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Imane Idris, Fazia Derridj, Thierry Roisnel, Henri Doucet, Jean-François Soulé. Quinoxaline as an integrated directing group in palladium-catalyzed ortho -C–H bond arylation of the aryl unit of 2-arylquinoxalines. New Journal of Chemistry, 2018, 42 (19), pp.16036 - 16039. 10.1039/C8NJ02713G . hal-01894687

**HAL Id: hal-01894687**

**https://univ-rennes.hal.science/hal-01894687**

Submitted on 15 Oct 2018

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# Quinoxaline as Integrated Directing Group in Palladium-Catalyzed Ortho C–H Bond Arylation of the Aryl Unit of 2-Arylquinoxalines

Imane Idris,[a,b] Fazia Derridj[b] Thierry Roisnel,[a] Henri Doucet[a*] and Jean-François Soulé[a*]

**We report the Pd-catalyzed C–H bond arylation at the *ortho*-position of the aryl unit of 2-arylquinoxalines. The reaction proceeds with complete regioselectivity using phosphine-free $Pd(OAc)_2$ as the catalyst and potassium acetate as inexpensive base. In contrast to previously employed directing groups, quinoxaline is an integrated directing group in the final product that only promotes *ortho* mono-arylation without formation of bis-arylated products. A wide variety of (hetero)aryl bromides, including bromopyridine derivatives has been successfully employed.**

Since a few decades, palladium-catalyzed C–H bond activation/functionalization has become a powerful method for the formation of C–C bonds, as it allows the preparation of organic molecules in more efficient and shorter ways with higher atom economy compared to the traditional cross-coupling reactions.[1] Among C–H bond transformations, the direct arylation has drawn a particular attention, as it allows the one-step formation of (hetero)biaryls,[2] which are important units in material and pharmaceutical chemistry owing their high stabilities.[3] It is now possible to regioselectively arylate 5-membered ring heterocycles at the desired positions using substrate or catalytic system control, due to the strong effect of the heteroatom.[4] However, the regioselective arylation of benzene rings is more challenging, and often required the use of a directing group to regioselectively promote the C–H bond cleavage.[5] This strategy has been widely applied using nitrogen atom containing heterocycles as directing groups (Figure 1). Among them, the most commonly employed contains a pyridine unit. For example, 2-phenylpyridine has been successfully arylated using palladium or ruthenium catalysts.[6] In most cases, it is difficult to stop the reaction at the monoarylation stage, and very often a substituent at the C3 position of the pyridine is required to prevent the diarylation. Quinolines[6] or purines (**II**)[7] have also been employed as directing groups in direct arylation reactions. 2-Arylpyrimidines have been arylated using Ru(II)-catalysis.[8] Moreover, 5-membered ring *N*-heterocycles such as pyrazoles (**III**),[6b, 6c] tetrazoles (**IV**),[9] benzoxazoles,[10] benzothiazoles,[11] and (benzo)imidazoles (**V**),[7b, 12] have been successfully used as directing groups in Pd-catalyzed C–H bond arylation. One of the major advantage to employ heterocycles as directing group is that they can be an integral part of the target final structure or did not required additional step to be removed.

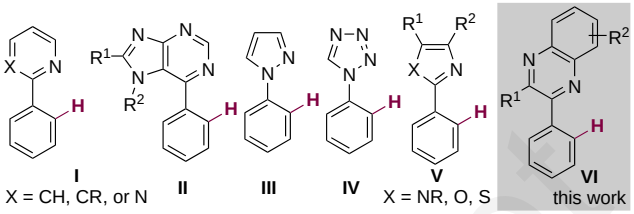



**Figure 1.** Non-Removable Directing Groups Containing Nitrogen atom in Direct Arylation

On the other hand, quinoxaline is an important motif, which has broad applications in materials sciences,[13] and it is a crucial structural scaffold present in plethora of therapeutically useful agents in medicinal chemistry.[14] As examples, the quinoxaline **I** is under evaluation as antineoplastic agent, and the quinoxalines **II** and **III** display inhibition effects of U tyrosine kinase (Figure 2).

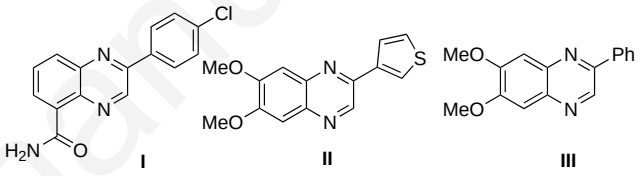



**Figure 2.** Examples of Bioactive Molecules Containing a Quinoxaline Unit.

However, to our knowledge there is no example of direct arylation where quinoxaline plays the role of an integrated directing group,[15] although it could provide an effective methodology to prepare a variety of biological active compounds and active materials in a single operation. Therefore, we propose herein to investigate the palladium-catalyzed C–H bond arylation of arenes using a quinoxaline as directing group.

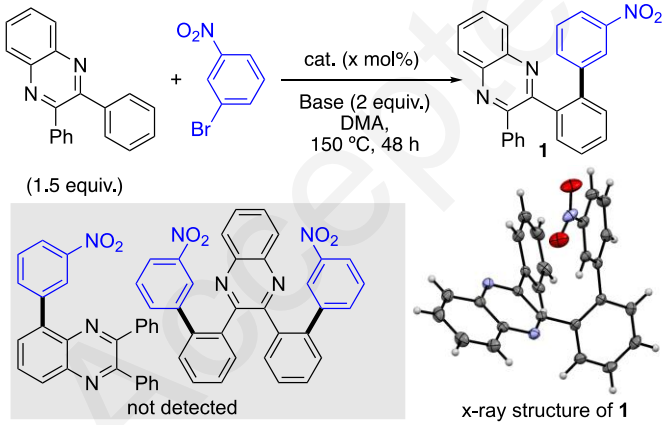
We selected 2,3-diphenylquinoxaline and 3-bromonitrobenzene in 1.5 to 1 ratio as model reaction and we applied our previous phosphine-free conditions for the Pd-catalyzed C–H bond arylation of 6-membered rings,[16] namely 2 mol% of $Pd(OAc)_2$ associated to potassium pivalate (PivOK) as base in DMA at 150 ºC. Under these conditions, we only observed the formation of regioisomer **1**, albeit in a poor yield of 38% (Table 1, entry 1). The C–H bond arylation takes place on one of the two phenyl groups, probably resulting from a *ortho*-directing effect of one of nitrogen atoms of the quinoxaline motif. The structure of **1** was confirmed by X-ray diffraction.[17] We should mention that arylation on the quinoxaline unit was not detected. In order to improve the yield in **1**, we evaluated the catalytic activity of other palladium catalysts (Table 1, entries 2-5). Unfortunately, $PdCl_2$, $[Pd(C_3H_5)Cl]_2$, $PdCl_2(CH_3CN)_2$, or even more stable diphosphine palladium catalyst $PdCl(C_3H_5)$(dppb) displayed lower reactivities. We next evaluated the effect of the nature of the

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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base (Table 1, entries 6-10). The use of a bulkier carboxylate such as adamantyl carboxylate ($AdCO_2K$) lead to a lower yield in **1**. In contrast, AcOK allowed the formation of desired arylated product **1** in 41% yields. Other acetate salts, such as cesium or sodium acetates gave lower yields, and potassium carbonate ($K_2CO_3$) was not operative in this system. Using KOAc as base, we studied the effect of palladium loadings. We had already observed that lower catalyst loadings often gave better results in C–H bond arylation of heteroarenes due to a reduction of the formation of homocoupling side-product of the aryl bromide.[18] Indeed, when we employed lower $Pd(OAc)_2$ loadings, higher yields in **1** were obtained. The best result was obtained using as little as 0.5 mol% of $Pd(OAc)_2$, and the arylated product **1** was isolated in 68% yield (Table 1, entries 11 and 12). A shorter reaction time of 24h lead to a lower yield (Table 1, entry 13). No reaction occurred using non-polar xylene solvent and a lower yield in **1** was obtained in DMF (Table 1, entries 14 and 15). The use of lower amount of 2,3-diphenylquinoxaline (1.2 equiv.) resulted in a lower yield of **1** (Table 1, entry 16). In addition, we did not observe the formation of diarylation product resulting from the activation of both phenyl groups, even in the presence of a larger amount of the aryl bromide (Table 1, entry 17). We explain this lack of reactivity of the second phenyl unit by the formation of a non-coplanar system between the second nitrogen and the second phenyl ring after the first arylation. It is well established that ruthenium(II) is able to catalyze *ortho*-directed arylations using nitrogen directing groups (e.g., pyridine, imines, etc.),[19] but there is no example using a quinoxaline motif as directing group. Therefore, we also employed $[RuCl_2(p\text{-cymene})]_2$ as catalyst for this transformation. Unfortunately, no reaction occurred (Table 1, entry 18).

**Table 1.** Optimization of the Reaction Conditions

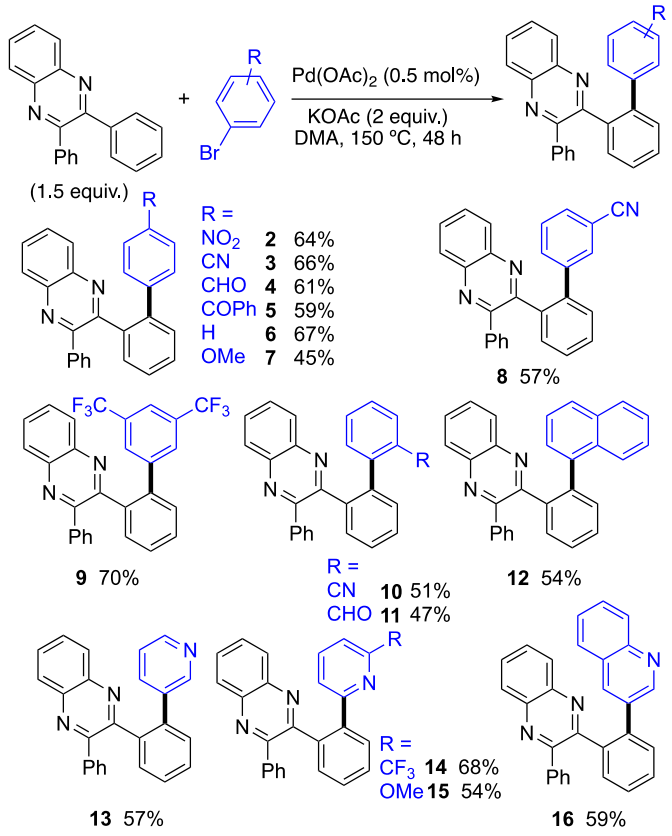



| Entry | Cat. (x mol%) | Base | Yield in **1** %[a] |
|---|---|---|---|
| 1 | $Pd(OAc)_2$ (2) | KOPiv | 38 |
| 2 | $PdCl_2$ (2) | KOPiv | 27 |
| 3 | $[Pd(C_3H_5)Cl]_2$ (2) | KOPiv | 25 |
| 4 | $PdCl_2(CH_3CN)_2$ (2) | KOPiv | 20 |
| 5 | $PdCl(C_3H_5)$(dppb) (2) | KOPiv | 24 |
| 6 | $Pd(OAc)_2$ (2) | $AdCO_2K$ | 26 |
| 7 | $Pd(OAc)_2$ (2) | KOAc | 41 |
| 8 | $Pd(OAc)_2$ (2) | CsOAc | 31 |
| 9 | $Pd(OAc)_2$ (2) | NaOAc | 22 |
| 10 | $Pd(OAc)_2$ (2) | $K_2CO_3$ | 8 |
| 11 | $Pd(OAc)_2$ (1) | KOAc | 52 |
| 12 | $Pd(OAc)_2$ (0.5) | KOAc | 72 (68) |
| 13[b] | $Pd(OAc)_2$ (0.5) | KOAc | 51 |
| 14[c] | $Pd(OAc)_2$ (0.5) | KOAc | 0 |
| 15[d] | $Pd(OAc)_2$ (0.5) | KOAc | 18 |
| 16[e] | $Pd(OAc)_2$ (0.5) | KOAc | 51 |
| 17[f] | $Pd(OAc)_2$ (0.5) | KOAc | 66 |
| 18[g] | $[RuCl_2(p\text{-cymene})]_2$ (5) | $K_2CO_3$ | 0 |

[a] Determined by GC-MS analysis using dodecane as internal standard. The isolated yield was shown in parentheses. [b] 24 h. [c] In xylene. [d] In DMF. [e] Using 1.2 equivalent of 2,3-diphenylquinoxaline. [f] Using 2.5 equivalent of ArBr. [g] In NMP.

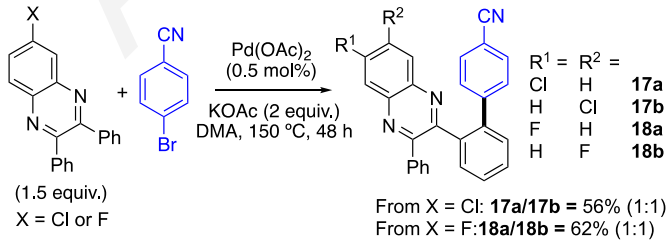
With the best conditions in hands, namely 0.5 mol% of phosphine-free $Pd(OAc)_2$ associated to KOAc as base in DMA at 150 ºC, we turned our attention to the scope of the reaction (Scheme 1). Aryl bromides bearing an electron-withdrawing group at *para* position, such as nitro, cyano, formyl, and benzoyl reacted nicely to afford the corresponding 2-biphenyl-3-phenylquinoxaline **2–5** in 59–66% yields. The reaction was not limited to the use of activated aryl bromides, as bromobenzene and 4-bromoanisole were successfully coupled with 2,3-diphenylquinoxaline affording **6** and **7** in 67% and 47% yields, respectively. The reaction also tolerated *meta*-substituents on the aryl bromide partner. From 3-bromobenzonitrile and 3,5-bis(trifluoromethyl)bromobenzene, the arylated products **8** and **9** were isolated in 57% and 70% yields, respectively. The reaction is slightly sensitive to the steric hindrance, as from 2-nitrile-, 2-formyl-bromobenzenes and 1-bromonaphtalene, lower yields into the *ortho*-arylated 2,3-diphenylquinoxalines **10**-**12** were obtained. *N*-containing heteroaryl bromides such as 3-bromopyridine, 2-bromo-6-(trifluoromethyl)pyridine, 2-bromo-6-(methoxy)pyridine or 3-bromoquinoline, also underwent oxidative addition to afford the desired products **13–16** in moderate yields.

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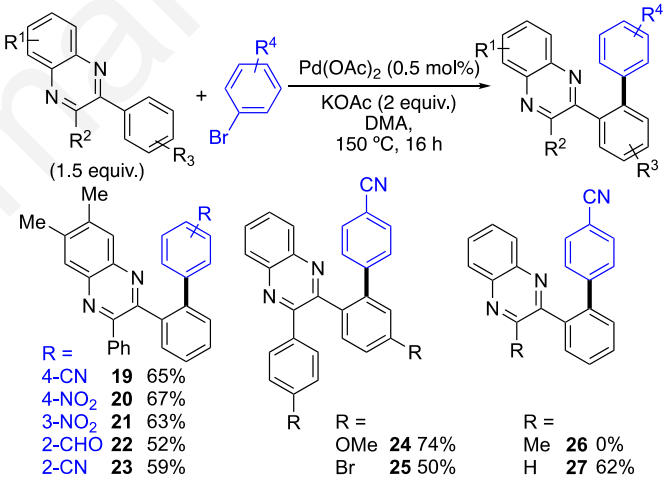

**Scheme 1.** Scope of (Hetero)Aryl Bromides in Palladium-Catalyzed *Ortho*-Directed (Hetero)Arylation of 2,3-Diphenylquinoxaline.

Next, we investigated the reactivity of 6-substituted 2,3-diphenylquinoxalines (Scheme 2). From the reaction of 6-chloro-2,3-diphenylquinoxaline with 4-bromobenzonitrile in the presence of 0.5 mol% $Pd(OAc)_2$ associated to KOAc as base in DMA at 150 ºC, an equimolar mixture of two regioisomer was obtained in 56% yield (Scheme 2, top). Both regioisomers **17a** and **17b** resulted from *ortho*-directed arylations. The two regioisomers have been isolated and characterized separately by $^{1}H$ and $^{13}C$ NMR, but we were not able to assign the corresponding structures of **17a** and **17b**. A similar reactivity was observed with 6-fluoro-2,3-diphenylquinoxaline with 4-bromobenzonitrile, which offered both isomers **18a** and **18b** in 62% yield in an equimolar ratio (Scheme 2, bottom). It is noteworthy that no product resulting from C–H bond activation at *ortho*-position of fluorine atom was detected, in contrast with previous reports on palladium-catalyzed C–H bond arylation of fluorobenzenes, which employed a similar catalytic system.[16a, 20]




**Scheme 2.** Reactivities of 6-Substituted 2,3-Diphenylquinoxalines in Palladium-Catalyzed Direct Arylation.

Using the same reaction conditions, we investigated the reactivity of a set of 2-arylquinoxalines in palladium-catalyzed *ortho*-C–H bond arylation (Scheme 3). From 6,7-dimethyl-2,3-diphenylquinoxaline and *para*-, *meta*- or *ortho*-substituted aryl bromides, the mono-arylation took place on one phenyl substituent allowing the formation of the 6,7-dimethyl-2-biphenyl-1,3-phenylquinoxalines **19**-**23** in 52-67% yields. The electronic properties of the phenyl ring which reacts in the C–H bond activation step was also studied with quinoxaline as directing group. An electron-donating substituent enhances the reactivity, as **24** was obtained in 74% yield. In contrast, when the reaction was performed from 2,3-bis(4-bromophenyl)quinoxaline, the desired product **25** was isolated in 50% yield. These results suggest that an electron-withdrawing group such as bromo makes the C–H bond functionalization more challenging. When 2-methyl-3-phenylquinoxaline was employed as starting material, no reaction occurred. This lack of reactivity might be due to the steric influence of the methyl substituent at quinoxaline C2 position, which prevents the formation of 5-membered palladacycle or due to its high acidity. In contrast, 2-phenylquinoxaline successfully underwent *ortho*-C–H bond arylation of the phenyl ring with 4-bromobenzonitrile to afford **27** in 62% yield.




**Scheme 3.** Reactivities of 2-Aryl-quinoxaline Derivatives in Palladium-Catalyzed Direct Arylation.

## Conclusions

In summary, we have shown that quinoxaline can be used as an efficient directing group in palladium-catalyzed *ortho*-C–H bond arylation. Quinoxaline unit is integrated in many important medicinal or material molecules; therefore, its use as integrated directing group allows the late-stage functionalization of 2,3-diarylquinoxalines. The reaction is regioselective in favor of the formation of the mono-arylated product, in contrast to the previously reported results using a pyridine, as directing group. The reaction operates under very simple conditions using phosphine–free $Pd(OAc)_2$ as catalyst and KOAc as inexpensive base. A wide range of functions such as methoxy, fluoro,

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formyl, propionyl, carboxylate, nitrile or nitro on the aryl bromide is tolerated.

## Acknowledgements

We thank the Algeria "Ministry of Higher Education and Scientific Research" for a fellowship to I.I.

## Conflicts of interest

"There are no conflicts to declare".

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