Summary of results:

The development of selective C-H arylation methodologies is highly desirable, as they would improve the access to biaryl motifs, which are ubiquitous in natural products, pharmaceuticals and organic materials, offering a more direct, economic and significantly greener approach. In this way, the main objective of metaCHaryl proposal was to develop a cascade process that would use CO_2 as an *invisible directing group* leading to a completely novel approach towards direct meta-arylation.

Phenols are exceptionally important chemical motifs, as they are present in many natural products, pharmaceuticals and polymers and they are key building blocks for synthesis. While the ortho and para direct functionalization of phenols is highly favored by the electron donating nature of the hydroxy group, the access to meta functionalized phenols from the corresponding phenols generally requires multiple synthetic operations.

During the course of this project, we have reported a novel procedure[1] that addressed the challenge of functionalising phenols at the electronically disfavoured meta position. CO_2 has been used to install a temporary and "traceless" directing group, a carboxylic acid, using a Kolbe–Schmitt type reaction. This ortho-carboxylated phenol is used to direct a C-H activation meta to the hydroxyl substituent (ortho to the acid group), overriding the inherent reactivity of the molecule (Figure 1). Thus, after Kolbe–Schmitt carboxylation, a tandem arylation–protodecarboxylation process regenerates CO_2 to give a meta-functionalised phenol, leaving no trace of the directing group. This represents the first meta-selective arylation of phenols in a one-pot operation, which uses CO_2 as a traceless directing group, allowing the synthesis of meta-arylphenols from phenols containing moderately electron-rich or electron-poor substitution at C2 and C3. The study was completed with an efficient three-step synthesis of a gamma-secretase inhibitor, starting from 3-bromo phenol in 41% overall yield, far surpassing the eight steps and 6% overall yield of the patented process[2].

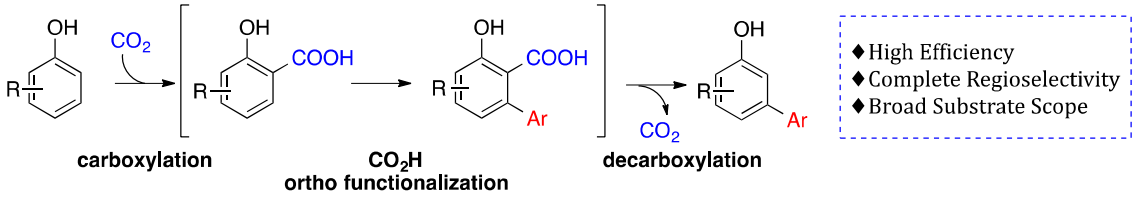

Figure 1. One pot *meta*-functionalization of phenol via installation of a secondary removable directing group

However, due to the intrinsic harsh requirements for the Kolbe–Schmitt carboxylation, these processes required the use of high pressures of CO_2 (25 atm), high temperatures (190 ºC) and, consequently, of specialized autoclave equipment. Furthermore, significantly electron-deficient phenols (such as 3-nitrophenol,

[1] Luo, J.; Preciado, S.; Larrosa, I. *J. Am. Chem. Soc.* **2014**, *136,* 4109.

[2] Wilson, F.; Reid, A.; Reader, V.; Harrison, R. J.; Sunose, M.; Hernandez-Perni, R.; Mayor, J.; Boussard, C.; Smelt, K.; Taylor, J.; Le Formal, A.; Cansfield, A.; Burckhardt, S. (Cellzome UK Ltd.) European Patent Appl. EP1849762A1, 2007

or 3-trifluoromethylphenol) were not suitable substrates due to lack of reactivity towards carboxylation. In this way, we decided to study the arylation of salicylic acids, which are readily available starting materials,[3] and also easily synthesised from phenols *via* a variety of routes. Therefore, we envisaged that an exploration of the suitability of salicylic acids for the general synthesis of meta- substituted biaryls would be of significant utility.

Thus, we identified efficient conditions for the arylation–decarboxylation process starting with salicylic acid and a iodoarene.[4] Our optimized reaction conditions for the reaction of salicylic acid (1.0 equiv.) with aryl iodides (3.0 equiv.) involved the use of 2 mol% PEPPSI-IPr as a catalyst, 0.5 equiv. each of K_2CO_3 and Ag_2CO_3, in AcOH at 150 ºC. We showed that both electron-rich and electron-poor salicylic acids react smoothly under our tandem arylation–protodecarboxylation leading to the corresponding meta-arylphenols with complete regioselectivity. Besides, a silver-free C-H arylation process, recently reported in our group[5] was applied for the synthesis of meta-substituted biaryls. Satisfyingly, the Ag-salt can be conveniently replaced by a cheap and readily available organic salt, NMe_4Cl, which makes these reactions increasingly attractive for large scale synthesis and industrial processes.

Furthermore, these substrates can then be easily functionalized at the C–O bond, resulting in a highly versatile and straightforward approach towards meta-biaryls, highlighting salicylic acids as attractive starting materials for the synthesis of these structural motifs (Figure 2).

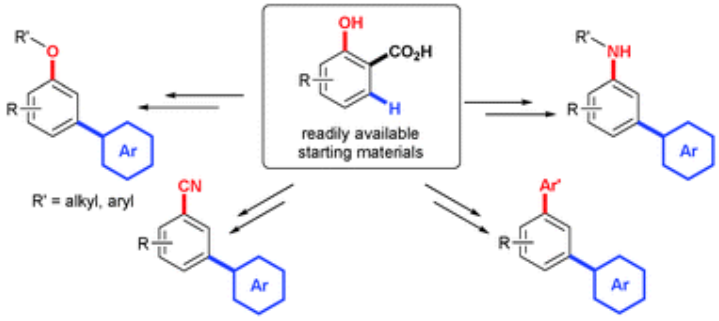

Figure 2. Transformations of salicylic acids into a variety of meta-functionalized biaryls

We envisage that this traceless directing group strategy will be applicable to the development of other useful one-pot meta-functionalization processes, opening a new route for the preparation of biaryls in a more efficient and simple manner than currently available methods. This is expected to have immediate impact by facilitating access to chemical compounds needed for research in other areas, such as medicinal chemistry and molecular biology, materials science, etc. Furthermore, the use of this methodology in industrial applications would reduce the number of operations needed for the preparation of a target compound, thus reducing the cost and favouring the sustainability of the overall process.

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[3] Reaxys indicates that over 1700 salicylic acids are commercially available

[4] Luo, J.; Preciado, S.; Larrosa, I. *Chem. Commun*., **2015**, *51*, 3127.

[5] C. Arroniz, J. G. Denis, A. Ironmonger, G. Rassias and I. Larrosa, *Chem. Sci*., **2014**, *5*, 3509.