

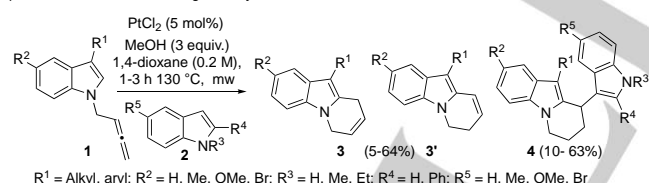
Heterobimetallic catalysis: Platinum-Gold-catalysed tandem cyclisation/C-X coupling reaction of (hetero)aryllallenes with nucleophiles

José Miguel Alonso^{‡a} and María Paz Muñoz^{*‡a}

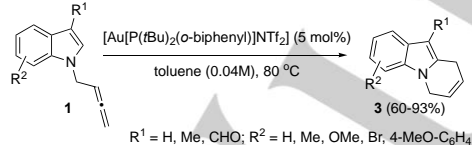
Abstract: Heterobimetallic catalysis offers new opportunities for reactivity and selectivity but still presents challenges and only a few metal combinations have been explored so far. We have developed a Pt-Au bimetallic catalyst system for the synthesis of a family of multi heteroaromatic structures through tandem cyclisation/C-X coupling reaction. Au-catalysed 6-*endo*-cyclisation takes place as the first fast step and Pt-Au clusters are proposed to be responsible for the increased activity of the intermolecular second nucleophilic addition that occurs through an outer-sphere mechanism by hybrid homo-heterogeneous catalysis.

Dual catalysis in well-defined homogeneous systems has appeared in recent years as a powerful tool to control selectivity in C-C coupling reactions.^[1] In this area, heterobimetallic systems that work cooperatively leading to improved reactivity have been reported, including examples in allene chemistry of Au-Pd dual synergistic catalysis.^[2] In most examples, a transmetalation step is involved as the link of two catalytic cycles, so the choice of redox compatible metal pairs with appropriate ligands and counterions is crucial for the success of the processes. Heterobimetallic homogeneous catalysis involving Au and Pt has not been explored in this context, although Pt(II)-to-Au(I) transmetalation of methyl groups has been reported to occur through bimetallic Pt-Au complexes.^[3] In contrast, there are increasing examples of heterogeneous catalysis involving Au and Pt, where the addition of small amounts of Au to the heterogeneous system greatly enhances the catalytic activity.^[4]

a) Previous work under Pt-single catalysis⁶



b) Previous work under Au-single catalysis⁶



Scheme 1. Previous work with *N*-indolylallenes **1** using single catalysis.

We thus decided to investigate a dual Pt-Au process in which the two metals could be either involved in a classic orthogonal catalysis,^[5] or where two catalytic cycles could be connected through a transmetalation step. Here we report the optimisation and scope of a new methodology using dual Pt-Au catalysis for the synthesis of a family of multi heteroaromatic structures from the reaction of hetero(aryl)allenes with nucleophiles.

N-indolylallenes **1** were selected as model substrates. Under single Pt catalysis in the presence of indoles as nucleophiles, **1** gives bisindolylmethanes (BIMs) **4**,^[6] a naturally occurring motif present in diverse biologically active molecules,^[7] in moderate yields. The process is limited to activated *N*-indolylallenes and activated indoles as nucleophiles, with intermediate cyclic alkenes **3** and **3'** recovered at short reaction times (Scheme 1a). The cyclisation reaction of **1** catalysed by Au complexes has been reported (Scheme 1b),^[8] but to the best of our knowledge, there are no examples of addition of external nucleophiles reported with these systems under Au catalysis.

To our delight, after a small screening of complexes and catalysts loadings, the desired BIM **4a** was obtained as the only product in higher yields when *N*-indolylallene **1a** was reacted with indole **2** in the presence of Ph₃PAuNTf₂ (2.5 mol%) and PtCl₂ (10 mol%) as catalytic pair (Table 1, entry 2). The high efficiency of the dual catalysis allowed us to lower the amount of indole, yielding BIM **4a** in 95% isolated yield (Table 1, entry 3).^[9] As already mentioned, although Au complexes are extremely efficient catalysts for the cyclisation of **1a**, the intermolecular nucleophilic attack does not occur and cyclic allyl indole **3a** is obtained as the only product under our reaction conditions (Entry 4, Table 1), emphasizing the divergent reactivity that Au and Pt exhibit in similar systems^[9] and the need for both metals^[11] for an efficient process.

Table 1. [Pt] vs [Pt]-[Au] catalysis in the reaction of **1a** with indole **2**.

Entry	Catalyst (mol%) ^[b]	Indole 2 (equiv.)	3a:3a' (%)	4a (%)
1 ^[a]	[Pt] (5)	3.0	5 (1:0.3)	61
2	[Pt](10)/[Au](2.5)	3.0	-	80
3	[Pt](10)/[Au](2.5)	1.0	-	95
4	[Au] (2.5)	1.0	98 (1:0)	-

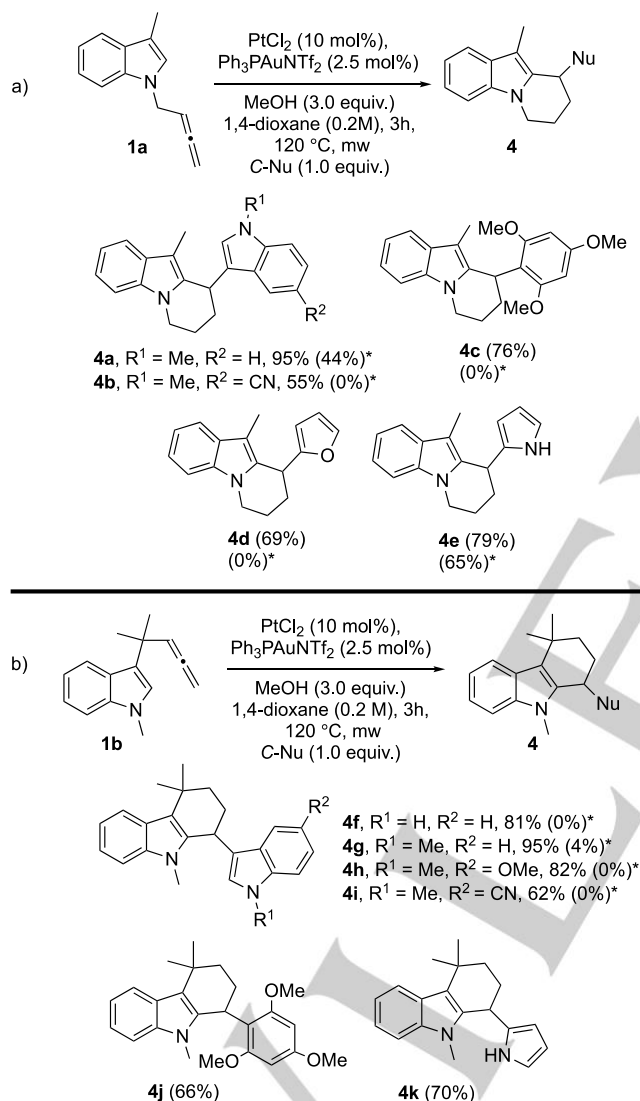
[a] Results from ref 6. [b] [Pt] = PtCl₂; [Au] = Ph₃PAuNTf₂.

Encouraged by these results, we extended the dual Pt-Au strategy to other C-nucleophiles, in particular to those that do not work under the single catalyst. Thus, reaction of *N*-indolylallene **1a** in the presence of deactivated 5-cyanoindole^[12]

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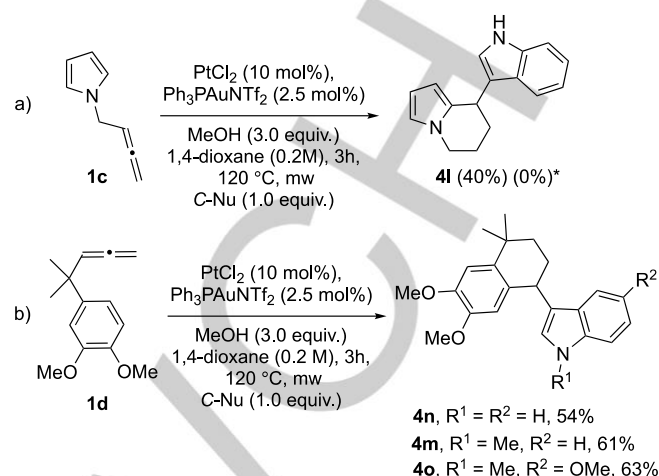
under optimised reaction conditions (as in entry 3, Table 1), generated the expected BIM adduct **4b**, not accessible by single catalyst methodology, in good yield. Moreover, reaction of **1a** with 1,3,5-trimethoxybenzene and furan as nucleophiles, also provided the expected adducts **4c** and **4d** respectively, undetected in the platinum single catalysis reaction (Scheme 2a). C3-indolylallenes such as **1b** are known to undergo 6-*endo* carbocyclisation in the presence of Au catalysts but are unreactive under single Pt catalysis.^[13] Taking advantage of this precedent, we explored the Pt-Au strategy on **1b** with different nucleophiles that gave the corresponding adducts (**4f-4k**) in good to excellent yields (Scheme 2b).



Scheme 2. Pt-Au catalyzed reaction of *N*-indolylallenes **1a** and **1b** with C-nucleophiles. (*Yields from Pt-single catalyst experiments).

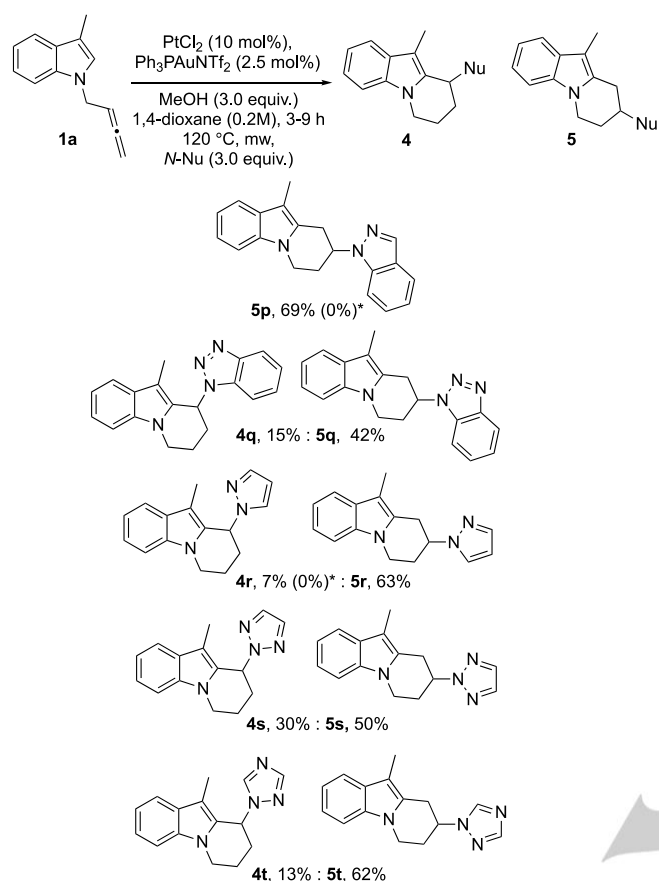
In addition, we were able to expand the reaction to pyrrole- and benzene-based allenes **1c** and **1d**, also unreactive substrates under Pt single catalysis, which led to the expected adducts **4l-4o** in good yields, providing a wide family of BIM

related structures through a versatile and efficient methodology (Scheme 3).^[14]



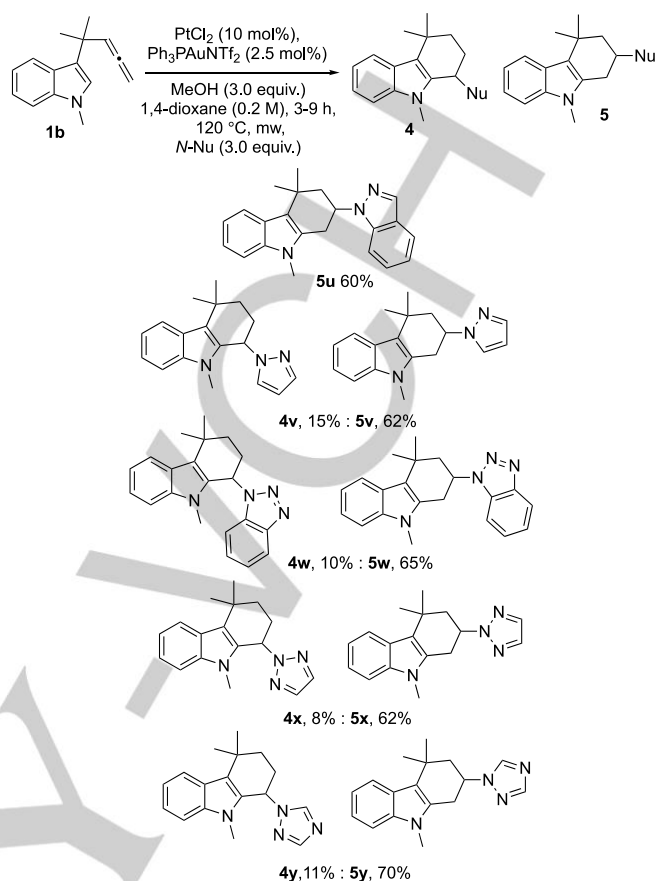
Scheme 3. Pt-Au catalyzed reaction of *N*-indolylallenes **1c** and **1d** with C-nucleophiles. (*Yield from Pt-single catalyst experiment).

N-heterocyclic nucleophiles have been scarcely explored in the Au- and Pt-catalyzed reaction with allenes,^[15] and do not work in the single catalyst reactions under our reaction conditions. Therefore, the tandem carbocyclisation/C-N coupling reaction was also explored using the dual Pt-Au strategy. *N*-indolylallenes **1a** (Scheme 4) and **1b** (Scheme 5) were submitted to Pt-Au reaction conditions in the presence of pyrazole, indazole, and triazoles. Surprisingly, in every case, C-N coupling reaction at the central carbon of the allene was preferred, opposite to the regioselective addition to the terminal allenic carbon observed in the C-C version. Thus, reaction with pyrazole or triazoles yielded mixtures of two isomers **4** and **5**, products of the nucleophilic attack to the terminal and central allenic carbon respectively. Interestingly, reaction with indazole yielded adducts **5p** and **5u** as the only isomers from reaction onto the central carbon of the allenes **1a** and **1b** respectively (Schemes 4 and 5).



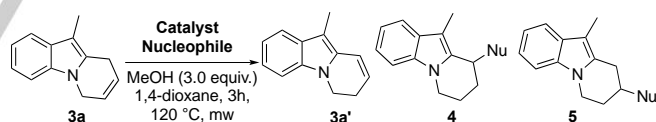
Scheme 4. Pt-Au catalysed reaction of *N*-indolylallene **1a** with *N*-nucleophiles. (*Yields from Pt-single catalyst experiments)

Previous studies have shown that Pt is able to promote the 6-*endo-trig* carbocyclisation in *N*-indolylallenes **1a**,^[6,16] and that alkenes **3** and **3'** are true intermediates of the reaction, with Pt-catalysed isomerisation of **3** to **3'** occurring before the intermolecular nucleophilic addition.^[6,17] Nevertheless, PtCl₂ is not able to promote the carbocyclisation of allenes **1b-d** in an efficient manner under our reaction conditions.^[9] The fact that Au-catalysed carbocyclisation of all substrates **1a-d** took place under milder reaction conditions and shorter reaction times to yield intermediates **3** (Au-catalysed process: 15 min at rt vs Pt-catalysed process: 3 h at 120 °C under mw irradiation, under same solvent and dilution conditions), supported a classic tandem orthogonal catalysis, with no considerable interference of the Pt in the first cycle or the Au in the second. However, different results obtained from isolated intermediate **3a** in the presence of Pt or Pt-Au catalysis and different nucleophiles (Table 2),^[9] suggest that Au is also involved in the second catalytic cycle and that Pt-Au interaction is needed to catalyse the intermolecular nucleophilic attacks efficiently, with [R-Pt-AuPPh₃] clusters as the proposed species involved.^[18,19]



Scheme 5. Pt-Au catalysed reaction of *N*-indolylallene **1b** with *N*-nucleophiles. (*Yields from Pt-single catalyst experiments)

Table 2. [Pt] vs [Pt]-[Au] catalysis in the reaction of cyclic alkene **3a** with nucleophiles.



Entry	Catalyst (mol%)	Nucleophile (equiv.)	3a' (%)	4 (%)	5 (%)
1	[Pt] (10)	5-CN-indole (1.0)	50	4b , 5	-
2	[Pt](10)/[Au](2.5)	5-CN-indole (1.0)	-	4b , 51	-
3 ^[a]	[Pt] (10)	Pyrazole (3.0)	30	4r , 8	-
4 ^[b]	[Pt](10)/[Au](2.5)	Pyrazole (3.0)	28	4r , 9	5r , 27

[a] 56% of **3a** recovered. [b] 32% of **3a** recovered. Full conversion at 9 h. See Schemes 4 and 5.

In all experiments a black solid was observed during and after the reaction, suggesting that heterogeneous Pt-Au particles could be responsible for the enhanced catalytic activity.^[4] This black solid did not catalyse the reaction from **1a**, but it was moderately active in the reaction from **3a**, suggesting that Pt-Au particles might be involved only in the second catalytic cycle.

Although this solid could be acting as a reservoir of the solution state Pt-Au catalyst, further evidence^[20] would support a hybrid homo-heterogeneous catalysis operating in this reaction, not reported to date in heterobimetallic systems, where both phases are needed for an efficient process.^[21,22]

Taking into account all the experimental evidence,^[6b, 20] we propose a fast homogeneous Au-catalysed 6-*endo-trig* carbocyclisation of the heteroarylallenes to furnish, after protodemetalation, compound **3**, the first reaction intermediate observed in the process (Scheme 6, cycle 1). Intermediate **3** would then enter into the second catalytic cycle (Scheme 6, cycle 2) promoted by [Pt-AuPPh₃] homogeneous clusters aided by Pt-Au particles in the heterogeneous phase, with heterobimetallic carbene **E** as the key intermediate. **E** could evolve by 1,2-H shift to a stable benzylic carbocation **F**, able to react with any nucleophile present to generate, after protodemetalation, product **4**. Intermediate **F** could also easily explain the generation of alkene **3'**, observed at shorter reaction times (Scheme 5, cycle 3). Product **5** could be formed by direct attack of *N*-nucleophiles into the bimetallic carbene carbon in **E**.^[23] This divergent reactivity could be rationalised by an increased α -metallocarbenium ion character of intermediate **E** due to the relativistic effect of the Au atoms in the heterobimetallic carbene,^[24] as well as the superior nucleophilicity of the *N*-nucleophiles (reacting through a very acidic N-H) compared with the *C*-based ones (reacting through an aromatic C-H).^[12,25] Deuterium labelling experiments (Scheme 6),^[26] as well as monitoring the reactions with pyrazole by ¹H NMR support that **3a** is an intermediate in the formation of **3a'** and **5r**, while **3a'** is an intermediate in the formation of **4r** as found with the *C*-based nucleophiles.^[6] Stoichiometric reactions with complex PtCl₂(pyrazole)^[27] showed that, although this complex is active in the isomerisation of **3a** to **3a'**, no products from the nucleophilic addition **4r** or **5r** were detected in the absence of Au. Besides, gold mirror appeared in the reaction vessel at short times in cases when *N*-nucleophiles were used.

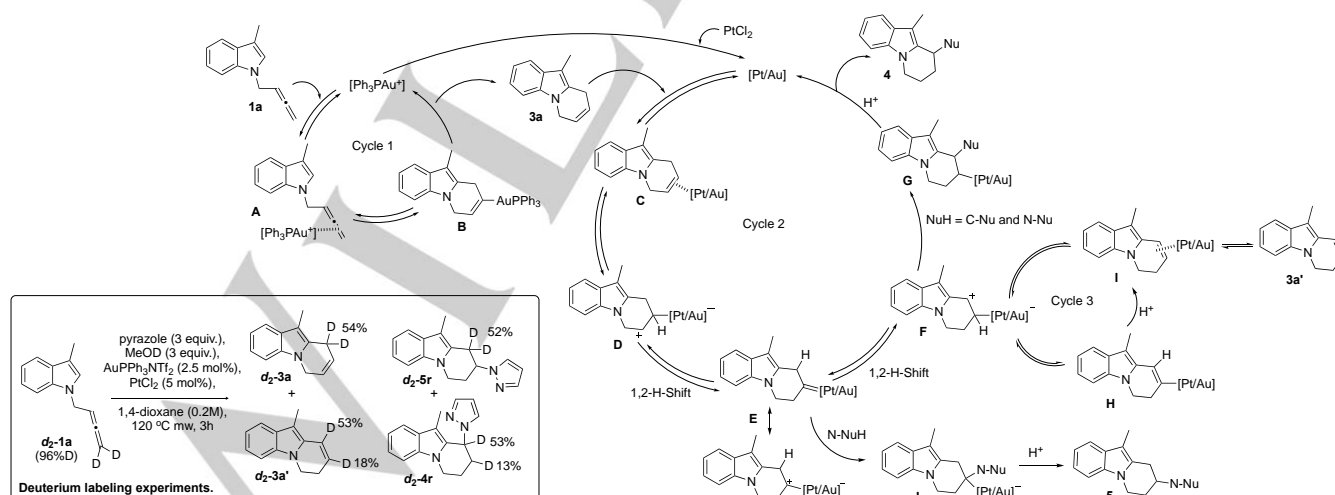
Cyclic voltammetric measurements of isolated complex PtCl₂(pyrazole)₂, that could be formed *in situ* in the catalytic reaction, revealed an irreversible oxidation at ~ +1.40-1.50 V vs NHE. This indicates that PtCl₂(pyrazole)₂ is capable of reducing Au⁺ to Au(0) (E₀ = +1.83 V vs NHE), highlighting the importance of redox compatible bimetallic pairs.^[28] In the cases where gold mirror was seen, worse conversion to products were observed, supporting the hypothesis that PtCl₂(azole)₂ formation inhibits the nucleophilic attack, and that Pt-Au interaction is needed first with an outer-sphere mechanism as the main pathway for the nucleophilic attacks.^[9]

In conclusion, an efficient example of Pt-Au bimetallic catalysis has been developed for the synthesis of a family of multi heteroaromatic structures with potential use in pharmaceutical industry. The first catalytic cycle seems to involve only homogeneous Au-catalysis to generate an intermediate that enters the second cycle in which hybrid homogeneous-heterogeneous catalysis by [Pt-Au] clusters is responsible for the high efficiency of the process. The methodology has been expanded to azoles as *N*-nucleophiles, which as well as the normal reactivity as seen with *C*-nucleophiles, are able to attack directly the bimetallic carbene carbon, opening new avenues for reactivity and molecular complexity in these and related systems.

Acknowledgements

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Keywords: heterobimetallic catalysis • platinum • gold • allenes • hybrid homogeneous-heterogeneous catalysis

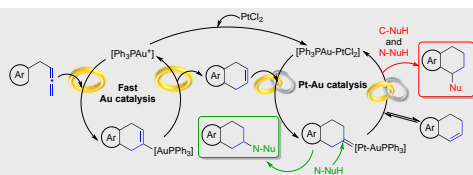


Scheme 6. Proposed mechanism for heterobimetallic catalysis with **1a** and deuterium labelling experiments in the reaction with pyrazole. Mechanism applicable to all substrates shown in the scope.

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José Miguel Alonso and María Paz Muñoz*

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