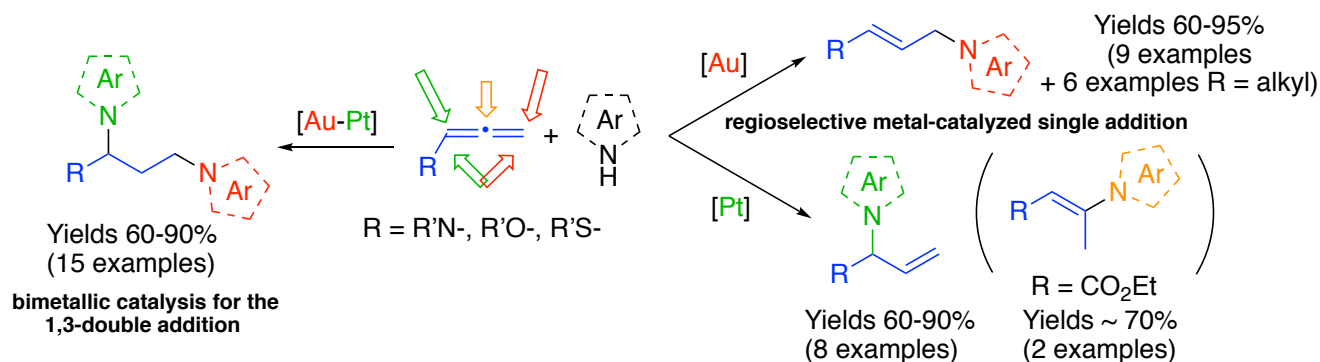
José Miguel Alonso[‡][a] and María Paz Muñoz[‡][*][a].

[a] School of Chemistry, University of East Anglia, Norwich NR4 7TJ (UK).

Scheme showing reactivity: bimetallic catalysis for the 1,3-double addition (Yields 60-90%, 15 examples) via [Au-Pt]; regioselective metal-catalyzed single addition via [Au] (Yields 60-95%, 9 examples + 6 examples R = alkyl) and [Pt] (Yields 60-90%, 8 examples; R = CO2Et Yields ~ 70%, 2 examples). R = R'N-, R'O-, R'S-.

ABSTRACT: Nucleophilic additions to allenes catalyzed by transition metals represent a powerful tool to get selective access to diverse structures with numerous applications. Reported here is a straightforward methodology to achieve selective addition of azoles to the proximal or distal carbon of activated allenes depending on the catalyst used, unravelling a gold-platinum bimetallic catalysis approach for the 1,3-double addition of azoles to activated allenes to give 1,3-bisazole derivatives, important scaffold in medicinal and organometallic chemistry.

Nucleophilic addition onto transition metal-activated C=C bonds represents an efficient methodology to gain access to a wide variety of functionalized molecules in an atom economic manner.[1] On this matter, allenes provide diverse advantages compared to alkenes or alkynes, as they present three reaction sites, and they offer the possibility to modulate the electrophilicity of each one of them. The reactivity pattern for any nucleophilic attack onto allene systems depends on the catalyst and the electronic nature of the allene. Distal, proximal and central carbon intermolecular single addition to yield derivatives **2**-**4** (Scheme 1a, right) have been described with a variety of allenes, nucleophiles and metals, where gold has been widely explored.[2] In the case of activated allenes the regioselectivity generally depends on the heteroatom present. For example, alkoxyallenes mostly favor the proximal attack to form analogues **3**,[3] while the most common reactivity of allenamides is the addition to the distal carbon to form derivatives **2**.[4] The Pt-catalyzed double distal addition of *C*- and *O*-based nucleophiles to simple allenes has been described to generate adducts **5** (Scheme 1a, left).[5] The Au-catalyzed double distal-proximal addition to allenamides has been reported in a single example with 2-methylfuran as nucleophile in moderate yield,[4d] and with phenol/allyltrimethylsilane to give adducts **6** (Scheme 1a, left).[6] There is one reported example of the Au-catalyzed double addition of thiols to the central carbon of aromatic allenes to give compounds **7** (Scheme 1a, left).[7]
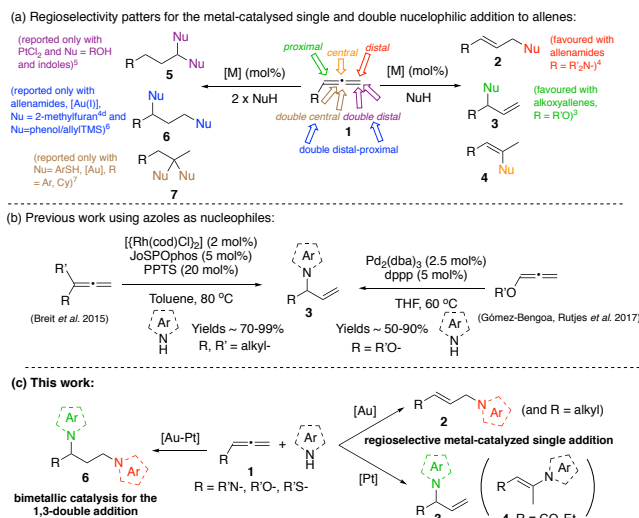
Among the transformations including allenes and nucleophiles, metal-catalyzed intermolecular hydroamination of al-

lenes are the more scarcely reported.[8] In particular, addition of azoles to allenes represents a powerful tool to generate highly heteroatom-enriched scaffolds with multiple applications in medicinal[9] and organometallic chemistry.[10] However, it has been limited so far to the use of Rh with alkyl allenes[11a] and Pd with alkoxyallenes[12] towards the proximal addition in both cases to generate adducts of type **3** (Scheme 1b), with no examples of addition of azoles to any other positions of the allene reported to date under any metal catalyst.

In recent years, bimetallic catalysis has appeared as a powerful tool to achieve challenging transformations.[13] In many of them, gold is used as one of the catalysts in combination with another metal.[14] In the context of allene chemistry, Au-Pd dual catalysis has been reported in the reaction of allenoates to form butenolides.[15] We have recently reported a dual Au-Pt strategy for the reaction of heteroarylallenes in the reaction with heteroaromatic nucleophiles, showing unprecedented reactivity not observed previously with single catalysis strategies.[16]
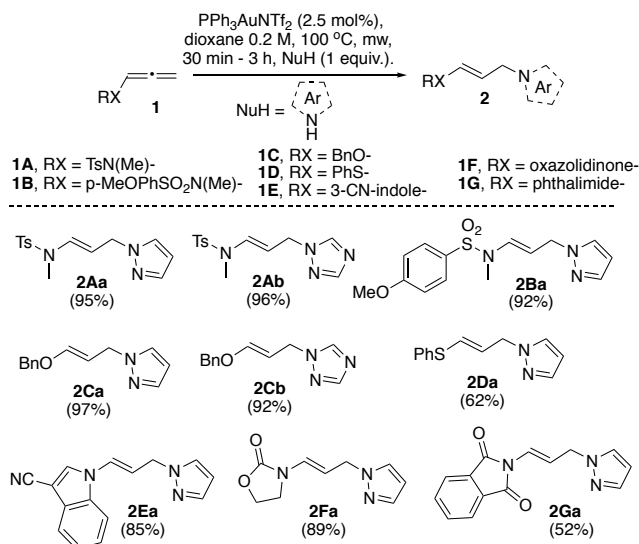
In this work, we report the effect of gold and platinum catalysis on the hydroamination of activated terminal activated allenes with azoles, unravelling a regioselective *à la carte* addition of azoles to give the products of the single addition, **2**-**4** depending on the single catalyst employed, and a novel bimetallic catalysis strategy for the double addition of azoles, to furnish 1,3-bisazole derivatives **6** (Scheme 1c).

Scheme 1. Previous reactivity pattern and present work.

(a) Regioselectivity patters for the metal-catalysed single and double nucleophilic addition to allenes:

(reported only with PtCl₂ and Nu = ROH and indoles)[5]

(reported only with allenamides, [Au(I)], Nu = 2-methylfuran[4d] and Nu=phenol/allylTMS)[6]

(reported only with Nu= ArSH, [Au], R = Ar, Cy)[7]

proximal central distal

5 2 x NuH [M] (mol%) **1** [M] (mol%) NuH **2** (favoured with allenamides R = R'₂N-)[4]

double central double distal

6 double distal-proximal

3 (favoured with alkoxyallenes, R = R'O)[3]

7

4

(b) Previous work using azoles as nucleophiles:

[{Rh(cod)Cl}₂] (2 mol%)
JoSPOphos (5 mol%)
PPTS (20 mol%)
Toluene, 80 °C
(Breit et al. 2015)
Yields ~ 70-99%
R, R' = alkyl-

Pd(dba)₃ (2.5 mol%)
dppp (5 mol%)
THF, 60 °C
(Gómez-Bengoa, Rutjes et al. 2017)
Yields ~ 50-90%
R = R'O-

3

(c) This work:

[Au-Pt] **6** bimetallic catalysis for the 1,3-double addition

1 R = R'N-, R'O-, R'S-

[Au] **2** (and R = alkyl) regioselective metal-catalyzed single addition
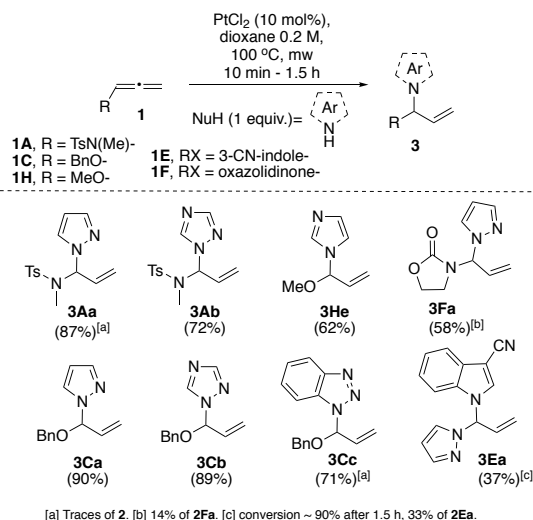
[Pt] **3** **4** R = CO₂Et

Reaction of allenylsulfonamide **1A** in the presence of 1 equiv. of pyrazole as nucleophile under Au(I) catalysis slowly generated distal addition allyl derivative **2Aa**, in line with other Au-catalyzed nucleophilic additions to allenamides,[4] but showing opposite and complementary regioselectivity to the previously described with Rh or Pd catalysts. Microwave irradiation at 100 °C decreased the reaction time to 30 min, providing **2Aa** in quantitative yield (Scheme 2). The scope was extended to different allenamides (**1B**, **1F**, **1G**). Interestingly, alkoxyallenes (**1C**) that generally favor proximal addition[3] also gave products **2**.[17] Phenylthioallene (**1D**) and N-indolylallene (**1E**) displayed the same regioselectivity. Different azoles were tested giving complete conversions and good yields.

Scheme 2. Au-catalyzed distal addition of azoles to allenes.

PPh₃AuNTf₂ (2.5 mol%),
dioxane 0.2 M, 100 °C, mw,
30 min - 3 h, NuH (1 equiv.).

1 NuH = **2**

1A, RX = TsN(Me)-
1B, RX = p-MeOPhSO₂N(Me)-
1C, RX = BnO-
1D, RX = PhS-
1E, RX = 3-CN-indole-
1F, RX = oxazolidinone-
1G, RX = phthalimide-

2Aa (95%) **2Ab** (96%) **2Ba** (92%)

2Ca (97%) **2Cb** (92%) **2Da** (62%)

2Ea (85%) **2Fa** (89%) **2Ga** (52%)

Remarkably, when PtCl₂ was used under the same optimized conditions as for Au(I) catalysis, the reaction of allenylsulfonamide **1A** gave isomer **3Aa** as a single product in good yield (Scheme 3) in an unusual regioselectivity for this type of substrates.[18] Different substituted allenamide (**1F**), N-indolylallene (**1E**) and alkoxyallenes (**1C**, **1H**)[3] showed the same regioselectivity in the presence of PtCl₂ and different azoles for the synthesis of allyl adducts of type **3** (Scheme 3).[19]

Scheme 3. Pt-catalyzed proximal addition of azoles to allenes.

PtCl₂ (10 mol%),
dioxane 0.2 M,
100 °C, mw
10 min - 1.5 h

1 NuH (1 equiv.)= **3**

1A, R = TsN(Me)-
1C, R = BnO-
1H, R = MeO-
1E, RX = 3-CN-indole-
1F, RX = oxazolidinone-

3Aa (87%)[a] **3Ab** (72%) **3He** (62%) **3Fa** (58%)[b]

3Ca (90%) **3Cb** (89%) **3Cc** (71%)[a] **3Ea** (37%)[c]

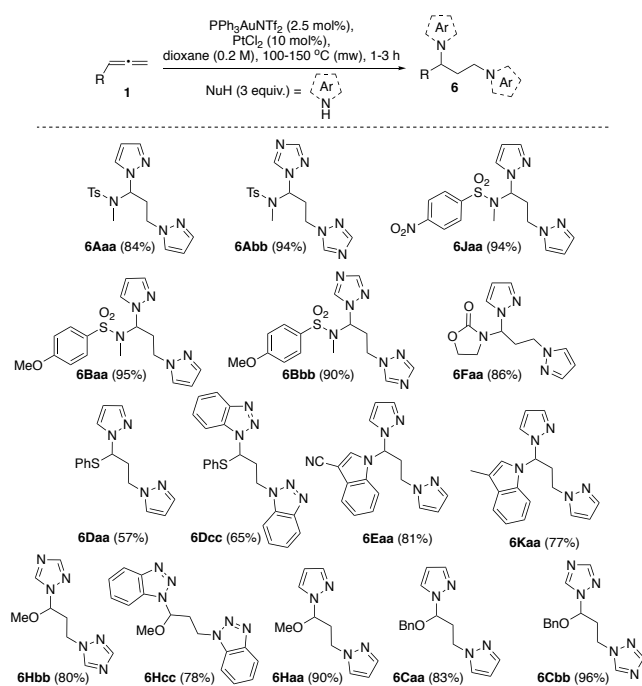[a] Traces of **2**. [b] 14% of **2Fa**. [c] conversion ~ 90% after 1.5 h, 33% of **2Ea**.

In light of these results, we envisioned the possibility of double addition processes to activated allenes using more powerful bimetallic Au-Pt strategies. To our delight, when allenylsulfonamide **1A** was treated with PtCl₂ and PPh₃AuNTf₂ as catalytic pair, excess of pyrazole as nucleophile, in a dioxane solution at 100 °C during 1 h under mw irradiation, 1,3-bispyrazole derivative **6Aaa** was obtained as sole reaction product in good yield, through double distal-proximal nucleophilic addition to the allene (Scheme 4). Allenamides **1B**, **1J** and **1F**, with different electronic properties, gave adducts **6** with the same regioselectivity and excellent yields. Alkoxyallenes **1C** and **1H**, phenylthioallene **1D**, and N-indolylallenes **1E** and **1K**, as well as different azoles, such as benzotriazole or 1,2,4-triazole, gave, under the optimized conditions and with good to excellent yields, a family of adducts **6** showing the attractive 1,3-bisazole motif, a recurring scaffold in medicinal chemistry[9] and in ligand design for metallic complexes, MOFs and COFs.[10] Metal complexes of Zn[20] and Ag[21] using **6Haa** and **6Hcc** were readily synthesized,[22] which highlights the synthetic utility of these 1,3-bisazoles incorporating an extra functionality and added complexity, not easy to achieve through conventional procedures, in the field of organometallic chemistry.

Interestingly, although C-substituted allenes have been reported to react towards the proximal addition of azoles in the presence of Rh catalysts,[11a] under single Au or Pt catalysts, cyclohexyl- (**1L**) and phthalimide-CH₂-based (**1M**) allenes were unreactive. The combination of Pt(II)-Au(I) or Pt(II)-Au(III) in a dual catalysis strategy favored the formation of the distal addition products **2** (see compounds **2La**, **2Lc**, **2Ld** and **2Ma-c** in the SI), but the double addition was not possible even under harsher conditions with these substrates.[22]

When a deactivated allenoic ester **1N** was used,[23] isomers **4**, from the metal-catalyzed conjugated addition of the azole to the central carbon, were obtained as the only isomers with Au(I)-Pt(II) bimetallic strategy under more forcing conditions (see compounds **4Na**, **4Na'**, **4Nc** in the SI). When Au(I)-Pt(IV) was used double addition to the central carbon was also found in the presence of pyrazole to give adduct **7Naa**.[22]

Scheme 4. Au-Pt-catalyzed 1,3-bisazole addition to allenes.

PPh$_3$AuNTf$_2$ (2.5 mol%),
PtCl$_2$ (10 mol%),
dioxane (0.2 M), 100-150 °C (mw), 1-3 h

NuH (3 equiv.) =

6Aaa (84%) **6Abb** (94%) **6Jaa** (94%)

6Baa (95%) **6Bbb** (90%) **6Faa** (86%)

6Daa (57%) **6Dcc** (65%) **6Eaa** (81%) **6Kaa** (77%)

6Hbb (80%) **6Hcc** (78%) **6Haa** (90%) **6Caa** (83%) **6Cbb** (96%)

Single catalyst reactions of activated allenes under harsher conditions (excess of azole, longer times, higher temperatures) led to mixtures of isomers **2-3** and uncompleted conversions towards **6**, highlighting the need for the bimetallic catalysis to provide 1,3-bisazoles efficiently and pointing to compounds **2** and **3** as possible intermediates in the double nucleophilic addition to form **6**.[22] Interestingly, **3Aa** generated **2Aa** in every experiment performed (even in the absence of azole), while the reverse process was not observed. This result points to an equilibrium between **3Aa** and **2Aa**, displaced towards **2Aa**, prior to the second nucleophilic attack to give **6Aaa**.

Cross-over experiments in the presence of two different azoles[22] support the equilibrium between intermediates **3** and **2** that under the reaction conditions, favors the thermodynamically more stable regioisomer **2**. Although studies on the gold-catalyzed hydroamination of allenes using hydrazides,[24] and hydrazines[25] as nucleophiles, as well as the examples of addition of azoles with Rh[11a] and Pd[12] showed no evidence of isomerization between allyl derivatives,[26] computational studies on the Au-catalyzed reaction of allenes with oxygen nucleophiles have shown that isomerization between regioisomers **3** and **2** can take place during the reaction via a six-membered cyclic gold intermediate in a process with two alcohols involved, to give predominantly the more stable regioisomer **2**.[27] A similar cyclic metallic intermediate involving two azoles could be proposed in our case.

Therefore, a possible reaction mechanism would start with coordination of the metal catalyst to the allene. In the case of activated allenes, the involvement of the heteroatom in the stabilization of the coordinated allene can influence de point of attack (1,2- or 1,4-addition to the proximal or distal carbons). Nucleophilic addition to the proximal carbon atom would generate vinyl-metal intermediate **A** that after protonolysis (with acidic protons of the azole) will give **B** and **3** in a process favored by Pt catalysts, while opposite regioselectivity towards the terminal carbon atom would generate intermediate **A'** that will give **C** and **2** in a process favored by Au complex-

es (Scheme 5). Isomerization between **B** and **C** can then occur via intermolecular attack of the second azole to either metal-activated double bond in **B** or **C** to form a protonated bisazole (bi)metallic intermediate **D**, resembling the proposed for the reaction with alcohols and gold.[27] In the presence of the more reactive Au-Pt bimetallic system, intermediate **D** could undergo protodemetallation via S$_E$OX process involving protonation of a bimetallic center to form metallic-hydride intermediate **E**, stabilized by the presence of the second metal. Reductive elimination from **E**, would form 1,3-bisazole products **6** (Scheme 5). In the presence of single catalysts, formation of the metal-hydride intermediate **E**, although possible is less favored,[28] and therefore the reaction stops to give **2** or **3** depending on the metal employed and only traces of **6** in more forcing conditions. The addition of the second azole from **3** and **2** can also be promoted by acid present in the media (excess pyrazole, Tf$_2$NH generated in situ), aided by the heteroatom. However, reactions only in the presence of acid are less clean, and decomposition of the product is observed, suggesting this is not the main pathway under bimetallic conditions.[29,22]

Formation of **6Aaa** from **1A** was quenched under optimized Au-Pt conditions and under Au and Pt single catalyst experiments with excess pyrazole in the presence of TEMPO (10 mol%), known to trap metal-hydrides.[30] However, mixtures of **2** and **3** where obtained in the presence of TEMPO in all cases.[22] Although TEMPO is also known to react with acids,[31] possibly quenching the second addition, protonolysis of **2** and **3** was not affected. Besides, the reaction showed higher conversion towards products **6** in the presence of an alternative hydride source (Et$_3$SiH), and gave complex mixtures in the presence of radical initiators (AIBN), supporting that intermediates **2** and **3** are generated without the involvement of metal-hydrides, and the bimetallic hydride as the main pathway for the second azole addition under bimetallic catalysis.[22]

Reaction using N-deuterated pyrazole led to final adduct d_2-**6Aaa** showing complete double transference of deuterium from the azole to the central carbon of the allene. Incorporation of the first deuterium can be explained by the protonolysis of **A/A'**. Incorporation of the second deuterium from the azole in the central carbon would also support metal-hydrides as the main species responsible for the second hydroamination reaction from intermediate **D**. Stabilization of Au-hydrides[32] in the presence of a second metal such as Pt has been reported,[33] which will further support the need for both metals for the more efficient double azole addition observed under bimetallic catalysis.

In conclusion, we have found that from the same starting material and under similar reaction conditions, simply modulating the catalyst used (platinum, gold or both) and the excess of nucleophile, we were able to tune the regioselective addition of azoles to activated allenes to be directed towards the proximal or distal allenic carbon. Remarkably, the combination of gold and platinum as bimetallic system was found to catalyze the double nucleophilic addition of azoles to terminal allenes in high efficiency to give 1,3-diazole derivatives, recurring and attractive scaffolds in catalysis, biological active molecules, and ligands for metal complexes. The divergent reactivity of platinum and gold and the higher efficiency shown towards novel processes in allene chemistry when both metals are used in combination, highlights the importance of

the understanding of metallic intermediates in synthesis and catalysis for the discovery of new processes.

Scheme 5. Mechanistic proposal for the bimetallic Au-Pt-catalyzed double azole addition to activated allenes.
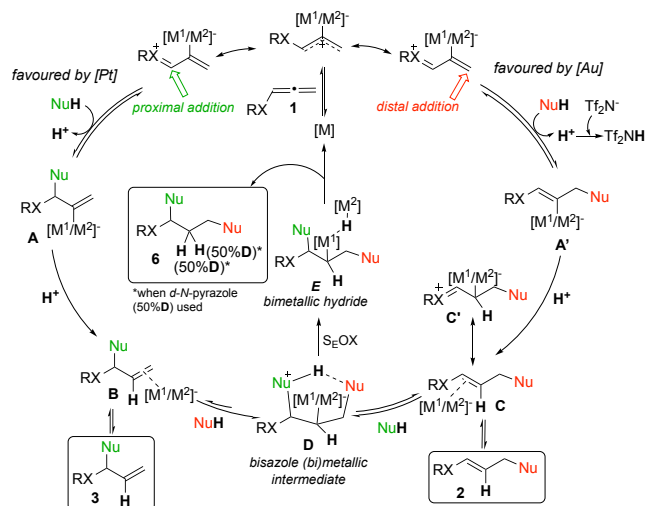
ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website: pdf containing experimental data, full characterization of compounds, details on the mechanistic investigations and copies of the NMR spectra of the new compounds.

AUTHOR INFORMATION

Corresponding Author

* E-mail: m.munoz-herranz@uea.ac.uk

Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript. / ‡These authors contributed equally.

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