Peroxide-Promoted Regioselective Arylation of 2-Phenylpyridines and Related Substrates with Aryl Iodides

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Abstract: The direct arylation of aryl iodides with 2-phenylpyridines and related substrates was carried out smoothly in the presence of 5 mol% $RuCl_3$ using benzoyl peroxide as a promoter to generate biarylated products in high yields. The method is simple, efficient, and regioselective, and employs only commercially available reagents.

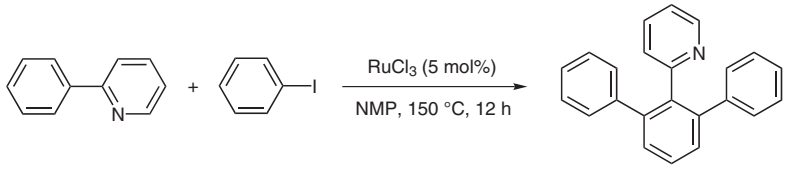
Key words: C–H activation, arylation, ruthenium homogeneous catalysis

The transition-metal-catalyzed aryl–aryl coupling reactions are powerful synthetic tools[1] and have been widely used for the synthesis of important organic molecules and natural products.[2] Among the various aryl–aryl coupling reactions, the catalytic direct arylations involving C–H activation is especially attractive due to the enhanced efficiency and little byproduct formation.[3] Nitrogen- and oxygen-coordinating functional groups are usually employed to direct the arylation and control the regioselectivity. For example, phenols,[4] ketones,[5] amides,[6] carboxylic acids,[7] and imines,[8] have been successfully employed as the directing groups in Ru-, Rh-, or Pd-catalyzed arylation reactions. In the case of pyridine, ruthenium(II) phosphine complex ($[RuCl_2(\eta^6\text{-}C_6H_6)]_2$ and $[RuCl_2(p\text{-cymene})]_2$) have been used as the catalysts and good selectivity was achieved.[9] Phosphine-free arylation procedure of pyridines was developed by Shabashov and Daugulis using acetic acid as the solvent in the presence of catalytic amount of $Pd(OAc)_2$.[10] Very recently, Sanford demonstrated that iodine(III) reagent $[Ar_2I]BF_4$ was very effective for the palladium-catalyzed direct arylation.[11] Although significant progress was achieved, efficient methods for biarylation of 2-phenylpyridine and related substrates in the absence of phosphine ligands are rare.[10]

In this paper, we describe our findings regarding the direct arylation of aryl iodides and 2-phenyl-pyridines and their related substrates catalyzed by $RuCl_3$ using benzoyl peroxide as a crucial promoter. The reactions could be performed in the absence of expensive ligands and did not require any precautions with regard to the exclusion of air and moisture, and biarylated products were obtained in high yields.

Our investigations into an efficient arylation catalyst began with the reaction of 2-phenylpyridine and iodobenzene in the presence of 5 mol% $RuCl_3$ (Scheme 1). Unfortunately, only trace of the desired product was detected at 150 °C for 12 hours in 1-methylpyrrolidin-2-one (NMP, Table 1, entry 1). $Ru(PPh_3)_3Cl_2$ and $Pd(PPh_3)_4$ were then chosen as catalyst precursors. However, in both cases, the arylation reactions were sluggish (Table 1, entries 2 and 3). Very recently, Ackermann and his co-workers reported the ruthenium-catalyzed direct arylation of bromides. Unfortunately, we could not obtain the desired products under their reaction conditions.[12] However, we were delighted to find that the rate of arylation reaction was markedly accelerated in the presence of one equivalent of *m*-chloroperbenzoic acid and the desired biphenylated product **1a** was isolated in 40% yield (Table 1, entry 4). The screening of various peroxides reviewed more successes (Table 1, entries 5–9) and benzoyl peroxide was found to be the best, and it could produce **1a** in 96% isolated yield (Table 1, entry 6). Notably, the reactivity could be extended to palladium catalysts, although $RuCl_3$ was still the best (Table 2).

The superior efficiencies obtained with $RuCl_3$ in the presence of benzoyl peroxide promoted us to select these catalytic conditions for further explorations. The scope of the



1a

Scheme 1

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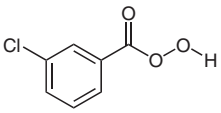
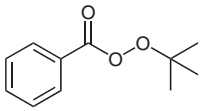
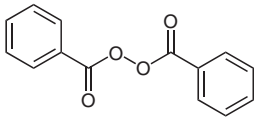
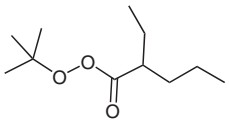
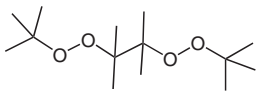
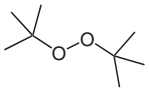
Table 1 Effect of Oxidants on the Arylation Reaction[a]

Entry	Oxidant	Yield (%)[b]
1	–	trace
2	–	trace[c]
3	–	trace[d]
4		40
5		91
6		96
7		89
8		76
9		78

[a] Reaction conditions: 2-phenylpyridine (1 mmol), PhI (2.4 mmol), $RuCl_3$ (5 mol%), oxidant (1 mmol), K_2CO_3 (2 mmol), NMP (5 mL), 150 °C, 12 h.
[b] Isolated yields.
[c] $Ru(PPh_3)_3Cl_2$ (5 mol%) was used.
[d] $Pd(PPh_3)_4$ (5 mol%) was used.

Table 2 Arylation Reaction in the Presence of Various Catalysts[a]

Entry	Catalyst	Yield (%)[b]
1	$RuCl_3$	96
2	$Ru(PPh_3)_3Cl_2$	85
3	$Pd(OAc)_2$	67
4	$PdCl_2$	65
5	$Pd(CH_3CN)_2Cl_2$	62
6	$Pd(PPh_3)_4$	45
7	$Pd_3(dba)_2$	39

[a] Reaction conditions: 2-phenylpyridine (1 mmol), PhI (2.4 mmol), catalyst (5 mol%), benzoyl peroxide (1 mmol), K_2CO_3 (2 mmol), NMP (5 mL), 150 °C, 12 h.
[b] Isolated yields.

arylation reaction with respect to the aryl iodide component was investigated (Table 3). A variety of aryl iodides that incorporate electron-donating and electron-withdrawing groups were well tolerated (Table 3, 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 3, entries 6–8). It should be noted that the clean biarylated products were delivered in these reactions. However, when a methyl group located at 3′-position of phenylpyridine, the monophenylated and diphenylated products were isolated in a ratio of 1:1 (Table 3, entry 9, 43% diphenylated and 44% 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 3, entry 10). 2-(Naphthalen-2-yl)pyridine also delivered the diarylated product in good yield (Table 3, 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 3, entries 12–15).

Table 3 $RuCl_3$-Catalyzed Arylation in the Presence of Benzoyl Peroxide[a]

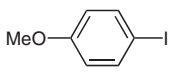
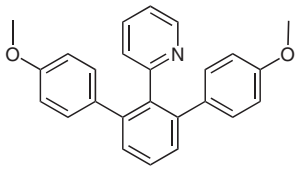
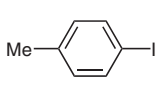
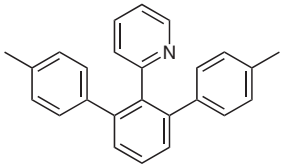
Entry	Aryl iodide	Product	Yield (%)[b]
1			82
2			89

Table 3 $RuCl_3$-Catalyzed Arylation in the Presence of Benzoyl Peroxide[a] (continued)

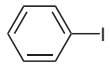
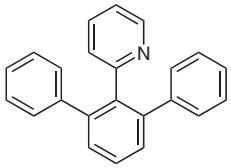
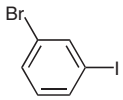
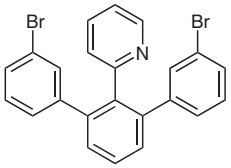
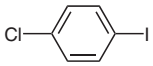
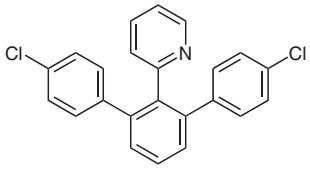
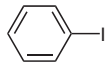
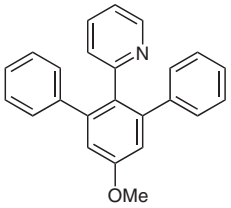
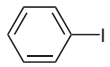
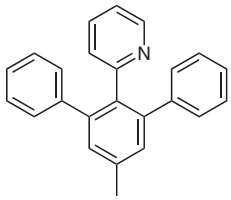
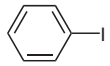
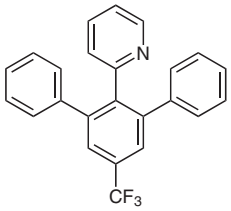
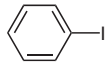
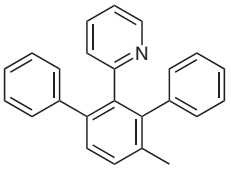
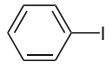
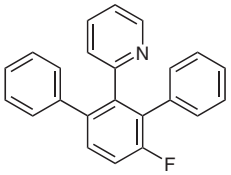
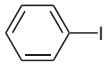
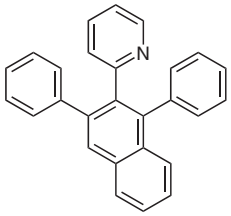
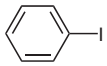
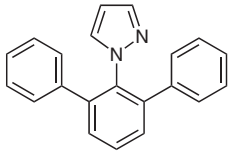
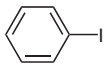
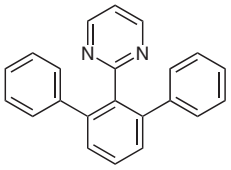
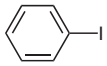
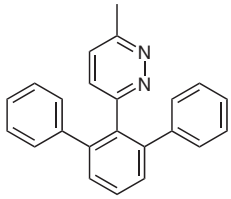
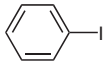
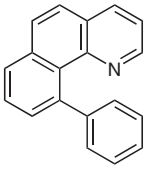
Entry	Aryl iodide	Product	Yield (%)[b]
3			96
4			88
5			74
6			87
7			77
8			93
9			43[c]
10			81

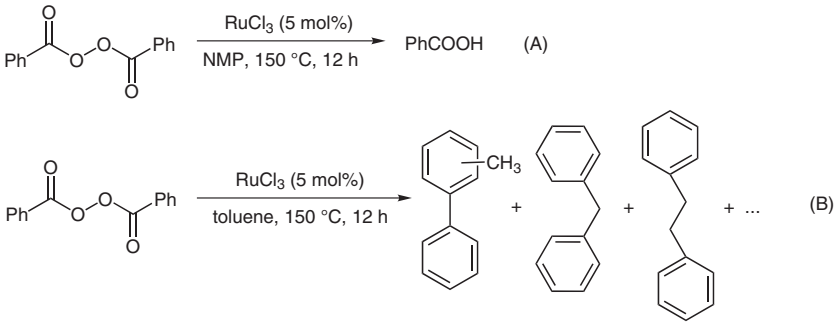
Table 3 $RuCl_3$-Catalyzed Arylation in the Presence of Benzoyl Peroxide[a] (continued)

Entry	Aryl iodide	Product	Yield (%)[b]
11			84
12			92
13			83
14			94
15			90

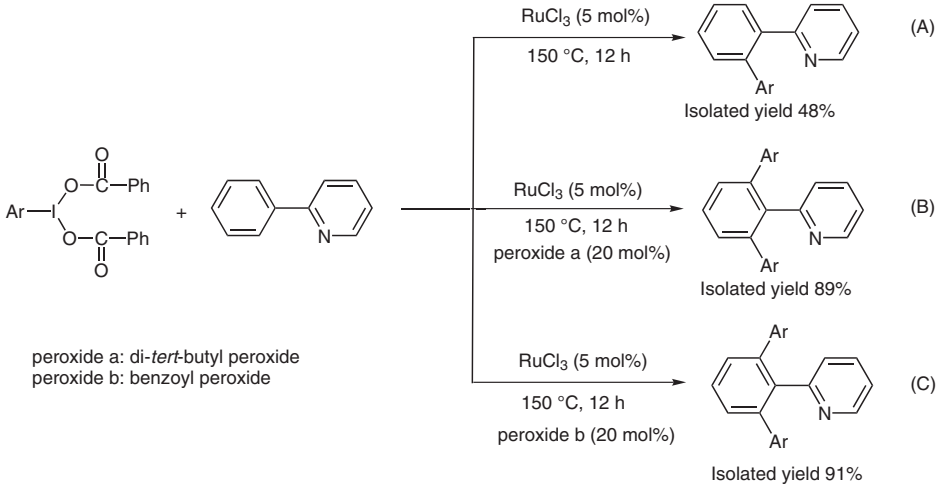
[a] Reaction conditions: 2-phenylpyridines and related substrates (1 mmol), aryl iodide (2.4 mmol), $RuCl_3$ (5 mol%), benzoyl peroxide (1 mmol), K_2CO_3 (2 mmol), NMP (5 mL), 150 °C, 12 h.
[b] Isolated yields.
[c] Monoarylated product was isolated in 44% yield.

Early works on benzoyl peroxide established that their thermolysis occurred at 95 °C to generate aryl radicals and the rates of decomposition was accelerated by transition metals.[13] Our experiments were carried out at 150 °C in the presence of $RuCl_3$ and the radical Ar might be involved in the arylation processes. We therefore performed the experiment in the absence of aryl iodides and pyridines. Interestingly, benzoic acid was isolated quantitatively and no products from radical reactions such as biphenyl were found (Scheme 2, A). In contrast, a large number of products generated from radical reactions were detected by GC-MS when toluene was employed as the solvent (Scheme 2, B). In this regard, it appeared that the thermolysis of benzoyl peroxide was restrained by NMP under the reaction conditions.

Sanford and co-workers reported that iodobenzene diacetate [$PhI(OAc)_2$] could be used as oxidant and promoted the regioselective C–H bond oxidation in the presence of Pd catalyst.[14] They found that the C–H activation and arylation reactions could be performed using phenyl iodonium salts $[Ph_2I]BF_4$ prepared from the reaction of $PhI(OAc)_2$ with $ArB(OH)_2$ in the presence of $BF_3{\cdot}OEt_2$.[11] In our experiments, the carboxylate oxidant might generate in situ under the reaction conditions and hence play a role to the direct arylation reaction. We therefore prepared 4-$MeC_6H_4I(O_2CPh)_2$ according to the literature procedure[15] and subjected it to the reaction in the absence of benzoyl peroxide. The results showed that no biarylation product was formed and only monoarylated product was isolated in 48% yield (Scheme 3, A). However, the biarylated product was isolated in high yield when 20 mol% of di-*tert*-butyl peroxide or benzoyl peroxide was added in the reaction (Scheme 3, B and C). These results indicated that carboxylate oxidant generated in situ under the reaction conditions might have implications with the arylation.



Scheme 2



Scheme 3

In conclusion, we have developed a novel catalyst system capable of activating C–H bond for direct arylation reactions to give clean biarylated products in high yields with a broad substrate scope.[16,17] The utilization of benzoyl peroxide as a crucial promoter might have implications with the development of novel C–H activation mechanism and methods. The mechanism studies and further application of present transformations are under way in our laboratories.

Acknowledgment

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References and Notes

(1) (a) de Meijere, A.; Diederich, F. *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; Wiley-VCH: Weinheim, **2004**. (b) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (c) Yin, L.; Liebscher, J. *Chem. Rev.* **2007**, *107*, 133.

(2) (a) Corbet, J. P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651. (b) Bringmann, G.; Mortimer, A. J. P.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 5384. (c) Xie, C.; Zhang, Y.; Huang, Z.; Xu, P. *J. Org. Chem.* **2007**, *72*, 5431.

(3) (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Campeau, L. C.; Fagnou, K. *Chem. Commun.* **2006**, 1253. (c) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731.

(4) (a) Bedford, R. B.; Coles, S. J.; Hursthouse, M. B.; Limmert, M. E. *Angew. Chem. Int. Ed.* **2003**, *42*, 112. (b) Bedford, R. B.; Limmert, M. E. *J. Org. Chem.* **2003**, *68*, 8669. (c) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1740.

(5) (a) Kakiuchi, F.; Matsuura, Y.; Kan, S.; Chatani, N. *J. Am. Chem. Soc.* **2005**, *127*, 5936. (b) Kakiuchi, F.; Kan, S.; Igi, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 1698. (c) Terao, Y.; Kametani, Y.; Wakui, H.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron* **2001**, *57*, 5967. (d) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360. (e) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473. (f) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 12382.

(6) (a) Zaitsev, V.; Shabashov, G. D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (b) Kametani, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **2000**, *41*, 2655. (c) Ferraccioli, R.; Carenzi, D.; Motti, E.; Catellani, M. *J. Am. Chem. Soc.* **2006**, *128*, 7229.

(7) Giri, R.; Maugel, N.; Li, J. J.; Wang, D. H.; Breazzano, S. P.; Saunders, L. B.; Yu, J. Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510.

(8) (a) Oi, S.; Ogino, Y.; Fukita, S.; Inoue, Y. *Org. Lett.* **2002**, *4*, 1783. (b) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2005**, *7*, 2229. (c) Park, Y. J.; Jo, E. A.; Jun, C. H. *Chem. Commun.* **2005**, 1185.

(9) (a) Ackermann, L.; Althammer, A.; Born, R. *Angew. Chem. Int. Ed.* **2006**, *45*, 2619. (b) Ackermann, L. *Org. Lett.* **2005**, *7*, 3123. (c) Oi, S.; Fukita, S.; Hirata, N.; Watanuki, N.; Miyano, S.; Inoue, Y. *Org. Lett.* **2001**, *3*, 2579.
(10) Shabashov, D.; Daugulis, O. *Org. Lett.* **2005**, *7*, 3657.
(11) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330.
(12) Ackermann, L.; Althammer, A.; Born, R. *Synlett* **2007**, 2833.
(13) (a) Leffler, J. E.; Story, L. J. *J. Am. Chem. Soc.* **1967**, *89*, 2333. (b) Wang, T. T.; Leffler, J. E. *J. Org. Chem.* **1971**, *36*, 1531.
(14) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300.
(15) Stang, P. J.; Boehshar, M.; Wingert, H.; Kitamura, T. *J. Am. Chem. Soc.* **1988**, *110*, 3272.
(16) **General Procedure**
Starting materials and solvents were purchased from common commercial sources and were used without additional purification. Column chromatography was carried out on SiO_2 (300–400 mesh). ^1H NMR spectra were recorded at 400 MHz, ^{13}C NMR spectra were recorded at 100 MHz, using TMS as internal standard. Mass spectrometry data of the product of direct arylation reaction were collected on an HRMS-EI instrument.
(17) **General Procedure for Direct Arylation Reaction**
A mixture of K_2CO_3 (2 mmol), $RuCl_3$ (11 mg, 5 mol%), 2-phenylpyridines (1 mmol), aryl iodines (2.4 mmol), peroxybenzoic (1 mmol), and NMP (5 mL) was stirred at 150 °C for 12 h. Afterwards, the reaction solution was cooled to r.t. and filtered through a filter paper. Brine (20 mL) was added to the filtrate and the mixture was extracted three times with EtOAc (3 × 15 mL). After washing with H_2O (3 × 20 mL) and brine (20 mL), the combined organic phase was evaporated under reduced pressure. The residue was purified on a SiO_2 column to afford the desired product.