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Palladium versus copper-catalyzed N-arylation towards an efficient access to polysubstituted dibenzophenanthrolines and carbazoles

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Abstract—The double amination of *meta*-diiodo and dibromobenzenes by anthranilic acid derivatives is described using palladium and/or copper catalysis. The resulting symmetrical and unsymmetrical phenylene diamines are key precursors to polyfunctional dibenzophenanthroline carboxaldehydes. In contrast, when *ortho*-dibromo benzene is used as substrate, the Pd-mediated process affords exclusively the functional carbazole.

The synthesis of polyfunctional heterocyclic compounds is a very active field of research since this class of compounds is of great interest for pharmacological applications[1] and for use in molecular electronics.[2] A particular feature of condensed aromatics is their ability for π-stacking that contributes to their binding affinity for biomacromolecules and gives rise to molecular ordering via self assembly in the solid state and on surfaces. With regards to their application, a critical issue is the solubility in water or in organic solvents of the aromatic system. This is usually resolved through the attachment of either hydrophilic or hydrophobic chains on the desired aromatic core, but in most cases, the construction of the latter relies on the same synthetic methodologies. In the aza-aromatic series this mainly proceeds via three well-established routes, namely, the Friedländer method,[3] the Skraup reaction[4] and the amination of aryl halides (Ullmann-type reaction)[5a] followed by an intramolecular cyclization. The two former are efficient one-step processes but are somewhat limited by the availability and the chemical stability of the starting materials. On the contrary N-arylation allows in principle the use of a variety of commercially available substrates. N-arylations can be mediated either by a copper or a palladium catalysis, but the copper process (Ullmann–Goldberg)[5b] has suffered a 'bad reputation' related to poor yields and a low reproducibility originating in the harsh conditions required. In the past decade, Pd-catalyzed cross-couplings have been spectacularly developed[6,7] leading to a broad panel of novel Pd-based catalytic systems, which are considered currently as unavoidable substitutes to copper catalysts.[8] However, recent investigations on the scope and limitations of both processes shed light on the interesting complementarity of the two catalytic systems with regards to the functional groups on the coupling partners.[9]

Amino dibenzophenanthrolines (namely quinacridines), have been developed in our group as multistranded DNA binders.[10] In particular the [1,7]-isomers (*meta*-quinacridine) display a high affinity for quadruplex DNA and are potent inhibitors of the telomerase enzyme.[10c] The original synthetic scheme[10a] was based on the copper-catalyzed N-arylation of a dihalogeno benzene ring by 2-amino-5-methyl benzoic acid (i.e. 5-methyl-anthranilic acid abbreviated 5Me-AA), which affords the phenylene diamine **1** (Scheme 1). **1** is further cyclized and functionalized through a four-step sequential process leading to a variety of water soluble polyamino dibenzophenanthrolines.

Here we report on the improved synthesis of **1** using Pd-catalyzed aryl amination and the obtention of novel polysubstituted dibenzo-phenanthrolines derivatives as well as functional carbazoles. In addition, a two-step

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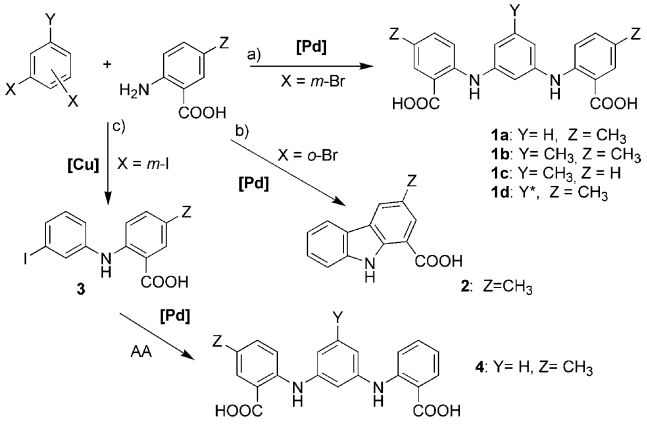


Scheme 1. Reagents: (a), (b) [Pd]: $Pd(OAc)_2$/BINAP, Cs_2CO_3, dioxane, reflux; (c) [Cu]: Cu/CuI, K_2CO_3, pentanol, reflux. *Trisubstituted product starting from 1,3,5-tribromobenzene.

access to nonsymmetrically substituted phenylene diamines based on the copper catalysis is described.

The condensation of our typical substrate 5-MeAA with various aryl halides (mono, di, trihalogeno benzene) was conducted in Ullmann–Goldberg conditions using Cu/CuI as the active catalytic species source. Previous work using these conditions allowed us to build monocondensation products (diphenyl amines) with a satisfactory yield.[11] However, the classical Ullmann conditions appeared more capricious when a dihalogeno benzene derivative was required for introducing the two amino phenyl groups on the aromatic ring. Firstly, when dibromobenzene was used, the evolution of the reaction was highly unpredictable and mixtures containing a low to variable proportion of the disubstituted product are systematically obtained. Therefore, the use of a diiodo derivative appears to be an absolute requirement. This is particularly pronounced in the *ortho* series where the double amination of 1,2-dibromobenzene hardly proceeded at all (<10%) whereas the use of 1,2-diiodobenzene allowed the formation of the double aminated product, albeit in low yield (see Table 1 entries 1 and 2). In the *meta* series, the second coupling is less disfavoured, as expected, and the double amination can be performed with a reasonable yield (45%, entry 4). Nevertheless, a significant decrease in reactivity is still observed when the reaction is carried out with the 1,3-dibromo derivative (entry 3). Also the presence of a methyl group (donor group) on the benzene ring (use of 3,5-dibromotoluene) induces a dramatic decrease in reactivity, the monoarylated product being quite exclusively formed in low yield (entry 5). Finally in the case of the 1,3,5-tribromo benzene the product of trisarylation was detected but not formed in isolable yield (entry 6). In addition, the suppression of the carboxylate function on the aryl-amine (use of *p*-toluidine) or its displacement in position β to the amino group (use of 3-amino benzoic acid) considerably decreased the reactivity (data not shown). This points to the essential role of the chelation of Cu(I) by the carboxylate function as has been observed in the case of the coupling with amino acids.[5] Several recent studies reported on the acceleration of the Ullmann condensation making use of various ligands to activate the copper(I) species.[12–15] Unfortunately, none of these modifications resulted in the significant increase of the biscoupling in our case. Regarding our unsuccessful attempts for improving the copper process, we turned to Pd catalysis.

A crucial factor for a successful catalyst is the choice of the right ligand, base and solvent. Although strong bases and in particular NaO-*t*Bu are the most effective bases, their use severely limits the tolerance to functional groups. This is why N-arylation using cesium carbonate has been further developed to improve the functional group compatibility.[16] Furthermore N-arylation of free carboxylate bearing substrates has been described only recently by Buchwald and co-workers and it has been suggested that binding of the deprotonated oxygen to the palladium centre could be compromising the success of the reaction.[17] Therefore, 5MeAA has been condensed onto *m*-dibromobenzene using the catalytic system $Pd(OAc)_2$/BINAP/Cs_2CO_3 (Scheme 1a). When toluene was used as solvent no improvement was

Table 1. Pd versus Cu-catalyzed N-arylation of dihalogeno benzene derivatives by 5MeAA (2-amino-5-methyl-benzoic acid)

Entry	Arylhalide	Catalyst	Yield[a] (%)	Mono/di [b] (%)
1	1,2-Dibromobenzene	Cu	0—10	50
2	1,2-Diodobenzene	—	20–30	20–50
3	1,3-Dibromobenzene	—	15–20	50
4	1,3-Diiodobenzene	—	30–45	10–20
5	3,5-Dibromotoluene	—	—	100[c]
6	1,3,5-Tribromobenzene	—	—	—[d]
7	1,3-Dibromobenzene	Pd/toluene	28	50
8	1,3-Dibromobenzene	Pd/dioxane	60–80	20
9	3,5-Dibromotoluene	—	87	Traces
10	1,3,5-Tribromobenzene	—	60[e]	Traces
11	1,2-Dibromobenzene	—	—[f]	—

A survey of the reaction conditions.
[a] Disubstituted product, isolated yield.
[b] Ratio of mono/disubstituted product measured by NMR analysis of the crude extract.[18]
[c] Isolated yield 25%.
[d] Mixture of starting material and substitution products.
[e] Trisubstituted product.
[f] Formation of carbazole.

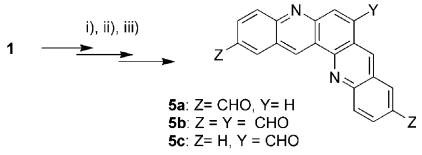
observed as compared to copper catalysis (entry 7). On the contrary, when the reaction was carried out in dioxane, the disubstitution compound was obtained in good to high yield (entry 8). The work up procedure[18] allows the removal of the excess or unreacted 5MeAA, thus the efficiency of the mono versus double amination is estimated on the crude extract through NMR analysis. After purification, a global yield of 60% is obtained (isolated yield) whether the reaction is carried out at 0.5 g or 5 g scale. This represents a remarkable improvement as compared to the copper-catalyzed reaction. This result also points out the importance of the solubility of the reagents or of the intermediate activated species as seen from the dramatic influence of the replacement of toluene by dioxane. Most importantly, the Pd catalysis is much more tolerant than the copper one to the presence of additional functional groups on the aryl halide. This is clearly shown by the reaction of 3,5-dibromotoluene, a poor substrate for disubstitution in the Ullmann conditions, which is converted with Pd to the dicondensation product **1b** in 85–90% yield with only traces of the monoarylated product (entry 9). Similarly a dramatic improvement provided by the use of Pd was also observed when the 1,3,5-tribromobenzene was reacted, since the product of the tris-coupling was formed in 60% yield (entry 10). Apparently, there is no or only slight influence by electronic nature of the aryl halide since no significant difference in reactivity has been observed between electron-rich and electron-deficient derivatives, which is not usually the case in Pd catalysis. This could mean that the steric hindrance of the partners is the dominant factor.

In contrast, we failed to apply the Pd-catalyzed protocol to the formation of the *ortho* phenylene diamine analogues of **1**. Indeed when 5MeAA was reacted with the *ortho* dibromo benzene a unique compound was isolated in high yield (86%, entry 11), which has been identified as being the carbazole derivative **2** (Scheme 1). This means that the intramolecular reductive elimination takes place instead of the second nucleophilic attack, which is disfavoured in this series.[19] Although Pd-catalyzed formation of carbazoles from oxidative cyclization of diphenyl amines is well known, it generally requires the construction of the suitable diarylamine precursors.[20] To our knowledge, only one example of one-pot process has been recently reported[20d] but it is restricted to N-alkylated anilines and requires the presence of halogen atoms of different reactivity on the two substrates. On the contrary, in our case the carbazole ring is obtained readily from the standard dibromobenzene and commercially available AA derivative. 3-methylcarbazole derivatives are key intermediates in the biogenesis of the naturally occurring carbazoles.[20d] Therefore it seems interesting to further investigate the generality of this one-step process.

We decided to take advantage of the predominance of the monoamination in the copper-mediated process (see Table 1) to prepare mixed phenylene diamines through a two step selective functionalization. To this end, 1,3-diiodobenzene has been condensed with a decreased amount of 5-MeAA (1 equiv) and with a shorter reaction time (4–5 h) (Scheme 1c). These conditions provide predominantly the monoarylated product **3**, the presence of the dicondensation product in the crude extract is detected (<10%) but it is easily eliminated by further purification leading to the isolation of **3** in a satisfactory yield (52%). In contrast, the similar variation of stoichiometry in the palladium mediated process led to the obtention of a mixture containing the disubstituted compound as the major product. This has been reported in similar studies[21] and confirms that the coupling of the second equivalent of amine to the monosubstituted intermediate is faster than the addition of the first equivalent to the starting dihalogenobenzene. Therefore, it appears that the monosubstitution of a dihalogeno benzene ring can be more easily performed when a copper catalyst is used rather than Pd. This result is in line to what has been recently reported on Cu-catalyzed N-arylations and might be explained in mechanistic terms favouring the oxidative addition/reductive elimination pathway rather than the involvement of a radical anion intermediate.[9c] Further coupling of **3** to anthranilic acid (AA) was examined using either Pd or Cu catalysis. The Pd catalysis appeared much more efficient and afforded the unsymmetrical phenylene diamine **4** in high yield (Scheme 1) (70% isolated). In the presence of Cu, compound **4** was obtained in satisfactory yield (52%) only when the reaction was boosted by operating in large excess of AA (>5 equiv). This two-step Pd/Cu catalyzed sequence is a simple route to nonsymmetrically substituted phenylene diamines. Its application to the further obtention of dibenzophenanthrolines bearing three different substituents on the external and central rings, respectively, is currently under investigation.

Finally, compounds **1** were submitted to the synthetic sequence cylization/reduction/oxidation previously described,[10a] which afforded the mono-, di- and tri-carboxaldehyde dibenzophenanthrolines **5a**–**c** (Scheme 2). These compounds are key precursors to water soluble derivatives and building blocks for the construction of multichromophoric architectures.[10a]

In summary, we have described an efficient route to polyfunctional dibenzophenanthroline and carbazole cores based on Pd and Cu-catalyzed N-arylation using commercially available dihalogenobenzenes and amino benzoic acids. This flexible process might lead to a large molecular diversity of both heterocylic series, which are of great potential interest for pharmacological and material applications.



Scheme 2. Reagents and conditions: (i) $P(O)Cl_3$ reflux; (ii) $LiAlH_4$, THF reflux, $FeCl_3$, (iii) SeO_2, naphthalene 220 °C.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.02.079.

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18. *Typical procedure of the Pd-catalyzed N-arylation*: Aryl dihalide (1 equiv), Cs_2CO_3 (3 equiv), $Pd(OAc)_2$ (0.04 equiv), BINAP (0.06 equiv), and 2-amino-5-methyl benzoïc acid (2.5 equiv) were introduced in a reaction flask under argon. The flask was evacuated, backfilled with argon and freshly distilled dioxane was added. After refluxing for 24 h under argon, the mixture was cooled down to room temperature and the solvent removed in vacuo. MeOH/H_2O 1/1 v/v was added and the pH of the solution was adjusted to 5 by adding concentrated hydrochloric acid. A precipitate was formed, which was filtrated and analyzed by NMR. The precipitate was then extracted with ether. The ether fractions were combined to give a solid, which was recrystallized in EtOH/H_2O. The Cu process is described in Ref. 12a.
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