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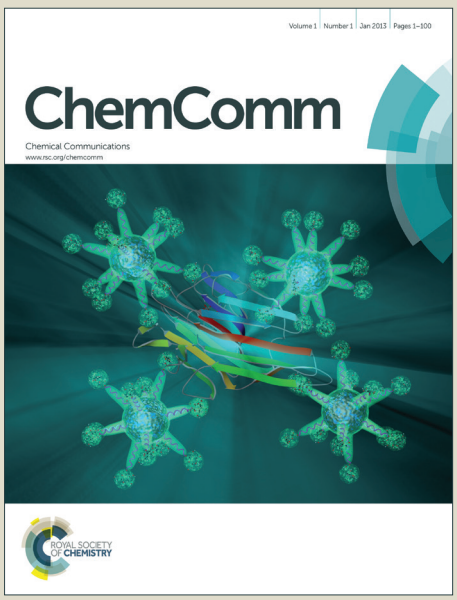

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Salicylic Acids as Readily Available Starting Materials for the Synthesis of meta-Substituted Biaryls

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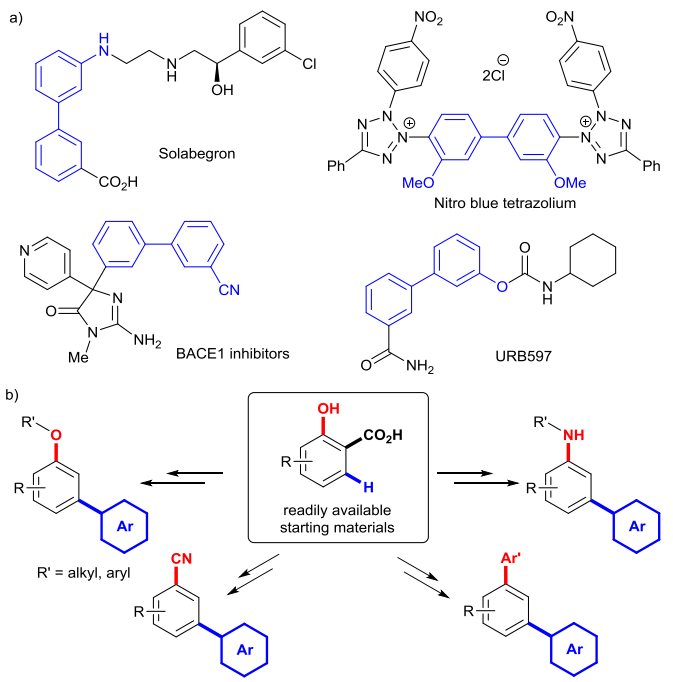
Salicylic acids are shown as readily available and versatile starting materials that easily undergo a tandem arylation / protodecarboxylation process under Pd-catalysis. The corresponding meta-arylphenols can subsequently be easily transformed into a variety of meta-functionalized biaryls, highlighting the versatility of this approach to access this structural motif.

Over the last decade, transition metal-catalysed C-H arylation of aromatic rings has received great attention due to its power and efficiency for accessing diversely functionalized aromatic motives from simple starting materials.[1] Thus, controlling the regioselectivity of functionalization has become one of the most important challenges in the field.[2] Whereas great many methods are now available for the synthesis of ortho-arylated arenes,[3] meta- and para-arylation methods are still significantly underdeveloped.[4,5] However, meta-substituted biaryl motifs are widely found in drug candidates and other bioactive molecules (Scheme 1a).[6] We recently reported a novel strategy for the meta-arylation of phenols in a one-pot operation involving a Kolbe-Schmitt carboxylation followed by a tandem arylation / protodecarboxylation process.[7,8] This methodology allowed the synthesis of meta-arylphenols from phenols containing moderately electron-rich or electron-poor substitution at C2 and C3. However, due to the intrinsic harsh requirements for the Kolbe-Schmitt carboxylation,[9] these processes required the use of high pressures of CO_2 (25 atm), high temperatures (190 °C) and, consequently, of specialized autoclave equipment. Furthermore, significantly electron-deficient phenols (such as 3-nitrophenol, or 3-trifluoromethylphenol) were not suitable substrates due to lack of reactivity towards carboxylation.

It is noteworthy that salicylic acids themselves are readily available starting materials,[10] and also easily synthesised from phenols via a variety of routes, including carboxylation, carbonylation/oxidation,[11] and ortho-lithiation of suitable O-substituted phenols, followed by reaction with CO_2.[12] Furthermore, salicylic acids are also available in one step through Pd-catalyzed hydroxylation of benzoic acids.[13] 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 (Scheme 1b). In this report, we show that both electron-rich and electron-poor salicylic acids react smoothly under our tandem arylation / protodecarboxylation leading to the corresponding meta-arylphenols. Furthermore, these substrates can then be easily functionalized at the C-O bond, resulting in a highly versatile and straightforward approach towards meta-biaryls.



Scheme 1. a) Representative examples of biologically active meta-substituted biaryls. b) This report: salicylic acids can be used as starting materials for the synthesis of a wide variety of meta-substituted biaryl motifs.

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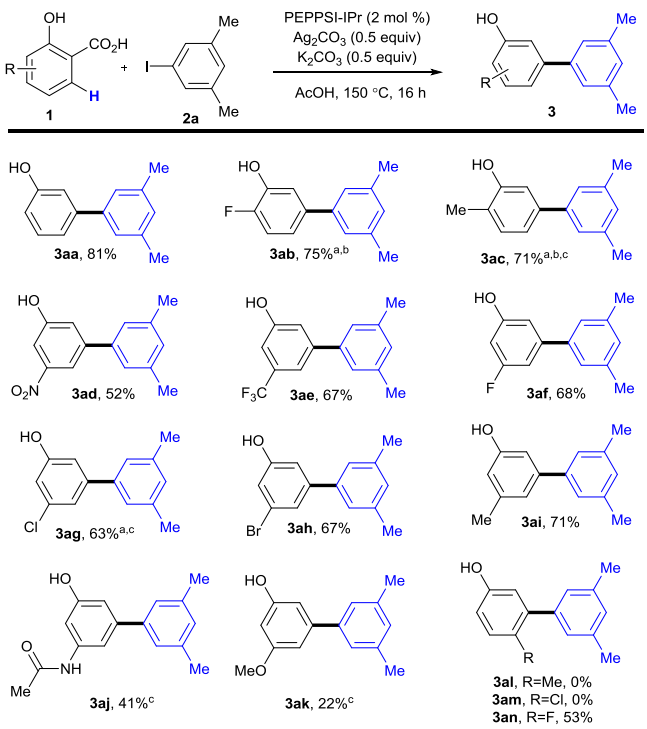
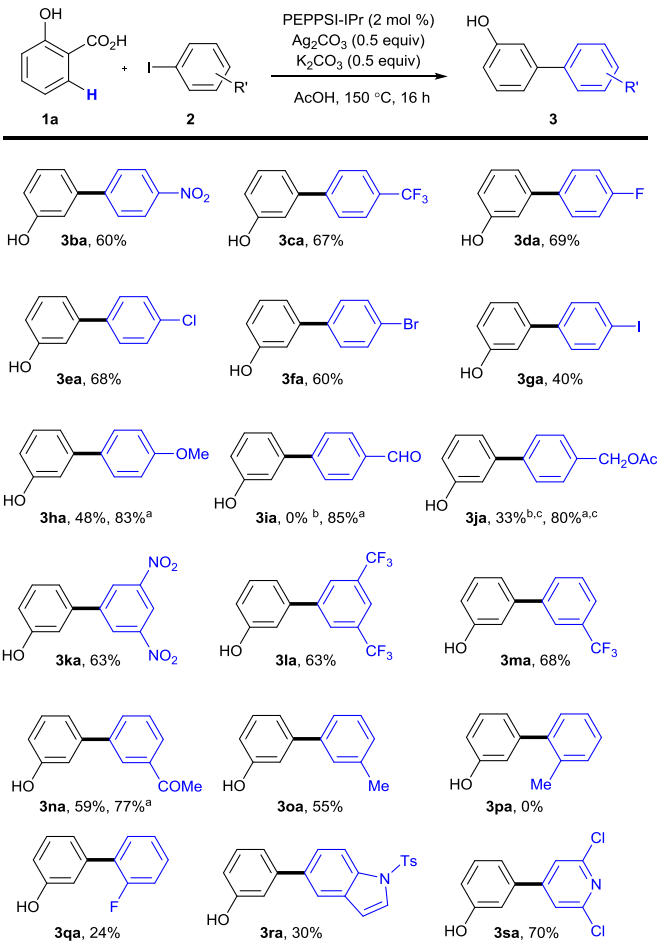
Our optimized reaction conditions for the reaction of salicylic acid **1** (1.0 equiv) with aryl iodides **2** (3 equiv) involved the use of 2 mol % PEPPSI-IPr as a catalyst, 0.5 equiv each of K_2CO_3 and Ag_2CO_3, in AcOH at 150 °C (Scheme 1).[14] Under these conditions a number of substituted salicylic acids were tested and both electron-withdrawing and electron-donating groups at C3 and C4 showed excellent compatibility with the reaction. It is important to note that in all cases the obtained yields were higher than those achieved in the one-pot methodology starting from phenols.[7] Gratifyingly, the highly electron-withdrawing NO_2 (**3ad**) and CF_3 (**3ae**) groups, which had been shown to be unreactive in the one-pot methodology, now furnished 52% and 67% isolated yields, respectively. In all cases, the expected meta-arylphenol product was obtained with complete regioselectivity. This was the case even in the presence of an acetamido group (**3aj**), which has been shown to be a good ortho-directing group, affording **3aj** in 41% yield. The highly electron-rich 4-MeO-salicylic acid afforded only 22% yield of the desired product **3ak**, due to competitive protodecarboxylation of the starting material, highlighting one of the limitations of the methodology. Furthermore, substitution at C5 of the salicylic acid is poorly tolerated, with Me and Cl not reacting at all due to steric hindrance. On the other hand, the smaller F substituent allowed the arylation to proceed, affording **3an** in 53% of yield.



Scheme 2. Scope of the tandem arylation / protodecarboxylation process on substituted salicylic acids (**1a-n**). Unless otherwise stated, all the reactions were carried out using 0.5 mmol of **1**, 1.5 mmol of **2a** and 0.5 mL of AcOH at 150 °C for 16 h. Yields are of isolated products. [a] The reaction was carried out at 160 °C. [b] 1.0 mL of AcOH were used. [c] K_2CO_3 was not used.

Substitution in the iodoarene coupling partner **2** was then examined (Scheme 3). The process is compatible with electron-withdrawing (**3ba-3ga**, **3ka-3na**) and electron-donating groups (**3ha**, **3oa**) in meta and para positions, leading to the corresponding meta-arylphenols in good yields. Remarkably, the monoarylated **3ga** was obtained selectively from *p*-diiodobenzene as coupling partner without any bisarylation product being observed.[15] An aldehyde substituent (**3ia**) led to no reaction under the standard conditions. This may result from the consumption of Ag_2CO_3 in an undesired aldehyde oxidation process. Surprisingly, when the salicylic acid was used in excess, **3ia** could be obtained in an excellent (85%) yield. Similarly, iodoarenes containing *p*-OMe (**3ha**), *p*-CH_2OH (**3ja**) and *m*-COMe (**3na**) proceeded in better yields when the iodoarenes were used as limiting reagents. Ortho-substitution at the iodoarene is not well tolerated, with only the smaller F substituent leading to appreciable reactivity (24% of **3qa**). Some heteroarenes such as iodoindole and iodopyridine were found to be compatible with the reaction, leading to the corresponding meta-heteroarylphenols **3ra** and **3sa** in 30% and 70% yields, respectively.



Scheme 3. Scope of the tandem arylation / protodecarboxylation process on substituted iodoarenes (**2b-s**). Unless otherwise stated, all the reactions were carried out using 0.5 mmol of **1a**, 1.5 mmol of **2** and 0.5 mL of AcOH at 150 °C for 16 h. Yields are of isolated products. [a] The reaction was carried out with 0.5 mmol of **1a** and 0.167 mmol of **2** at 130 °C. [b] Yield determined by ^{1}H NMR analysis using an internal standard. [c] *p*-iodobenzyl alcohol was used as starting material.

The great majority of reported methods for C-H arylation that use iodoarenes as coupling partners require the stoichiometric use of Ag-salts.[16] We have recently shown that for a range of such methodologies, 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.[17] We therefore tested if NMe_4Cl could also be a suitable replacement for Ag_2CO_3 in the present methodology (Scheme 4). Gratifyingly, good yields of the desired products could be obtained without any optimization in a silver-free process.

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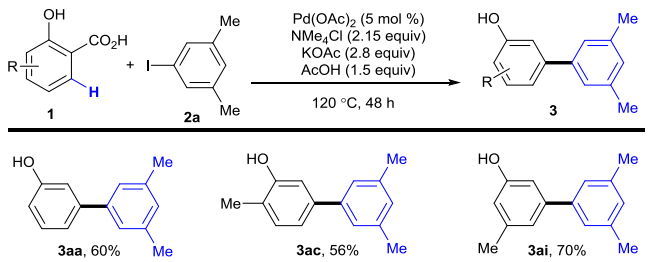
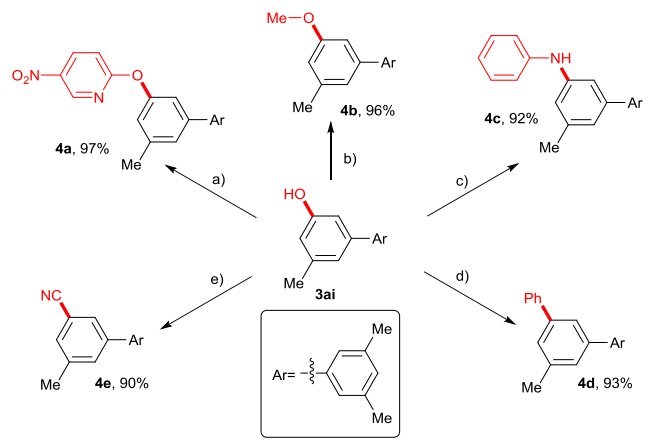


Scheme 4. Silver-free method for the tandem arylation / protodecarboxylation of salicylic acids.

Taking advantage of the myriad of methodologies available for the functionalization of (and at) aromatic C-O bonds, the meta-arylphenols here described are highly attractive intermediates towards the synthesis of meta-functionalized biaryls providing an efficient alternative to the most widely used Suzuki coupling. Thus, the meta-arylphenol **3ai** can be reacted with alkyl and aryl electrophiles in the presence of bases to form, in good yields, O-arylated **4a** and O-alkylated **4b**. Both of these motifs are common in natural products and pharmaceuticals. [18] On the other hand, transforming the OH into a triflate group, allowed a subsequent Buchwald-Hartwig amination[19] to **4c** and Suzuki[20] coupling to the unsymmetrical meta-triaryl **4d** to occur in 92% and 93% yields, respectively. Finally, a cyano group could be easily installed in 90% yield by preforming the tosylate of **3ai**, followed by Pd-catalyzed coupling.



Scheme 5. Transformations of **3ai** into a variety of meta-functionalized biaryls. Reagents and conditions: a) 2-chloro-5-nitropyridine, NaH, DMF, rt, 16 h; b) MeI, K_2CO_3, acetone, rt, 16 h; c) Tf_2O, Pyridine, DCM, rt, 1 h; Then, aniline, $Pd(OAc)_2$, BINAP, Cs_2CO_3, PhMe, 120 °C, 16 h; d) Tf_2O, Pyridine, DCM, rt, 1 h; Then, $PhB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, monoglyme/H_2O, 95 °C, 2.5 h; e) TsCl, Et_3N, MeCN, rt, 1 h; Then, $Pd(OAc)_2$, cm-Phos, $K_4[Fe(CN)_6]\bullet 3H_2O$, K_2CO_3, $^tBuOH/H_2O$, 80 °C, 18 h.

In conclusion, we have demonstrated that salicylic acids can undergo facile Pd-catalyzed tandem arylation/decarboxylation leading to meta-arylated phenols with complete regioselectivity. These products can be further transformed into a variety of meta-functionalized biaryls highlighting salicylic acids as attractive starting materials for the synthesis of these structural motifs.

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