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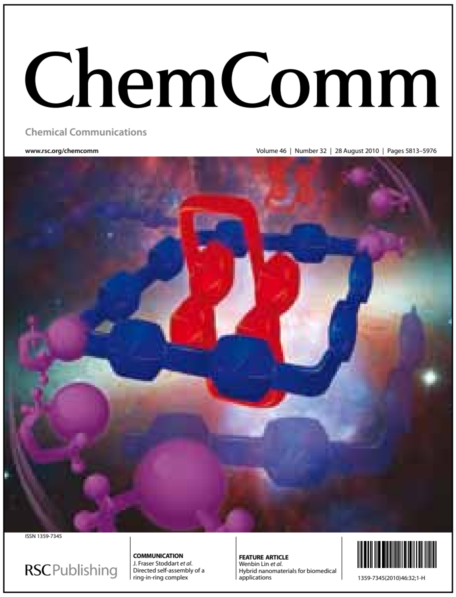

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ARTICLE TYPE

Copper-Catalyzed Free-Radical C-H Arylation of Pyrroles

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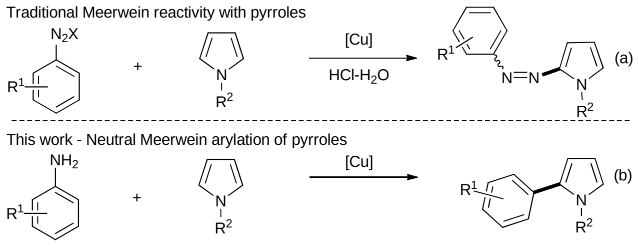
A room temperature copper-catalyzed radical arylation of pyrroles with anilines, through *in situ* generated aryl diazonium salts, has been developped under neutral conditions. Experimental and theoritical studies explained the crucial role of $CaCO_3$ and the high regioselectivity observed.

The transition-metal-catalyzed C-H arylation of heteroarenes with haloarenes has recently attracted considerable attention[1] as such approach allows the preparation of ubiquitous structures found in many organic materials[2] and pharmaceuticals, e.g., Atorvastatin, Tanaproget and Fendosal, without a prefunctionalization step. While these approaches changed the way chemists design chemical routes, forcing conditions are usually required due to the inertness of the C-H bond. On the other hand, free-radical C-H arylation of heteroarenes through both metal- and non-metal-mediated processes has recently emerged as a valuable alternative enabling mild conditions.[3] Amongst others, aryl diazonium salts are well-known species giving free-radical aryl intermediates through a homolytic dediazoniation mechanism.[4] The copper redox process involving aryl diazonium salts, known as the Meerwein-type arylation[5] has been reported on several occasion for the arylation of furanes and thiophenes.[6,7] Unfortunately, the strong acidic conditions required for this transformation precluded the arylation of electron-rich heteroarenes such as pyrroles.[8] From, preliminary studies we observed that the C2-azo adduct was obtained instead (Scheme 1a). With the aim of developping copper-catalyzed C-H arylations of pyrroles[9] under neutral conditions at room temperature in aqueous solvents, we reinvestigated the Meerwein-type arylation and unveiled several interesting features (Scheme 1b).

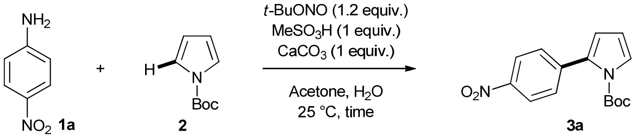


Scheme 1 Meerwein-type arylation of pyrroles

Aryl diazonium salts are traditionally used under their tetrafluoroborate form as crystalline salts but their high reactivity and hazardous profile make these compounds unsuitable for a safe handling, especially on large scale.[10] Alternatively, they can be prepared in aqueous HCl, but this approach reduces the window of compatible chemical reactions due to harsh conditions. Recently we have contributed to the use of aryl diazonium salts under unusual and safe conditions for Pd-catalyzed reactions[11] and to the copper-catalyzed Meerwein-type arylation of highly sensitive quinones.[12] Inspired by these studies we developped an unprecedented copper-catalyzed arylation of pyrroles with *in situ* generated aryl diazonium salts under neutral conditions.[13]

Initial investigations focused on the arylation of acid-sensitive *N*-Boc-pyrrole **2** with 4-nitroaniline **1a**, through an *in situ* generated aryl diazonium salt with only one equivalent of $MeSO_3H$ and *t*BuONO (Table 1) in aqueous acetone. $CaCO_3$ (1 equiv) was used as a mild base in order to avoid any acid-mediated azo compound formation. During our optimization studies, we assessed various copper catalysts from which $Cu(OAc)_2.H_2O$ emerged as the best one (entry 5). Although, $CuCl_2$ was the standard catalyst for the copper-catalyzed Meerwein arylation,[14] it frequently led to Sandmeyer-type side-products contrary to $Cu(OAc)_2.H_2O$.[15] The reaction was highly regioselective at C2 provided that an excess of pyrrole **2** was used to avoid the double arylation at C2/C5. After extensive experimentation and evaluation of key parameters including temperature, solvent system, concentration and reaction time, we discovered that degassed and more concentrated solutions allowed the C-H arylation of pyrrole **2** (4 equiv) in 1 hour at 25°C with 83% yield, unreacted pyrrole **2** being easily recovered by bulb to bulb distillation or flash chromatography (entry 6). Other combinations of solvents including DMSO, and CH_3CN in association with H_2O gave lower yields. When $CaCO_3$ was omitted (entry 7), the yield of **3a** significantly decreased (55% *vs* 83%). This result hints a twofold role for $CaCO_3$ since it acts as a buffer additive suppressing the formation of azo compounds but also steps in the catalytic cycle (vide infra) to improve the reaction efficiency. Importantly, the use of the commercially available 4-nitrophenyl diazonium tetrafluoroborate instead of our *in situ* protocol dramatically decreased the reaction yield (entry 8). These last results also explain the failures encountered in the literature for the Meerwein-type arylation of sensitive heteroarenes since both neutral conditions and a specific *in situ* diazonium salt generation are required for a successful coupling.[8]

Table 1 Optimization studies.



Entry	Conditions[a]	Yield (%)[b]
1	10% Cu(acac)$_2$, **2** (6 equiv), [0.1 M], 12 h	44
2	10% CuO, **2** (6 equiv), [0.1 M], 12 h	45
3	10% CuCl$_2$.2H$_2$O, **2** (6 equiv), [0.1 M], 12 h	57
4	10% CuSO$_4$.5H$_2$O, **2** (6 equiv), [0.1 M], 12 h	59
5	10% Cu(OAc)$_2$.H$_2$O, **2** (6 equiv), [0.1 M], 12 h	65
6	10% Cu(OAc)$_2$.H$_2$O, **2** (4 equiv), [0.3 M], 1 h	83[c]
7	10% Cu(OAc)$_2$.H$_2$O, **2** (4 equiv), [0.3 M], 1 h	55[d]
8	10% Cu(OAc)$_2$.H$_2$O, **2** (4 equiv), [0.3 M], 1 h	35[c,e]

[a] Reactions performed on 1 mmol scale. Concentration of the diazonium salt in brackets. [b] Isolated yield. [c] Degassed solvents. [d] CaCO$_3$ was omitted. [e] 4-Nitrophenyl diazonium tetrafluoroborate was used.

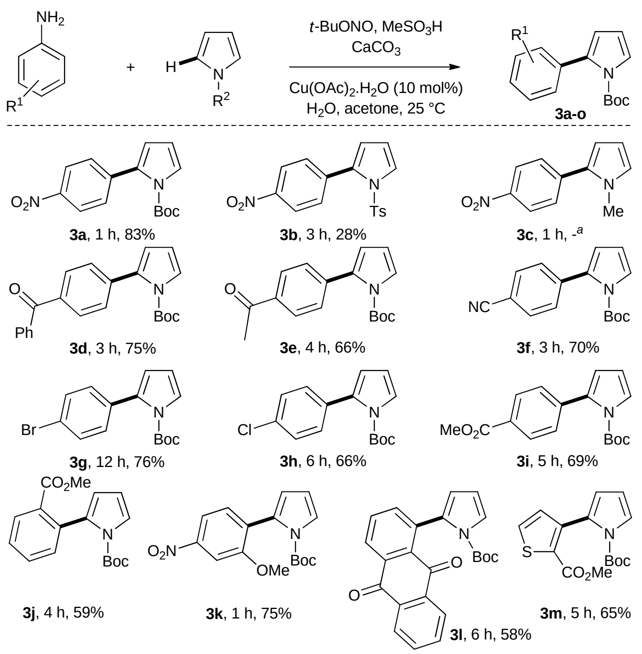
With a solid set of optimized conditions, we evaluated the scope of this methodology on a wide range of anilines (Table 2). The reaction time was based on the observation of the nitrogen evolution. The electrophilic character of aryl radicals could explain their low reactivity with strongly electron-deficient pyrroles (**3b**). By contrast, electron-rich pyrrole only reacted as a nucleophile onto the diazonium function to furnish the unwanted azo adduct as the only isolable product (**3c**). This highlights the fine tuning of the pyrrole properties required for succeeding the arylation. This process was found to be tolerant to a variety of functional groups including nitro (**3a**, **3k**), ketone (**3d-e**), ester (**3i-j**, **3m**), cyano (**3f**), methoxy (**3k**) and quinone (**3l**). Moreover, the halogen containing-motifs, such as Br (**3g**) and Cl (**3h**), were compatible despite the free-radical conditions, opening the door for further functionalization. Heteroarylation of pyrrole **2** was also successful with a thiophene derivative, leading to the structurally interesting thiophenylpyrrole **3m** in good yield.[16]

We also explored the opportunity for preparing diarylated pyrroles (Scheme 2). For instance, in the presence of 4-nitroaniline **1a**, the pyrrole **3a** can be arylated in 53% yield to give the expected symmetrical pyrrole **4a**. Unsymmetrical structures can be obtained as well following the same strategy (see **4b**).

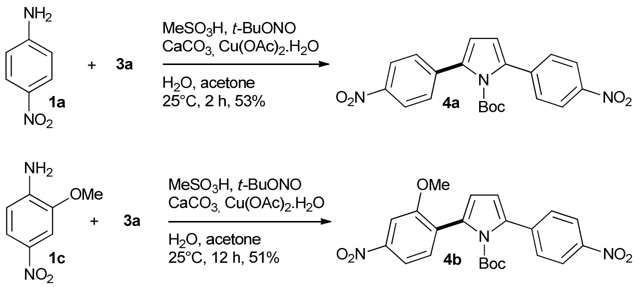
We assumed that the C-H arylation of pyrroles followed a free-radical pathway and experimental evidences supported this hypothesis. Indeed, when the arylation of pyrrole **2** with 4-aminobenzophenone **1b** was conducted in the presence of the persistent nitroxide radical TEMPO (1.5 equiv), the expected coupling product **3d** was not formed and the O-aryl-TEMPO adduct was detected by mass spectroscopy. This result confirms the involvement of free-radical intermediates. On the basis of our experimental observations and assisted by literature, the following catalytic cycle should account for the mechanism involved in this transformation (Scheme 3). The Cu(I)-catalyzed homolytic dediazoniation of the *in situ* generated diazonium salt **A** gives the corresponding highly reactive aryl radical **B**, quickly intercepted by the pyrrole **C**. The radical intermediate **D** is further oxidized by Cu(II) species into the corresponding cation **E** which upon deprotonation provides the expected coupling products **3a-m**. The high regioselectivity of the arylation process at C2 *versus* C3 was further explored with the assistance of DFT calculations (see below). A similar regioselectivity has been described for the Pd-catalyzed arylation of pyrrole due to electronic preference for generating Pd-σ-heteroaryl complexes at C2 and the higher acidity of the C$_2$-H bond favoring the initial palladation at this site. However, this interpretation cannot account for our free-radical C-H arylation process where the C-C bond is initially formed by addition of an aryl radical onto pyrrole.

The regioselectivity was explained by examining the stability of the radical intermediate (of type **D**) and the corresponding transition states for the reaction of **1a** (R$_1$=NO$_2$) with **2** (R$_2$=H). The radicals **D** present much lower Gibbs energies for the C2 than the C3 products, the estimated difference being 10.7 kcal.mol^{-1}. The same holds for the transition states with a relative Gibbs energy of 4.2 kcal.mol^{-1} in favour of the attack on C2.

Table 2 C-H Arylation of pyrroles



[a] : The C2-azo adduct was isolated in 72% yield.



Scheme 2 Synthesis of diarylated pyrroles

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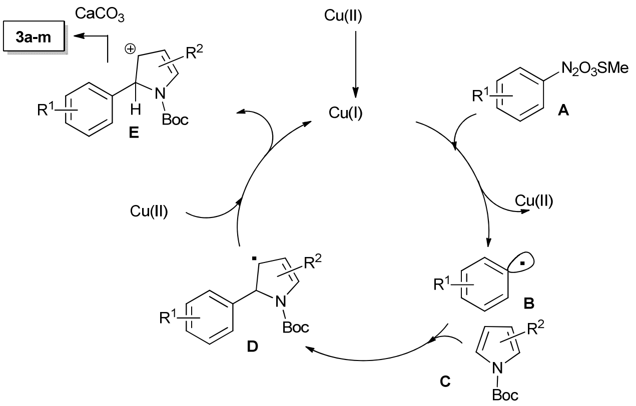
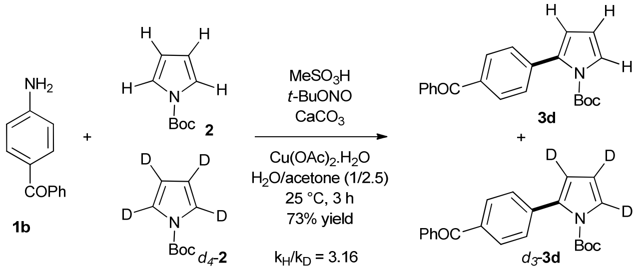


Scheme 3 Proposed catalytic cycle.

The corresponding imaginary frequency mode that characterizes the transition state presents a frequency of 384 cm^{-1} (see ESI). We also note that the **1a**+**2**→**D** reaction is exergonic with a ΔG of -24.7 kcal.mol^{-1}. Therefore both thermodynamic and kinetic criteria go in the same direction and indicate a preferred C2 attack.



Scheme 4 Kinetic isotope effect.

The role of CaCO$_3$ was also investigated with labelled experiments (Scheme 4). A kinetic isotope effect (k_H/k_D = 3.16) was observed between pyrrole **2** and its deuterated analogue d_4-**2**, indicating that the C-H bond cleavage could be involved in a rate limiting step. Thereby, we suggest that CaCO$_3$ could facilitate the deprotonation of the pyrrolo cation **E** which likely follows undesirable pathways decreasing the reaction yield in the absence of a base. Theoretical calculations of the transition states corresponding to deprotonation could be found with both OH$^-$ and HCO$^-_3$ anions (see ESI) but not for MeSO$^-_3$, hinting that a sufficiently efficient base is indeed necessary.

In summary, we have developped a Meerwein-type arylation of pyrroles under very mild conditions. The methodology features aqueous solvents, room temperature, inexpensive reagents and catalysts, as well as experimental simplicity. Experimental and theoritical studies provided mechanistic insights.

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† Electronic Supplementary Information (ESI) available: Experimental procedures for all new compounds and computational details are provided. See DOI: 10.1039/b000000x/

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