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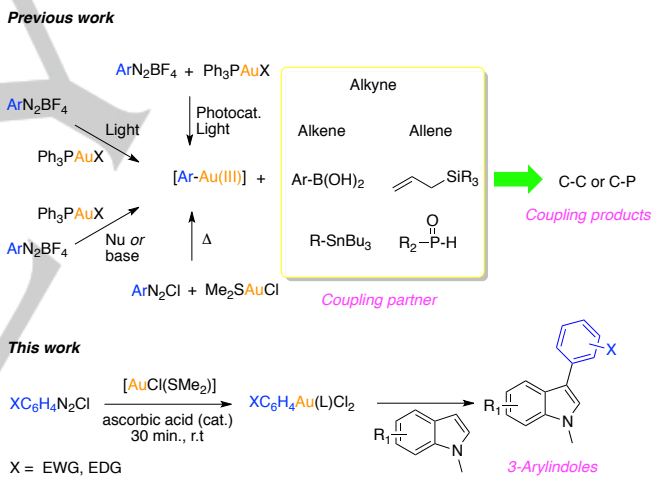
Ascorbic Acid as an Aryl Radical Inducer in the Gold Mediated Arylation of Indoles with Aryldiazonium Chlorides

Ignacio Medina-Mercado,[a] Eric Omar Asomoza-Solís,[a] Eduardo Martínez-González,[b] Victor Manuel Ugalde-Saldívar,[b] Lydia Gabriela Ledesma-Olvera,[a] José Enrique Barquera-Lozada,[a] Virginia Gómez-Vidales,[a] Joaquín Barroso-Flores, [a],[c] Bernardo A. Frontana-Uribe, [a],[c] and Susana Porcel*[a]

Abstract: In recent years has increased the interest in developing protocols that facilitate the oxidative addition of gold, for getting access to mild cross-coupling processes mediated by this metal. In this sense, we report herein, that ascorbic acid, a natural and readily accessible antioxidant, is able to accelerate the oxidative addition of aryldiazoniun chlorides onto Au(I). The arylAu(III) species generated in this way, have been used for preparing 3-arylindoles in a *one-pot* protocol starting from anilines and *para*- *meta*- and *ortho*- substituted aryldiazonium chlorides. The mechanism underlying the oxidative addition have been accurately examined through EPR analyses, cyclic voltammetry and DFT calculations. Interestingly, we have found that in this protocol, the chloride atom induces the Au(II)/Au(III) oxidation step.

Introduction

The largely proved proficiency of gold to activate C-C multiple bonds toward nucleophilic attack,[1] is being complemented with the ability of this metal to participate in cross-coupling reactions, under certain conditions. Initial endeavours employed stoichiometric amounts of strong oxidants to realize Au(I)/Au(III) oxidation,[2] but soon appeared appealing alternatives based on the development of suitable ligands that activate gold,[3] or that utilize reactive electrophiles. In the latter case, diazonium salts have been the electrophiles of preference.[4] Initial reports dealing with diazonium salts, performed the Au(I) oxidation via two single electron oxidation mechanism, mediated by a photocatalyst under irradiation. More recently, some alternative protocols that avoid the use of the photocatalyst were developed. In these cases, the Au(I) oxidation is promoted by simple irradiation, thermally or by a base, but the mechanism underlying remains elusive.[5] In particular, our group showed that aryldiazonium chlorides are able to oxidize Au(I) complexes under thermal conditions.[6] In order to extend the application of this chemistry, and shed light on the operating mechanism, we decided to explore the arylation of indoles. Gold has been used before to address this transformation, employing alkynyliodonium salts, arylsilanes or electrondeficient arenes as coupling partners.[7,8] The examples mentioned show that the aryl moiety is transferred to the C3 position, thus complementing the performance of palladium which usually lead to 2-arylindoles.[9,10]



Scheme 1. Modes of aryldiazonium salts activation for the oxidation of Au(I) in cross-coupling processes.

Results and Discussion

We started our investigation by examining the arylation of 1-methylindole (**1a**) with *p*-nitroaniline in a *one-pot* sequence (Table 1). To this end we prepared *in situ* 4-NO_2-$C_6H_4N_2Cl$, and generated the required arylAu(III)complex, following the protocol previously reported by us.[6a] Next, we added **1a** and let evolved the reaction at rt for 18 h. After this time, 1-methyl-3-(2-nitrophenyl)-1*H*-indole (**1b**) was isolated in 69% yield (entry 1) over three steps (diazotization, oxidative addition and arylation). The position of the new aryl moiety was corroborated by comparison with NMR reported data,[11] and it is in accordance with that expected for Au(III).[7,12] In order to improve the yield, we examined the effect of using Ph_3P as a ligand (entry 2), and the effect of increasing the temperature up to 50 °C (entry 3), but the

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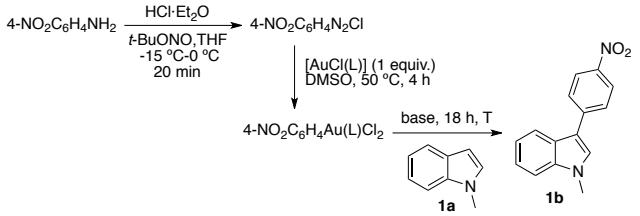
yields turned lower. Then we analyzed the influence of adding bases such as Li_2CO_3 or dtbpy (entries 5 and 6). In this case, the yields remained in the same order, pointing that indole deprotonation is not a rate limiting step of the reaction.

Table 1. Optimization of the arylation of 1-methylindole.



Entry[a]	L	base	T[c]	Yield [%][b]
1	SMe_2	-	25 °C	69
2	PPh_3	-	25 °C	60
3	SMe_2	-	50 °C	63
4	PPh_3	Li_2CO_3	25 °C	67
5	SMe_2	dtbpy	50 °C	68

[a] [AuCl(L)] = 0.085 mmol/ml, [1-methylindole]= 0.085 mmol/ml. [b] isolated yield.

In spite that the oxidative addition step is done in the absence of radical inducers, in previous works we got some insights about the participation of aryl radicals.[6b] This time in order to accelerate the oxidative addition, we decided to study the effect of adding some natural reducing agents such as ascorbic acid or gallic acid. Accurate investigations from the groups of Reszka and Bravo-Diaz, have stablished that both compounds are capable of reducing aryldiazonium ions, producing aryl radicals.[13] Moreover, they have already been employed in metal-free arylations of hetero(arenes),[14] and in the coupling of terminal alkynes with diazonium salts.[15] Nevertheless, to the best of our knowledge, their role as radical inducers in the oxidative addition of gold with arenediazonium salts, have not been explored before.

In this sense, we inspected the reaction of 4-NO_2-$C_6H_4N_2Cl$ with [$AuCl(SMe_2)$] in the presence of ascorbic acid (10 mol%) or gallic acid (10 mol%) at rt. Immediate gas evolution was observed in both experiments. A ^{1}H NMR control after 1 h, revealed that at this point the diazonium salt was completely consumed in both cases (Fig 1b,c). The spectrum of the sample containing ascorbic acid, showed a main compound consisting of two doublets [7.45 (d) and 7.94 (d) ppm] (Fig 1b). These signals were also present in the spectrum of the sample containing gallic acid, but along with a variety of signals of similar intensity (Fig 1c). A second experiment with ascorbic acid, showed that the diazonium salt was consumed after 30 min (Fig 1d). This finding excited us, since in the absence of ascorbic acid, it was necessary to heat 4 h at 50 °C to achieve the complete consumption of the diazonium salt,[6a] (in Fig 1f is shown the evolution of the reaction after 2.5 h in the absence of radical inducers at r.t.). Analyzing the crude mixture by mass spectrometry (FAB, [M +H]), we could identify a peak corresponding to [4-$NO_2C_6H_4AuCl_2$ + H]: 391(m/z). For comparative reasons we also examined the reaction of 4-NO_2-$C_6H_4N_2BF_4$ with [$AuCl(SMe_2)$] in the presence of ascorbic acid. However, with this counteranion, the diazonium salt was consumed after 3 h, and needed a higher amount of ascorbic acid (20 mol%) (Fig 1e).

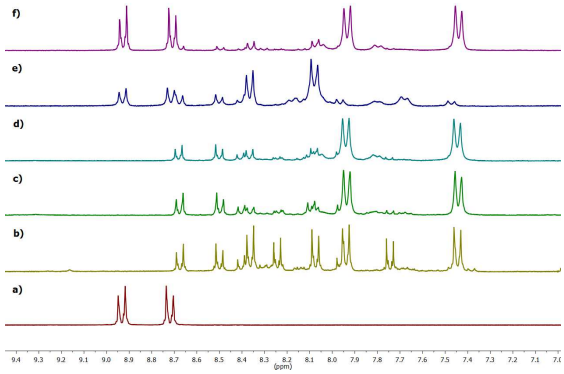
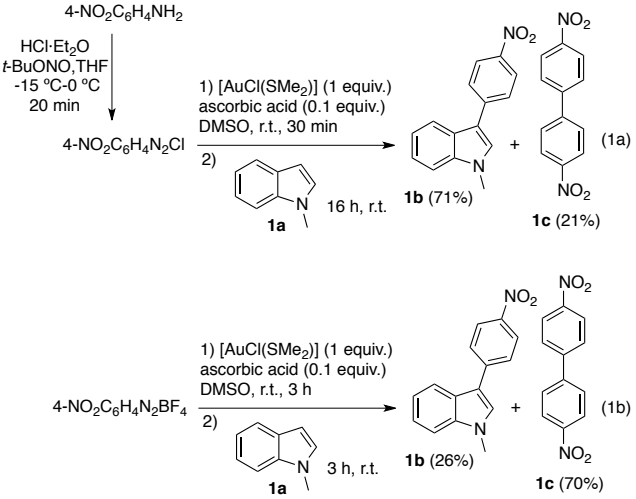


Figure 1. Screening of the reaction of 4-$NO_2C_6H_4N_2Cl$ with [$AuCl(SMe_2)$] by ^{1}H NMR: b) in the presence of gallic acid (10 mol%), after 1 h.; c) in the presence of L-ascorbic acid (10 mol%) after 1 h; d) in the presence of L-ascorbic acid (10 mol%), after 30 min; f) in the absence of radical inducers after 2.5 h. e) Monitoring of the reaction of 4-$NO_2C_6H_4N_2BF_4$ with [$AuCl(SMe_2)$] in the presence of L-ascorbic acid (20 mol%) after 3 h.

With these results in hand, we decided to test the *one-pot* arylation protocol of *N*-methylindole, adding ascorbic acid in the oxidative addition step. As displayed on Scheme 2a, when 4-NO_2-$C_6H_4N_2Cl$ was used as starting material, **1b** was formed in 71% yield along with 4,4'-dinitrobiphenyl (**1c**) in 21%. This experiment pleasantly evidenced, that ascorbic acid accelerates the formation of the arylAu(III) intermediate, without interfering in the arylation step. On the other hand, when 4-NO_2-$C_6H_4N_2BF_4$ was used as starting material, **1b** was isolated in only 26% yield, along with **1c** in 70% yield (Scheme 2b). The latter shows that the nature of the counteranion is an important factor, impacting on the amount of the homocoupling process.[16]



Scheme 2. Effect of adding ascorbic acid to the arylation protocol.

According to the above points, we chose 4-NO_2-$C_6H_4N_2Cl$ to examine the scope of the arylation reaction over a variety of indole

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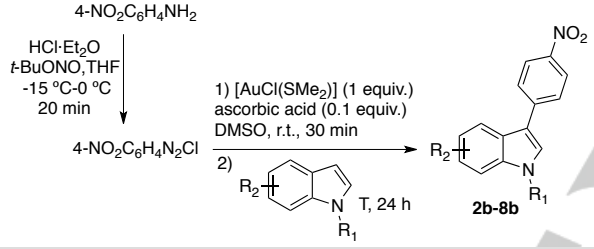
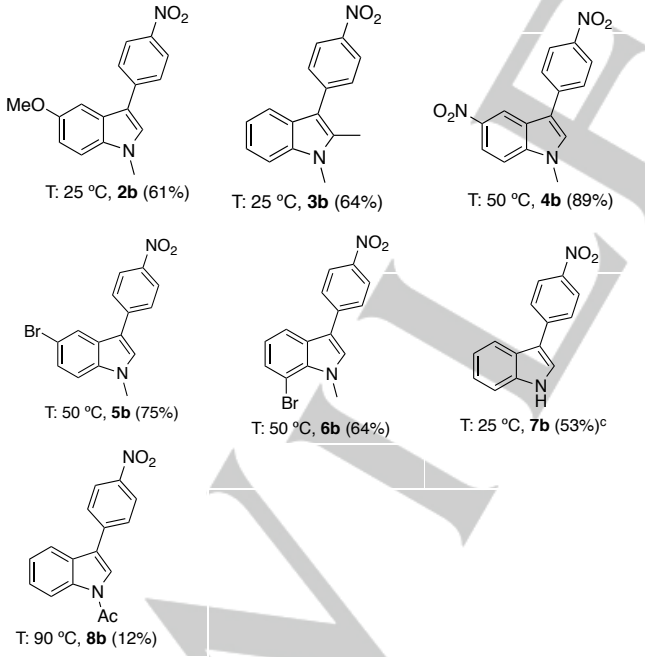
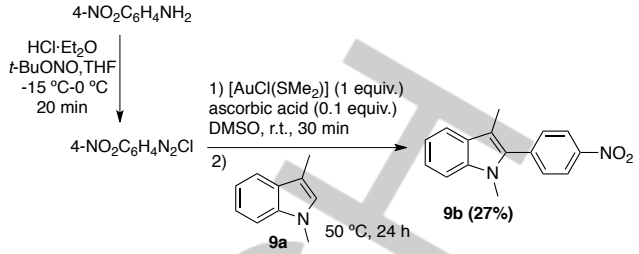
derivatives (Table 2). Indoles substituted with electron-donor substituents like **2a** (5-OMe) and **3a** (2-Me), reacted at r.t. in yields of 61% and 64% respectively. Comparatively, indoles bearing electron-withdrawing substituents such as 5-NO_2, 5-Br and 7-Br (**4a-6a**), required an increase of the temperature up to 50 °C for accelerating the arylation step, what is otherwise expected for an electrophilic aromatic substitution onto Au(III). Under these conditions, the corresponding arylated indoles (**4b-6b**) were obtained in 64-89 % yield. We also studied the effect of replacing the methyl at nitrogen by a TBDPS or an acetyl group. In the former case (**7a**), the free (*NH*)-indole derivative **7b** was recovered in 52%, whereas for the latter (**8a**), the reactivity diminished significantly, **8b** being obtained in low yield (12%). Interestingly, the group of Gaunt reported that the arylation of **8a** with diaryl-iodine(III) reagents catalyzed by Cu(II),[10] delivers the C2 arylated regioisomer, that it is not observed in our case. In order to study the possibility of forcing the arylation at C2, we tested the reactivity of 1,3-dimethylindole (Scheme 3). To our delight the arylation took place, but in only 27% yield, what it is in accordance with the less nucleophilic character of C2.

Table 2. Scope of the arylation over various indole derivatives.





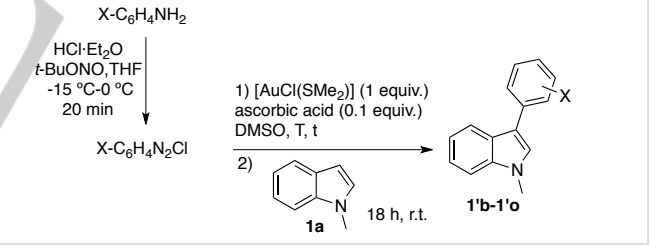
[a] [AuCl(L)] = 0.085 mmol/mL [Indole]= 0.085 mmol/mL. [b] isolated yield. [c] R_1= TBDPS for **7a**.

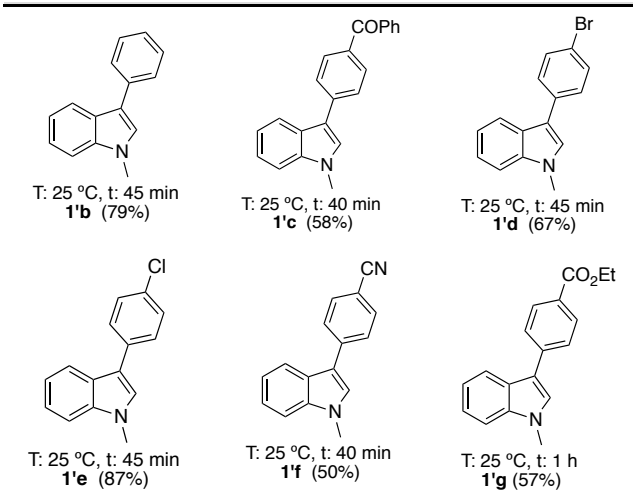


Scheme 3. Arylation of 1,3-dimethylindole.

Once examined the scope of the reaction over the indole scaffold, we studied the scope over a variety of aryldiazonium chlorides (Table 3). Benzenediazonium chloride furnished 1-methyl-3-phenyl-1*H*-indole in 79%. Aryldiazonium chlorides bearing a substituent at the *para* position, reacted in yields ranging from 53% to 87%. Special attention required 4-MeO-$C_6H_4N_2Cl$, which showed a marked reluctance to undergo the oxidative addition. Under our previously reported thermal conditions, this aryldiazonium chloride required heating at 50 °C for 48 h to complete the oxidative addition step.[6a] Adding ascorbic acid, this step finished in 12 h, and the corresponding arylated compound was obtained in 53%. 3-Substituted aryldiazonium chlorides reacted in yields from 40-84%, the lower yield corresponding to 3-Me and the best to 3-Cl. Finally, 2-substituted aryldiazonium chlorides (2-NO_2 and 2-Cl) reacted in 37% and 27% respectively, probably due to steric reasons. It is important to note that under the thermal conditions previously reported by us, both 2- and 3-substituted aryldiazonium salts failed to react.[6b]

Table 3. Scope of the arylation over various aryldiazonium chlorides.





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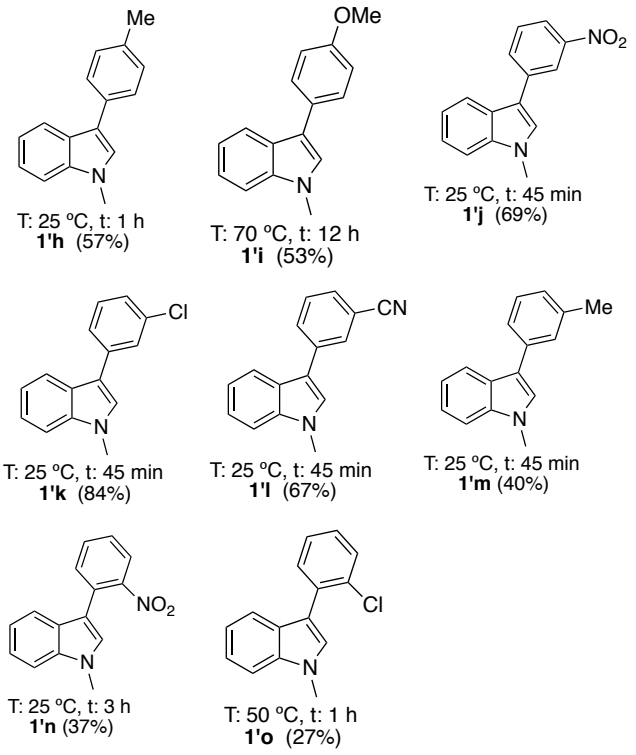

[a] [AuCl(L)] = 0.085 mmol/ml, [**1a**]= 0.085 mmol/ml. [b] isolated yield.

Having optimized and inspected the scope of the arylation protocol, we got interest in studying the mechanism of the oxidative addition step in more details. First, we wanted to corroborate that ascorbic acid induces the formation of aryl radicals employing EPR. Earlier, Reszka and coworkers used the spin trapping technique to this end.[13a] With this in mind, we dissolved freshly prepared 4-nitro-benzenediazonium chloride in DMSO, and added ascorbic acid (0. 1 equiv.) and 5,5-dimethyl-1-pyrroline N-oxide (DMPO, 0.02 equiv.). The EPR spectrum of the mixture is displayed on Figure 2A. Two set of signals were observed, a sextuplet and a triplet. With the time (25 min) the sextuplet evolved to the triplet. The sextuplet signal is consistent with a carbon-centered radical and corresponds to the DMPO/4-NO_2-C_6H_4· radical adduct (a_N = 14.3 G, a_H = 20.9 G). The gradual disappearance of the sextuplet and the increase in the intensity of the triplet signal suggests possible quenching or degradation of the spin-adduct (DMPO/4-NO_2-C_6H_4·), detecting a radical specie of open ring with g=2.0056 and a_N=13.9 G.[17] In the absence of ascorbic acid (Figure 2B), the same set of signals is observed, but the sextuplet in a lower intensity, thus confirming that ascorbic acid induces the formation of the 4-NO_2-C_6H_4· aryl radical. As DMSO is a source of methyl radicals, we also examined the EPR spectrum of a solution containing only ascorbic acid and DMPO (Supporting info. Figure S6). In this case it was observed a sextuplet consistent with the presence of a carbon-centered radical but with slightly different values of a_N and a_H (a_N = 14.8 G, a_H = 20.0 G). Additionally, this sextuplet was stable and did not evolve to a triplet. These evidences support that the observed sextuplet in the presence of 4-nitro-benzenediazonium chloride, corresponds to a DMPO/4-NO_2-C_6H_4· adduct and not to a DMPO/CH_3·adduct.

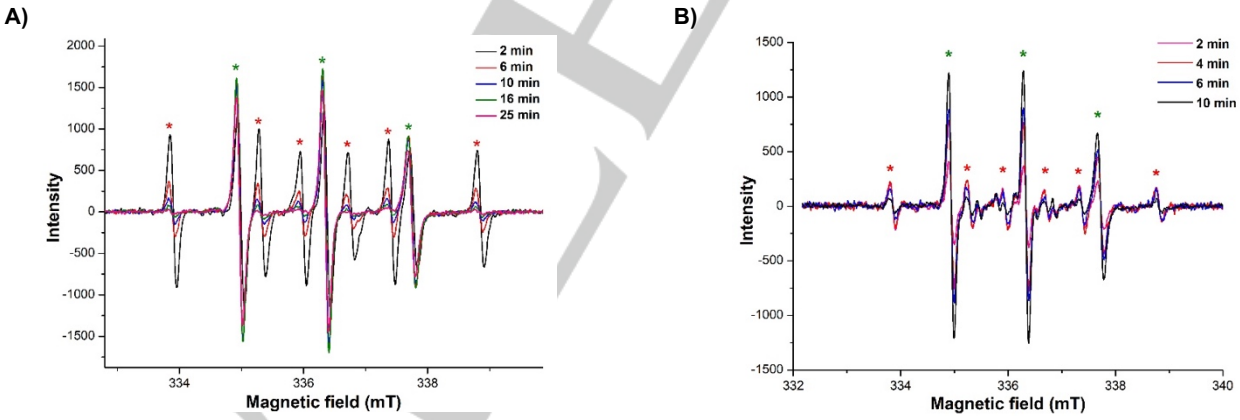

Figure 2. A: EPR spectrum of *p*$NO_2C_6H_4N_2Cl$, ascorbic acid and DMPO. B: EPR spectrum of *p*$NO_2C_6H_4N_2Cl$, and DMPO

Next, we underwent some electrochemical studies to shed light on some aspects, using DMSO as solvent and Bu_4NPF_6 (0.1 mol L^{-1}) as the electrolyte in all measurements. First, we were intrigued by the effect of the substituent and the counteranion over the reduction potential of the diazonium salts. For this reason, we analyzed the cyclic voltammograms of 4-MeO-$C_6H_4N_2BF_4$, $C_6H_5N_2BF_4$, 4-NO_2-C_6H_4-N_2BF_4, 4-NO_2-C_6H_4-N_2Cl and 4-MeO-$C_6H_4N_2Cl$ (Fig 3):

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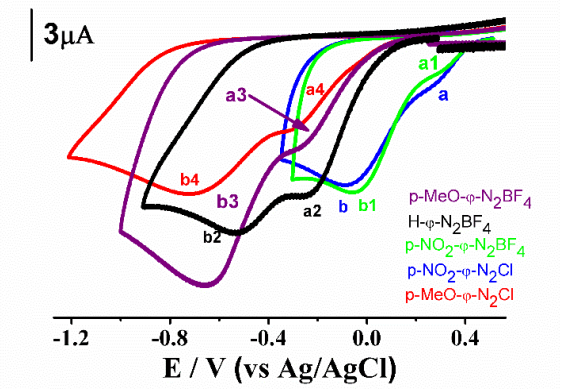
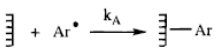


Figure 3. Cyclic voltammograms of 4-MeO-C_6H_4-N_2BF_4, C_6H_5-N_2BF_4, 4-NO_2-C_6H_4-N_2BF_4, 4-NO_2-C_6H_4-N_2Cl, and 4-MeO-C_6H_4-N_2Cl in DMSO (5 mmol L^{-1}) using Bu_4NPF_6 (0.1 mol L^{-1}) as electrolyte. Scan rate: 0.1 V s^{-1}.

All the compounds examined exhibited a typical CV behavior for reduction reactions of diazonium salt solutions at a fully polished GC electrode.[18] The two irreversible waves detected (denoted by **a** and **b**), are consistent with one-electron reduction reactions of electroactive molecules, that form aryl radicals, which covalently attached to the electrode. The set of chemical equations occurring at the electrodes are depicted in Scheme 4:

X-C_6H_4-N_2 + e^- → X-$C_6H_4^\bullet$ + N_2 **E1**, α (transfer coeff.) **Eq. 1**



Eq. 2

Scheme 4. Reduction reactions at electrodes

As it has been previously demonstrated by Downard,[18c] this binding process involves the formation of multilayer films at two different thermodynamic conditions: the first grafted molecules directly interact with GC, being reduced at less negative potential values (peak **a**) than those transformed when the electrode surface is fully modified (peak **b**).

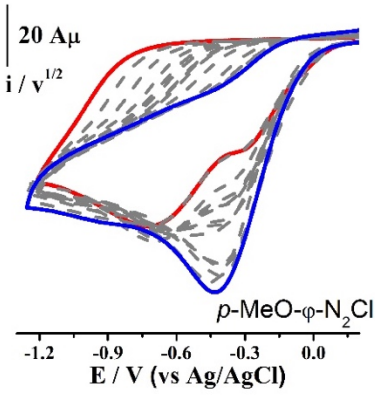
In Table 4 are presented the values of the diazonium salts reduction potentials at unmodified (**E1**, peak **a**) and modified (**E2**, peak **b**) GC electrode. As can be noted, these values are modulated by the presence of the different substituents according to the Hammett´s model.[19] Thus 4-NO_2-C_6H_4-N_2BF_4, and 4-NO_2-C_6H_4-N_2Cl containing the electro-withdrawing group -NO_2 are reduced at lower potentials than 4-MeO-$C_6H_4N_2BF_4$, and 4-MeO-$C_6H_4N_2Cl$ (entries 3 and 4 *vs* entries 1 and 5), whereas $C_6H_5N_2BF_4$ is reduced at middle values (entry 2). From a thermodynamic viewpoint, this explains that the NO_2 group favors the generation of aryl radicals (Eq. 1) and its adsorption (Eq. 2), because of its high affinity for receiving electrons. On the other hand, the nature of the counter anion that interacts with the diazo group, does not affect significantly the reduction potential values (entries 1 *vs* 5, and 3 *vs* 4).

Table 4. Experimental values of reduction potential of diazonium salts to produce aryl radicals (Eq.1). The adsorptive peak values at unmodified (**E1**) and modified (**E2**) GC electrode are presented.

Entry	Substrate	**E1** (V) (peak **a**)	**E2** (V) (peak **b**)
1	4-MeO-$C_6H_4N_2BF_4$	-0.224	-0.652
2	$C_6H_5N_2BF_4$	-0.149	-0.502
3	4-NO_2-C_6H_4-N_2BF_4	0.333	-0.050
4	4-NO_2-C_6H_4-N_2Cl	0.296	-0.087
5	4-MeO-$C_6H_4N_2Cl$	-0.276	-0.734

In order to elucidate other molecular effects controlling the reactivity of the diazonium salts upon receiving electrons, we undertook a kinetic analysis strategy, based on estimations of the transfer coefficient α (Eq. 1). For dissociative electron transfer reactions, such as those described by Eq. 1, α values can be estimated from the peak width data of voltammograms obtained at different scan rates (Fig. 4) using Equation 3 (where E_p is the reduction potential peak of the system).[18b,20]

$$\alpha = \frac{RT}{F}\frac{1.85}{E_{p/2} - E_p} \qquad (Eq.\,3)$$



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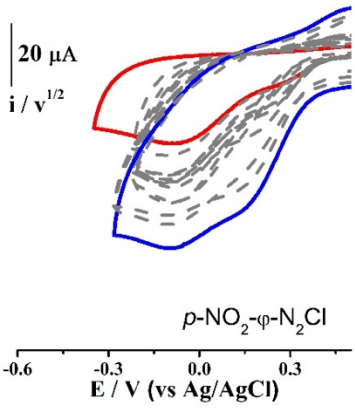

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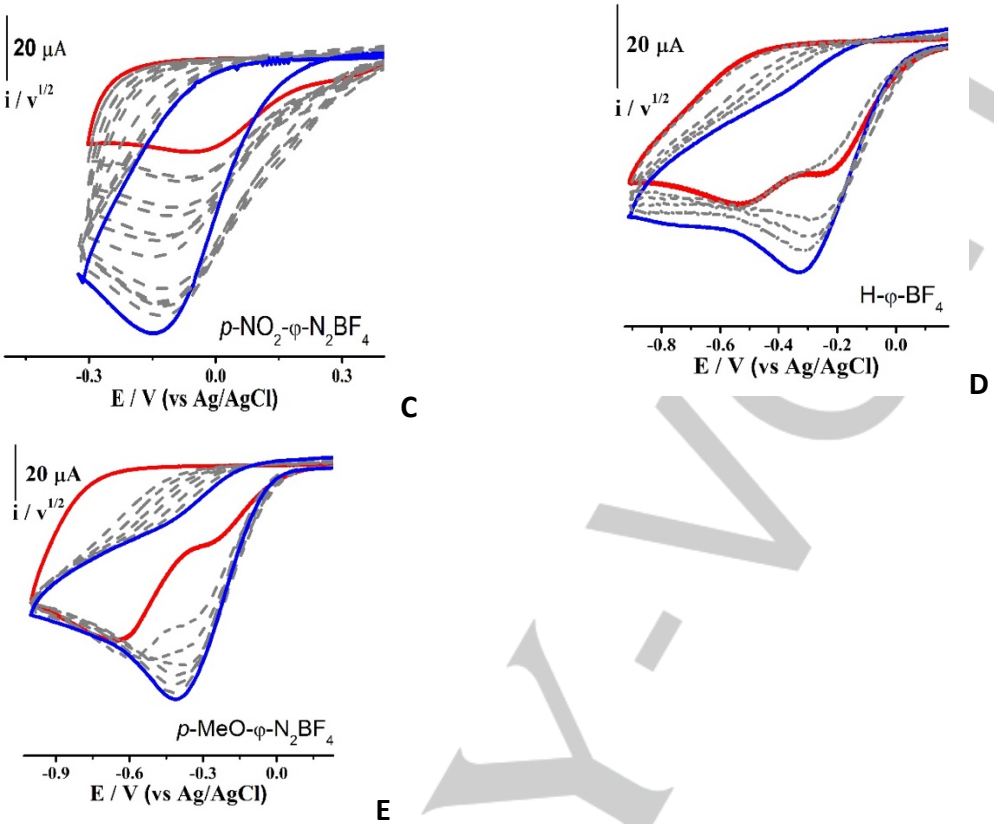

Figure 4. Cyclic voltammograms of 4-MeO-C_6H_4-N_2Cl (A), 4-NO_2-C_6H_4-N_2Cl (B), 4-NO_2-C_6H_4-N_2BF_4 (C), C_6H_5-N_2BF_4 (D), and 4-MeO-C_6H_4-N_2BF_4 (E) in DMSO (5 mmol L^{-1}), using Bu_4NPF_6 (0.1 mol L^{-1}) as electrolyte, at differents scan rates (red line, 0.1 V s^{-1}.; blue line, 10 V s^{-1}). Current is in Amperes and normalized /$v^{1/2}$

Upon analyzing the cyclic voltammograms of 4-MeO-$C_6H_4N_2BF_4$, $C_6H_5N_2BF_4$, 4-NO_2-C_6H_4-N_2BF_4, 4-NO_2-C_6H_4-N_2Cl and 4-MeO-$C_6H_4N_2Cl$, at different scan rates (Fig 4), we note that an increase in the scan rate enhances the intensity of peak **a** at the expense of peak **b**, which tends to decrease. Such behavior occurs because under these conditions the amount of diffusing material is small relative to the amount of material reacting near and directly with GC electrode.[18c,21] For this reason, and in order to analyze the species interacting directly with the GC electrode, α values were estimated at peak **a,** from responses obtained at high scan rates, except in the case of compounds containing nitro groups on their structures, because in these cases the first wave (peak **a,** Figs. 3 and 4) is not well defined even at high scan rates (10 V s^{-1}). The resulting transfer coefficient calculated from Eq. 3 are: ~ 0.20 for 4-MeO-$C_6H_4N_2BF_4$, ~ 0.26 for $C_6H_5N_2BF_4$ and ~ 0.23 for 4-MeO-$C_6H_4N_2Cl$. These values are extremely small to consider a sequential mechanism (determined by α > 0.5)[21] in the reactions occurring at the electrode upon reducing diazonium salts, therefore a concerted pathway is proposed, what implies that the aryl-azo bond breaking is extremely fast and exceeds the electron transfer rate.

Next, we analyzed the effect of adding ascorbic acid to a solution of 4-$NO_2C_6H_4N_2BF_4$ as model diazonium salt (Fig 5). The addition of 0.1 equivalent of ascorbic acid to a solution of 4-$NO_2C_6H_4N_2BF_4$, produced the disappearance of the reduction potentials of this diazonium salt (peaks **a** and **b)**, after 1 h. This show that under these conditions, there are no longer molecules to be reduced, since they were previously reduced by ascorbic acid, thus confirming its reducing power.

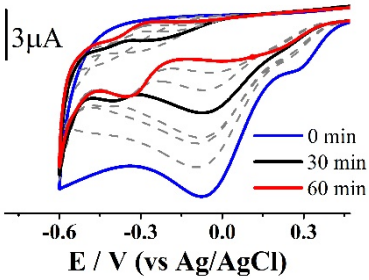

Fig. 5. CVs for reduction reactions of of 4-$NO_2C_6H_4N_2BF_4$ (5 mmol L^{-1}) in the absence and in the presence of ascorbic acid (0.5 mmol L^{-1}) as a function of time, using DMSO as solvent, and Bu_4NPF_6 (0.1 mol L^{-1}) as electrolyte. Scan rate: 0.1 V s^{-1}.

To continue with the electrochemical study of the system, as no significant effects of the counterion on the reactivity and stability of electrogenerated aryl radicals were detected, we were curious to examine if the presence of chloride ions had an impact on the oxidation of the gold atom. For this purpose we first studied the voltammetric oxidation of the gold compound [AuCl(SMe_2)]. However, no signals were detected upon scanning in a positive direction (Fig. S8). Most likely the oxidation process Au(I)/Au(III) occurs at higher potential values

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than those detected for solvent oxidation reactions. In contrast, by adding solutions of different concentrations of Et_4NCl (as source of chloride ions) to a solution of [$AuCl(SMe_2)$], appeared two oxidation waves at positive potential values (aprox. 1.1V and 1.3 V, Fig. 6b). The peak closest to the solvent oxidation belong to the oxidation process of chloride ions, as was corroborated upon reducing Et_4NCl in the absence of [$AuCl(SMe_2)$] (Fig. 6a). On the other hand, the peak at 1.1 V can be related to a Au(I)/Au(III) oxidation process.[22] In the presence of Et_4NCl it is favored the formation of a stable Au(III) specie, what modifies the redox properties of the couple Au(I)/Au(III), and depends upon the concentration of the chloride ions in the solution. This evidence is in line with the experimental observation that the oxidative addition of [$AuCl(SMe_2)$] is faster with 4-NO_2-$C_6H_4N_2Cl$ than with 4-$NO_2C_6H_4N_2BF_4$.

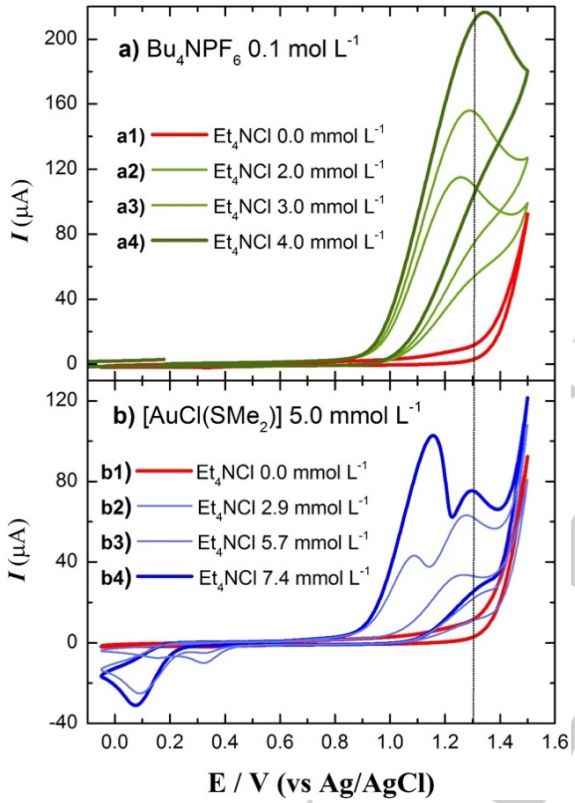

Fig.6. a) CVs of oxidation reactions of Et_4NCl using DMSO as solvent and Bu_4NPF_6 as electrolyte. Scan rate: 0.1 V s^{-1}; b) CVs of oxidation reactions of solutions of [$AuCl(SMe_2)$] in the presence of increasing concentrations of Et_4NCl, using DMSO as solvent and Bu_4NPF_6 as electrolyte. Scan rate: 0.1 V s^{-1}.

At this point we had no evidence of the specie ultimately responsible for the oxidation of gold. The addition of an aryl radical specie onto Au(I) to deliver an arylAu(II) intermediate, has been calculated to be a very favourable pathway,[22] however, in the most part of the reports dealing with diazonium salts, the single electron oxidation Au(II)/Au(III), is proposed to arise from a photoredox catalyst. Under our experimental conditions, this single electron oxidation could occur by direct reaction of the transient arylAu(II) complex with the starting aryldiazonium salt.[23] In order to ascertain this hypothesis, we decided to examine the energy profile of the reaction of the aryl radical 4-NO_2-C_6H_4· with [$AuCl(DMSO)$] by DFT calculations at the M06/Def2TZVP level of theory (See SupInfo for details). As shown in Scheme 4, the addition of 4-NO_2-C_6H_4· to [$AuCl(DMSO)$] led to the T-shape gold complex 4-NO_2-C_6H_4AuCl. This step is exogernic by 5.6 kcal/mol and proceeds without activation barrier. An energy scan of the Au---C distance was performed. The energy continuously decreases until it reaches the minimum of the T-shape Au(II) complex. Subsequently 4-NO_2-C_6H_4AuCl reacts with the starting aryldiazonium which unexpectedly evolved transferring a chloride atom onto the Au(II) center, to furnish 4-NO_2-$C_6H_4AuCl_2$ and an aryldiazonium radical. This step is exorgernic by -19.7 kcal/mol and surprisingly proceeds also without activation barrier. Again, an energy scan of the Au---Cl distance produce a potential energy surface where the energy decreases if the Au---Cl distance decreases as well. It seems to be triggered by the high affinity of the chloride atom for the Au(II) center. A molecular orbital (MO) analysis of the Au---Cl distance PES shows that the oxidation of the Au(II) to Au(III) occurs only when the Cl atom is very close to the Au atom. During most of the approach of the Cl to Au(II) the single occupied molecular orbital (SOMO) is mainly around the metal and only when the Cl is at ~2.5 Å from Au(II) the oxidation takes place (Fig 7). These results evidence that the role of the chloride ion is non innocent and are in line with the electrochemical studies, which pointed that the oxidation of gold is favoured in the presence of chloride ions that can access the coordination sphere of the metal. Finally, the aryldiazonium radical breaks into the initial aryl radical and nitrogen. This last step has a transition state (TS) with a relative energy of 7.3 kcal/mol. According to the aforementioned, the oxidative addition of 4-NO_2-C_6H_4· to [$AuCl(DMSO)$] in the presence of chloride ions, is a very favoured process that proceeds with only one energy barrier, which TS has an energy of 7.3 kcal/mol. For comparative reasons we also calculated the reaction path when the substituent at the aryl ring is OMe. The reaction path is very similar, the energy of the TS only increases to 9.5 kcal/mol. That means that independently of the nature of the substituent at the aryl ring, the oxidative addition of aryl radicals to [$AuCl(DMSO)$] in the presence of chloride ions is very favoured energetically. Interestingly, the radical adduct **3** is significantly more stable for NO_2 than for OMe (6.8 kcal/mol). This could be due to electronwithdrawing nature of the NO_2 group, which allows a better delocalization of the unpaired electron.

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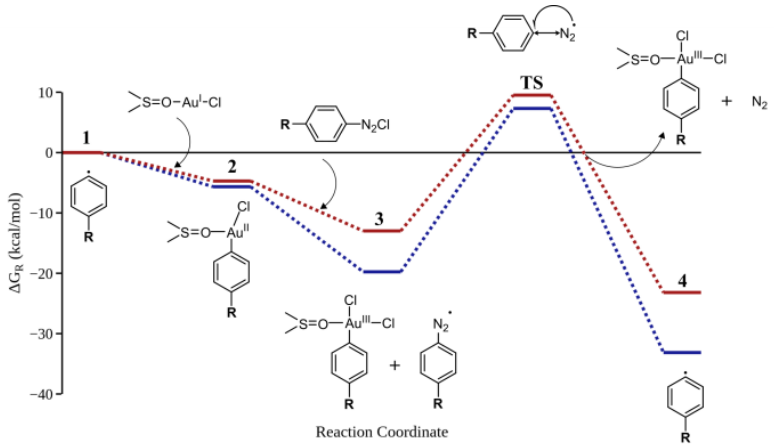

Scheme 4. Reaction path of the radical propagation mechanism of 4-NO_2-C_6H_4· (blue) and 4-OMe-C_6H_4· (red).

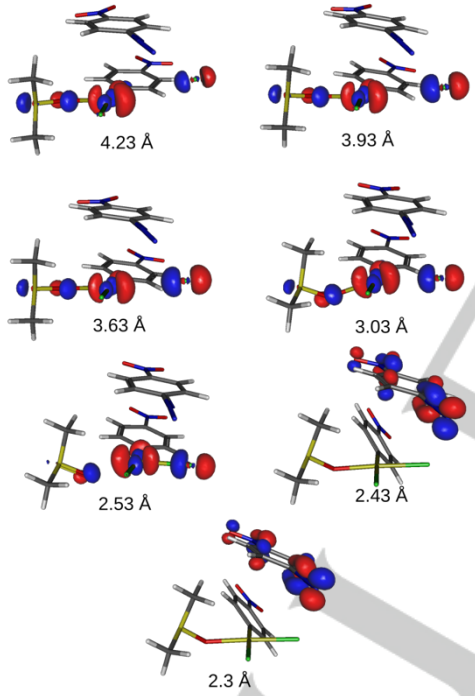

Fig. 7. SOMOs of the [4-NO_2-C_6H_4AuCl][4-NO_2-$C_6H_4N_2$Cl] adduct with Au---Cl fixed at different distances. Isosurface at 0.075 a.u.

Conclusions

We have found an efficient and economical way to facilitate the oxidative addition of Au(I) with aryldiazonium salts, by using ascorbic acid as an aryl radical inducer. The protocol described is operationally simple and avoid the use of sophisticated ligands. 3-Arylindoles have been successfully synthesized using this methodology in a *one-pot* reaction from 1-methylindoles and anilines. The coupling works for *para*-, *meta*-, and *ortho*- substituted aryldiazonium salts, tolerating the presence of electronwithdrawing and electrondonating groups, at both the indole and the diazonium salt structure. We also thoroughly examined the mechanism of the oxidative addition by EPR analysis, cyclic voltammetry experiments and DFT calculations. The results obtained are in agreement with a two single oxidation mechanism, where the Au(II)/Au(III) oxidation come from the reaction of an arylAu(II) intermediate with the starting aryldiazonium salt, and it is facilitated by the affinity of the chloride ion to the Au(II) center.

Acknowledgements

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Keywords: aryldiazonium salts • ascorbic acid • gold • oxidative addition • indoles

[1] Recent reviews: a) A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2010**, *49*, 5232; b) A. S. K. Hashmi, *Acc. Chem. Res.* **2014**, *47*, 864; *c*) A. Fürstner, *Acc. Chem. Res*. **2014**, *47*, 925; d) Y. Zhang, T. Luo, and Z. Yang, *Nat. Prod. Rep*. **2014**, *31*, 489; e) R. Dorel and A. M. Echavarren, *Chem. Rev*. **2015**, *115*, 9028; f) J. A. Goodwin and A. Aponick, *Chem. Commun*. **2015**, *51*, 8730; g) V. K.-Y. Lo, A. O.-Y. Chan and C.-M. Che, *Org. Biomol. Chem*. **2015**, *13*, 6667; *h*) W. Zi

and F. D. Toste, *Chem. Soc. Rev*. **2016**, *45*, 4567; i) D. Plästerer and A. S. K. Hashmi, *Chem. Soc. Rev*. **2016**, *45*, 1331.

[2] a) B. Sahoo, M. N. Hopkinson, F. Glorius, *J. Am. Chem. Soc*. **2013**, *135*, 5505; b) X.-Z. Shu, M. Zhang, Y. He, H. Frei, F. D. Toste, *J. Am. Chem. Soc.* **2014**, *136*, 5844; Selected reviews: a) P. García, M. Malacria, C. Aubert, V. Gandon and L. Fensterbank, *ChemCatChem*, **2010**, 493; b) M. N. Hopkinson, A. D. Gee and V. Gouverneur, *Chem. – Eur. J*., **2011**, *17*, 8248; c) H. A. Wegner and M. Auzias, *Angew. Chem., Int. Ed*., **2011**, *50*, 8236.

[3] a) M. D. Levin and F. D. Toste, *Angew. Chem., Int. Ed*., **2014**, *53*, 6211; b) M. Joost, A. Zeineddine, L. Estévez, S. Mallet-Ladeira, K. Miqueu, A. Amgoune, D. Bourissou, *J. Am. Chem. Soc*. **2014**, *136*, 14654; c) J. Serra, C. J. Whiteoak, F. Acuña-Parés, M. Font, J. M. Luis, J. Lloret-Fillol, and X. Ribas, *J. Am. Chem*. Soc. **2015**, *137*, 13389; d) A. Zeineddine, L. Estévez, S. Mallet-Ladeira, K. Miqueu, A. Amgoune and D. Bourrissou, *Nat. Commun*., **2017**, *8*, 565; e) J. Serra, T. Parella and X. Ribas, *Chem. Sci*. **2017**, *8*, 946.

[4] Recent reviews: a) M. N. Hopkinson, A. Tlahuext-Aca, F. Glorius, *Acc. Chem. Res*. **2016**, *49*, 2261; b) M. O. Akram, S. Banerjee, S. S. Saswade, V. Bedi, N. T. Patil, *Chem. Commun.* **2018**, *54*, 11069.

[5] a) L. Huang, M. Rudolph, F. Rominger, A. S. K. Hashmi, *Angew. Chem., Int. Ed.,* **2016**, *55*, 4808; b) L. Huang, F. Rominger, M. Rudolph, A. S. K. Hashmi, *Chem. Commun.*, **2016**, *52*, 6435; c) S. Witzel, J. Xie, M. Rudolph, A. S. K. Hashmi, *Adv. Synth. Catal.*, **2017**, *359*, 1522; d) J.-R. Deng, W.-C. Chan, N. C.-H. Lai, B. Yang, C.-S. Tsang, B. C.-B. Ko, S. L.-F. Chan, M.-K. Wong, *Chem. Sci*., **2017**, *8*, 7537; e) R. Cai, M. Lu, E. Y. Aguilera, Y. Xi, N. G. Akhmedov, J. L. Petersen, H. Chen, X. Shi, *Angew. Chem., Int. Ed*., **2015**, *54*, 8772; f) H. Peng, R. Cai, C. Xu, H. Chen, X. Shi, *Chem. Sci*., **2016**, *7*, 6190; g) B. Dong, H. Peng, S. E. Motika, X. Shi, *Chem.-Eur. J*., **2017**, *23*, 11093; h) M. Barberoa, S. Dughera, *Org. Biomol. Chem*., **2018**, *16*, 295; i) M. O. Akran, P. S. Shinde, C. C. Chintawar, N. T. Patil, *Org. Biomol. Chem*., **2018**, *16*, 2865; A. A. Jimoh, S. Hosseyni, X. Ye, L. Wojtas, Y. Hu, X. Shi, *Chem. Commun.* **2019**, *55*, 8150.

[6] a) E. O. Asomoza-Solís, J. Rojas-Ocampo, R. A. Toscano, S. Porcel, *Chem. Commun*. **2016**, *52*, 7295; b) U. A. Carrillo-Arcos, S. Porcel, *Org. Biomol. Chem*., **2018**, *16*, 1837.

[7] a) J. P. Brand, J. Charpentier, J. Waser, *Angew. Chem. Int. Ed*. **2009**, *48*, 9346; b) M. Hofer, C. Nevado, *Tetrahedron* **2013**, *69*, 5751; c) K. Hata, H. Ito, Y. Segawa, K. Itami, *Beilstein J. Org. Chem.* **2015**, *11*, 2737; d) X. C. Cambeiro, N. Ahlsten, I. Larrosa, *J. Am. Chem. Soc.* **2015**, *137*, 15636; e) A. J. Cresswell, G. C. Lloyd-Jones, *Chem. Eur. J*. **2016**, *22*, 12641; f) J.-R- Liu, Y.-Q. Duan, S.-Q. Zhang, L.-J. Zhu, Y.-Y. Jiang, S. Bi, X. Hong, *Org. Lett*. **2019**, *21*, 2360.

[8] When this work was under review, the group of Bourissou reported the catalytic arylation of *N*-methyl indoles with iodoarenes: J. Rodriguez, A. Zeineddine, E. D. Sosa Carrizo, K. Miqueu, N. Saffon-Merceron, A. Amgoune, D. Bourissou, *Chem. Sci.* **2019**, *10*, 7183-7192.

[9] Selected examples: a) B. S. Lane, D. Sames, *Org. Lett*. **2004**, *6*, 2897; b) N. R. Deprez, D. Kalyani, A. Krause, M. S. Sanford, *J. Am. Chem. Soc*. **2006**, *128*, 4972; c) S.-D. Yang, C.-L. Sun, Z. Fang, B.-J. Li, Y.-Z. Li, Z.-J. Shi, *Angew. Chem. Int. Ed*. **2008**, *47*, 1473; d) N. Lebrasseur, I. Larrosa, *J. Am. Chem. Soc*. **2008**, *130*, 2926; e) R. Vicente, *Org. Biomol. Chem.* **2011**, *9*, 6469; f) Y. Huang, Z. Lin, R. Cao, *Chem. Eur. J*. **2011**, *17*, 12706; g) S. Islam, I. Larrosa*, Chem. Eur. J.* **2013**, *19*, 15093; h) Z. Xum Y. Xu, H. Lu, T. Yang, X. Lin, L. Shao, F. Ren, *Tetrahedron* **2015**, *71*, 2616; i) S. Cacchi, G. Fabrizi, *Chem. Rev*. **2015**, *105*, 2873; j) A. H. Sandtorv, *Adv. Synth. Catal*. **2015**, *357*, 2403; k) L. Duan, R. Fu, B. Zhang, W. Shi, S. Chen, Y. Wan, *ACS Catal*. **2016**, *6*, 1062; l) H.P. L. Gemoets, I. Kalvet, A. V. Nyuchev, N. Erdmann, V. Hessel, F. Schoenebeck, T. Noel, *Chem. Sci*., **2017**, *8*, 1046; m) O. Moncea, D. Poinsot, A. A. Fokin, P. R. Schreiner, J.C. Hierso, *ChemCatChem* **2018**, *10*, 2915.

[10] Under certain conditions the 3-arylated regioisomer is preferred. a) D. R. Stuart, K. Fagnou, *Science* **2007**, *316*, 1172; b) G. Cusati, L. Djakovitch, *Tetrahedron Lett*. **2008**, *49*, 2499; c) J. Cornella, P. Lu, I. Larrosa, *Org. Lett.* **2009**, *11*, 5506; d) L. Joucla, N. Batail, L. Djakovitch, *Adv. Synth. Catal.* **2010**, *352*, 2929; e) H. Veisi, N. Morakabati, *N. New J. Chem*. **2015**, *39*, 2901; (*f*) M. Yamaguchi, K. Suzuki, Y. Sato, K. Manabe, *Org. Lett*. **2017**, *19*, 5388.

[11] R. J. Phipps, N. P. Grimster, M. J. Gaunt, *J. Am. Chem. Soc*. **2008**, *130*, 8172.

[12] 3-Arylated indoles are also obtained by reaction of indoles with aryldiazonium salts in the presence of Rhodamine B as photocatalyst: Y.-P. Zang, X.-L. Feng, Y.-S. Yang, B.-X. Cao, *Tetrahedron Letters* **2016**, *57*, 2298.

[13] a) K. J. Reszka, C. F. Chignell, *Chem.-Biol. Interact.* **1995**, *96*, 223; b) U. Costas-Costas, E. González-Romero, C. Bravo-Díaz, *Helv. Chim. Acta* **2001**, *84*, 632; c) S. Losada-Barreiro, V. Sánchez-Paz, C. Bravo-Díaz, *Helv. Chim. Acta*, **2007**, *90*, 1559.

[14] a) F. P. Crisóstomo, T. Martín, R, Carrillo, *Angew. Chem. Int. Ed.* **2014**, *53*, 2181; b) M. D. Perretti, D. M. Monzón, F. P. Crisóstomo, V. S. Martín, R. Carrrillo, *Chem. Commun*. **2016**, *52*, 9036.

[15] B. Alcaide, P. Almendros, I. Fernández, F. Herrera, A. Luna, *Chem. Eur. J*. **2007**, *23*, 17227.

[16] a) M. Trinchillo, P. Belanzoni, L. Belpassi, L. Biasiolo, V. Busico, A. D'Amora, L. D'Amore, A. Del Zotto, F. Tarantelli, A. Tuzi, D. Zuccaccia, *Organometallics* **2016**, *35*, 641-654; b) L. D'Amore, G. Ciancaleoni, L. Belpassi, F. Tarantelli, D. Zuccaccia, P. Belanzoni, *Organometallics* **2017**, *36*, 2364-2376.

[17] J. M. Fontmorin, R.C. Burgos-Castillo, W.Z. Tang, M. Sillanpää, *Water Res*. **2016**, *99*, 24-32.

[18] a) M. Delamar, R. Hitmi, J. Pinson, J.M. Savéant. *J. Am. Chem. Soc*. **1992**, *114*, 5884-5886; b) P. Allongue, M. Delamar, B. Desbat, O. Fagebaume, R. Hitmi, J. Pinson, J. M. Savéant. *J. Am. Chem. Soc*. **1997**, *119*, 201-207; c) L. Lee, P. A. Brooksby, P. Hapiot, A. Downard. *Langmuir*. **2016**, *32*, 468-476.

[19] C. Hansch, A. Leo, R. W. Taft. *Chem. Rev*. **1991**, *91*, 165-195.

[20] J. M. Savéant. *Acc. Chem. Res*. **1993**, *26*, 455-461.

[21] R. H. Wopschall, I. Shain. *Anal. Chem.* **1967**, *39*, 1514-1527.

[22] Chloride ions can have strong effects on the thermodynamic and kinetics of oxidation of some metals, such as those observed in the oxidative addition of iodobenzene to low-ligated zerovalent palladium complexes: C. Amatore, M. Azzabi, A. Jutand. *J. Am. Chem. Soc*. **1991**, *113*, 8375-8384.

[23] The group of Yu has previously studied by DFT the mechanism of the light-mediated gold-catalyzed oxyarilation of alkenes: Q. Zhang, Z.-Q. Zhang, Y. Fu, H.-Z. Yu, *ACS Catal*. **2016**, *6*, 798.

[24] The group of Toste has proved very recently (using quantum yield determinations), that arylgold(II) intermediates can be oxidizes by diazonium salts. S. Kim, F.D. Toste, *J. Am. Chem. Soc*. **2019**, *141*, 4308-4315.

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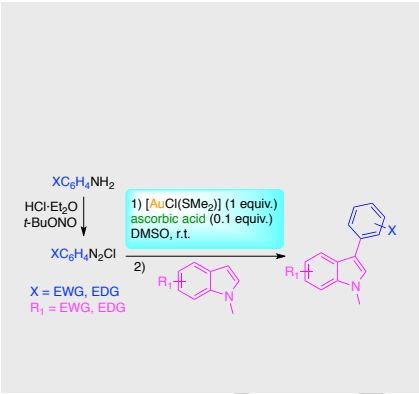
Layout 1:

FULL PAPER

Ascorbic acid, a natural and readily accessible antioxidant, is able to accelerate the oxidative addition of aryldiazoniun chlorides onto Au(I). The arylAu(III) species generated in this way, have been used for preparing 3-arylindoles in a *one-pot* protocol. In addition, the mechanism underlying the oxidative addition have been examined through EPR analyses, cyclic voltammetry and DFT calculations.



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Ascorbic acid as an aryl radical inducer in the gold mediated arylation of indoles with aryldiazonium chlorides