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Ruthenium-Catalyzed Oxidative Homo-Coupling of 2-Arylpyridines

Xiangyu Guo,[a] Guojun Deng,[a,b,*] and Chao-Jun Li[a,*]

[a] Department of Chemistry, McGill University, Montreal, QC, H3A 2K6, Canada
Fax: (+1)-514-398-3797; e-mail: cj.li@mcgill.ca
[b] School of Chemistry, Xiangtan University, Xiangtan, Hunan 411105, People's Republic of China
Fax: (+86)-732-8292477; e-mail: gjdeng@xtu.edu.cn

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Abstract: A ruthenium-catalyzed oxidative homo-coupling reaction of 2-arylpyridines *via* C–H activation was developed. The reaction could tolerate various functional groups on both the aryl and the pyridyl rings to afford a series of dimerized products with iron(III) chloride ($FeCl_3$) as a stoichiometric oxidant. A tentative mechanism was proposed for this oxidative C–H/C–H homo-coupling.

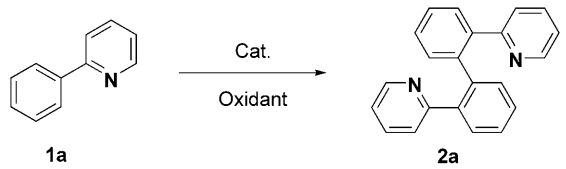
Keywords: C–H activation; oxidative coupling; 2-phenylpyridines; ruthenium

The biaryl moiety is a common structural motif in natural products, agrochemicals, chiral ligands and pharmaceuticals.[1] Many methodologies have been developed to achieve the synthesis of both symmetrical and unsymmetrical biaryls.[2] In the past two decades, transition metal-catalyzed C–H bond activation followed by C–C bond formation has emerged as a powerful synthetic methodology,[3] which is more efficient and simpler than the traditional metal-catalyzed cross-coupling reaction by avoiding the necessity of preparing functionalized substrates.[4] Furthermore, when this strategy is applied to both substrates, using C–H bonds as the only starting functionality can further simplify the syntheses. Such reactions will only require one to remove 2 H atoms from the reactants by using a hydrogen acceptor.[1a,5] Therefore, the synthesis of biaryls using oxidative C–H/C–H coupling is attracting increasing attention.[5]

For the oxidative homo-coupling of aryls *via* the direct reaction of C–H/C–H bonds, classical examples are the oxidative dimerization of various phenols and their analogues to generate various biphenol and polyphenol products.[6] For the homo-dimerization of arenes in the absence of a phenol group, Sanford and Hull recently reported that 2-arylpyridines underwent a highly regioselective Pd-catalyzed oxidative C–C coupling at room temperature with oxone as a terminal oxidant.[7] On the other hand, Yu and Chen discovered that such a reaction could be carried out with an *in situ* iodination followed by a $Cu(OAc)_2$-mediated Ullmann coupling to give the homodimerized product.[8]

During our recent studies on the ruthenium-catalyzed *cross-dehydrogenative coupling* (CDC) of 2-phenylpyridine with cycloalkanes mediated by peroxides,[9] we observed a trace amount of the oxidative homo-coupling product of 2-phenylpyridine. Subsequently, various conditions regarding the ruthenium catalyst and the oxidant were examined to optimize the formation of this homo-coupling product (Table 1). It was found that using $FeCl_3$, instead of peroxide, as the stoichiometric oxidant, increased the product yield to 27% (Table 1, entry 1). No reaction was observed in the absence of the ruthenium catalyst (Table 1, entry 2). Other ruthenium catalysts were also examined (Table 1, entries 3–7). Whereas $Ru_3(CO)_{12}$ was inactive, the use of $Ru(acac)_3$, $RuCl_2(PPh_3)_3$, and $[Ru(benzene)Cl_2]_2$ increased the product yield to 60%, 77%, and 59%, respectively. The combination of $[Ru(p\text{-cymene})Cl_2]_2$ with $FeCl_3$ gave an 84% yield of the desired product (Table 1, entry 7). Other oxidants were also examined (Table 1, entries 8–12), and all led to lower product yields. The reaction temperature and solvents were also investigated (Table 1, entries 13–18) with the optimal conditions being 2.5 mol% $[Ru(p\text{-cymene})Cl_2]_2$ with 0.8 equiv. of $FeCl_3$ in chlorobenzene at 110 °C under air for 16 h, giving the product in 87% NMR yield (Table 1, entry 20). Reasonable yields can also be obtained when conducting the reaction in other common solvents, such as toluene, benzene and anisole. A lower reaction temperature resulted in a lower yield (Table 1, entries 7, 13 and 14). Decreasing

Table 1. Reactions of 2-phenyl pyridine **1a** under various conditions.[a]



1a 2a

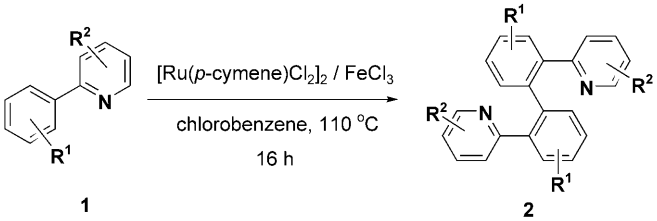
Entry	Catalyst	Oxidant	Yield [%][b]
1	$RuCl_3$	$FeCl_3$	27
2	–	$FeCl_3$	0
3	$Ru_3(CO)_{12}$	$FeCl_3$	0
4	$Ru(acac)_3$	$FeCl_3$	60
5	$RuCl_2(PPh_3)_3$	$FeCl_3$	77
6	$[Ru(benzene)Cl_2]_2$	$FeCl_3$	59
7	$[Ru(p\text{-cymene})Cl_2]_2$	$FeCl_3$	84
8	$[Ru(p\text{-cymene})Cl_2]_2$	benzoquinone	43
9	$[Ru(p\text{-cymene})Cl_2]_2$	$[t\text{-BuO}]_2$	18
10	$[Ru(p\text{-cymene})Cl_2]_2$	$FeCl_3{\cdot}6H_2O$	66
11	$[Ru(p\text{-cymene})Cl_2]_2$	$Fe(acac)_3$	trace
12	$[Ru(p\text{-cymene})Cl_2]_2$	O_2	30[c]
13	$[Ru(p\text{-cymene})Cl_2]_2$	$FeCl_3$	87[d]
14	$[Ru(p\text{-cymene})Cl_2]_2$	$FeCl_3$	74[e]
15	$[Ru(p\text{-cymene})Cl_2]_2$	$FeCl_3$	68[f]
16	$[Ru(p\text{-cymene})Cl_2]_2$	$FeCl_3$	80[g]
17	$[Ru(p\text{-cymene})Cl_2]_2$	$FeCl_3$	81[h]
18	$[Ru(p\text{-cymene})Cl_2]_2$	$FeCl_3$	74[i]
19	$[Ru(p\text{-cymene})Cl_2]_2$	$FeCl_3$	72[j]
20	$[Ru(p\text{-cymene})Cl_2]_2$	$FeCl_3$	87[k]

[a] *Conditions:* **1a** (0.5 mmol), catalyst (0.0125 mmol), chlorobenzene (1 mL), oxidant (1.0 equiv. = 0.5 mmol), 110 °C, 16 h in air unless otherwise noted.
[b] 1H NMR yield [%].
[c] O_2 1 atm.
[d] 130 °C.
[e] 100 °C.
[f] In anisole.
[g] In benzene.
[h] In toluene.
[i] In dichloroethane.
[j] $FeCl_3$ 0.5 equiv.
[k] $FeCl_3$ 0.8 equiv.

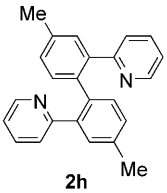
the amount of the $FeCl_3$ to 50% decreased the yield (Table 1, entry 19); more oxidant amount did not help the reaction either (compare entries 7 and 20). We reasoned that with more $FeCl_3$ being added, it coordinated with the nitrogen atom in 2-phenylpyridine, which prevented ruthenium from coordinating to the same site, and thus reduced the efficiency of the C–H activation. Interestingly, when only 0.8 equiv. of $FeCl_3$ is used, an 87% yield is obtained rather than the expected 80% (the highest theoretical yield). This unexpected "higher" yield is most likely due to the fact that the reaction was conducted under air and O_2 (in the air) acted as an extra oxidant (Table 1, entries 12 and 20).

With the optimized reaction conditions in hand, different substituted 2-arylpyridines were investigated using this reaction (Table 2). No significant change was observed with 4-phenylphenylpyridine (compare entries 1 and 2). Electronic effects of the phenyl ring of the substrates did not have a great impact on the reaction (Table 2, entries 1–7). Substrates with halide substituents also proceeded in this reaction (Table 2, entries 5 and 6). The location of substituents on both rings also played an important role in this reaction. A good yield was obtained with 2-(4-methylphenyl)pyridine (Table 2, entry 7). With two potential reaction sites on the phenyl ring of 2-(3-methylphenyl)pyridine, the reaction took place regioselectively at the

Table 2. Substrate scope of ruthenium-catalyzed homo-coupling of substituted 2-arylpyridines.[a]



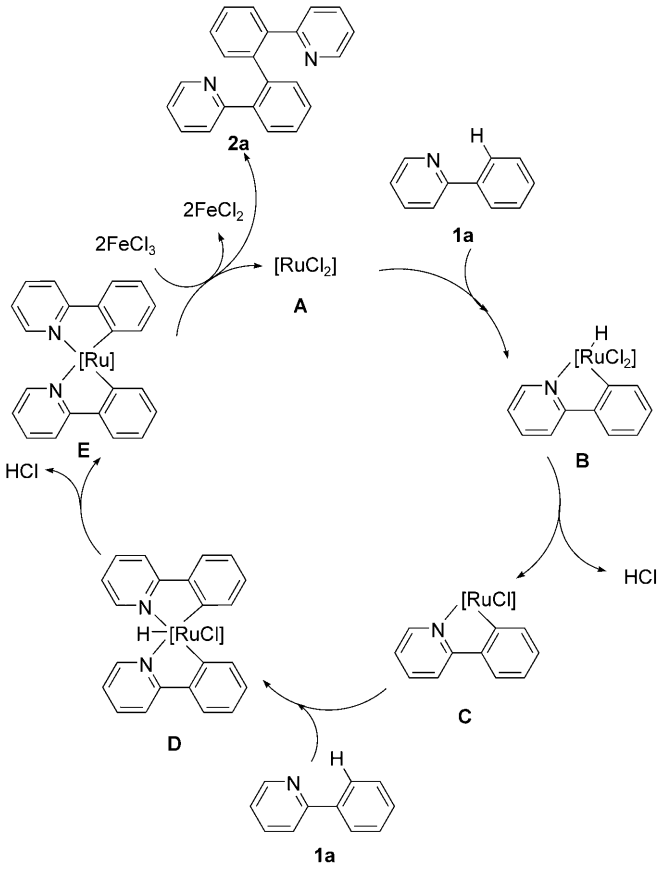
1 2

Entry	Substrate	Product	Yield [%][b]
1	R^1 = H, R^2 = H	**2a**	84
2	R^1 = 4-Ph, R^2 = H	**2b**	80
3	R^1 = 4-CO_2Et, R^2 = H	**2c**	67
4	R^1 = 4-OMe, R^2 = H	**2d**	54
5	R^1 = 4-F, R^2 = H	**2e**	71
6	R^1 = 4-Cl, R^2 = H	**2f**	42
7	R^1 = 4-Me, R^2 = H	**2g**	74
8	R^1 = 3-Me, R^2 = H	 **2h**	78
9	R^1 = 2-Me, R^2 = H	**2i**	12
10	R^1 = 2-Me, R^2 = H	**2i**	30[c]
11	R^1 = H, R^2 = 3-Me	**2j**	66
12	R^1 = H, R^2 = 4-Me	**2k**	66
13	R^1 = H, R^2 = 6-Me	**2l**	0

[a] *Conditions:* **1** (0.5 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (0.0125 mmol), $FeCl_3$ (0.4 mmol), chlorobenzene (1 mL), 110 °C, 16 h in air unless otherwise noted.
[b] Isolated yield [%], average yield of two parallel reactions.
[c] 48 h.

less hindered C–H bond (Table 2, entry 8). However, when changing the location of the methyl group on the phenyl ring from *para*- or *meta*-substituted to *ortho*-substituted, the yield decreased dramatically. This might be due to the increased steric compulsion between the methyl group and the hydrogen atom on the C-3 position on the pyridine ring during the nitrogen-directed C–H activation process in 2-(2-methylphenyl)pyridine (Table 2, entries 9 and 10). The reaction also proceeded well when changing the substituents on the pyridine ring. When the methyl group is at the 3- and 4- sites, reasonable yields were also obtained (Table 2, entries 11 and 12). However, a substrate with a methyl group at the *ortho*-position on the pyridine ring could not undergo this reaction which could also be explained by the steric effect in which the methyl group next to the nitrogen atom blocked ruthenium from coordination (Table 2, entry 13).

A tentative mechanism to rationalize the dimerized product formation is illustrated in Scheme 1. The active ruthenium species **A** reacts with 2-phenylpyridine **1a** (and other arenes) by a chelation-directed C–H activation to generate intermediate **B**.[10] After loosing HCl *via* a reductive-elimination, intermediate **C** is formed.[7] Subsequently, a second 2-phenylpyridine **1a** reacts with intermediate **C** and undergoes the same process forming intermediate **E**. Finally, reductive elimination affords the oxidative coupling product, and ruthenium catalyst **A** was regenerated *via* oxidation by $FeCl_3$.



Scheme 1. Proposed mechanism for the ruthenium-catalyzed dimerization of 2-arylpyridines.

In summary, we have developed a homo-coupling of 2-arylpyridines using a ruthenium complex as the catalyst and $FeCl_3$ as the oxidant to generate biaryls efficiently and regioselectively. The reaction proceeded well for a range of different substrates. A tentative mechanism for this reaction was also proposed.

Experimental Section

Representative Experimental Procedure (2a)

An oven-dried reaction vessel was charged with [{Ru(*p*-cymene)Cl_2}$_2$] (7.6 mg, 0.0125 mmol), 2-phenylpyridine (**1a**, 77.5 mg, 0.5 mmol), $FeCl_3$ (65 mg, 0.4 mmol), and chlorobenzene (1.0 mL). The reaction vessel was then sealed and the resulting solution was stirred at 110 °C for 16 h. After cooling to room temperature, triethylamine (1.0 mL) and dichloromethane (1.0 mL) were added to the mixture and the resulting solution was stirred at room temperature for 30 min. Then the resulting mixture was filtered through a short silica gel plug in a filter by using dichloromethane as the eluent. The volatiles were removed under vacuum and the residue was purified by column chromatography (SiO_2, hexane/diethyl ether = 1:1) to give **2a** as a yellow solid; yield: 65 mg (84%).

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