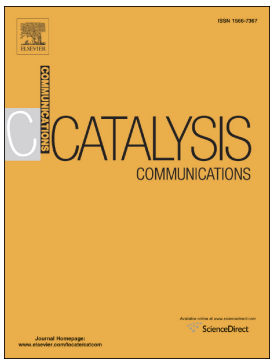

Ruthenium-catalyzed Suzuki coupling of anilines with alkenyl borates via selective aryl C-N bond cleavage

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Ruthenium-Catalyzed Suzuki Coupling of Anilines with Alkenyl Borates via Selective Aryl C-N Bond Cleavage

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Keywords: Ruthenium Catalyst; Aniline; Alkenes; C-Coupling; Alkenyl Borates; C-N Bond Cleavage

Abstract: Herein, we developed a new ruthenium(0)-catalyzed Suzuki-coupling of *N,N*-dimethyl-2-(pyridin-2-yl) anilines with alkenyl borates to synthesize 2-phenylolefins via the cleavage of neutral aryl C-N bond. In the absence of ligand and additives, by using pyridine as the directing group, the desired 2-phenylolefins were obtained in good to excellent yields with high stereoselectivity (*E*/*Z* > 20:1).

Transition-metal catalyzed functionalization of non-activated bonds, such as C-H, C-C, C-F, and C-N bonds has become one of the most powerful protocols in modern organic synthesis.[1] Among the substrates, anilines are versatile chemical building blocks for many organic molecules in the manufacture of advanced materials, pharmaceuticals and agricultural chemicals.[2] Due to the accepted importance, numerous synthetic approaches have been developed for the aryl C-N bond formation during the past decades, such as Buchwald-Hartwig amination,[3] Ullmann cross-coupling reaction,[4] C-H amination and etc.[5] In contrast, the functionalization of anilines via cleavage of the aryl C-N bond is much less reported. Given the abundance and wide availability of anilines, it is important and attractive to develop new methods for their synthetic transformations. Many other useful functionalized organic molecules can be obtained by cleavage of the aryl C-N bond. Such process can open possibilities on using amino group as a site for the late-stage functionalization of molecules. However, the aryl C-N bond usually has high dissociation energy, and chemically inert which lead the direct transformation challenge.[6] Conventionally, activation of the aryl C-N bond is conversing the aryl C-N bond into the corresponding diazonium salts,[7] or ammonium salts,[8] which contain much higher reactivity (Figure 1, eq a). Remarkably, this challenge has been partly overcome by the research groups of Chatani, Shi, and Xia (Figure 1, eq b).[9] Suzuki-coupling, Kumada-coupling, borylation and reduction reactions of neutral anilines via the direct aryl C-N bond cleavage have been successfully developed with nickel as the catalyst without directing group.

On the other hand, chelation-assisted inert bonds cleavage at 2-position of the directing groups has been identified as a powerful strategy for regioselective C-X (X = H, C, F, N, etc.) bond functionalization.[10] This strategy has also been successfully explored in the functionalization of neutral aryl C-N bonds (Figure 1, eq c).[11] To date, four examples have been successfully developed on the chelation-assisted inert neutral aryl C-N bond cleavage. In 2007, Kakiuchi and co-workers reported a $RuH_2(CO)(PPh_3)_3$-catalyzed Suzuki-coupling of o-NMe_2 substituted pivalophenones.[11a,11b] By using ketone as the directing group (DG), organic boronic acid 2,2-dimethyl-1,3 propanediol esters were coupled via aryl carbon–nitrogen bond cleavage in refluxing toluene. Later on, the research groups of Snieckus and Szostak successfully used amides[11c] and imines[11d] as the DGs for this Suzuki-type C(aryl)–N bond cleavage reaction. In 2017, Zeng and co-workers also reported a mild chromium-catalyzed Kumada-coupling of neutral anilines using imine as the directing group.[11e] Herein, we developed a new ruthenium(0)-catalyzed Suzuki-coupling of *N,N*-dimethyl-2-(pyridin-2-yl) anilines with alkenyl borates to synthesize 2-phenylolefins via the cleavage of neutral aryl C-N bond by using pyridine as the directing group. The desired 2-phenylolefins can be obtained in good to excellent yields with high stereoselectivity by using $Ru_3(CO)_{12}$ as the only catalyst.

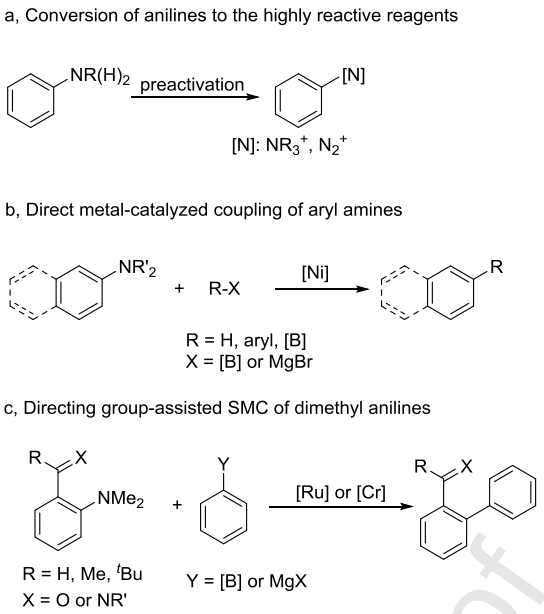
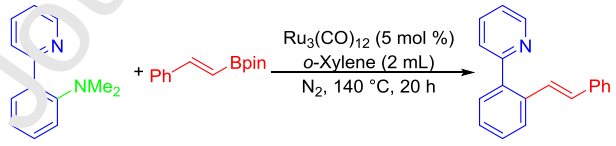


Figure 1. The methods to active aryl C-N bonds. (a) Converse the aryl C-N bond into the corresponding highly reactive ammonium salts or diazonium salts; (b) Nickel-catalyzed direct coupling of relatively reactive neutral amines; (c) DG assisted cross-coupling reaction of neutral anilines.

To begin this study, we chose *N,N*-dimethyl-2-(pyridin-2-yl) aniline (**1a**) and (*E*)-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolaneas (**2a**) as the model substrate to establish the reaction conditions. After extensive experimentation, we found that the (*E*)-2-(2-styrylphenyl) pyridine (**3a**) was obtained in 89% yield with $Ru_3(CO)_{12}$ (5 mol %) as the catalyst in o-Xylene under Argon at 140 °C without any ligand or additives (Table 1, entry 1). Here, it is worthy to mention that almost quantitative yield of the desired product could be obtained with 0.5 equivalent of the catalyst. Other ruthenium catalysts, such as $[Ru(p\text{-cymene})Cl]_2$, $Ru(PPh_3)_3Cl_2$, and $RuH_2(CO)(PPh_3)_3$ were submitted to the transformation to replace $Ru_3(CO)_{12}$. However, only $RuH_2(CO)(PPh_3)_3$ delivered **3a** in moderate yield (Table 1, entries 2-4), which was an efficient catalyst in the other catalytic cleavage of aryl C-N bond reactions.[11a,b,c] We also investigated other metal catalysts, including $NiCl_2(PCy_3)_2$, $Rh_4(CO)_{12}$, $Re_2(CO)_{10}$, and $Co_2(CO)_8$ (Table 1, entries 5-8). Unfortunately, these catalysts are not able to break the aryl C-N bond and substrate stays non-converted. In addition, other solvents such as toluene, anisole or chlorobenzene were less effective than o-xylene for this transformation (Table 1, entry 9). Different styrylboron reagents were also examined, and organoboronic esters show good results than the corresponding boronic acid which may be caused by the difference on the stability of the boron reagents (Table 1, entries 10-11). Other additives such as CsF, KF, usually act as accelerators in Suzuki-coupling reactions, is disadvantageous for this transformation (Table 1, entry 12). Furthermore, decreasing the catalyst loading led to reduced yield of **3a** (Table 1, entry 13).

Table 1. Optimization of the Reaction Conditions.[a]



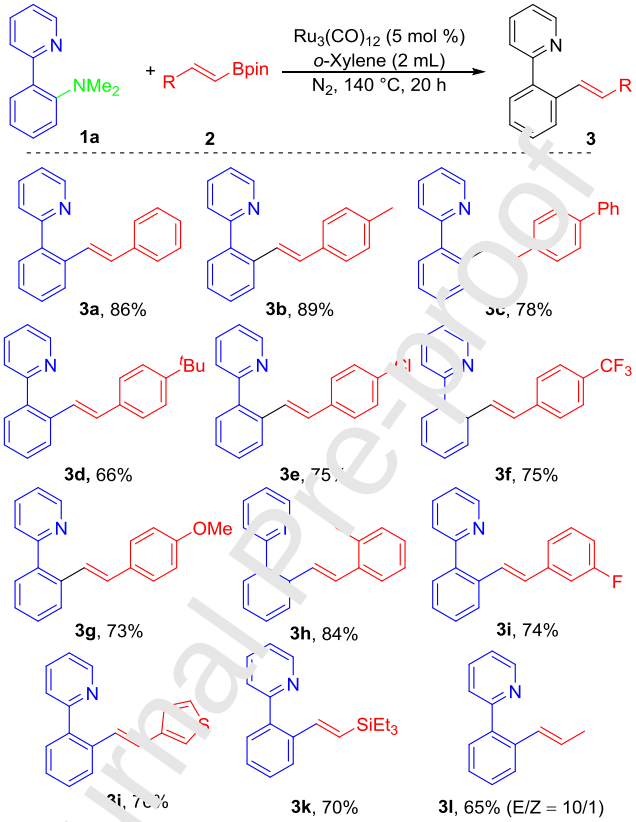
1a **2a** **3a**

entry	variation from the standard conditions	yield (%)[b]
1	-	89
2	$[Ru(p\text{-cymene})Cl]_2$ instead of $Ru_3(CO)_{12}$	n.r.
3	$Ru(PPh_3)_3Cl_2$ instead of $Ru_3(CO)_{12}$	n.r.
4	$RuH_2(CO)(PPh_3)_3$ instead of $Ru_3(CO)_{12}$	59
5	$NiCl_2(PCy_3)_2$ instead of $Ru_3(CO)_{12}$	n.r.
6	$Rh_4(CO)_{12}$ instead of $Ru_3(CO)_{12}$	n.r.
7	$Re_2(CO)_{10}$ instead of $Ru_3(CO)_{12}$	n.r.
8	$Co_2(CO)_8$ instead of $Ru_3(CO)_{12}$	n.r.

9	toluene, anisole, or PhCl instead of *o*-xylene	73, 69, 86
10	(*E*)-styrylboronic acid instead of **2a**	51
11	(*E*)-5,5-dimethyl-2-styryl-1,3,2-dioxaborinane instead of **2a**	88
12	CsF, or KF(1.5 equiv.) as additive	43,47
13	2.5 mol% $Ru_3(CO)_{12}$	71

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), $Ru_3(CO)_{12}$ (5 mol %), N_2, *o*-Xylene (2 mL), 140 °C, 20 h. [b]Determined by GC using hexadecane as the internal standard. n.r. is no reaction.

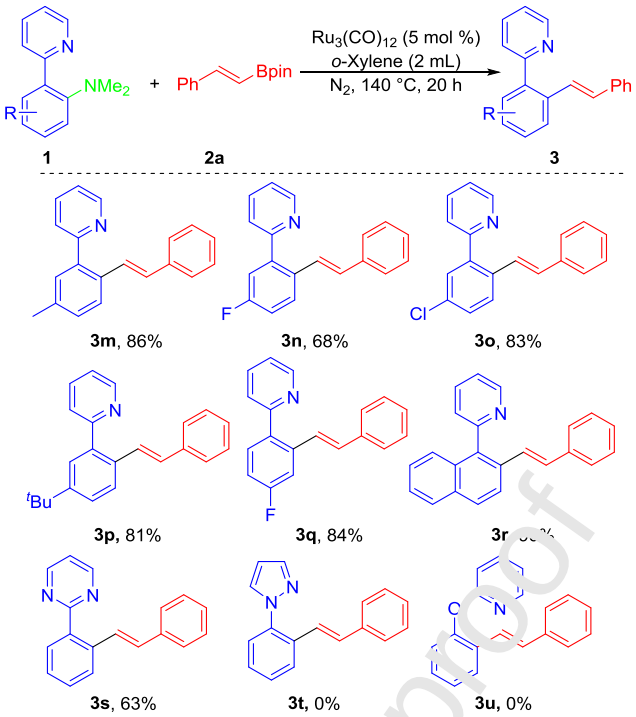
Scheme 1. The scope of various alkenyl borates in ruthenium-catalyzed coupling cleavage of aryl C-N bond. Reaction conditions: 1a (0.2 mmol), 2 (0.24 mmol), $Ru_3(CO)_{12}$ (5 mol %), N_2, o-Xylene (2 mL), 140 °C, 20 h, isolated yields.



With the optimized reaction condition in hand, we next investigated the scope of substrates for this catalytic system. Firstly, a range of alkenyl borates were tested in this cross-coupling reaction. As shown in Scheme 1, the styrylboronic acid pinacol esters with electron-neutral groups gave the desired styrylbenzene in excellent yields (**3b**, **3c**, and **3h**), except **3d** was achieved in 66% yield. Other synthetically valuable functionalized groups, such as fluoro-(**3i**), chloro-(**3e**), trifluoromethyl-(**3f**), methoxy-(**3g**), were also well tolerated in this catalytic system. Furthermore, heterocyclic alkenyl borates, 2-(thiophen-3-yl) vinyl boronic acid pinacol ester can also gave the desired product in high yield (**3j**). Besides, 2-(triethylsilyl) vinyl boronic acid pinacol ester able to give the corresponding **3k** in good yield as well, and **3k** is a very useful synthetic intermediate for late-stage functionalization of alkylsilyl.[12] Interestingly, when we used allyl boronic acid pinacol ester as the reagent, the corresponding 2-(2-(prop-1-en-1-yl) phenyl) pyridine(**3l**) as the single product was isolated in 65% yield (E/Z = 10:1), no product with terminal alkene was detected. Moreover, phenylboronic acid ester was tested under the optimized conditions as well, only a trace amount of the target biphenyl product was observed.

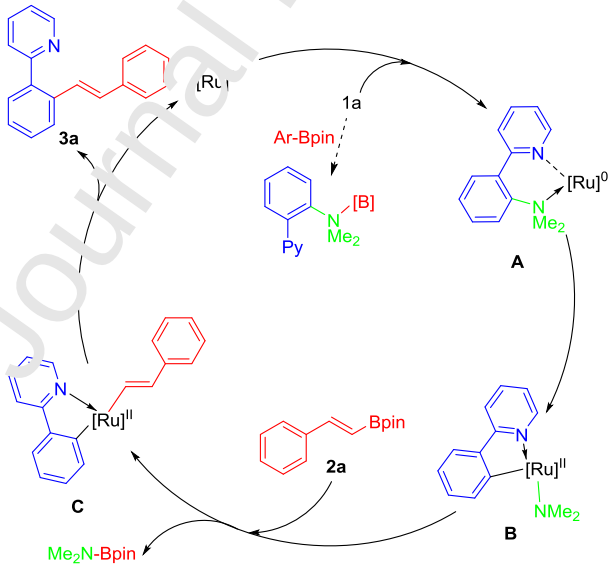
We then examined various *N,N*-dimethylanilines under our standard conditions (Scheme 2). Both alkyl- and halogen-substituted substrates can be applied in this catalytic system and gave the corresponding diaryl alkenes products in good to excellent yields (**3m**-**3q**). Naphthalene-2-amine is a highly reactive starting material, and the desired product was obtained in excellent yield under the standard conditions (**3r**). Pyrimidine, considered as an analogue group of pyridine, can be applied as directing group here as well and gave the corresponding product with moderate yield (**3s**). However, other directing groups, such as pyrazole (**3t**) and 2-hydroxypyridine (**3u**), can't promote the cleavage of aryl neutral C-N bond under our conditions.

Scheme 2. The scope of various *N,N*-dimethylanilines in ruthenium-catalyzed coupling cleavage of aryl C-N bond. Reaction conditions: 1a (0.2 mmol), 2 (0.24 mmol), $Ru_3(CO)_{12}$ (5 mol %), N_2, o-Xylene (2 mL), 140 °C, 20 h, isolated yields.



Based on the above results and previous studies,[9b,11,13] a plausible reaction pathway is proposed (Scheme 3). Firstly, substrate **1a** coordinate with carbonyl ruthenium to give intermediate complex **A**. Then, intermediate **B** was generated through the activation of C-N bond. After transmetlation, the intermediate **C** was achieved. Finally, the desired product **3a** can be eliminated through reductive elimination and the catalytic active ruthenium can be regenerated for the next catalytic cycle.

Scheme 3. Proposed Mechanism.



In summary, we have developed a ruthenium(0)-catalyzed Suzuki-coupling of *N,N*-dimethyl-2-(pyridin-2-yl) anilines with alkenyl borates to synthesize 2-phenylolefins via the cleavage of neutral aryl C-N bond using pyridine as directing group. In the absence of ligand and additives, various 2-phenylolefins were obtained in good to excellent yields with high stereoselectivity (*E/Z* > 20:1).

Conflicts of interest

There are no conflicts to declare.

Acknowledgment

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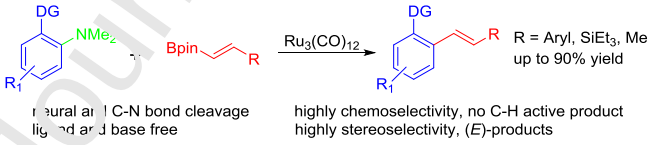
Graphic abstract:



Credit Author Statement

X.W. directed the project. J.X. and F. Z. performed all the experiments. R. F. joined in the discussion. J. X., F. Z. and X. W. prepared and revised the manuscript.

We have no conflict of interest to declaration!

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