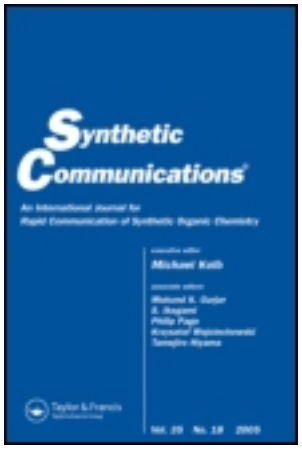

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$RuCl_3$-Catalyzed Regioselective Diarylation with Aryl Tosylates via C-H Activation

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Baoli Zhao
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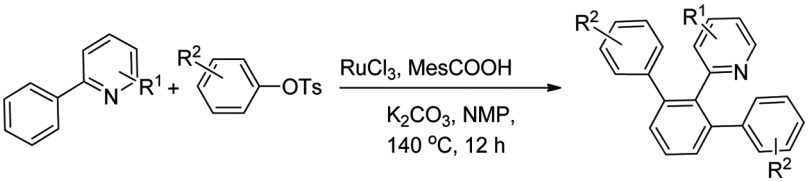
GRAPHICAL ABSTRACT



Abstract *The direct arylation of arylpyridines with aryl tosylates was carried out smoothly in the presence of 2.5 mol% $RuCl_3$ using MesCOOH as crucial promoter to generate biarylated products. The method is simple, efficient, safe, and regioselective, can be performed in the absence of expensive ligands, and does not require any precautions with regard to the exclusion of air and moisture. The biarylated products were obtained in good yields.*

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Keywords Aryl tosylates; C–H activation; diarylation; ruthenium catalysis

INTRODUCTION

Transition-metal-catalyzed C-C bond-forming reactions have emerged as a powerful tool in organic synthesis, allowing access to structural backbones with high selectivity and efficiency. Suzuki–Miyaura, Heck, and Stille reactions are the most often used examples of this synthetic strategy.[1] More recently, much attention has been paid to green and sustainable reactions for developing environmentally friendly processes. Catalytic processes involving C-H bond activation are highly desirable, not only because they allow the functionalization of more readily available starting materials[2] but also because they produce clean products.[3] Nowadays, formally unactivated C-H bonds are used as the functionalization site on the nucleophilic coupling partner in transition-metal-catalyzed direct arylation.[4] Regioselective

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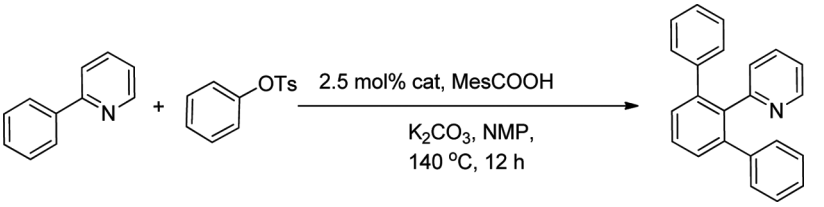
conversion of C-H to C-C bonds would result in shortening of synthetic schemes by allowing the use of readily available starting materials.[5–16]

The research focus has shifted to the direct arylation of aromatic substrates by C-H bond functionalizations to make aryl–aryl linkages ecologically and economically friendly alternatives, which sets the stage for novel routes to substituted biaryls. The intermolecular coupling of arenes with aryl halides is a principal reaction system in the rapidly growing area of transition-metal-catalyzed direct arylation. Among the known direct arylations of arenes, the majority have been accomplished applying aryl halides/pseudohalides as electrophiles.[17–20] The possibility of using aryl tosylates, which can be easily prepared from readily available corresponding phenols or ketones as electrophiles in cross-coupling chemistry is very attractive because they are convenient to use. However, the great stability makes aryl tosylates less reactive in transition-metal-catalyzed processes. Methods for cross-coupling reactions between aryl tosylates and organometallic complexes have been developed.[21–25] Direct arylations through C-H bond activation using tosylates under catalyses have proven rare. Ackermann and co-workers[26] reported an example for nitrogen-coordinating functional groups that employed direct mono-arylation and controlled the regioselectivity. Pyridine has been proven to be an effective directing group for C-H bond activation, usually using ruthenium(II) complex ($[RuCl_2(\eta^6\text{-}C_6H_6)]_2$ and $[RuCl_2(p\text{-cymene})]_2$) as catalysts, and good selectivity was achieved.[27–37] Very recently, $RuCl_3$ has shown catalytic activity to achieve biarylated products.[38–42] In 2010, Arackiam et al. reported a transformation by C-H bond functionalization catalyzed by carboxylato ruthenium(II) systems in water.[43] In this article, we describe our findings regarding the direct arylation of aryl tosylates and arylpyridines substrates catalyzed by $RuCl_3$ using simple carboxylic acids such as MesCOOH (2,4,6-trimethylbenzoic acid) as promoters. The reactions can be performed in the absence of expensive ligands and do not require any precautions with regard to the exclusion of air and moisture, and biarylated products were obtained in good yields.

Our investigations into the development of an efficient arylation catalyst began with the reaction of 2-phenylpyridine and phenyl 4-methylbenzenesulfonate in the presence of 2.5 mol% $[RuCl_2(PPh_3)_3]$ at 120 °C for 12 h in NMP (1-methylpyrrolidin-2-one), which afforded no arylation products. After the addition of 1 equiv MesCOOH, 53% of the desired product was detected when the mixture was heated at 140 °C for 12 h (Table 1, entry 1). Use of $[RuCl_2(p\text{-cymene})]_2$ increased the yield to 60%. However, we were delighted to find that the rate of arylation reaction was markedly accelerated in the presence of $RuCl_3$, and the biphenylated product was isolated in 85% yield (Table 1, entry 4). $PdCl_2$, $Pd(OAc)_2$, $Pd(PPh_3)_4$, and $Pd_2(dba)_3$ were then chosen as catalyst precursors. However, in all cases, the arylation reactions were sluggish (Table 1, entries 4–7). $[RhCl(PPh_3)_3]$ was ineffective under these conditions (Table 1, entry 8).

The screening of various acids summarized in Table 2 revealed MesCOOH was the best. The steric effect and electronic properties of the arene did not significantly influence the arylation (Table 2, entries 1–10). Many aliphatic acids were also tested, and the arylation reactions were sluggish (Table 2, entries 11–13). The effect of base was also investigated (Table 3). The additions of acid and base are indispensable to the reaction.

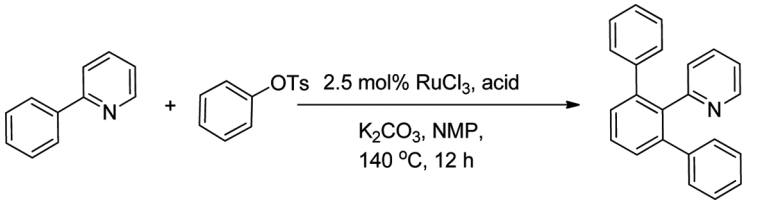
Table 1. Arylation reaction in the presence of various catalysts[a]



Entry	Catalyst	Yield (%)[b]
1	$[RuCl_2(PPh_3)_3]$	53
2	$[RuCl2(p\text{-cymene})]_2$	60
3	$RuCl_3$	85
4	$PdCl_2$	35
5	$Pd(OAc)_2$	32
6	$Pd(PPh_3)_4$	25
7	$Pd_2(dba)_3$	22
8	$[RhCl(PPh_3)_3]$	—

[a]Reaction conditions: 2-phenylpyridine (1 mmol), 4-methylbenzenesulfonate (2.2 mmol), catalyst (2.5 mol%), MesCOOH (1 mmol), K_2CO_3 (2 mmol), NMP (5 mL), 140 °C, 12 h.
[b]Isolated yields.

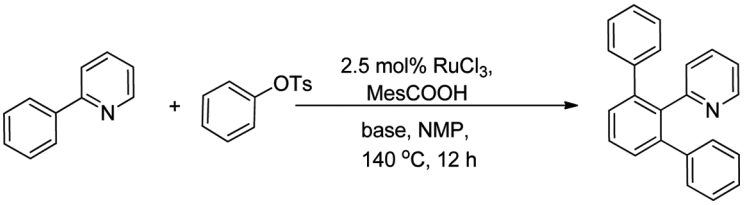
Table 2. Screening of various acids[a]



Entry	Acid	Yield (%)[b]
1	Benzoic acid	56
2	2-Methylbenzoic acid	72
3	3-Methylbenzoic acid	71
4	4-Methylbenzoic acid	70
5	2-Nitrobenzoic acid	65
6	3-Nitrobenzoic acid	71
7	4-Nitrobenzoic acid	67
8	4-Aminobenzoic acid	71
9	4-Aminobenzenesulfonic acid	43
10	2,4,6-Trimethylbenzoic acid	85
11	Octanoic acid	22
12	Acetic acid	—
13	2-Phenylacetic acid	29
14	—	—

[a]Reaction conditions: 2-phenylpyridine (1 mmol), 4-methylbenzenesulfonate (2.2 mmol), $RuCl_3$ (2.5 mol%), acid (1 mmol), K_2CO_3 (2 mmol), NMP (5 mL), 140 °C, 12 h.
[b]Isolated yields.

Table 3. Base effect of the arylation in the presence of MesCOOH[a]



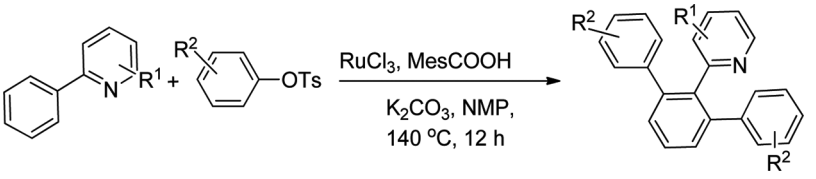
Entry	Base (mol %)	Yield (%)[b]
1	K_2CO_3	85
2	K_3PO_4	70
3	KOH	61
4	KF	53
5	KOAc	51
6	Na_2CO_3	44
7	NaOAc	42
8	$NaBF_4$	33
9	Et_3N	—
10	—	—

[a]Reaction conditions: 2-phenylpyridine (1 mmol), 4-methylbenzenesulfonate (2.2 mmol), $RuCl_3$ (2.5 mol%), MesCOOH (1 mmol), base (2 mmol), NMP (5 mL), 140 °C, 12 h.
[b]Isolated yields.

The superior efficiencies obtained with $RuCl_3$ in the presence of MesCOOH prompted us to select this reagent combination for further exploration. The scope of the arylation reaction with respect to the aryl tosylate component was investigated (Table 4). A variety of aryl tosylates that incorporate electron-donating and electron-withdrawing groups were well tolerated (Table 4, entries 1–5). In addition, the electronic properties of the substituents on arylpyridines proved to have little effect on the arylation processes, and good to excellent yields were obtained (Table 4, entries 6–8). It should be noted that the clean biarylated products were delivered in these reactions. However, when a methyl group was located at the 3-position of phenylpyridine, the monophenylated and diphenylated products were isolated in a ratio of 1:1 (Table 4, entry 9, 36% diphenylated and 37% monophenylated product), showing that the steric effect influenced the arylation. Placing the less bulky fluoride attenuated the steric effect, and the biarylated product could be isolated as the main product (Table 4, entry 10). 2-(Naphthalen-2-yl)pyridine also delivered the diarylated product in good yield (Table 4, entry 11). As expected, the arylation proceeded in comparable yield and efficiency when structurally diverse heterocycles, including pyrazole, pyrimidine, pyridazine, and quinoline, were used as the substrates (Table 4, entries 12–15).

The experimental evidence at present to explain the exact reaction pathway for the direct arylation processes is rare. When equimolar quantities of aryl tosylates and 2-arylpyridine are employed under the reaction condition, we can afford corresponding monoarylated and diarylated products in the ratio of 36:64. (The total yield is 69%.) The monoarylation may occur first and then another arylation at the

Table 4. $RuCl_3$-catalyzed arylation in the presence of MesCOOH[a]



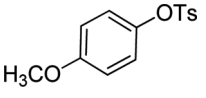
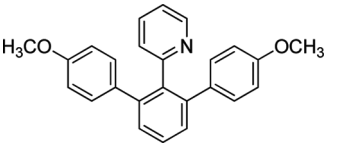
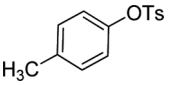
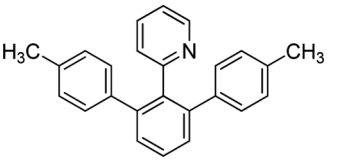
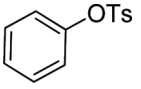
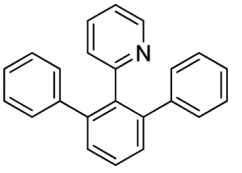
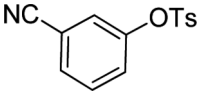
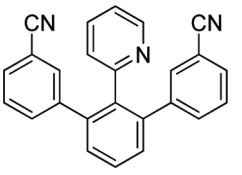
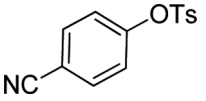
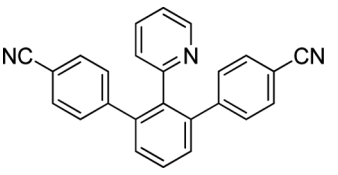
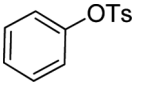
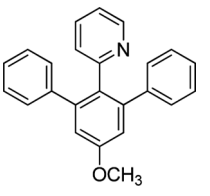
Entry	Aryl iodide	Product	Yield (%)[b]
1			67
2			80
3			85
4			72
5			66
6			71

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Table 4. Continued

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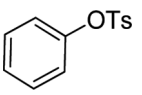
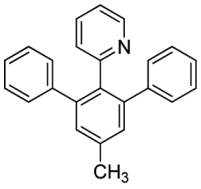
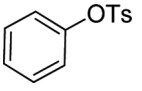
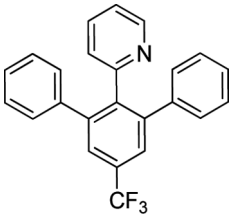
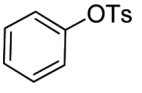
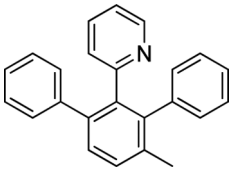
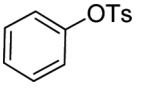
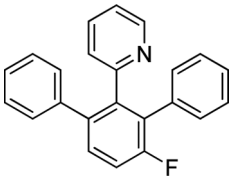
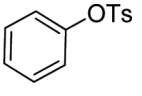
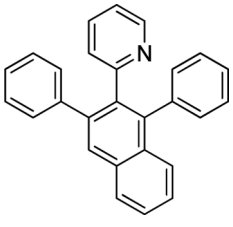
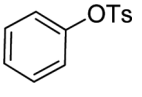
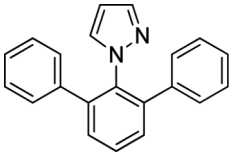
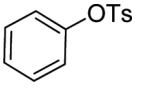
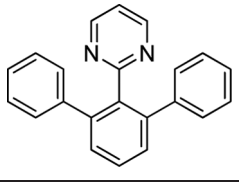
7			73
8			67
9			36[c]
10			77
11			71
12			69
13			68

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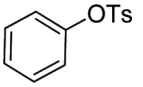
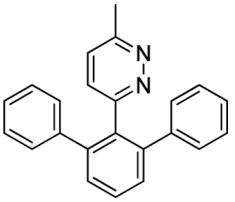
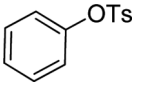
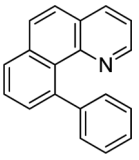
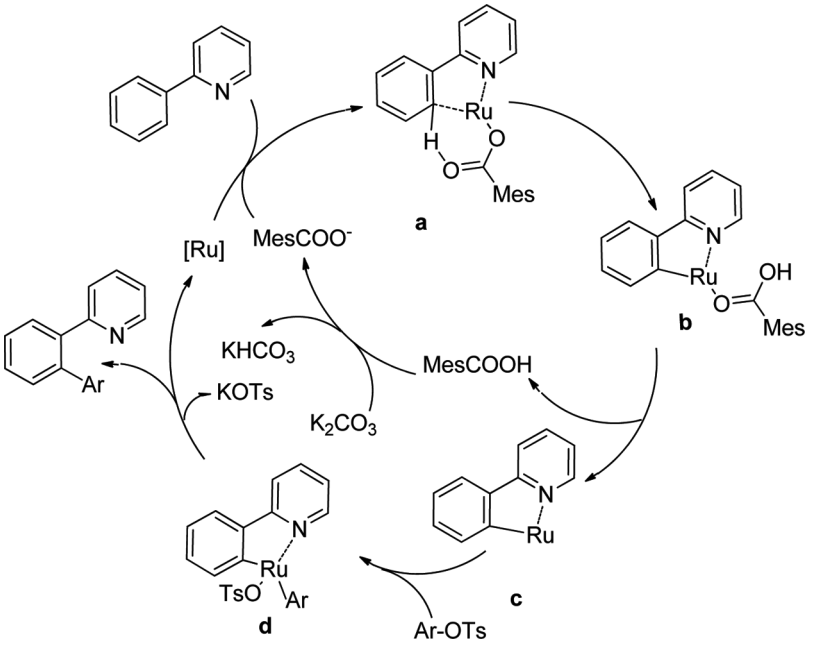
Table 4. Continued

Entry	Aryl iodide	Product	Yield (%)[b]
14			78
15			80

[a]Reaction conditions: substrate (1 mmol), aryl tosylates (2.2 mmol), $RuCl_3$ (2.5 mol%), MesCOOH (1 mmol), K_2CO_3 (2 mmol), NMP (5 mL), 140 °C, 12 h.
[b]Isolated yields.
[c]Monoarylated product was isolated in 37% yield.

6-position C-H bond. Ackermann proposed a proton abstraction mechanism, which provides a satisfactory explanation for the Ru-catalyzed arylation via C-H bond activation.[44–47] On the basis of this C-H bond activation chemistry and our results, a plausible mechanism for the diarylation process is shown in Scheme 1. Proton



Scheme 1. Mechanism proposed.

abstraction by the benzoate anion coordinated to ruthenium results in intermediate **b**. Afterward, dissociation of $MesCO_2H$ to form intermediate c, followed by insertion of ArOTs, leads to intermediate d, which liberates the arylated product and ruthenium catalyst by protodemetalation. Then a similar process occurs at another C-H bond.

The research herein used directing groups for C-H bond cleavage with a special focus on utilizing simple carboxylic acids such as MesCOOH to promote the diarylation of 2-arylpyridines. We have developed a new selective $RuCl_3$-catalyzed C-H functionalization process that can arylate arylpyridines without the use of additional ligands with high regioselectivity with aryl tosylates as electrophiles. The scope of the arylation is broad and tolerates a variety of functional groups. Further mechanistic studies of the activation pathways are still in progress in our laboratory.

EXPERIMENTAL

MesCOOH (1 mmol) was added to a mixture of the 2-arylpyridine (1 mmol), aryl tosylates (2.2 mmol), anhydrous $RuCl_3$ (2.5 mol%), and NMP (3 mL). The solution was stirred at 140 °C under air for 12 h, then cooled to rt and filtered through a filter paper. Brine (25 ml) was added to the solution, which was extracted with Et_2O (3×20 mL). After washing with H_2O and brine, the combined organic phases were evaporated under reduced pressure, and the residue was subjected to flash column chromatography to obtain the desired product.

Complete experimental details are available online in the Supplemental Materials.

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