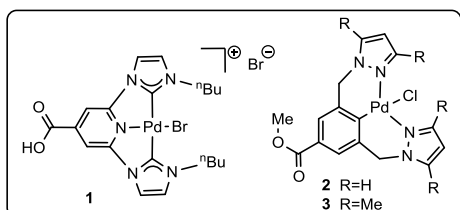
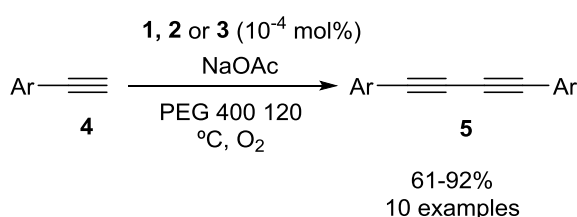


## Diyne formation from alkynes in the presence of palladium pincer complexes

Garazi Urgoitia (garazi.urgoitia@ehu.eus), Raul SanMartin (raul.sanmartin@ehu.eus)\*,  
 María Teresa Herrero (mariateresa.herrero@ehu.eus) and Esther Domínguez  
 (esther.dominguez@ehu.eus)\*

\* *Department of Organic Chemistry II, Faculty of Science and Technology, University of the Basque Country (UPV/EHU), 48940 Leioa, Spain.*

### Graphical Abstract



### Abstract.

1,3-Diynes are valuable building blocks for biologically active molecules and precursors of polymers, macrocycles and supramolecular structures. The combination of metal catalysts and molecular oxygen is considered a suitable protocol for the direct homocoupling of alkynes leading to diynes. Regarding the catalyst, palladium species have proved to be efficient and selective, but copper salts as co-catalysts and/or stoichiometric amounts of reoxidants are often needed. Palladium pincer complexes are presented as alternative palladium sources for the homocoupling of alkynes in an environmentally friendly solvent as polyethylene glycol, in the absence of any other co-catalyst and under aerobic conditions.

### Introduction

1,3-Diyne compounds are important building blocks for many natural, pharmacological active products as well as for oligomers and polymers.<sup>[1]</sup> Back in the XIX century Carl Glaser<sup>[2]</sup> reported the synthesis of 1,3-diynes from terminal alkynes through an oxidative process mediated by copper(I) chloride exposed to air. Although classical Glaser conditions for the homocoupling of terminal alkynes is still used, other protocols can be found in the literature about this specific and useful reaction. Regarding the oxidant, even when molecular oxygen<sup>[3]</sup> is considered as the most suitable one due to its availability, low cost and harmless by-product, other oxidants have been explored (I<sub>2</sub>, Na<sub>2</sub>CO<sub>3</sub>·1.5 H<sub>2</sub>O, Ag, chloroacetone, etc.).<sup>[4]</sup>

In relation to the catalyst and even when other metal have been tested in the aforementioned transformation<sup>[5]</sup> palladium catalysed homocoupling of terminal alkynes is considered the most suitable, but co-catalyst as copper and/or stoichiometric amounts of reoxidants are often required.<sup>[6]</sup>

However, a few examples about palladium solely mediated homocoupling of alkynes have been reported, but in all of the high amounts of catalytic loading are required.<sup>[7]</sup> For these reason and taking into account the experience of the group in palladium pincer complexes as catalytic species in organic transformations we envisioned that these kind of complexes could also be suitable in the above transformation and if it is possible in a green media.

### Materials and Methods

A round bottom flask equipped with a magnetic stirrer bar was charged with the alkyne (1 mmol), NaOAc (8.0 mg, 0.1 mmol), pincer compound (**1**, **2** or **3**) (20  $\mu$ L of a  $5 \times 10^{-5}$  M solution in PEG 400,  $10^{-6}$  mmol) and PEG 400 (1mL per mmol of the substrate) at room temperature. The system was purged with molecular oxygen, and an oxygen-filled balloon (1-1.2 atm) was connected. The mixture was heated at 120°C under continuous stirring for 24 hours. The reaction outcome was monitored by <sup>1</sup>H-NMR. Upon completion, the mixture was cooled to room temperature and water was added (50 mL aprox.). The resulting solution was acidified with HCl 1M (pH $\approx$ 1-2) and extracted with Et<sub>2</sub>O (4 x 6 mL), and the combined organic layers were washed with brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and evaporated in vacuo to give a residue which was purified by flash column chromatography using hexane:ethyl acetate as eluent.

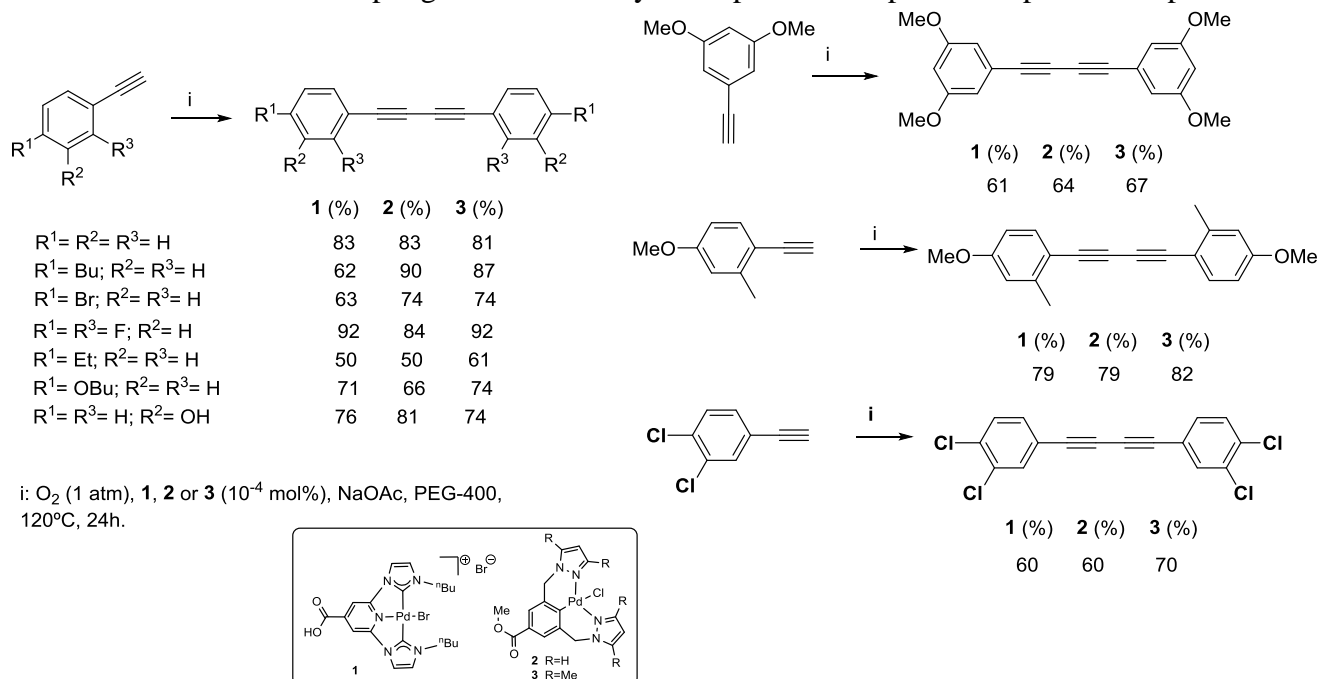
### Results and Discussion

In order to improve the catalytic activity of some of the palladacycles prepared in the research group (CNC **1**, NCN **2** and NCN **3**)<sup>[8]</sup> there were applied in the homocoupling of terminal aromatic alkynes. Phenylacetylene (**4a**) was chosen as model substrate, after a variety of optimization assays in which a catalytic loading of 0.01 mol% of the pincer complexes 1-3 was employed and in which priority was given to environmentally friendly solvents (polyol solvents, water, etc) in order to the typical reaction medias (acetonitrile, DCM, DMF, etc). We decided to use **1**, **2** or **3**, O<sub>2</sub>, NaOAc, PEG 400 and 120 °C and decrease the catalytic loading down to  $10^{-4}$  mol%. In order to verify if addition of a substoichiometric amount of a copper salt could improve results, phenylacetylene was again submitted to the above conditions adding 0.1 equiv. of CuBr<sub>2</sub> as co-catalyst, surprisingly no improvement was observed. Blank experiments also confirmed the crucial role of the palladium pincer complexes, since no product was detected when commercially available palladium source was employed or even when the pincer type ligands were tested.

The afore mentioned optimized conditions were respectively applied to a number of aromatic acetylenes, proving good result regardless the nature of the substrate as summaries in Table 1. No steric hindrance was observed in the coupling of *ortho*-substituted aromatic acetylenes. Furthermore, different halogens as F, Cl or Br or relatively acidic protons were also tolerated obtaining good yields in all the cases. Regarding the catalyst, no clear trend or marked differences was observed for complexes **1-3**.

Finally, the recycling of the palladium pincer complexes was as well carried out using the homocoupling reaction of the model substrate **4a**. To be able to reuse the reaction media it was necessary to replace the workup procedure with an extraction at low temperature (-78 °C). With this small modification several runs were performed (4 times) in the same PEG media without observing any decrease in the product yield.

Table 1. Oxidative homocoupling of terminal alkynes in presence of palladium pincer complexes.



## Conclusions

To sum up, palladium pincer complexes constitute a highly active catalytic species for the aerobic homocoupling of aromatic terminal alkynes. In addition, the presence of metal traces in the final product has been thereby minimized to values below legal limits for food and drug products. Furthermore, it has been proven not only that the presented method was performed in a sustainable media but also that the catalysts can be effectively reused.

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