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# Palladium-catalyzed direct deprotonative arylation of 2-pyridylacetonitriles: Facile synthesis of alpha-aryl-2-pyridylacetonitrile

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ABSTRACT



## Introduction

α-Aryl-2-pyridylacetonitriles play an important role in the development of new drugs and carrier materials [1]. Gulick's work revealed that some α-aryl-2-pyridylacetonitrile derivatives had a strong inhibition effect of PvdQ enzyme (Fig 1-a,b), and it could be used to develop news drugs for small molecule inhibition of Pseudomonas aeruginosa which can replace the antibiotics [2]. In the synthesis of 5-HT1A receptors ligands (Fig 1-c), Krol's work showed α-aryl-2-pyridylacetonitrile derivatives were the crucial fragments for the synthesis of important intermediates [3]. All of these illustrate that it was very important to synthesize α-aryl-2-pyridylacetonitrile derivatives in the process of developing new drugs and screening of lead compounds by using highly selective and efficient synthesis methods. Unfortunately, it has been observed that there is a lack of efficient synthetic methods of α-aryl-2-pyridylacetonitrile derivatives. Up to now, α-aryl-2-pyridylacetonitriles can only be obtained by $S_N2$ intermolecular reactions using potassiophenylacetonitrile or phenylacetonitrile as substrates (Scheme 1-A, B) [4,5]. In the above process, due to the sensitivity of substituents to reaction conditions, the chemical diversity of derivatives is limited. Moreover, the low utilization rate of raw. Moreover, the low utilization rate of raw materials and the yield of target products are also important problems. Considering a number of our completed work about deprotonative-coupling reactions, we envisioned a unified approach to access these important structural motifs based on a non-traditional approach [6–8]. In this work, we also used palladium-catalyzed deprotonative cross-coupling process (Scheme 1-C). For the first time, a series of α-aryl-2-pyridylacetonitrile derivatives were synthesized via palladium catalyzed coupling reaction using 2-pyridylacetonitrile derivatives as starting materials. Moreover, by extending the substrate we found that this condition was resistant to multiple functional groups attached to the core. It indicated that this work offers great help to the construction of α-aryl-2-pyridylacetonitrile derivatives, as well as to the synthesis of lead compounds and the development of new drugs with inhibitory activity of PvdQ enzyme and bio-active compounds such as 5-HT1A receptors ligands [2,3].

## Results and discussion

Because of strong coordination between N of pyridine and Pd catalysts, the α-arylation in 2-pyridylacetonitrile cores becomes very difficult [9]. One of strategies to address this potential problem includes adding Lewis acid to bind N in the pyridine group and to increase the reactivity of the pyridine benzyl C—H [10].

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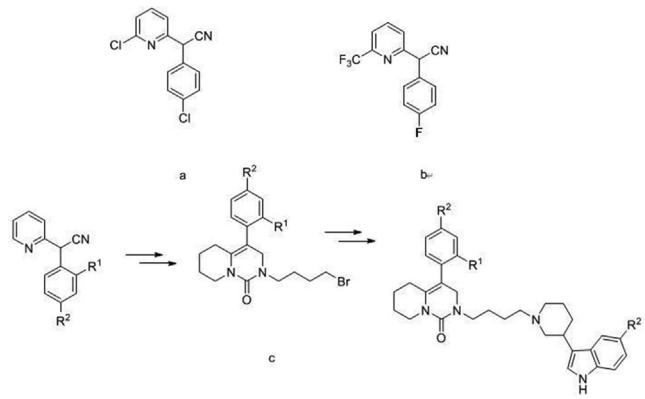
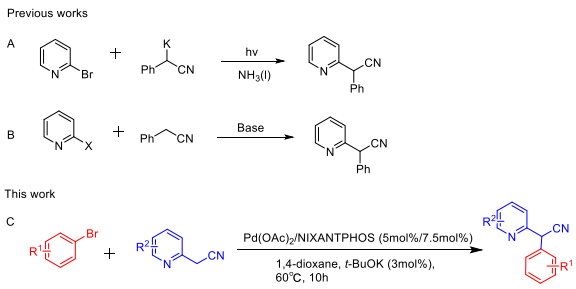


**Fig. 1.** α-aryl-2-Pyridylacetonitrile derivatives were used as active lead compounds and significant intermidate.



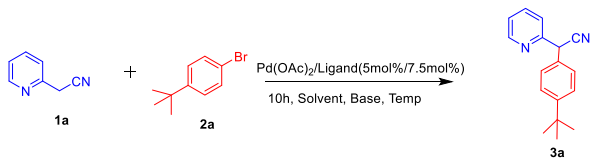

**Scheme 1.** Synthesis of α-aryl-2-pyridylacetonitriles.

Instead in our strategy, we chose strong bases such as *t*-BuOK and KHMDS to enhance the reactivity of α-H. Moreover, in our previous work, [6–8]we found that due to palladium complexes of van Leeuwen's NixantPhos's stronger coordination ability than N of pyridine, good results can be obtained by building sp3-sp2 C—C bond in the deprotonative-coupling process of low-acidic substrates [11,12]. At the same time, the α-H of 2-pyridyl acetonitrile derivatives tends to leave under the interaction of strong electron withdrawing group CN and electron deficient aromatic ring. Therefore, NixantPhos was chose as our preferred ligand.

Our study began with the evaluation of the reaction condition of palladium-catalyzed deprotonative arylation of 2-pyridylacetonitrile (Table 1). Firstly, with 2-pyridylacetonitrile **1a** and 4-*tert*-butyl bromobenzene **2a** as substrates, we used *t*-BuOK as a strong base to deprotonate α-H of 2-pyridylacetonitrile. We used Pd $(OAc)_2$ as catalyst in dipolar aprotic solvent 1,4-dioxane and heated at 60 ℃ for about 10 h, so that the substrate 2-pyridylacetonitrile **1a** was completely consumed. The effects of different ligands on the reaction were also observed by comparing the monodentate phosphate ligands tricyclic hexylphosphine ($PCy_3$) (Entry 1), triphenylphosphine ($PPh_3$) (Entry 2), the bidentate phosphate ligands bis(diphenylphosphino)-1,1′-BINAPhthyl (BINAP) (Entry 3), and 4,6-bis(diphenylphosphino)phenoxazine (NixantPhos) (Entry 4). Among the screening experiments, $Pd(OAc)_2$/NixantPhos (5 mol %/7.5 mol%) (Entry 4) obtained a higher yield of product **3a** than other ligands. This also confirmed the conclusion obtained in our previous work [6–8]. In order to explore the influence of different solvents on the reaction process, we used another three solvents to conduct control experiments with Entry 4 without changing other reaction conditions. We used dipolar aprotic solvents THF (Entry 6), ethylene glycol dimethyl ether (DME) (Entry 7) and nonpolar solvents cyclopentyl methyl ether (CPME) (Entry 8). The results showed that there was no reaction took place in the nonpolar solvent CPME (Entry 8), while the reaction in the other two dipolar aprotic solvents gave lower yields compared to 1,4-dioxane. That suggested that the reaction should be carried out in a dipolar aprotic solvent and 1,4-dioxane was very suitable.

Subsequently, the effects of temperature and base were screened. By comparison, the yield of product **3a** was generally higher in the strong alkali environment (Entry 4, 10, 13, 14) when *t*-BuOK, KHMDS, LiHMDS and $K_2CO_3$ were used. The above results indicated that under the reaction condition of 1,4-dioxane, a small steric strong base should be coordinately used to achieve a better activation of α-H, and *t*-BuOK was the most suitable. The yields of products **3a** obtained by the reaction were 92% (Entry 4) and

**Table 1**
Optimization of direct 2-pyridylacetonitrile **1a** with 1-bromo-4-*tert*-butylbenzene **2a.**




| Entry | Ligand | Solvent | Base | Temp (°C) | Yield(%) |
|---|---|---|---|---|---|
| 1 | $PCy_3$ | 1,4-dioxane | *t*-BuOK | 60 | 80 |
| 2 | $PPh_3$ | 1,4-dioxane | *t*-BuOK | 60 | 88 |
| 3 | BINAP | 1,4-dioxane | *t*-BuOK | 60 | 84 |
| 4 | NixantPhos | 1,4-dioxane | *t*-BuOK | 60 | 92 |
| 5 | NixantPhos | 1,4-dioxane | *t*-BuOK | R.T. | 46 |
| 6 | NixantPhos | THF | *t*-BuOK | 60 | 80 |
| 7 | NixantPhos | DME | *t*-BuOK | 60 | 77 |
| 8 | NixantPhos | CPME | *t*-BuOK | 60 | NR |
| 9 | NixantPhos | 1,4-dioxane | $Cs_2CO_3$ | 60 | 29 |
| 10 | NixantPhos | 1,4-dioxane | KHMDS | 60 | 84 |
| 11 | NixantPhos | 1,4-dioxane | KHMDS | R.T. | 55 |
| 12 | NixantPhos | 1,4-dioxane | *t*-BuOK | 90 | 34 |
| 13 | NixantPhos | 1,4-dioxane | LiHMDS | 60 | 88 |
| 14 | NixantPhos | 1,4-dioxane | $K_2CO_3$ | 60 | NR |

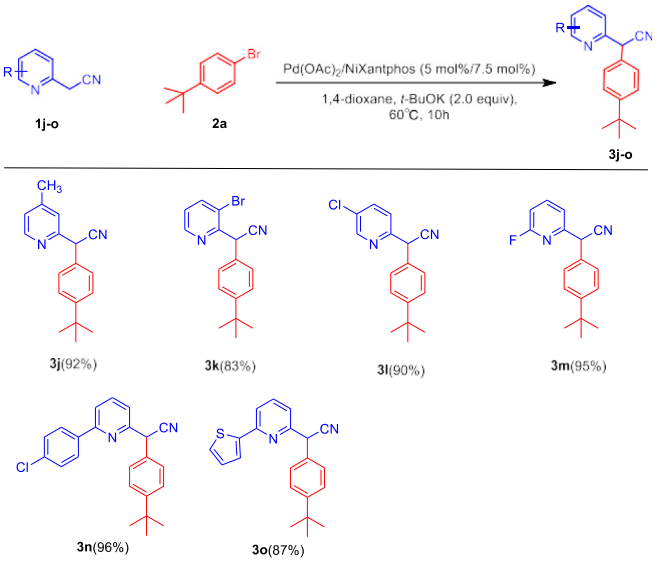
[a]Reactions conditions: **1a** (1.0 mmol, 1.0 equiv), **2a** (1.5 mmol, 1.5 equiv), *t*-BuOK (2 mmol, 2.0 equiv), and every 1 mmol **1a** reacted with solvents (3 mL), 10 h.
[b]Yield confirmed by $^1$H NMR, CH2Br2 was taken as the internal standard substance.

84% (Entry 10) respectively under the conditions of proper heating to 60 ℃. Entry 5, 11 and 12 showed that lower or higher reaction temperature displayed negative effect on the yields of coupling product **3a**. Therefore, properly heating to 60 ℃ was suitable for our reaction. In summary, 2-pyridineacetonitrile **1a** and 1-bromo-4-*tert*-butylbenzene **2a** were used as substrates, $Pd(OAc)_2$/NixantPhos (5 mol%/7.5 mol%) was used as the catalyst system. Under the influence of basic *t*-BuOK in solvent 1,4-dioxane, the reaction was the most suitable. When heated to 60 ℃ for about 10 h, the substrate 2-pyridylacetylene **1a** completely disappeared.

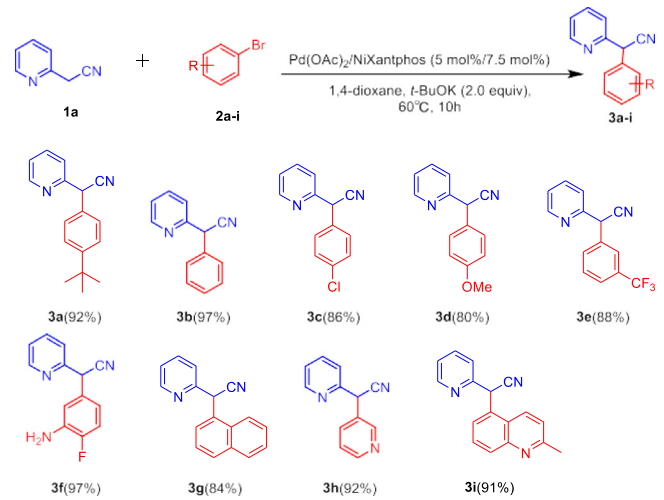
After screening the reaction conditions, 2-pyridyl acetonitrile **1a** and a series of aryl bromide **2a-i** were used as substrates to investigate the applicable range of reaction conditions (Scheme 2). Generally, high yield products can be obtained from substrates with electron withdrawing or electron donating groups and substituents such as small steric hindrance groups. From the experimental results of **3a-f**, we knew that examined reaction conditions had good adaptability and tolerance for bromobenzene compounds with electron-withdrawing and electron-donating groups. In addition, 1-bromonaphthalene **2g**, 3-bromopyridine **2h** and 5-bromo-2-methylquinoline **2i** were coupled with 2-pyridylacetonitrile **1a** to investigate the adaptability of different brominated aromatic compounds to reaction conditions, especially the substrates with sterically hindered substituents. Under the optimized conditions, the yields of **3g**, **3h** and **3i** were 84%, 92% and 91%, respectively. In conclusion, for brominated aromatic compounds with general steric hindrance, the reaction conditions determined by us are generally tolerable.

After studying the arylation of 2-pyridylacetonitrile **1a** with a variety of brominated aryl compounds **2a-i**, we briefly explored the arylation of 2-pyridylacetonitrile derivatives **1j-o** and 4-*tert*-butyl-1-bromobenzene **2a** substrates with substitutive groups to understand the universal applicability of $Pd(OAc)_2$/NixantPhos catalytic conditions (Scheme 3). Successfully, 2-pyridylacetonitrile derivatives **1j-o** and 4-*tert*-butyl-1-bromobenzene **2a** as substrates got ideal yields in 83%-96% for products **3j-o**. To begin with, we tried to react 4-methyl-2-pyridine acetonitrile **1j** with the substrate 4-*tert*-butyl-1-bromobenzene **2a** under optimized condition. The high yield of product **3j** was 92%. At the same time, taking the trend of widespread application of electron-withdrawing groups such as halogen atoms in drug development into consideration, we selected 3-bromo-2-pyridine acetonitrile **1k**, 5-chloro-2-pyridine acetonitrile **1l** and (6-fluoropyridine-2-yl)acetonitrile **1m** as substrates to combine 4-*tert*-butyl-1-bromobenzene **2a**. Products **3k**, **3l** and **3m** obtained high yields of 83% , 90% and 95% respectively. Finally, 2-(6-(4-chlorophenyl) pyridine-2-)acetonitrile **1n** and 6-(2-thiophenyl)-2-pyridine acetonitrile **1o** were coupled with 4-*tert*-butyl-1-bromobenzene **2a** to investigate the effects of steric hindrances on the reaction of electron-rich aromatic rings. Unsurprisingly, products **3n** and **3o** were obtained in high yields of 96% and 87% respectively. These **3j-o** experimental results indicated that some common substituents on the pyridine group had little effect on the reaction, and the reaction conditions we selected could provide high yield for the combination of 2-pyridylacetonitrile derivatives and aryl brominated derivatives.

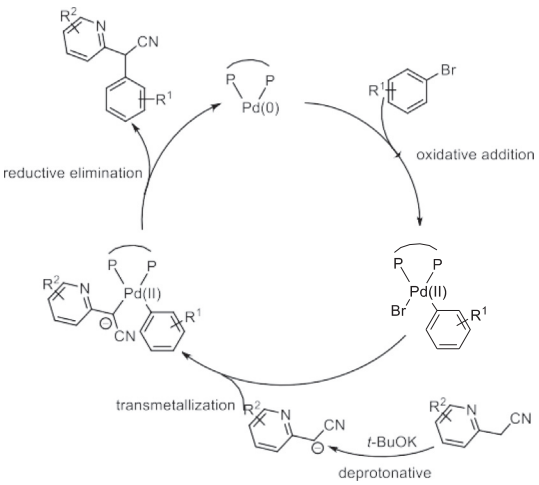
In 2015, Walsh et al. reported that $Pd(OAc)_2$/NixantPhos was used as catalytic system to construct $sp^3$-$sp^2$ C—C bond through deprotonative cross-coupling [13]. By comparison, we found that the two works were very similar. Therefore, we inferred that our mechanism was credible by referring to the mechanism they pro-




**Scheme 3.** Range of 4-*tert*-1-bromobenzene **2a** in direct α-arylationof 2-pyridylacetonitrile derivatives **1j-o.**




**Scheme 2.** Range of bromoaryl compound **2a-i** in direct α-arylation of 2-pyridylacetonitrile**1a.**




**Scheme 4.** Proposed mechanism [13].

posed (Scheme 4). The catalytic cycle begins with $Pd(OAc)_2$/NixantPhos pre-Pd (0) catalyst. The brominated aryl compound **2a** constructs Pd complexes by oxidative addition. Then, the exposed electron-rich C **1a** extracted by *t*-BuOK builds Pd complexes with the -Ar in **2a** by means of transmetallization. Finally, through reduction and elimination, we gain the target product **3a** and the Pd (0) catalysis which entered into the catalytic cycle.

In summary, we successfully developed the method of catalyzing the deprotonative grade-arylation of 2-pyridylacetonitrile derivatives with the help of $Pd(OAc)_2$/NixantPhos. The success of this reaction will provide an efficient scheme for the synthesis of bioactive new chemical entities and important intermediate fragment, which included α-aryl-2-pyridylacetonitrile derivatives. Moreover, it also provides a new method for the synthesis of amides and carboxylic acids with a as upstream substrate.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgement

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152534.

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