# Final report

## 1. Summary of results:

Cross-coupling methodologies proceeding *via* two-fold C-H activation have the potential to become a new generation of cross-coupling type reactions for the synthesis of biaryls.[1] Such motifs are ubiquitous in natural products, pharmaceuticals and organic materials but today their synthesis mainly rely on the use of pre-functionalised starting materials such as arylhalides and aryl organometallic species (Figure 1a). By comparison, procedures in which two aryl C-H bonds are directly cross-coupled in the presence of an oxidant could offer more direct, more economic and significantly greener approaches than current methods as pre-functionlisation is avoided and waste is minimized. However, all C-H activation methodologies face the difficulty of breaking poorly reactive C-H bonds, and reactions proceeding *via* two-fold C-H activation must in addition overcome the challenge of favoring the formation of cross-coupled products over homo-coupled by-products (Figure 1b). Thus, the main objective of the Au-doubleC-H proposal was to develop the first example of a Au-catalysed oxidative biaryl cross-coupling *via* two-fold C-H activation, and to take advantage of the specific properties of Au in order to achieve high selectivity for cross- over homo-coupled biaryls.

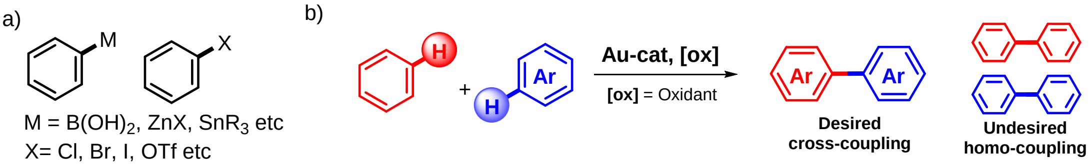

***Fig 1.*** *a) Traditional cross-couping partners containing metal and halides; b) Oxidative cross-coupling of arenes via double C-H activation, and possible homo-coupling by-products*

Our interest in using Au as the catalyst for this transformation was prompted by intrinsic differences in reactivities of the Au(I) and (III)oxidation states towards electron-deficient and electron-rich arenes, respectively, which in our view held great promise for developing selective cross-couplings and minimizing homocoupling side-products. [2] We recently reported a stoichiometric cross-coupling of Aryl-Au(I) complexes with electron-rich arenes in the presence of an iodine(III) oxidant.[2b] However, a catalytic version had not been realized, likely due to the significant challenge of combining in one pot the elementary steps of this reaction in the presence of a strong oxidant required for overcoming the high oxidation potential of the Au(I/III) redox couple, in order to achieve turnover under catalytic conditions. We have now reported a novel catalytic procedure that addresses the challenge of cross-coupling polyfluoroarenes with electron-rich hetero- and carbocyclic arenes in an efficient manner (Figure 2a).[3] The developed cross-coupling is the first of its kind with respect to using Au-complexes as catalyst in double C-H functionalization biaryl cross-coupling reactions.[4] A new iodine(III) oxidant was synthesized which showed the desirable compatibility with reagents while at the same time efficiently oxidizing Au(I) to Au(III). The reaction showed a large substrate scope, and tolerated substrates containing halogens as well as oxidation sensitive functional groups such as aldehydes, benzylic alcohols and thioethers. Indoles reacted selectively at the C3-position thus avoiding formation of regioisomeric products which are difficult to separate. Furthermore, not only indoles, but other heterocyclic arenes such as pyrroles, furans, thiophenes and electron-rich carbocyclic arenes were also reactive (Figure 2b). Importantly, high cross- vs homocoupling selectivity was retained even at close to stoichiometric ratio of the two arenes. Thus, under the standard reaction conditions, a 5-fold to 10-fold excess of polyfluoroarene was used, however in examples we showed that this could be reduced to a 1.5-fold excess while maintaining high yields and selectivity, which is a promising result for approaching greener and more efficient couplings of this type.

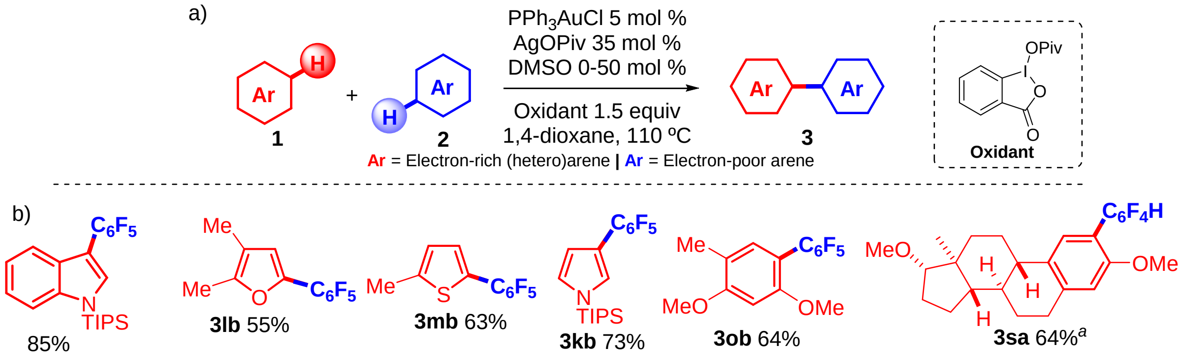

*Figure 2. a) General conditions for the Au-catalysed oxidative coupling; b) Representative examples for coupling of hetero- and carbocyclic arenes with pentafluorobenzene ($C_6F_5H$) and 1,2,4,5-tetrafluorobenzene ($C_6F_4H_2$). [a] 10 mol % $PPh_3AuCl$, 40 mol % AgOPiv, 120 °C*

We hope that the developed methodology described herein will encourage further exploration of the use of gold in cross-coupling reactions, in trying to address future greener methodologies for the preparation of biaryl scaffolds, and inspire research both in academic and industrial settings within the EU economic area.

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[1] For reviews, see for example: Yeung, C. S.; Dong, V. M. Chem. Soc. Rev. **2011**, *111*, 1215–1292; b) Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem. Int. Ed.* **2012**, *51*, 10236–10254.

[2] a) Lu, P.; Boorman, T. C.; Slawin, A. M. Z.; Larrosa, I. *J. Am. Chem. Soc.* **2010**, *132*, 5580–5581; b) Cambeiro, X. C.; Boorman, T. C.; Lu, P.; Larrosa, I. *Angew. Chem. Int. Ed.* **2013**, *52*, 1781–1784; c) Ahlsten, N.; Perry, G. J. P.; Cambeiro, X. C.; Boorman, T. C.; Larrosa, I. *Catal. Sci. Technol.* **2013**, 2892-2897

[3] Cambeiro, X. C.; Ahlsten N.; Larrosa, I. *J. Am. Chem. Soc*., **2015**, *137*, 15636-15639.

[4] For a related alkynylation methodology, see: De Haro, T.; Nevado, C. *J. Am. Chem. Soc.* **2010**, *132*, 1512–1513.