C–H Arylation

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# Ascorbic Acid as an Initiator for the Direct C–H Arylation of (Hetero)arenes with Anilines Nitrosated In Situ**

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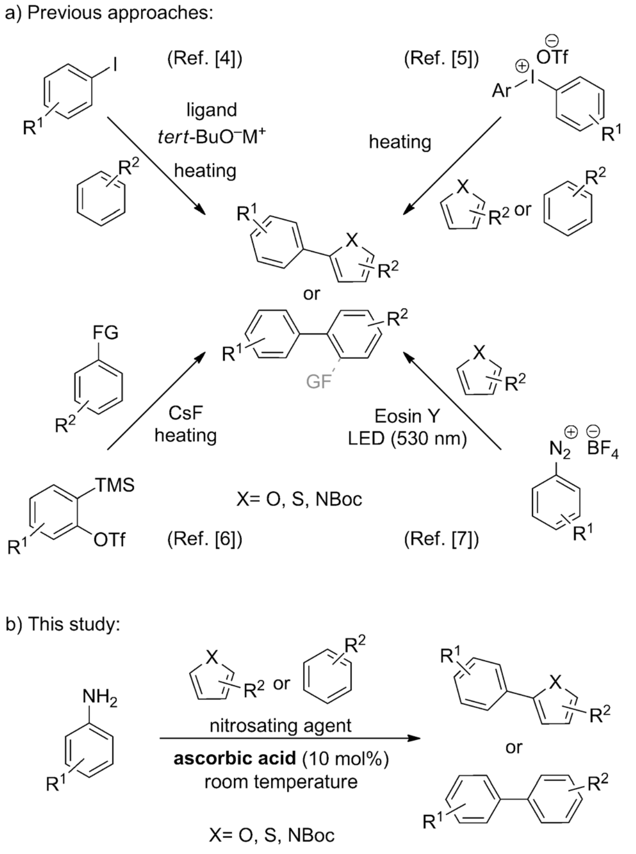
***Abstract:*** *Ascorbic acid (vitamin C) has been used as a radical initiator in a metal-free direct C–H arylation of (hetero)arenes. Starting from an aniline, the corresponding arenediazonium ion is generated in situ and immediately reduced by vitamin C to an aryl radical that undergoes a homolytic aromatic substitution with a (hetero)arene. Notably, neither heating nor irradiation is required. This procedure is mild, operationally simple, and constitutes a greener approach to arylation.*

The synthesis of (hetero)biaryl compounds has become one of the most important reaction types in organic synthesis owing to the high incidence of the biaryl structural motif in biologically active molecules, natural products, and materials chemistry.[1] In this regard, the direct C–H arylation of arenes is particularly attractive, because it avoids the traditional double preactivation of the coupling partners. As a consequence, the number of steps is reduced, less or no manipulation of sensitive and often toxic reagents is required, and less waste is generated. Numerous examples of the direct C–H arylation of arenes by the use of transition metals have been reported.[2] However, their cost effectiveness and the presence of transition-metal impurities in the final product affect the practical applicability of transition-metal-mediated reactions. Such environmental and economic concerns have motivated the development of plenty of transition-metal-free synthetic methods.[3] Regarding intermolecular C–H arylation reactions of (hetero)arenes, there are a few reported metal-free variants,[4–6] but in most cases harsh conditions, such as the use of strong bases and high temperatures, are required (Scheme 1a). Recently, an elegant and mild approach was suggested by König and co-workers: photochemical reduction of arenediazonium ions by an organic photocatalyst (Scheme 1a).[7] Indeed, arenediazonium ions function as one-electron oxidizing agents, and therefore, in reactions with suitable reducing agents, free radicals are generated,[8] which can undergo a homolytic aromatic substitution (Gomberg–Bachmann reaction).[9] In this regard, there is solid evidence that L-*threo*-ascorbic acid (hereafter referred to as ascorbic acid or vitamin C) is able to act as a reductant towards arenediazonium ions to generate aryl radicals in the absence of metals.[10] Surprisingly, the synthetic applicability of ascorbic acid as a radical promoter has never been evaluated, even though it is a perfect candidate for an environmentally benign synthetic procedure. We herein describe an operationally simple metal-free direct C–H arylation of (hetero)arenes with anilines that is promoted by catalytic amounts of ascorbic acid, with no heating or irradiation required (Scheme 1b).



***Scheme 1.*** a) Previous strategies for metal-free intermolecular direct C–H arylation of (hetero)arenes, and b) our method. Boc = *tert*-butoxycarbonyl, FG = functional group, TMS = trimethylsilyl, Tf = trifluoromethanesulfonyl.

As a proof of concept, 4-chlorobenzenediazonium tetrafluoroborate in dimethyl sulfoxide (DMSO) was treated with ascorbic acid (0.1 equiv)[11] in the presence of an excess

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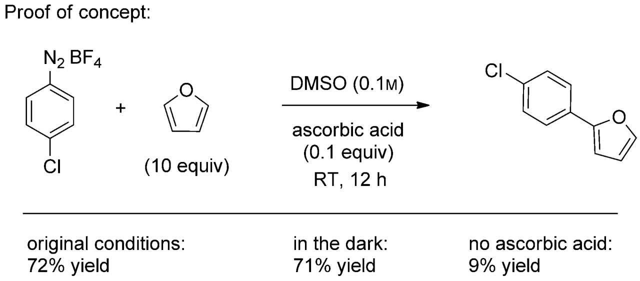


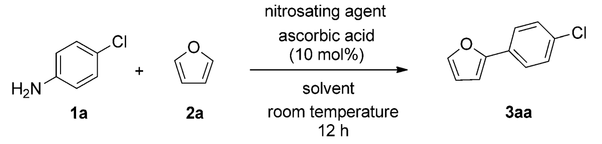
**Scheme 2.** Ascorbic acid as a radical initiator for the arylation of furan with 4-chlorobenzenediazonium ion.

amount of furan (Scheme 2). We found that furan arylation proceeded well in good yield. The reaction proceeded equally well in the dark, whereas poor yields were observed when no ascorbic acid was added. On the basis of these initial findings, it was thought more convenient to explore the arylation with anilines, from which the corresponding arenediazonium ion could be generated in situ,[12] not only because just a few diazonium salts are commercially available, but particularly because of the considerable explosion hazard associated with the use of large amounts of dry diazonium salts. Furthermore, anilines are usually inexpensive and readily available.

Optimization studies were performed for the arylation of furan (**2a**) with 4-chloroaniline (**1a**) as a model reaction (Table 1). The best nitrosating agent was found to be *tert*-butyl nitrite (Table 1, entry 4). Remarkably, no acid was added to the reaction mixture, but just a catalytic amount of ascorbic acid. Probably the lack of a stronger acid is the reason why traditional nitrosating agents, such as sodium nitrite, were least effective (Table 1, entry 1). The best solvent was acetonitrile (Table 1, entry 10); other solvents led to significantly lower yields. Water, which has been reported to be one of the best solvents for this kind of reaction because of its poor hydrogen-atom-donor ability,[8b,c] also led to a lower yield than acetonitrile (Table 1, entry 9). An excess amount of furan was found to be required because double arylation had to be minimized. Finally, the reaction was tested in an open flask, which resulted in a decrease in the yield (Table 1, entry 13), because oxygen can react with the radicals formed during the reaction. The arylation with anilines also proceeded in the dark (Table 1, entry 14). In contrast, when no ascorbic acid was added, the reaction led to a complex mixture of products, and only a small amount of heteroaryl **3aa** was found (Table 1, entry 15).[13] Finally, several other commonly used reducing agents were tested in this reaction; in all cases, yields were lower than that observed with ascorbic acid (see Table S1 in the Supporting Information).

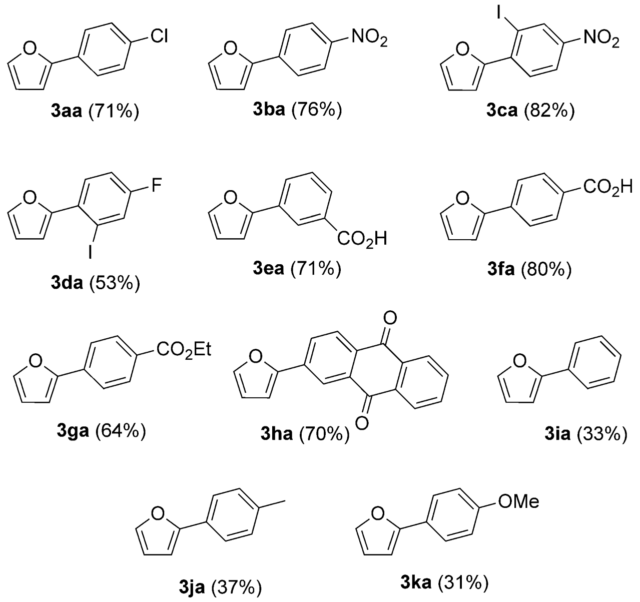
Having optimized the reaction conditions, we examined the scope of the arylation of furan **2a** with different anilines. It was clearly observed that electron-withdrawing substituents on the aniline led to higher yields than electron-donating substituents (Scheme 3), in agreement with the occurrence of a radical reaction controlled by the SOMO–HOMO interaction.[14] Indeed, electron-withdrawing groups on the aniline will lower the SOMO level of the corresponding aryl radical, and therefore, the interaction with the HOMO of furan will be more effective. Moreover, such an interaction also explains the regioselectivity of the arylation: The C2 atom of furan has the largest HOMO coefficient;[15] therefore, the arylation

**Table 1:** Optimization of the reaction conditions.[a]



| Entry | Nitrosating agent | Solvent | Amount of **2a** [equiv] | Yield of **3aa** [%][b] |
|---|---|---|---|---|
| 1 | $NaNO_2$ | DMSO | 10 | 34 |
| 2 | $TBANO_2$ | DMSO | 10 | 45 |
| 3 | *i*AmONO | DMSO | 10 | 59 |
| 4 | *t*BuONO | DMSO | 10 | 63 |
| 5 | *t*BuONO | THF | 10 | 11 |
| 6 | *t*BuONO | DMF | 10 | 41 |
| 7 | *t*BuONO | $CH_2Cl_2$ | 10 | 32 |
| 8 | *t*BuONO | $CH_3NO_2$ | 10 | 67 |
| 9 | *t*BuONO | $H_2O$ | 10 | 57 |
| **10** | ***t*BuONO** | **$CH_3CN$** | **10** | **71** |
| 11 | *t*BuONO | $CH_3CN$ | 5 | 62 |
| 12 | *t*BuONO | $CH_3CN$ | 20 | 71 |
| 13[c] | *t*BuONO | $CH_3CN$ | 10 | 59 |
| 14[d] | *t*BuONO | $CH_3CN$ | 10 | 70 |
| 15[e] | *t*BuONO | $CH_3CN$ | 10 | 11 |

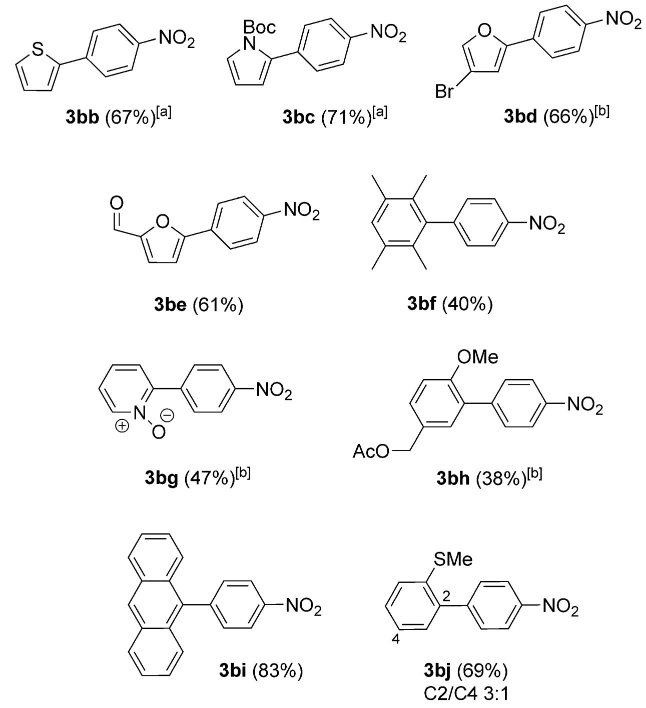
[a] Unless otherwise stated, reactions were performed under nitrogen by the addition of the nitrosating agent (1.5 equiv) and then a solution of ascorbic acid (0.05 mmol) in DMSO (0.1 mL) to a mixture of **1a** (0.5 mmol) and excess **2a** in the solvent (5 mL); the reaction mixture was left for 12 h at room temperature. [b] Yield of the isolated product. Conversion was complete in all cases. [c] The reaction was performed under air. [d] The reaction was performed in the dark. [e] No ascorbic acid was added. Am = amyl (pentyl), DMF = *N*,*N*-dimethylformamide, $TBANO_2$ = tetrabutylammonium nitrite.



**Scheme 3.** Products of the arylation of furan with different anilines. All reactions were performed under nitrogen with 5 mmol of furan (**2a**; see the Experimental Section for details). The yields given are for the isolated product. Conversion was complete in all cases.

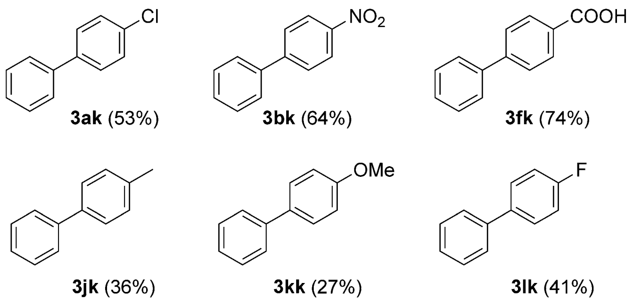
takes place at this carbon atom. On the other hand, several functional groups are compatible with the reaction conditions (Scheme 3). Particularly interesting is the observation that halogen substituents are not affected, which allows for further functionalization reactions.

This metal-free arylation was also tested on several other (hetero)arenes. The reaction was particularly effective with electron-rich aromatic rings (Scheme 4), which have a higher-energy HOMO. The arylation of unactivated benzene was studied separately, as it is usually considered a more complicated reaction. As Scheme 5 shows, the arylation of benzene gave biphenyl products in moderate to good yield. The yield was higher for reactions with anilines bearing electron-withdrawing groups.



***Scheme 4.*** Products of the arylation of different (hetero)arenes with 4-nitroaniline. Reactions were performed under nitrogen with 1 mmol of arene **2** (see the Experimental Section for details). The yields given are for the isolated product. Conversion was complete in all cases. [a] The reaction was carried out with 10 equivalents of the heteroarene. [b] No other regioisomers were detected by NMR spectroscopy.

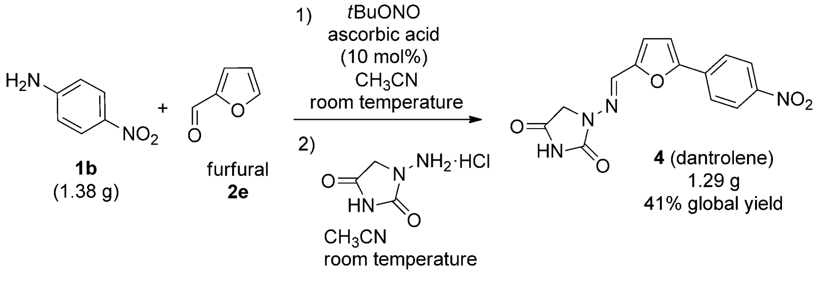
As seen in Schemes 3–5, the arylation yields are comparable to those observed for other metal-free procedures.[4–7] Thus, to further demonstrate the synthetic potential of our methodology, we undertook a metal-free gram-scale synthesis of dantrolene (**4**) in two steps (Scheme 6).[16] The arylation of furfural (**2e**) with 4-nitroaniline (**1b**), followed by condensation of the resulting aldehyde **3be** with 1-aminohydantoin hydrochloride, gave dantrolene in 41 % global yield.



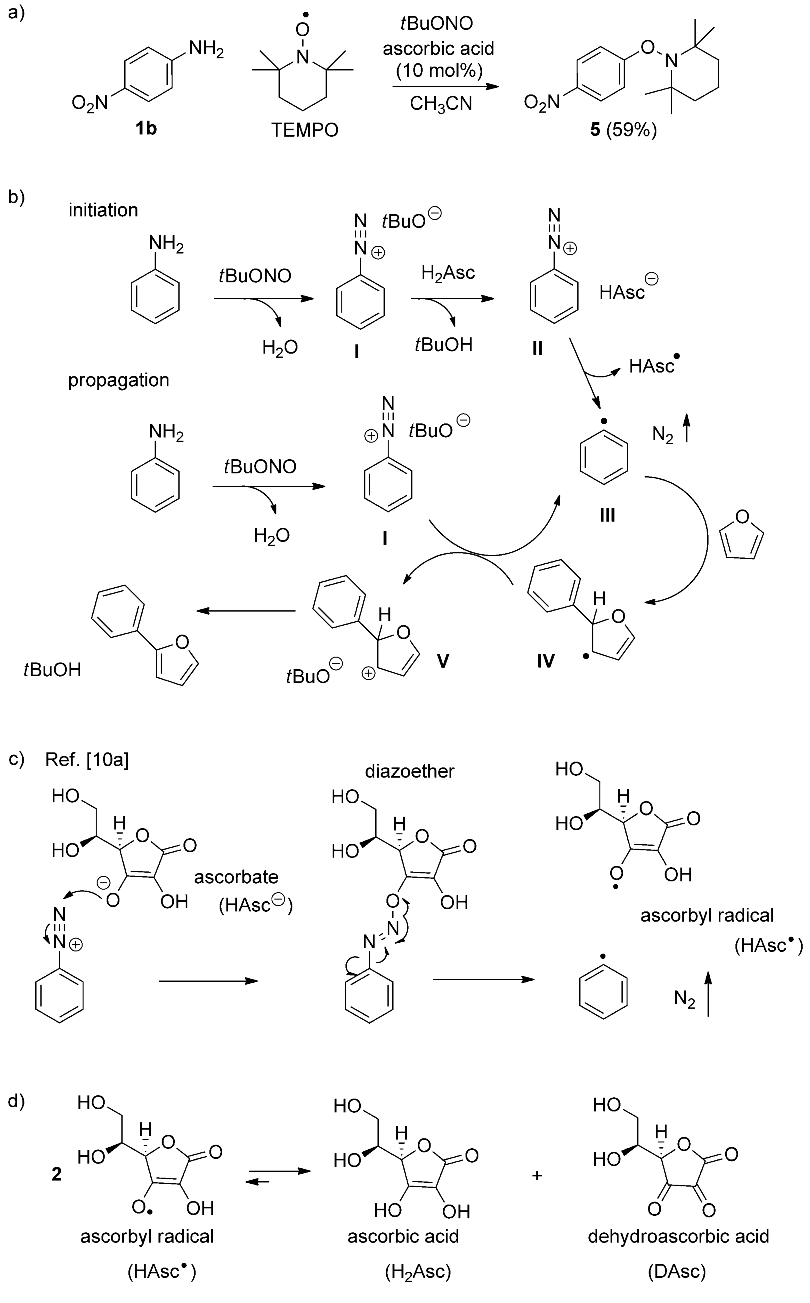
***Scheme 5.*** Products of the arylation of benzene with different anilines. All reactions were performed under nitrogen by adding *t*BuONO (1.5 mmol) to the aniline (1 mmol) in benzene (2 mL), followed by a solution of ascorbic acid (0.1 mmol) in DMSO (0.2 mL). [b] The yields given are for the isolated product. Conversion was complete in all cases.

Several pieces of evidence suggest a radical mechanism. To confirm this hypothesis, we added 2,2,6,6-tetramethylpiperidine-1-oxy radical (TEMPO) to the reaction mixture (Scheme 7a), whereupon the aryl radical was efficiently trapped, and the resulting product **5** was isolated in 59 % yield.[17]

On the basis of the above observations and previous reports,[7,8,10] a tentative mechanism is proposed in Scheme 7b for the arylation of furan. First, the aniline reacts with *tert*-butyl nitrite to yield the diazonium salt **I**.[12b,c] In the initiation step, ascorbic acid protonates a small part of **I**, which results in a change of the anion to ascorbate and leads to diazonium salt **II**. Ascorbate then reduces the arenediazonium ion by a single-electron transfer through an inner-sphere mechanism, as proposed by Bravo-Díaz and co-workers (Scheme 7c).[10a] This reduction consists of a nucleophilic addition of ascorbate to the diazonium moiety to afford a diazoether, which has previously been isolated,[18] followed by a homolytic rupture to generate nitrogen, ascorbyl radical, and the aryl radical **III**. Ascorbyl radical tends to dismutate into dehydroascorbic acid and ascorbic acid, which can reduce another arenediazonium ion (Scheme 7d).[19] On the other hand, the aryl radical **III** undergoes a homolytic aromatic substitution to yield initially radical **IV**, which propagates the reaction by losing one electron to reduce another molecule of diazonium salt **I** with the formation of the carbocation **V**, whose counterion, *tert*-butoxide, immediately abstracts a proton to yield the final product by rearomatization of the furan ring.



***Scheme 6.*** Gram-scale synthesis of dantrolene.



***Scheme 7.*** Mechanistic proposal. a) Aryl-radical entrapment by TEMPO. b) Suggested mechanism of the arylation of furan. c) Mechanism of inner-sphere single-electron transfer for the reduction of arenediazonium ions by ascorbate. d) Dismutation of ascorbyl radical.

In summary, ascorbic acid has been successfully employed as a radical initiator in a metal-free intermolecular direct C–H arylation of (hetero)arenes with anilines. The reaction is mild, operationally simple, and constitutes a greener approach to arylation. Indeed, ascorbic acid is edible, as is its decomposition product, dehydroascorbic acid. Additionally, this methodology is energy-efficient because it requires neither heating nor irradiation. Finally, very remarkable is the use of vitamin C as a radical initiator, which paves the way for milder and environmentally friendly radical reactions. This study indicates the huge potential application of ascorbic acid or its derivatives in almost any Meerwein/Sandmeyer-type reaction and in many other radical processes.

## Experimental Section

Standard procedure: The aniline (0.50 mmol) and the (hetero)arene (5 or 1 mmol) were placed in an oven-dried 10 mL round-bottomed flask with a Teflon-coated stirrer bar under an atmosphere of dry nitrogen. Acetonitrile (5 mL) was added with a syringe, and the resulting solution was stirred at room temperature until the reagents had dissolved. *t*BuONO (0.75 mmol) was then added with a syringe, and finally 0.1 mL of a freshly prepared solution of L-ascorbic acid in DMSO (0.5 M) was added with a syringe. A fine bubbling was observed thereafter. The reaction mixture was stirred at ambient temperature for 12 h. The crude product was adsorbed on silica gel and purified by flash chromatography ($SiO_2$, hexane/ethyl acetate gradient) to yield the corresponding (hetero)biaryl compound.

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