Rhodium-catalysed Regioselective Alkylation of the Phenyl Ring of 2-Phenylpyridines with Olefins

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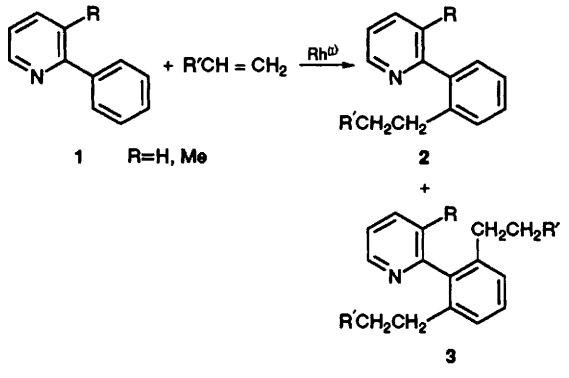
2-Phenylpyridines react with olefins in the presence of rhodium(I) as a catalyst to give 2-(2-alkylphenyl)pyridines by a regioselective alkylation at the *ortho* position of the phenyl ring.

There is currently great interest in transition metal mediated C–H bond activation.[1] One goal is to develop new routes for selective C–C bond formation.[1b] Although there are numerous cases of stoichiometric C–H bond activation, catalytic functionalization of the C–H bond is still a relatively rare phenomenon.[2] Recently, ruthenium-catalysed highly regioselective coupling reaction of aromatic C–H bonds to olefins has been reported.[3] Cyclometallation is well known as a good method for intramolecular activation of C–H bonds in transition metal complexes.[4] 2-Substituted pyridines are good substrates for the cyclometallation.[4b,c,5] The *ortho* aromatic C–H bond of the phenyl ring in 2-phenylpyridine is easily cleaved by transition metal complexes.[4] The selective functionalization of 2-phenylpyridine **1** has been the concern of many organic chemists.[6] There is no report to deal with the direct alkylation to aromatic ring by the aromatic C–H bond cleavage from the rhodium complexes. We have found that 2-phenylpyridines reacted with olefins in the presence of a rhodium(I) complex as catalyst to give the anti-Markownikoff *ortho* alkylated product **2**. Here we report the regioselective alkylation of the phenyl ring of 2-phenylpyridines with olefins.



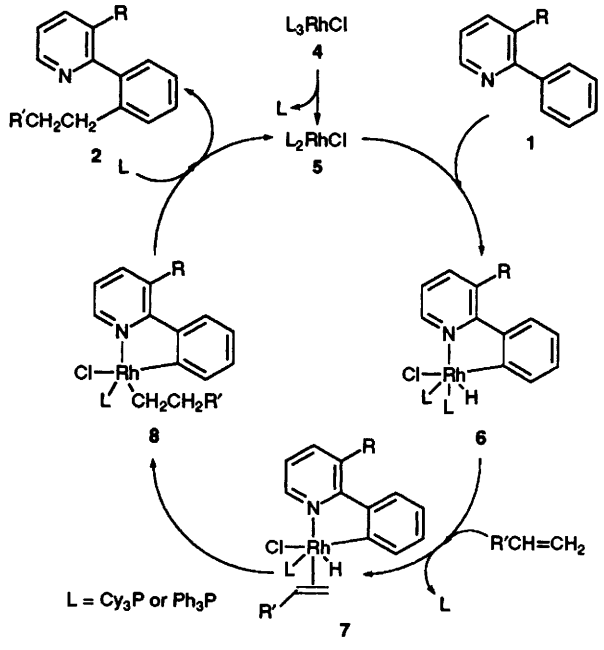
Scheme 1

In a typical experimental procedure, a screw-capped pressure vial was charged with chlorobis(cyclooctene)rhodium dimer (5 mol%, as catalyst) and tricyclohexylphosphine (0.192 mmol) in THF. After the reaction mixture was stirred at room temperature for 5 min, 2-phenylpyridine (ppy) (0.64 mmol) and 3,3-dimethylbut-1-ene (3.2 mmol) was added. The reaction mixture was heated at 100 °C for 22 h with stirring. The reaction mixture was concentrated under reduced pressure and then purified by column chromatography (silica gel, ethyl acetate–hexane, 1:10) to give 2-(2-neohexylphenyl)-pyridine (79%, 122 mg) and 2-(2,6-dineohexylphenyl)pyridine (7%, 14 mg). Satisfactory spectral data were obtained for both compounds.

1-Olefins reacted with 2-phenylpyridines to give the anti-Markownikoff addition product exclusively. The Markownikoff addition products are not detected in all the cases. When the reactions were carried out below 100 °C, the reaction proceeded slowly. In the case of 3-methyl-2-phenylpyridine (mppy), **2** was obtained as the product. Double alkylated product **3** could not be detected, probably due to the interference of rotation of the carbon–carbon bond between the pyridine and phenyl rings in **2** by the steric hindrance of the 3-methyl group in the pyridine ring and the alkyl in the phenyl group. Accordingly, **2** could not form metal complexes with doubly alkylated phenyl rings.

1-Linear alkyl olefins such as hex-1-ene and pent-1-ene are isomerized to the 2-olefin during the reaction.† This isomerization competes with the coupling reaction between the olefin and 2-phenylpyridine. Since the coordination into the metal complex formed by isomerization with 2-olefin is more difficult than with 1-olefin, the coupling reaction gives a moderate yield and needs a longer reaction time. 3,3-Dimethylbut-1-ene and vinylsilanes cannot be isomerized under the same conditions. Thus coupling without competition affords high yields of the alkylated product (Table 1).

A possible mechanism for this reaction can be postulated from the results (Scheme 2). Tris(tricyclohexylphosphine) rhodium (I) chloride[7] (B) and Wilkinson's catalyst (A) were used as the catalysts. The reaction appears to be initiated *via* formation of the highly reactive rhodium complex **5** by one ligand liberation and **5** reacts with 2-phenylpyridine to form the rhodium(III) hydride complex **6** by cleavage of an aromatic C–H bond at the *ortho* position of phenyl ring in 2-phenyl pyridine. The formation of the rhodium(III) complex from rhodium(I) and arenes are well documented in the reviews.[4a,b] The insertion of a hydride from **7** into the coordinated olefin may form anti-Markownikoff hydrometallated complex intermediates **8**. The intermediate complex **8** converts to the alkylated product **2** and **5**. The alkylated product **2** may further couple with an olefin to give the doubly alkylated



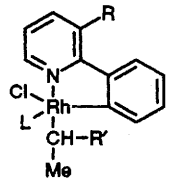
Scheme 2 A possible mechanism of the *ortho* position alkylation by C–H bond activation

Table 1 The results of the *ortho*-alkylation for 2-phenylpyridines[a]

Run	Substrate	Olefin	Catalyst[b]	Reaction temperature /°C	Reaction time/h	Yield[c] (%)	Ratio of isomer 2:3[d]
1	2-phenylpyridine	neohexene	A	120	48	79	95:5
2		neohexene	B	100	22	86 (98)[e]	92:8
3		pent-1-ene	B	120	96	64	94:6
4		hex-1-ene	B	120	144	35	100:0
5		oct-1-ene	B	120	144	33	100:0
6	3-methyl-2-phenyl pyridine	neohexene	B	110	21	99	100:0
7		pent-1-ene	B	110	48	55	100:0
8		hex-1-ene	B	110	48	54	100:0
9[f]		CH_2=$CHSi(OEt)_3$	B	120	4.5	96	100:0
10[f]		CH_2=$CHSi(OMe)_3$	B	120	5	95	100:0

[a] 2-Phenylpyridine (ppy or mppy):olefin:catalyst = 1:5:0.1 (scale:0.64 mmol), solvent THF. [b] Catalyst system, A: $(Ph_3P)_3$-RhCl; B: $1/2[RhCl(C_8H_{14})_2]_2/3Cy_3P$. [c] Isolated yield based on ppy or mppy. [d] Ratio of isomers was determined by GC-MS or ^1H NMR [e] GC-Yield. [f] mppy:olefin:catalyst = 1:5:0.15.

product **3**. The Markownikoff addition product was not detected, probably due to the unstability of intermediate **9**, which returns to **5** and 1-olefin (or 2-olefin) by β-elimination.[8]



9

As the catalyst ligand, tricyclohexylphosphine was found to be more effective than triphenylphosphine. THF was the better solvent for this reaction than toluene.

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Footnote

† The proton peaks of 2-olefin were checked by ^1H NMR spectra (300 MHz, $CDCl_3$) from time to time from the reaction mixture in a NMR tube

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