Base-Mediated Direct Arylation of Pyrrole Derivatives

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Abstract: It appears that transition metal catalysts are not necessary to perform the direct arylation of electron-rich heterocycles with aryl iodides and bromides. Lithium *tert*-butoxide in DMF promotes this reaction for a variety of *N*-alkyl- and *N*-arylpyrroles as well as for benzofuran and some other electronrich aromatic compounds and provides the desired products in moderate to high yields. In contrast to all previous reports on the Pd-catalyzed direct arylation of indolizine, the reaction mediated by lithium *tert*-butoxide proceeds selectively at position 5.

Keywords: aryl halides; C–C coupling; C–H activation; heterocycles; pyrroles

Recently, much attention has been paid towards searching for new and environmentally friendly alternatives for the construction of biaryl linkages between various homo- and heterocyclic units, which are ubiquitous as medicinal compounds.^[1] These are also fundamental building blocks in the synthesis of more complex molecules which possess interesting photophysical and biological properties.^[2]

Although, currently, numerous synthetic procedures are extensively used,^[3] most of them utilize expensive transition metal catalysts and require preactivation of both reaction partners. Consequently, due to the lack of greener alternatives, synthetic chemists have started to pay significant attention towards the use of aryl C–H bonds as functional groups.^[4,5] Such oxidative intermolecular coupling can be attractive and the simplest alternative to classical methods such as Suzuki– Miyaura, Stille and Negishi reactions. This process, however, is unfavourable from a thermodynamic perspective due to the strength of the aryl C–H bond.^[6] An interesting solution to this issue can be preactivation of one of the coupling partners, that is, direct arylation, a process which has undergone significant development in the last decade.^[7]

One of the fundamental heterocyclic skeletons is that of pyrrole and its importance is difficult to overestimate. Over the last few years, our team^[8] as well as other researchers,^[9] have developed Pd-based conditions for the direct coupling of pyrrole derivatives with aryl halides. The importance of the pyrrole skeleton combined with the lack of an environmentally friendly methodology prompted us to further focus on this problem. Therefore, the central theme of our research is the development of new competitive systems for the direct arylation of pyrroles.

Recently, there has be some development in copper-, iron- and nickel-based procedures for the arylation of various heterocycles.^[10,11] Amongst these discoveries, it was found that copper-mediated coupling reactions demonstrated efficiency for both C- and N-arylation of various aromatic skeletons.^[10] This approach appeared to be a valuable alternative to Pd-catalyzed direct arylation. A model reaction was investigated with N-methylpyrrole (1) and 4-iodobenzonitrile (2) using a variety of published catalytic systems (Table 1).

Conditions revealed by Do and Daugulis for the direct arylation of benzoxazoles^[12] offered only 2% of the desired product. Reactions performed according to the procedure described by Miura and co-workers, consisting of a copper-based methodology for the direct arylation of 1,3,4-oxadiazole and 1,2,4-triazole cores with aryl iodides,^[13] showed traces of both mono- and bis-arylated products. Other screened catalytic systems provided only miniscule amounts of the desired product **3**. Finally, a methodology originally published for the *N*-arylation of pyrazole,^[14] based on copper(I) oxide and Cs₂CO₃, provided the desired compound in 5% yield. Replacing Cs₂CO₃ with *t*-

Table 1. Influence of the reaction conditions on the coupling of *N*-methylpyrrole (1) with 4-iodobenzonitrile (2).^[a]



Entry	Catalyst	Base	Solvent	Yield [%]
1	Cu ₂ O	t-BuOLi	DMF	8
2	Cu_2O	<i>n</i> -BuLi	DMF	4
3	Cu_2O	LDA	DMF	4
4	Cu_2O	DBU	DMF	trace
5	Cu_2O	NaOH	DMF	0
6	none	t-BuOLi ^[b]	DMF	31
7	none	none	DMF	0
8	none	<i>t</i> -BuOLi ^[c] (1 equiv.)	DMF	13
9	none	<i>t</i> -BuOLi ^[c] (4 equiv.)	DMF	31
10	none	t-BuOLi ^[d]	DMF	5
11	none	t-BuOLi ^[c]	DMSO	23
12	none	t-BuOLi ^[c]	DMA	13
13	none	t-BuOLi ^[c]	dioxane	7
14	none	t-BuOLi ^[c]	NMP	11
15 ^[e]	none	t-BuOLi ^[c]	None	0
16 ^[f]	none	t-BuOLi ^[c]	DMF	15
17 ^[g]	none	t-BuOLi ^[c]	DMF	25
18 ^[h]	none	t-BuOLi ^[c]	DMF	49
19 ^[i]	none	t-BuOLi ^[c]	DMF	87

^[a] If not noted otherwise, reactions were performed under the following conditions: 4-iodobenzonitrile (1 equiv.), *N*methylpyrrole (5 equiv.), base (2 equiv.) catalyst (20 mol%), 145 °C, 17 h; yields were determined by HPLC.

^[b] *t*-BuOLi was used as an aged solution.

- ^[c] *t*-BuOLi was used as preheated stock solution.
- ^[d] *t*-BuOLi was used as a freshly prepared solution.
- ^[e] The reaction was performed in the absence of DMF with 20 equiv. of *N*-methylpyrrole.
- ^[f] The reaction was performed at 100 °C.
- ^[g] Yield was measured after 5 h.
- ^[h] For 10 equiv. of *N*-methylpyrrole.
- ^[i] For 15 equiv. of *N*-methylpyrrole.

BuOLi increased the yield of compound **3** up to 8% (Table 1, entry 1).

Inspired by these preliminary results, we initiated a systematic study of the reaction conditions. The first experiments were aimed towards optimization; specifically, by focusing on the type and amount of base used. Bases such as *n*-BuLi, LDA, DBU and NaOH showed less efficiency in comparison to t-BuOLi (Table 1, entries 2–5). Other easily available sources of copper were also investigated (Table in the Supporting Information), but a significant difference in catalytic activity was not noted. Subsequently, other metal oxides were examined as catalysts (Table in the Supporting Information). To our great surprise, yields remained consistent and led us to hypothesize that Cu₂O does not participate in the catalytic cycle. An experiment where only a solution of t-BuOLi was used supported our theory (Table 1, entry 6).

Compound 3 was not produced when the reaction was performed without any base (Table 1, entry 7). Changing the amount of base (Table 1, entries 8 and 9) also did not led to an increase in vield. Unexpectedly, the yield of the model reaction dropped to 8% when an aged solution of t-BuOLi (previously used for convenience) was replaced with the addition of that base as a freshly prepared solution (Table 1, entry 10). The decrease of the yield could be explained either by the formation of a 'complex' between DMF and the base or by the decomposition of t-BuOLi in solution. To provide evidence supporting one of these concepts, additional experiments were conducted. The addition of either Li₂CO₃ or LiOH resulted in a decrease in the yield of product 3 (Table in the Supporting Information). However, simple preheating the solution of t-BuOLi in DMF provided us with the desired product in a 31% yield. With this result in hand, we focused on screening other polar aprotic solvents; however, no improvement in yield was observed (Table 1, entries 11-14). When an experiment was performed in neat N-methylpyrrole, no evidence of compound 3 was found (Table 1, entry 15). Other parameters, such as time and temperature were also altered, but did not offer any improvement (Table 1, entries 16 and 17). Finally, by using a larger excess of one of the coupling partners (Table 1, entry 18 and 19), the desired product 3 was isolated in a satisfactory yield. Other modifications to the reaction conditions did not bring any further improvement (Table in the Supporting Information).

After establishing the optimal conditions (entry 19, dry DMF, 2 equiv. of *t*-BuOLi solution prepared by heating the base in DMF at 80 °C for 16 h, 15 equiv. of pyrrole) for the desired transformation, the scope and limitations of this approach were investigated by synthesizing a broad range of 2-arylpyrroles and testing a variety of iodoarenes with *N*-substituted pyrroles (Table 2).

Aryl iodides with various substituents were reacted with N-methyl-, N-benzyl- and N-phenylpyrrole, leading to products **13–21** in yields ranging from 53% to 92%. In all cases, complete regioselectivity was observed. The reaction was found to be more effective when electron-withdrawing substituents were present on the aryl iodide. Interestingly, aryl bromides turned out to be very efficient substrates for the described system (Table 2). However, direct coupling of 4chlorobenzonitrile with N-methylpyrrole (**1**) yielded only 16% of the desired product **3**.

Unfortunately, pyrrole itself and its derivatives bearing *N*-electron-withdrawing protecting groups (Ts, Boc), as well as *N*-TIPS-pyrrole, were unreactive, probably due to the lability of these groups under the reaction conditions. **Table 2.** Scope of the optimized conditions for the arylation of pyrrole derivatives.^[a]

N R	+	R'	<u><i>t</i>-BuOLi, DN</u> 145 °C, 17	h N	F	2'
Entry	Pyrrole	R	Aryl iodide	R'	Product	Yield ^[b] [%]
1	1	Ме	2	4-CN	3	90 (90) ^[c]
2	1	Ме	6	4-NO ₂	13	92 (78) ^[c]
3	1	Me	7	3-CN	14	70 (88) ^[c]
4	1	Me	8	3-NO ₂	15	83
5	1	Me	9	2-CN	16	55
6	1	Me	10	2-NO ₂	17	61
7	1	Me	11	4-OMe	18	52 (45) ^[c]
8	1	Me	12	_[d]	19	77
9	4	Ph	2	4-CN	20	82
10	5	Bn	2	4-CN	21	78

^[a] If not noted otherwise, reactions were performed under the following conditions: iodide (1 equiv.), *N*-methylpyrrole (15 equiv.), base (2 equiv.), DMF.

- ^[b] Yields of isolated products after column chromatography.
- ^[c] Yields in brackets correspond to bromides.

^[d] 4-Iodo(phenylethynyl).

It is worth mentioning that, for the reaction between N-phenylpyrrole (4) and 4-iodobenzonitrile (2), we were able to recover 85% of 4.

Intrigued by the fact that base alone could mediate direct arylation of certain *N*-substituted pyrrole derivatives, we resolved to attempt the same conditions for other electron-rich compounds.

Various aromatic compounds were tested in reactions with 4-iodobenzonitryle, under optimized reaction conditions. It was found that reactions with such substrates as benzene, 1,2-dimethoxybenzene, anthracene and benzothiophene did not lead to products of direct arylation. On the other hand, more electronrich substrates like benzofuran, *N*-methylindole 1,3,5trimethoxybenzene, indolizine gave the products **22– 26**, although the yields were rather moderate (Figure 1).

It is noteworthy to emphasize that the arylation of indolizine proceeded selectively at position 5, leading to the strongly fluorescent product **25**. This is very interesting, since all previous Pd-catalyzed arylations of this heterocycle proceeded selectively at position 3.^[15] The direct arylation of 1,3,5-trimethoxybenzene with aryl halides has never been reported before, although similar reactions have been developed.^[16]

It is known that impurities present in commercially available metal salts can catalyze various reactions.^[17]



Figure 1. Structures of products 22-26.

Taking into consideration that trace amounts of transition metals, which are known to catalyze direct arylation, can be present in t-BuOLi, some additional experiments were done to examine this issue. No difference in yield was noted in experiments when t-BuOLi from different sources was used. Additionally, to eliminate this possibility, a detailed analysis of lithium tert-butoxide via ICP-AES (inductively coupled plasma-atomic emission spectrometry) was conducted. The results clearly showed that the concentrations of most of the transition metals (Pd, Fe, Cu, Rh and Ru) in the *t*-BuOLi employed in our study were in the range of 0.07–0.13 ppm (see the Supporting Information for details). Among metals which are known to catalyze certain coupling reactions, only nickel was present at the level of 9 ppm. Experiments with the addition of nickel, palladium, copper and iron salts to the model reaction showed no improvement in the yield of product 3. No difference was observed when the model reaction was performed in brand-new glassware. Still, in view of the fundamental study by Leadbeater^[18] showing that Suzuki coupling is catalyzed by palladium, present in sodium carbonate at the level of 50 ppb, a definitive conclusion cannot be drawn as to whether or not the studied process is metal-free. A very recent report by Shi and co-workers has described the direct arylation of benzene and some other aromatic compounds with aryl iodides and bromides, mediated by t-BuOK and 1,10-phenanthroline.^[19] In conjunction with our findings, a significant excess of arene had to be used in order to achieve good yields. It is notable, however, that unlike in our case, electron-deficient aryl iodides displayed diminished reactivity. Although the role of the latter is unclear at this moment, the authors claim that this remarkable transformation was not catalyzed by transition metals.

Four recent reports have described the metal-free arylation as well as alkylation of electron-poor heterocyclic compounds and benzene, which according to the authors, proceeds via a radical mechanism.^[19,20] Initially, we assumed that, in the case of arvlation of N-alkylpyrroles, the same mechanism was valid as well. The addition of *tert*-butyl peroxide and tert-butyl peroxybenzoate, sometimes used as radical scavengers, stopped the model reaction only when they were used in an equimolar ratio to N-methylpyrrole. The control experiments clearly showed that when N-methylpyrrole alone was heated with these radical scavengers in a 1:1 ratio at 145°C, complete decomposition occurred within 15 min. The utilization of another radical scavenger such as 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) did not completely hinder the reaction either. The decrease of the yield of **3** to 23% with 3 equiv. of TEMPO was probably due to side reactions of the same type. In further experiments, it turned out that N-phenylpyrrole was more resistant to oxidation promoted by TEMPO (in comparison to N-methylpyrrole). In the reaction of N-phenylpyrrole with 4-iodobenzonitrile (2) in the presence of 3 equiv. of TEMPO, the yield of product **20** decreased, but only to 30%. Finally, the influence of galvinoxyl on the rate of reaction was studied. The model reaction carried out in the presence of 3 equiv. of galvinoxyl did not afford the desired product. Again, however, some side reactions took place. The analogous reaction with N-phenylpyrrole was also quenched with 3 equiv. of galvinoxyl and N-phenylpyrrole was not decomposed.

Additionally, the attempts to carry out the model reaction by the addition of metallic sodium, which can act as an electron donor and promoter in radical-type mechanisms, did not result in the formation of the desired compound. Consequently, it seems that it is rather impossible to obtain final proof of a radical mechanism for our system, due to the rapid interaction of radical scavengers with the substrates. Although the exact reaction pathway is not clear at this stage, there is no direct evidence that the reaction proceeded *via* a radical-type mechanism. In the attempted reaction of 4-fluorobenzonitryle with *N*-methylpyrrole, product **3** was not detected, which demonstrates that the studied reaction does not proceed *via* an addition-elimination mechanism.

In summary, we have discovered that lithium *tert*butoxide alone can promote the arylation of electronrich heterocycles with aryl iodides and bromides. The reaction affords 2-arylated products in good yields and with high regioselectivity, although the mechanism of this process is currently unclear. In the case of indolizine an unprecedented, intriguing regioselectivity of the arylation is observed, which holds promise for its utilization in the synthesis of previously inaccessible molecules. These results are not only of theoretical significance in that they provide new insights into factors influencing the course of the reaction of electron-rich aromatic compounds with aryl halides, but they may also open the door to practical applications and become a convenient pathway to a variety of compounds bearing aryl-aryl linkages.

Experimental Section

Representative Procedure

Iodoarene (0.6 mmol, 1 equiv.) and pyrrole (9 mmol, 15 equiv.) were placed into a glass tube, flushed with argon. Subsequently 750 μ L of stock solution of the base in DMF (containing 1.2 mmol of *t*-BuOLi) were added. The resulting reaction mixture was stirred overnight at 145 °C. Subsequently, it was evaporated under reduced pressure and purified by column chromatography.

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