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

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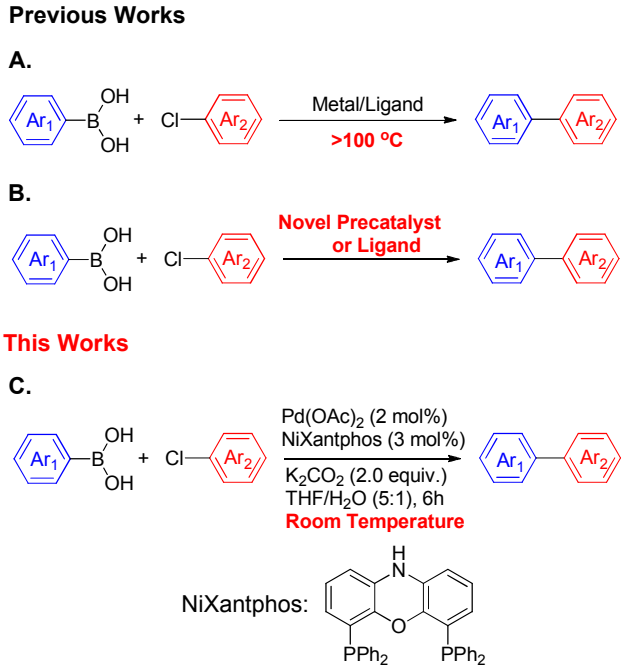
An efficient room-temperature Pd-catalyzed Suzuki-Miyaura cross-coupling reaction of arylboronic acids with aryl chlorides is communicated here. The Pd(OAc)2/NiXantphos catalyst system enables the coupling reaction at room temperature in good to excellent yields (average yield＞90%).

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 sp^2 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, agrochemicals[4] 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 ℃), 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.



Scheme 1 Suzuki-Miyaura coupling of aryl chlorides

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 sp^3-sp^2 C-C formation by promoting several arylation reactions,[10] yet its application in sp^2-sp^2 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

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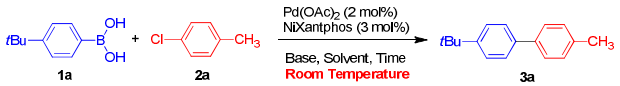
Table 1 Optimization of Suzuki coupling of 4-tert-butylphenylboronic acid (**1a**) with 1-chloro-4-methylbenzene (**2a**) [a]



Entry	Base	Solvent (ratio)	Time	Yield (%)[b]
1	KF	H_2O/THF (1:5)	3h	58
2	$CsCO_3$	H_2O/THF (1:5)	3h	55
3	K_2CO_3	H_2O/THF (1:5)	3h	88
4	KF	H_2O/THF (1:5)	6h	60
5	$CsCO_3$	H_2O/THF (1:5)	6h	80
6	K_2HPO_3	H_2O/THF (1:5)	6h	85
7	$KHCO_3$	H_2O/THF (1:5)	6h	90
8	KH_2PO_3	H_2O/THF (1:5)	6h	90
9	K_2CO_3	H_2O/THF (1:5)	6h	95
10	K_2CO_3	H_2O/PhH (1:5)	6h	75
11	K_2CO_3	H_2O/DME (1:5)	6h	92
12	K_2CO_3	H_2O/Dioxane (1:5)	6h	90

[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.

are communicating the efficient $Pd(OAc)_2$/NiXantphos-catalyzed room-temperature Suzuki-Miyaura coulping of arylboronic acids with aryl chlorides (Scheme 1C).

Our research started from the screening of bases (KF, $CsCO_3$, K_2HPO_3, K_2CO_3, $KHCO_3$, KH_2PO_3), adopting $Pd(OAc)_2$/NiXantphos-based catalytic system with H_2O/THF (1:5) as solvent (Table 1). Results showed that with K_2CO_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'-methylbiphenyl **3a** in 88% yield after 3 h (Table 1, entry 3). And when the reaction time was prolonged to 6h, the conversion rate was significantly improved. Then the scope of solvents (H_2O/THF，H_2O/PhH，H_2O/DME，H_2O/1,4-Dioxane) were tested adopting K_2CO_3 as base at room temperature for 6h. With H_2O/THF (1:5) as solvent, **3a** was afforded in near quantitative yield after 6 h (Table 1, entry 9).

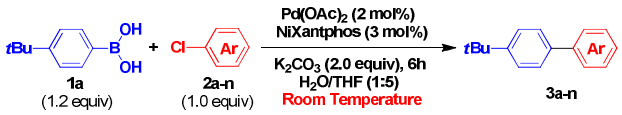
The substrate scope of aryl chlorides **2a-n** (1.0 equiv) with 4-*tert*-Butylphenylboronic acid **1a** (1.2 equiv) was investigated (Scheme 2) under the optimized reaction conditions as $Pd(OAc)_2$ (2 mol%), NiXantphos (3 mol%)，K_2CO_3 (2.0 equiv) in H_2O/THF (1:5) at room temperature for 6 h, and gave 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, **3e**, **3i**, **3j**, **3k**). As is shown in 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[13]. 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.

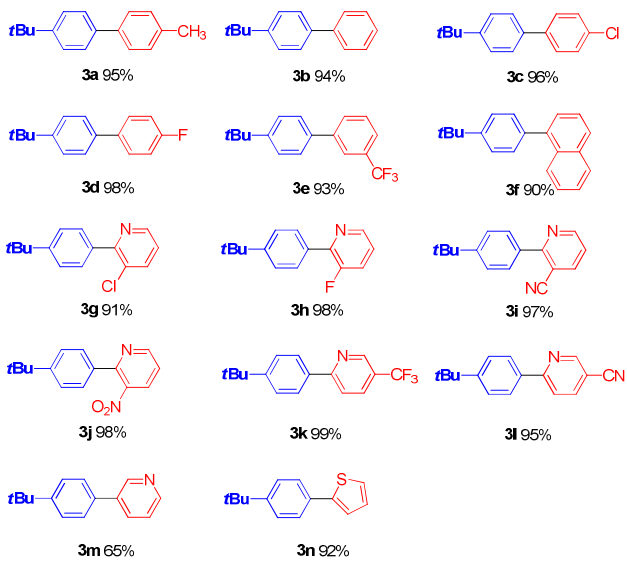
2-phenyl-5-(trifluoromethyl) pyridine derivatives were reported to have various bioactivities[15], like g-secretase modulation, antimalarial activity, P2X3 receptor antagonism, Glucagon receptor antagonism, etc. Therefore, it was chosen in the scope investigations of arylboronic acids **1b-o** (1.2 equiv) (Scheme 3) under the optimized reaction conditions as $Pd(OAc)_2$ (2 mol%), NiXantphos (3 mol%)，K_2CO_3 (2 equiv) in H_2O/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, **4e**). Among the coupling products, **4m** and **4n** were afforded from 2-furanboronic acid **1n** and 2-thiophenylboric 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*-butylphenylboronic acid, providing products in yields from 65% to 99%. Similarly, *para* and *meta* substituents in arylboronic acids were well tolerable, and afforded products in yields from 70% to 96%.

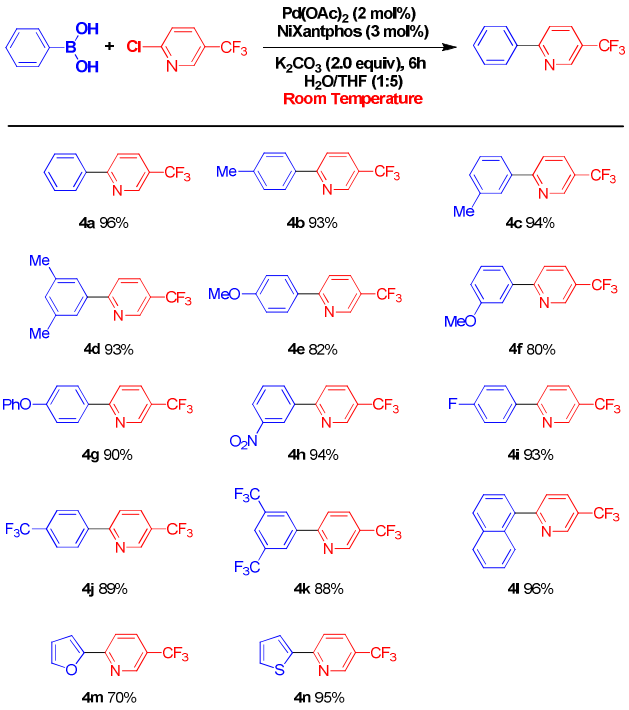
We also evaluated the scalability of this method by performing the coupling of 3-chloropyridine **2m** with 4-methoxyphenylboronic acid **1f** on gram scale. The coupling product, 3-(4-methoxyphenyl)pyridine **5a** was isolated in 60% yield. This yield is

Scheme 2 Scope of aryl chloride in the room-temperature Suzuki coupling with 4-*tert*-Butylphenylboronic acid (**1a**)



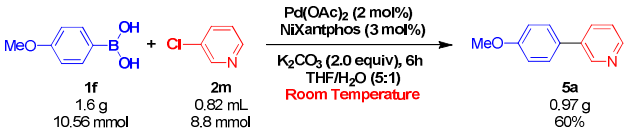


Scheme 3 Scope of aryl boronic acid in the room-temperature Suzuki coupling with 2-chloro-5-(trifluoromethyl) pyridine (**2k**)



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



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

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