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Room-Temperature Palladium-Catalysed Suzuki-Miyaura Coupling of Arylboric Acid with Aryl Chlorides†

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An efficient room-temperature Pd-catalyzed Suzuki-Miyaura cross-coupling reaction of arylboronic acids with aryl chlorides is communicated here. The Pd(OAc)2/NiXantphos catalyst system enables the coupling reaction at room temperature in good to excellent yields (average yield > 90%).

The construction of C-C bond is considered to be an important issue in transition-metal catalyzed organic reactions.1 With the discovery of Suzuki-Miyaura cross-coupling of arylboronic acids with aryl halides in 1981,2 a convenient and selective sp3 C-C bond forming method was established.3 As boron is similar to carbon in size and electronegativity, both boronic acids and boronate esters are highly nucleophilic, display excellent and broad functional group tolerance. In addition, structurally diverse biaryl motifs obtained from Suzuki reaction are important structural elements of massive natural products, pharmaceuticals, agrochemicals4 as well as many bioactive polymers.5 It is for these reasons that Suzuki reaction has emerged as a favorite tool in both industrial and academic fields.

Although aryl chlorides have been proved to be inactive in Suzuki reaction since the very beginning, numerous low-cost compounds available in this class still attract many researchers’ attention.6 To address this issue, high temperature (> 100 °C), along with commercial metal/ligand, was generally employed in early protocols,7 which inevitably limits the substrate scope with heat-intolerant heterocyclic aryl halides, such as furans and thiophenes (Scheme 1A); Later, to achieve room-temperature Suzuki coupling reaction with aryl chlorides, some novel ligands/precatalysts were successfully designed and prepared.8 However, these studies shared drawbacks like difficult preparation procedures for the ligands/precatalysts (Scheme 1B). It is worth mentioning that some ligand-free researches were highlighted as they achieved room temperature Suzuki reactions in PEG.

But unfortunately, they were all confined to phenylboronic acid.6,9 Therefore, it is still practically and theoretically significant to develop novel synthetic method for room-temperature Suzuki-Miyaura cross-coupling of aryl chlorides.

van Leeuwen’s NiXantphos (see Scheme 1 for structure) has been proved to be an efficient ligand in sp3-sp2 C-C formation by promoting several arylation reactions10 yet its application in sp2-sp2 has not been reported. In our preliminary work, we have disclosed the first direct 2-arylation of benzoxazoles catalyzed by Pd/NiXantphos at room temperature.11 Recently, Zhang reported that aryl chlorides could be activated by NiXantphos at room temperature.12 So we surmised that NiXantphos might be active in room-temperature Suzuki cross coupling of aryl chlorides. Here, we...
are communicating the efficient Pd(OAc)$_2$/NiXantphos-catalyzed room-temperature Suzuki-Miyaura coupling of arylboronic acids with aryl chlorides (Scheme 1C).

Our research started from the screening of bases (KF, CsCO$_3$, K$_2$HPO$_4$, K$_2$CO$_3$, KHCO$_3$, KH$_2$PO$_4$) adopting Pd(OAc)$_2$/NiXantphos-based catalytic system with H$_2$O/THF (1:5) as solvent (Table 1). Results showed that with K$_2$CO$_3$ as base, 4-tert-Butylphenylboronic acid 1a (1.2 equiv) and 1-chloro-4-methylbenzene 2a (1.0 equiv) could access to 4-tert-butyl-4’-methylphenyl 3a in 88% yield after 3 h (Table 1, entry 3). And when the reaction time was prolonged to 6 h, the conversion rate was significantly improved. Then the scope of solvents (H$_2$O/THF, H$_2$O/PhH, H$_2$O/DME, H$_2$O/1,4-Dioxane) were tested adopting K$_2$CO$_3$ as base at room temperature for 6 h. With H$_2$O/THF (1:5) as solvent, 3a was afforded in near quantitative yield after 6 h (Table 1, entry 9).

The substrate scope of aryl chlorides 2a-n (1.0 equiv) with 4-tert-Butylphenylboronic acid 1a (1.2 equiv) was investigated (Scheme 2) under the optimized reaction conditions as Pd(OAc)$_2$ (2 mol%), NiXantphos (3 mol%). K$_2$CO$_3$ (2.0 equiv) in H$_2$O/THF (1:5) at room temperature for 6 h, and gave corresponding products 3a-n in yields from 65% to 99%. In general, the reaction could be facilitated by strongly electron-withdrawing groups like trifluoromethyl, cyano group, nitro group, etc. (Scheme 2, heteroaryl compounds, mainly 2-phenylpyridines, account for half of the products. It is worth to mention that 2-phenylpyridine derivatives were widely reported to show antitumor and anticancer activity$^{12}$. Since our group has been conducting research on the design and synthesis of anti-cancer molecules with simple structures$^{14}$, 2-chloro pyridines were preferred substrates in this work.

2-phenyl-5-(trifluoromethyl) pyridine derivatives were reported to have various bioactivities$^{15}$, like g-secretase modulation, antimalarial activity, P2X3 receptor antagonism, Glucagon receptor antagonism, etc. Therefore, it was chosen in the scope investigations of arylboronic acids 1b-o (1.2 equiv) (Scheme 3) under the optimized reaction conditions as Pd(OAc)$_2$ (2 mol%), NiXantphos (3 mol%). K$_2$CO$_3$ (2 equiv) in H$_2$O/THF (1:5) at room temperature for 6 h, and gave corresponding products 4a-n in yields from 70% to 96%. It could be seen that the reaction could be suppressed when possessing substrates with strongly electron-donating groups like ether group (Scheme 3, 4m). Among the coupling products, 4m and 4n were afforded from 2-furanboronic acid 1n and 2-thiophenylboronic acid 1o with 2k, respectively, proving the successful application of heteroarylboronic acids.

Para, meta and ortho substituents in aryl chlorides were all well tolerated in the room-temperature Suzuki coupling with 4-tert-butyphenylboronic acid, providing products in yields from 65% to 99%. Similarly, para and meta substituents in arylboronic acids were well tolerated, and afforded products in yields from 70% to 96%.

We also evaluated the scalability of this method by performing the coupling of 3-chloropyridine 2m with 4-methoxyphenylboronic acid 1f on gram scale. The coupling product, 3-(4-methoxyphenyl)pyridine 5a was isolated in 60% yield. This yield is

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent (ratio)</th>
<th>Time</th>
<th>Yield (%)</th>
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<td>1</td>
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<td>H$_2$O/THF (1:5)</td>
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<td>5</td>
<td>CsCO$_3$</td>
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<td>7</td>
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<td>H$_2$O/Dioxane (1:5)</td>
<td>6h</td>
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</table>

$^a$Reactions performed using 1.2 equiv of 1a, 1.0 equiv of 2a and 2.0 equiv of base on a 0.2 mmol scale.

$^b$Isolated yields.
relatively high, proving that the Pd(OAc)$_2$/NiXantphos based catalyst could stay active in room-temperature Suzuki cross coupling of aryl chlorides without chelating with Nitrogen atom in pyridine.

**Scheme 3** Scope of aryl boronic acid in the room-temperature Suzuki coupling with 2-chloro-5-(trifluoromethyl) pyridine (2k)

![Scheme 3](image)

**Scheme 4** Room-temperature Suzuki coupling of 3-Chloropyridine with 4-Methoxyphenylboronic acid on gram scale

![Scheme 4](image)

In summary, Pd(OAc)$_2$/NiXantphos-catalyzed Suzuki-Miyaura cross-coupling reaction of arylboronic acids with aryl chlorides were realized at room temperature in high yields (average yield >90%). In our method, a broad range of substrates could be adopted to afford diverse products with minor limitations. The success of this method attributes to the application of commercially available ligand NiXantphos. Next, we will continue our exploration for cross coupling reaction of aryl chlorides using NiXantphos as ligand.

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**Notes and references**

† D.W. and H.-G.C. contributed equally.


The first room-temperature Suzuki-Miyaura coupling of arylboric acid with aryl chlorides catalyzed by Pd(OAc)$_2$/NiXantphos-based system is communicated.

\[
\text{Ar}_1\overset{\text{OH}}{\text{B}}\overset{\text{OH}}{\text{OH}} + \text{Cl}\text{Ar}_2 \xrightarrow{\text{Pd(OAc)}_2 (2 \text{ mol\%}) \text{ NiXantphos (3 mol\%})} \overset{\text{K}_2\text{CO}_3 (2.0 \text{ equiv.}) \text{ H}_2\text{O/THF (1:5), 6h}}{\text{Room Temperature}} \overset{29 \text{ examples up to 99\% yield}}{\text{Ar}_1-\text{Ar}_2}
\]