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Rhodium(I)-catalyzed *ortho*-alkenylation of 2-phenylpyridines with alkynes

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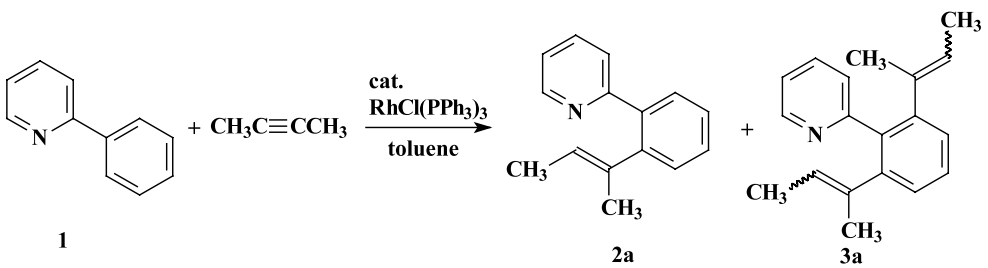
Abstract—2-Phenylpyridines reacted with internal alkynes via C–H bond activation by a catalyst, $RhCl(PPh_3)_3$, to give the *ortho*-alkenylated products.

Recently, the C–C bond coupling reaction through C–H bond activation by transition metal complexes has become a useful method in synthetic organic chemistry.[1] Even though many coupling reactions with alkenes via C–H bond activation by transition metal complexes have been reported by several groups,[2–9] the coupling reaction with alkynes is still rare. Ruthenium complexes such as $Ru(H_2)(CO)(PPh_3)_3$ and $Ru_3(CO)_{12}$ have been used as catalysts for the coupling reaction of aromatic ketones and aldimines with alkynes,[10,11] and iridium(I) complexes such as $[IrCl(cod)]_2/PR_3$ have been used as catalysts for the coupling reaction of 1-naphthols.[12] Rhodium complexes such as $Rh_4(CO)_{12}$[13] and $RhCl(PPh_3)_3$,[14b,c] as well as cobalt complexes[14a,c] have also been used for the coupling reaction of benzene and azobenzenes with diphenylacetylene, respectively. During the course of our studies of C–C bond coupling reaction by rhodium metal catalysts, we have found that the coupling reaction of 2-phenylpyridines with alkynes via C–H bond activation by a rhodium catalyst, $RhCl(PPh_3)_3$, gives alkenylated products. Herein, we report the preliminary results of a C–C coupling reaction at the *ortho* position of the phenyl ring of 2-phenylpyridines with various alkynes by the Wilkinson catalyst.

2-Phenylpyridine **1** (0.3 mmol) reacted with 2-butyne (2 equiv.) in the presence of $RhCl(PPh_3)_3$ (10 mol%) and 10 mol% of PPh_3 in toluene (2 ml) for 20 h at 140°C in a 2.5 ml vail reactor with stirring to give the double *ortho*-alkenylated product **3a** as the major product together with the mono-alkenylated product **2a** (**2a**:**3a** = 19:81, 64% isolated yield, run 1), as shown in Scheme 1. The mono-alkenylated product **2a** can be separated easily from the double alkenylated product **3a** by column chromatographic isolation (SiO_2, *n*hex:EtOAc = 10:1). When 3 equiv. of 2-butyne were used, **3a** was obtained as the sole product (run 2; *E*,*E*:*E*,*Z* = 85:15, 96%). The structure of the major part of **3a** is confirmed as *E*,*E*-isomer by analyses of ^1H NMR and NOE difference experiments (see Scheme 2). This result implies that a hydride inserts into coordinated alkyne by the *syn* manner. The additional PPh_3 led to higher conversion yield than the case of using Wilkinson catalyst only. The role of additional PPh_3



Scheme 1.

Keywords: rhodium catalyst; alkenylation; C–H bond activation; 2-phenylpyridines.
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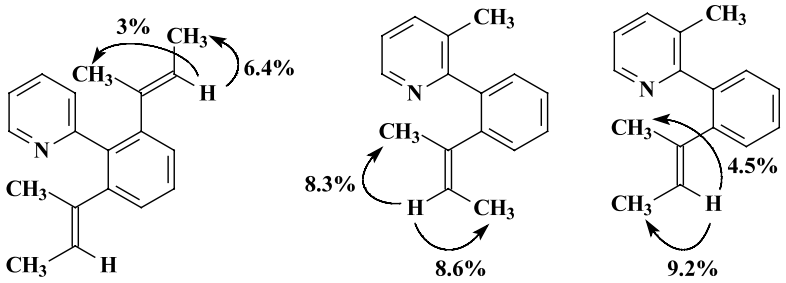


Scheme 2.

may be regeneration of reactive catalyst by the exchange of PPh_3=O formed during the catalytic reaction. When the bis-cyclooctene rhodium chloride dimer (5 mol%) was used without phosphine ligands, the reaction proceeded slowly (26% isolated yield). The $[RhCl(coe)_2]_2/Cy_3P$ system, which is good for the alkylation of phenylpyridines with alkenes, showed low activities in this coupling reaction (28%, mono:double = 4:96). The results of alkenylation are listed in Table 1.

In general, alkynes convert easily to benzene derivatives by transition metal catalyst.[15] Fortunately, the cyclotrimerized products of 2-butyne were not detected under these reaction conditions.

Another alkyne, 3-hexyne, gave a mixture of regioisomers of **2b** and **3b** under the same reaction conditions (**2b**:**3b** = 25:75, 86% isolated yield, run 3).

Unfortunately, 1-alkynes such as 1-hexyne and 1-phenylacetylene gave trace amounts of alkenylated products and unknown polymeric materials.

2-(*o*-Tolyl)pyridine **4**, having one site for alkenylation, reacted with 2-butyne (2 equiv.) under the same reaction conditions to give the mono *ortho*-alkenylated product **5a** in 96% isolated yield (run 4). The coupling reaction of 3-hexyne, 4-octyne and diphenylacetylene with **4** gave **5b**, **5c** and **5d** in 89, 97 and 74% isolated yields, respectively (runs 5–7). Some of the regioisomers, formed by isomerization of double bond to internal alkyl group, were found in the alkenylated products **5b** and **5c**.

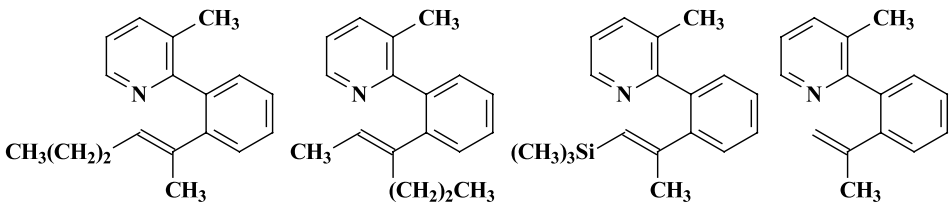
2-[2-(3,3-Dimethylbutyl)phenyl]pyridine **6** having a bulky substituent at the *ortho* position led to low conversion yield because of steric hindrance (33% isolated yield, run 8). To obtain a high conversion yield, longer reaction times and high reaction temperature were applied to the coupling reaction. However, the enhancement of yield failed and the isomerization of the product took place (41%, *E*:*Z* = 81:19).

Another substrate, 3-methyl-2-phenylpyridine **8** reacted with 2-butyne to give the mono-alkenylated product **9a** (molecular weight 223) as the major product, together with unexpected alkenylated product having a molecular weight of 277 (run 9). Surprisingly, the double *ortho*-alkenylated product **10a** is established by analyses of ^1H and ^{13}C NMR. This type of double coupled product is not detected in the coupling reaction with alkenes because of the limitation of rotation of the C–C bond between the pyridine group and phenyl group by methyl and alkyl groups in the *ortho*-alkylated product.[3a,c] These results imply that the rotation of the C–C bond between the pyridine group and phenyl group in the alkenylated product is easier than that in the alkylated product. The alkynes such as 3-hexyne, 4-octyne and diphenylacetylene also worked well (runs 10–12).

When 3 equiv. of 2-butyne were used, 2-(*p*-tolyl)pyridine **11** gave the double *ortho*-alkenylated product **13b** in only 89% isolated yield (run 13).

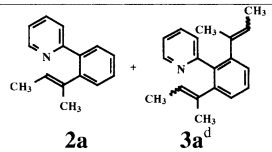
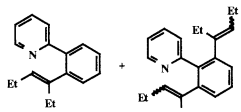
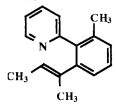
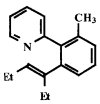
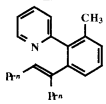
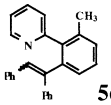
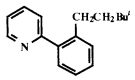
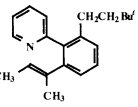
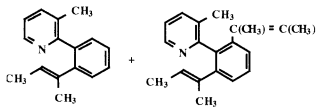
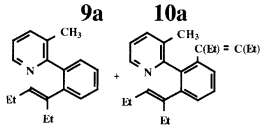
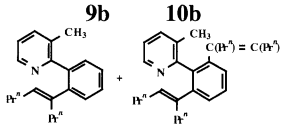
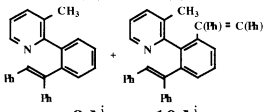
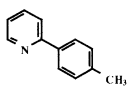
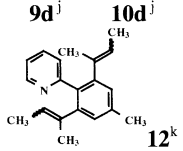
To discover the regioselectivity of alkyne, unsymmetric alkyne such as 2-hexyne (2 equiv.) was applied to the reaction. Unfortunately, the coupled products after the coupling were obtained at nearly equal ratio (**14**:**15** = 56:44, 52%). Another unsymmetric alkyne having a bulky group such as 3-trimethylsilyl-2-propyne (2 equiv.) was applied to this coupling reaction. This alkyne showed high regioselectivity and gave the regioisomer **16** together with **17** formed by Si–C bond cleavage in 90% isolated yield which contained 8% of the double alkenylated product (**16**:**17** = 42:58).

Finally, 2-phenylquinoline was applied to these coupling reactions. Unfortunately, 2-phenylquinoline did not work with 2-butyne under the same reaction conditions.



14 **15** **16** **17**

Table 1. The results of the alkenylation of 2-phenylpyridines with alkynes[a]

Run	Substrate	Alkyne (Equiv)	Product	Yield[b] (%)	Mono : double[c]
1	 **1**	CH_3CCCH_3 (2)	 **2a** **3a**[d]	64	19 : 81
2		CH_3CCCH_3 (3)	**3a**[e]	96	0 : 100
3		EtCCEt (3)	 **2b** **3b**	86	25 : 75
4	 **4**	CH_3CCCH_3 (2)	 **5a**	96	100 : 0
5		EtCCEt (2)	 **5b**	89[f]	100 : 0
6		Pr^nCCPr^n (2)	 **5c**	97[g]	100 : 0
7		PhCCPh (2)	 **5d**	74[h]	100 : 0
8	 **6**	CH_3CCCH_3 (2)	 **7**	33	100 : 0
9	 **8**	CH_3CCCH_3 (2)	 **9a** **10a**	92	58 : 42
10		EtCCEt (2)	 **9b** **10b**	96[i]	73 : 27
11		Pr^nCCPr^n (2)	 **9c** **10c**	99[i]	60 : 40
12		PhCCPh (2)	 **9d**[j] **10d**[j]	57	73 : 27
13	 **11**	CH_3CCCH_3 (3)	 **12**[k]	89	0 : 100

[a]Substrate : $RhCl(PPh_3)_3$: PPh_3 = 1 : 0.1 : 0.1, toluene, 140°C, 20h. [b]Isolated yields. [c]The ratios were determined by ^1H NMR or GC. [d]*E,E:E,Z* = 86:14. [e]*E,E:E,Z* = 85:15. [f]Yield contained 5% of regioisomer. [g]Yield contained 20% of regioisomer. [h]*E:Z or Z:E* = 7:3, 24% of **4** were remained. [i]A mixture of regioisomers. [j]one isomer, but the structure could not be determined. [k]*E,E:E,Z* = 73:27

In conclusion, we found that 2-phenylpyridines reacted with internal alkynes by the Wilkinson catalyst to give the alkenylated products in high yields. Unfortunately, terminal alkynes did not work under these coupling reactions. Unsymmetric alkyne having a bulky group showed high regioselectivity.

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