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$RuCl_3$-Catalyzed Alkenylation of Aromatic C−H Bonds with Terminal Alkynes

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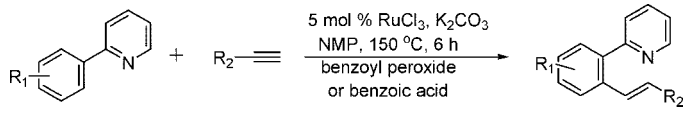
ABSTRACT



$RuCl_3$-catalyzed regio- and/or stereoselective alkenylation reactions of a variety of arylpyridines proceeded efficiently with terminal alkynes or allylic compounds in the presence of benzoyl peroxide or benzoic acid.

Transition metal-catalyzed C−H activation has currently aroused considerable interest since it avoids the otherwise necessary prefunctionalization such as halogenation and metalation.[1,2] In particular, the chelation-assisted cleavage of C−H bonds at the ortho-position of directing groups has been recognized as one of the most powerful strategies applicable to the functionalization of unreactive C−H bonds. For example, the chelation-assisted reactions of aromatic compounds bearing oxygen- or nitrogen-containing groups with organohalides, organometals, and internal alkynes have been successfully developed.[3] Alkenylation of arenes is among the most important transformations in organic synthesis. The first example of carbonyl-directed alkenylation of α-tetralone with internal alkynes catalyzed by $Ru(H)_2(CO)(PPh_3)_3$ was reported by Murai and co-workers.[4] Later, Miura et al. reported the iridium-catalyzed reactions of 1-naphthols and internal alkynes, in which alkenylation occurs regioselectively at the spatially neighboring position

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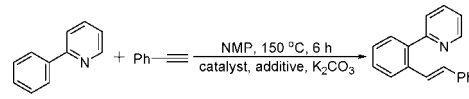
of phenolic function to give the corresponding 8-substituted 1-naphthol derivatives.[5] They also found recently that the carboxylate group was a good directing group for the alkenylation of internal alkynes at an ortho C−H bond in benzoic acids in the presence of rhodium/copper catalyst.[6] Very recently, the nickel-catalyzed alkenylation of N-protected 3-cyanoindoles was described by Nakao and co-workers[7] and the ruthenium-catalyzed reaction of arylpyridine and alkenyl ester gave rise to site-selective alkenylation at an ortho C−H bond in the aryl ring.[8] Despite these important advances, terminal alkynes are rarely used as alkenylation substrates in chelation-assisted aromatic C−H bond reactions,[9] and they were reported to be inactive in ruthenium-catalyzed carbonyl directed alkenylation reactions.[4b] To the best of our knowledge there is no example of alkenylation in chelation-assisted C−H bond activation using terminal alkynes. Herein, we report our efforts to develop a new catalytic method for the alkenylation of arylpyridines at the ortho C−H bond in the aryl ring with terminal alkynes in the presence of 5 mol % of $RuCl_3$ and 1 equiv of benzoyl peroxide or/and benzoic acid. Markedly high stereoselectivity was obtained in good to high yields with (*E*)-stereoisomers as the predominant alkenylation products. The catalytic system could also be extended to the alkenylation of arylpyridines with allylic compounds, which provide new protocols for the synthesis of arylalkenes.

We first examined the effects of various additives toward the reaction of 2-phenylpyridine and phenylacetylene in the presence of 5 mol % of $RuCl_3$ in NMP at 150 °C for 6 h. It was found that additive and solvent played the crucial role in the reaction efficiency (Table 1). In the absence of additives, no alkenylated product was observed (Table 1, entry 1). Promising results were obtained upon examining a variety of commercially available peroxides and a remarkable positive effect was observed when 1 equiv of benzoyl peroxide was presented in the reaction (Table 1, entries 2−4). Under these conditions, a satisfactory 76% isolated yield of the alkenylated product 2-(2-styrylphenyl)pyridine was obtained (Table 1, entry 2). With $RuCl_2(PPh_3)_3$ as catalyst, the yield was decreased to 55% (Table 1, entry 5). The palladium catalysts had a poor effect on the alkenylation reaction (Table 1, entries 6 and 7). The use of NMP as solvent proved to be the most adequate compared to other solvents tested such as CH_3CN, toluene, DME, and THF. GC-MS analysis revealed that excellent stereoselectivity was obtained with this transformation, in which only (*E*)-stereoisomers were observed. In addition, the reaction was highly regioselective to give the monoalkenylated product without the suffering of double alkenylation.

Table 1. The Optimization of Reaction Conditions[a]



entry	catalyst	additive	yield (%) [b]
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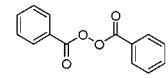
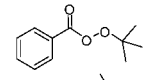
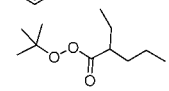
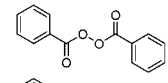
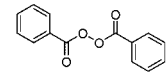
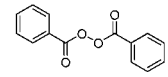
2	$RuCl_3$		76
3	$RuCl_3$		65
4	$RuCl_3$		51
5	$RuCl_2(PPh_3)_3$		55
6	$PdCl_2$		trace
7	$Pd(PPh_3)_4$		trace
8	$RuCl_3$		62

[a] Reaction conditions: 2-phenylpyridine (1 mmol), phenylacetylene (1.2 mmol), catalyst (5 mol %), additives (1 mmol), base (2 mmol), NMP (5 mL), 150 °C, 6 h. [b] Isolated yields.

In an earlier paper, we reported the $RuCl_3$-catalyzed arylation of arylpyridines with aryl iodides in the presence of peroxides in NMP.[10] We established that the decomposition of benzoyl peroxide to Ar• radicals was supressed under the reaction conditions, and quantitive amounts of benzoic acid were generated rapidly. Therefore, it became interesting

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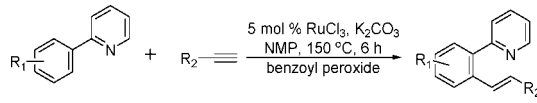
Table 2. Scope of the Alkenylation Reaction[a]



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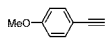
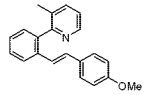
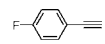
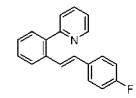
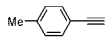
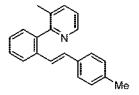
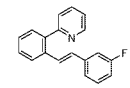
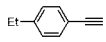
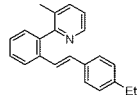
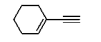
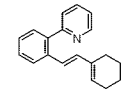
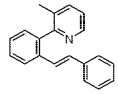
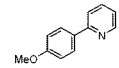
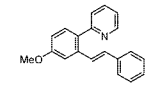
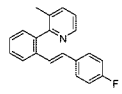
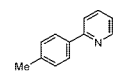
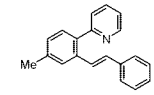
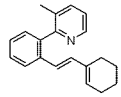
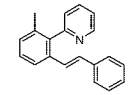
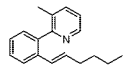
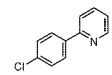
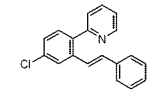
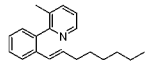
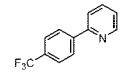
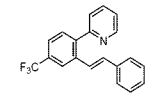
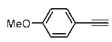
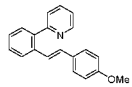
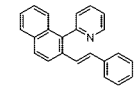
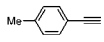
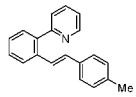
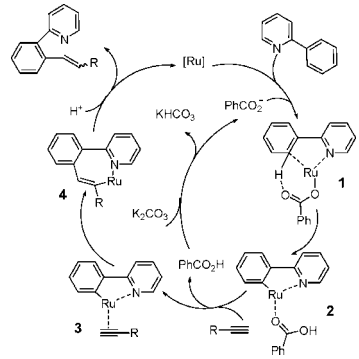
1	 **a**			96 (79)	12	**b**			83 (63)
2	**a**			86 (77)	13	**b**			67 (51)
3	**a**			93 (78)	14	**b**			61 (47)
4	**a**			94 (77)	15	 **c**			80 (61)
5	**a**			91 (72)	16	 **c**			79 (60)
6	**a**			83 (66)	17	 **c**			73(52)
7	**a**	1-Hexyne		86[c]	18	 **c**			72 (56)
8	**a**	1-Octyne		93[d]	19	 **c**			70(56)
9	 **b**			77 (63)	20	 **c**			71 (53)
10	**b**			89 (63)	21	**c**			68 (49)
11	**b**			76 (63)	22	**c**			61 (47)

[a] Reaction conditions: arylpyridine (1 mmol), alkyne (1.2 mmol), $RuCl_3$ (5 mol %), benzoyl peroxide (1 mmol), K_2CO_3 (2 mmol), NMP (5 mL), 150 °C, 6 h. [b] Isolated yields. The yields with benzoic acid (1 mmol) in place of benzoyl peroxide are in parentheses. [c] E/Z = 62/38. [d] E/Z = 52/48.

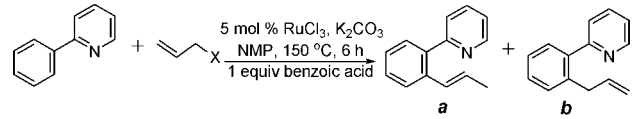
to examine the effect of benzoic acid on the reaction. Significantly, we discovered that benzoic acid indeed promoted the transformation and a 62% isolated alkenylation product was obtained (Table 1, entry 8). The combination of $RuCl_3$ catalyst and benzoic acid also allowed the arylation of arylpyridines under the reaction conditions. Although the replacement of benzyl peroxide with benzoic acid led to the lower yields, the results were still valuable considering the benzoyl peroxide was not easy to handle at high temperatures.

We then proceeded to evaluate the generality of these reaction conditions with a variety of terminal alkynes and arylpyridines as shown in Table 2. The electron-donating and electron-withdrawing substituents in the aryl ring of aryl alkynes were well tolerated to give moderate to high yields (Table 2, entries 1−5 and 9−13). The conjugated enyne smoothly underwent a selective reaction and afforded the diene derivative (Table 2, entries 6 and 14). The electronic properties of the substituents on arylpyridines proved to have little effect on the alkenylation processes, and good yields were obtained (Table 2, entries 15−19). 3-Methyl-2-phenylpyridine showed a relatively better reactivity (Table 2, entries 1−8). The alkenylation reaction was highly stereoselective and only (*E*)-alkenylated products were isolated.

Scheme 1



Scheme 2



X	*a* : *b*	yield (%)
Cl	77 : 28	84
Br	82 : 18	76
OAc	79 : 21	73

The alkyl alkynes were also suitable for the alkenylation reaction as revealed with the two examples in entries 7 and 8, generating the desired products in good yields (Table 2). However, in these cases, (*Z*)-stereoisomers was observed although (*E*)-stereoisomers were the major products (Table 2, entries 7 and 8). As depicted in Table 2, the arylpyridine-related substrates, including naphthalenepyridine, phenylpyrimidine, and phenylpyridazine, proved to be adaptable to these conditions, producing the alkenylation products in comparable yields (Table 2, entries 20−22). In general, the replacement of benzoyl peroxide with benzoic acid led to lower yields (Table 2, entries 1−22, the yields in parentheses). The internal alkynes were inactive under the reaction conditions.

There is little experimental evidence at present to elucidate the exact reaction pathway for the direct alkenylation processes. Since arylpyridines with electron-withdrawing substituents (Table 2, entries 18 and 19) also give good alkenylation yields, an electrophilic aromatic substitutioin mechanism is not favored. Recently, Echavarren and Maseras proposed a proton abstract mechnism, which provides a satisfactory explanation for the Pd-catalyzed arylation via C−H bond activation.[11] On the basis of this C−H bond activation chemistry and our results, a plausible mechanism for the alkenylation process was suggested as shown in Scheme 1. A proton abstract by the benzoic anion coodinated to ruthenium results in intermediate **2** and the exchange of benzoic acid with terminal alkynes to form intermediate **3**. The subsequent migratory insertion leads to intermediate **4**, which liberates the alkenylated product and ruthenium catalyst by protodemetalation.

Finally, this catalytic system was extended to the alkenylation of arylpyridine with allylic compounds such as allyl chloride, allyl bromide, and allyl acetate (Scheme 2). In these cases, however, the regioisometric products of ***a*** and ***b*** were isolated, while the alkenylated isomer ***a*** was the major product.

In conclusion, we have developed a new selective $RuCl_3$-catalyzed C−H functionalization process that can alkenylate arylpyridines without the use of ligands with high regioselectivity and/or stereoselectivity. The scope of the alkenylation and arylation is broad and tolerates a variety of functional groups. Mechanistic studies toward the detailed understanding of the activation pathways are in progress in our laboratory.

Acknowledgment. Funding from Zhejiang Provincial Natural Science Foundation of China (R407106) and Natural Science Foundation of China (No. 205710631) is acknowledged.

Supporting Information Available: The experimental procedure and spectroscopic data (^{1}H NMR, ^{13}C NMR, and HRMS) for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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