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Radical C-H arylations of (hetero)arenes catalysed by gallic acid†

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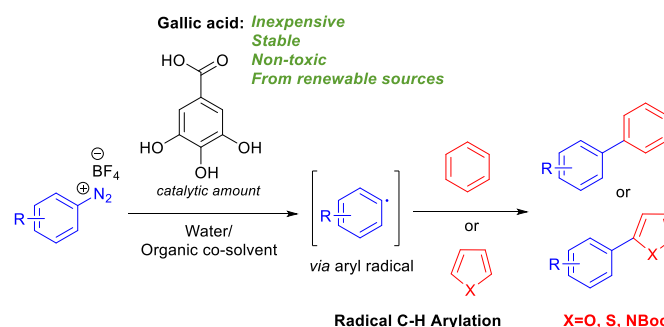
Gallic acid efficiently catalyses radical arylations in water-acetone at room temperature. This methodology proved to be versatile and scalable. Therefore it constitutes a greener alternative to arylations. Moreover, considering that gallic acid is an abundant vegetable tannin, this work also unleashes an alternative method for the reutilisation of bio-wastes.

Arylations are undoubtedly one of the most important synthetic methodologies nowadays. The reason seems obvious, taking into account the plethora of biaryl compounds which found applicability in many different fields from biomedicine to materials science.[1] At the same time, greener and more sustainable chemical methodologies are demanded in order to meet the increasing social and legal standards.[2] Regarding arylations, several metal-free processes have appeared recently, being particularly attractive the direct C-H arylations.[3] Indeed, the benefits of a metal-free methodology, are reinforced due to the fact that no double functionalization of the reacting points is required. Therefore less steps are necessary and less waste is generated. An interesting approach to such direct C-H arylations is the reduction of arenediazonium ions by a suitable reducing agent.[4,5,6,7,8,9,10] The aryl radical thus generated can then undergo a homolytic aromatic substitution.[11] Obviously, the optimal scenario would make use of a non-toxic reducing agent, from a renewable source. Gallic acid seems to fit perfectly well: It is an inexpensive antioxidant commonly used as food additive, which is present in considerable amounts in bio-waste such as grape pomace or oak bark.[12,13,14] Moreover, there is evidence that gallic acid derivatives can reduce arenediazonium ions, leading to an aryl radical.[15] Such solid starting point led us to develop a mild

radical arylation at room temperature promoted by catalytic amounts of gallic acid in sustainable solvents.

Scheme 1 Gallic acid as promoter of radical arylations

As a first attempt, 4-chlorobenzenediazonium tetrafluoroborate (0.5mmol) was treated with 10mol% of gallic acid in acetone (0.1M) in the presence of an excess of furan (5mmol) to avoid 2,5-diarylations (Table 1). The yield of arylated furan was disappointingly low (entry 1). However, when the reaction was submitted exactly in the same conditions but in acetone/water (3:1), then the yield obtained was much higher (entry 2). Indeed, Bravo et al. have already pointed out the relevance of some particular ionization forms of gallates in the reduction of arenediazonium ions.[15] Thus the role of water could be allowing such ionization equilibria. As expected, the same reaction with 1M aqueous solution of acetic acid led to poor yield (entry 3). On the other hand, by using 1M aqueous solution of $NaHCO_3$ instead of water, a more violent reaction led to no arylated compound (entry 4), but the reagents were decomposed into unidentified polar products.[16] Subsequently, a series of experiments were performed in order to optimize the solvent mixture. Reactions on water gave low yields (entry 5), and acetone proved to be the best among all the different co-solvents screened. Fortunately, the mixture acetone-water is an acceptable option from an environmental point of view.[17]

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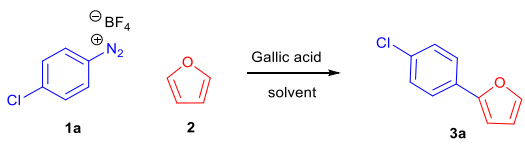‡ These authors contributed equally to this work.
†Electronic Supplementary Information (ESI) available: [Experimental details, characterization of the products and spectra]. See DOI: 10.1039/x0xx00000x

Modification of the amount of gallic acid was detrimental for the yield.[18] Importantly, when no gallic acid was employed, only traces of final compound were obtained (entry 14). Additionally, when the reaction was performed in the dark, yields were unchanged, revealing that light has no effect on the coupling (entry 15). Reducing the amount of furan to 2eq. led to slightly lower yields (entry 16).[19] And shorter reaction times were also counterproductive (entry 17). Worth to mention, other polyphenolic compounds were tested, and in all cases they were less efficient initiators than gallic acid.[20]

Table 1 Optimization studies[a]

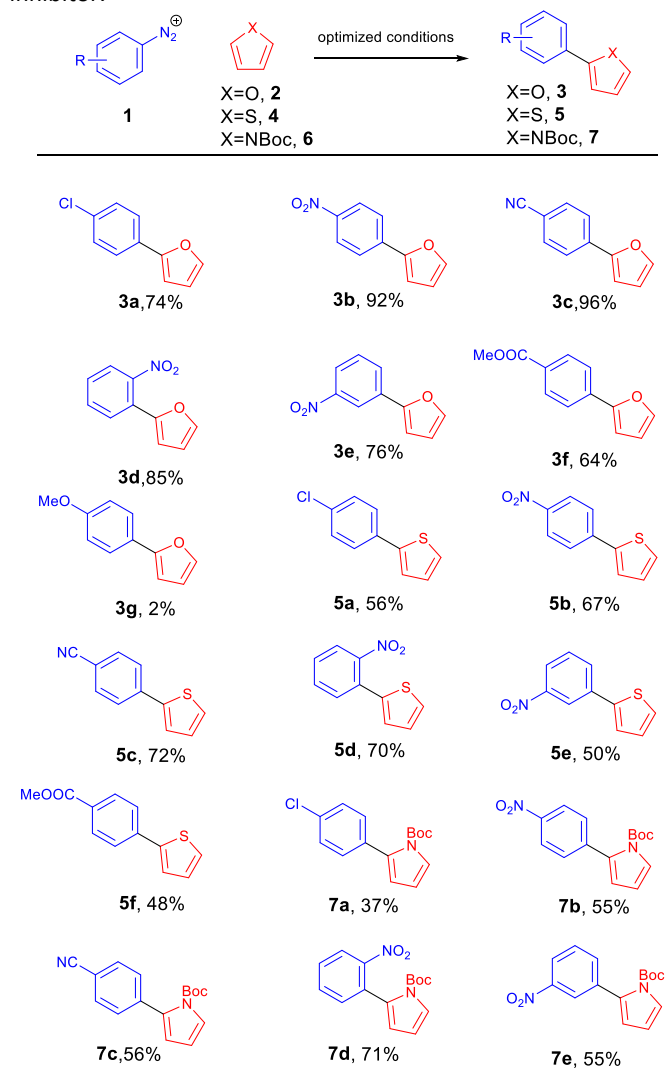| Entry	Solvent	Gallic acid[b]	Yield (%)[c]
1	Acetone	10 mol%	14
2	**Acetone/water (3:1)**	**10 mol%**	**74**
3	Acetone/AcOH$_{aq}$ (1M) (3:1)	10 mol%	27
4	Acetone/NaHCO$_3$ (1M) (3:1)	10 mol%	traces
5	Water	10 mol%	32
6	DMSO/water (3:1)	10 mol%	53
7	Acetonitrile/water (3:1)	10 mol%	44
8	DMF/water (3:1)	10 mol%	36
9	Ethanol/water (3:1)	10 mol%	41
10	Acetone/water (3:1)	20 mol%	55
11	Acetone/water (3:1)	5 mol%	66
12	Acetone/water (3:1)	2 mol%	48
13	Acetone/water (3:1)	1 mol%	45
14	Acetone/water (3:1)	0	traces
15	Acetone/water (3:1)	10 mol%	74[d]
16	Acetone/water (3:1)	10 mol%	69[e]
17	Acetone/water (3:1)	10 mol%	68[f]

[a] Reaction conditions: 0.5 mmol of diazonium salt, 5 mmol of furan, 4 ml of solvent, 12 h. [b] mol% respect to diazonium salt. [c] isolated yield. [d] In the dark. [e] With 1 mmol of furan. [f] Reaction time 2h.

Having optimized the reaction conditions, the scope of this arylation was examined. Firstly heteroarenes such as furan, thiophene and pyrroleBoc,[21] were reacted with different diazonium salts. The results are compiled in Scheme 2. As a general trend, furan gave better yield than the other two aromatic heterocycles. Indeed, in some cases excellent yields, up to 96%, were achieved. Moreover, it is clearly seen that electron withdrawing groups on the diazonium salts favour the reaction and improve the yields, while electron donating groups led to traces of product.[22]
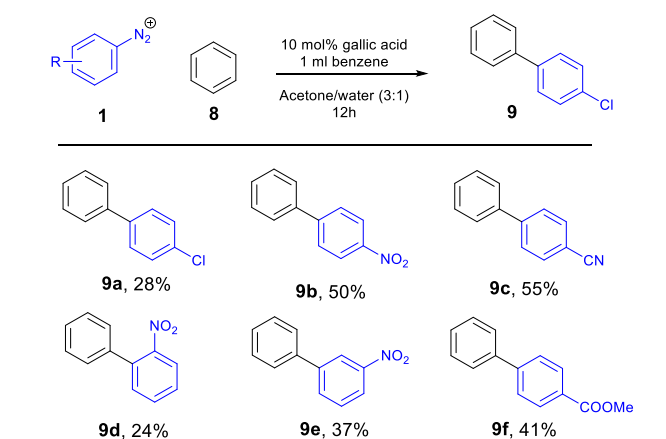
The arylation of non-activated benzene is usually considered a relatively complicated reaction. As Scheme 3 shows, the arylation of benzene gave biphenyl products in yields analogous to those obtained by other metal-free methodologies.[3]

As a further proof of the synthetic potential of this methodology, the arylation of thiophene with p-fluorobenzenediazonium tetrafluoroborate was tested in a gram scale (Scheme 4). Those precise reagents were chosen because the final product is a precursor of canagliflozin, a new kind of antidiabetes compound which acts as a selective SGLT2 inhibitor.[23]
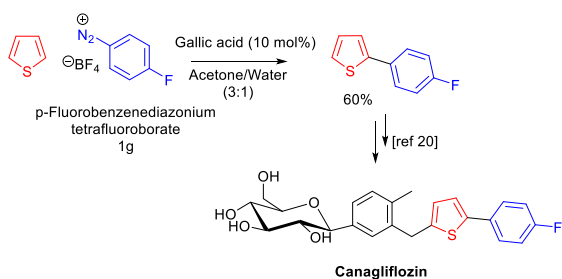

Scheme 2 Scope of the arylation of heteroarenes with various diazonium salts under the optimised conditions . The yields are given for the isolated products.
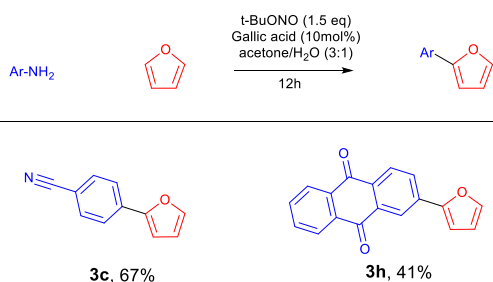

Scheme 3 Arylation of benzene with various diazonium salts. The yields are given for the isolated products.
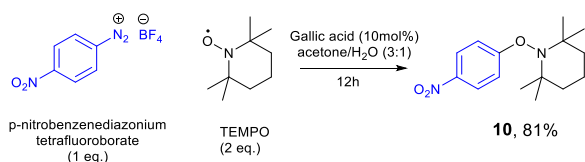
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Scheme 4 Gram-scale synthesis of canagliflozin precursor

As it is seen in Scheme 4, this scaled-up reaction proceeded nicely in a reasonably good yield. Indeed, the analogous palladium-based coupling, starts from 2-thienyl boronic acid,[24] which requires at least two step of synthesis with a moderate yield, and thus the global yield is lower than that presented herein. Additionally, a one pot procedure from the aniline, by generating the diazonium salt in situ, was assayed. Tert-butyl nitrite was added to a solution of the aniline and furan in acetone. Then, a solution of gallic acid (10 mol%) in water/acetone (1:1) mixture was added dropwise. As it is shown in Scheme 5, the yields obtained with such one pot methodology are considerable lower, and yet it is very useful for those anilines whose diazonium salts are unstable or difficult to isolate, like the anthraquinone derivative **3h**.
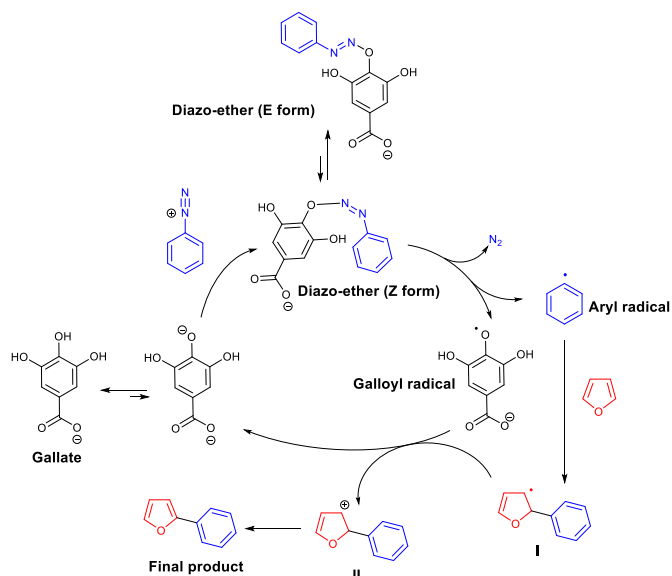

Scheme 5 One pot arylation from anilines.

In order to trap the hypothesized aryl radical generated in the reaction, we added 2,2,6,6-tetramethylpiperidine-1-oxy radical (TEMPO) to the reaction mixture (Scheme 6), and product **10** was successfully isolated in 81% yield.
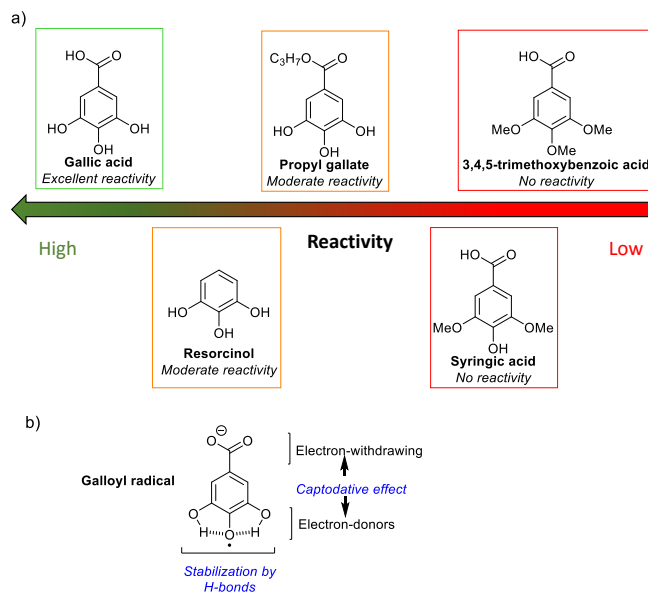

Scheme 6 Aryl-radical entrapment by TEMPO

While further mechanistic studies are required, a tentative mechanism is depicted in Scheme 7, inspired by previous reports. It is proposed that gallate undergoes a nucleophilic addition with the diazonium salt through the hydroxy group at the *para* position. Indeed, 3,4,5-trimethoxybenzoic acid presents no reactivity with diazonium salts, while resorcinol and

propyl gallate give moderate yields (Scheme 8a).[20] These control experiments imply that the carboxylate is not directly involved in the reactivity and prove the key role of a free hydroxy group at the *para* position. It is known that the radical at 4OH in galloyl radical is stabilized by two hydrogen bond interactions and by the captodative effect (Scheme 8b).[25] In fact, syringic acid, which lacks of H-bond stabilization, leads to just traces of product (Scheme 8a).

Scheme 7 Suggested mechanism

Scheme 8 (a) Modifications on gallate vary reactivity. (b) Stabilization of galloyl radical.

According to previous studies,[15,26] the kinetic product of the nucleophilic addition is the Z-diazo-ether, which can isomerize into the thermodynamic E form, or decompose homolytically to the corresponding aryl radical, nitrogen and galloyl radical. Stabilization of galloyl radical makes it a good homolytic leaving group, and therefore the homolytic degradation of Z-diazo-

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ether is more favourable than other competitive pathways. Analysis of the crude mixture by NMR and MS shows that gallic acid is present in the reaction mixture after full conversion has been reached,[20] thus proving its catalytic behaviour. Therefore, once the aryl radical undergoes a homolytic aromatic substitution giving radical **I**, the gallate ion is regenerated by means of the one electron oxidation of **I** to cation **II** mediated by galloyl radical.[27] After re-aromatization, the final product is obtained.

In summary, a greener and operationally simple direct C-H arylation has been developed: Catalytic amounts of gallic acid are able to promote a radical arylation of several heteroarenes and benzene with arenediazonium salts. This metal-free methodology is carried out at room temperature in acetone-water. Sustainability of this arylation is reinforced due to the fact that gallic acid is the simplest prototype of vegetable tannins and it is considerable abundant in several bio-waste. Actually, preliminary results prove that bio-waste rich in gallic acid such as grape pomace can also promote this arylation.[20] Therefore, the methodology herein described not only offers a greener approach to arylations by using an inexpensive and underexploited reagent in organic synthesis such as gallic acid; it also paves the way for novel methods of waste utilization and valorisation.

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