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Rhodium-catalyzed *ortho*-alkylation of aromatic aldimines and ketimines via C–H bond activation

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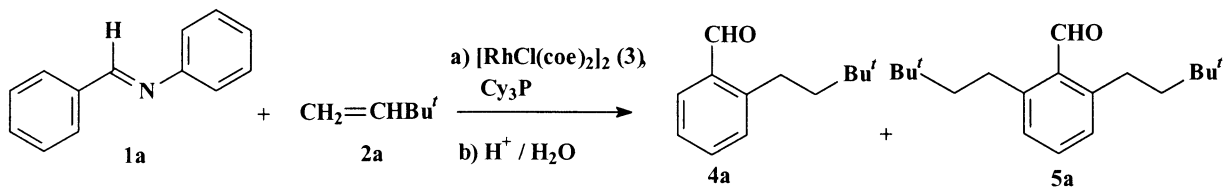
Abstract—The aldimines reacted with alkenes under a rhodium catalytic system, $Rh[(coe)_2Cl]_2$ and Cy_3P, to give mainly the double alkylated products with moderate to high yields. On the other hand, the ketimine **9** gave the mono alkylated product predominantly.

Recently, the C–C bond formation as a result of C–H bond activation by transition-metal complexes has become a useful synthetic method for chemists.[1] The activation of inactive C–H bonds has been achieved by many research groups.[2] By using the C–H bond activation, alkylation of the aromatic ring through the coupling reaction with alkenes and alkynes has been reported by us[3] and other groups.[4–10] In spite of many reports of C–C bond formation, the alkylation of aldimines and ketimines is still rare. The alkylation of aromatic aldimines by a ruthenium complex has been reported by the Murai group.[4f] Moreover, the alkylation of aldimines and ketimines using Wilkinson's catalyst has been reported very recently by Jun.[10] However, while the Ru-catalyzed alkylation of aldimines shows a high reactivity for vinyl siloxanes, it has some problems; for example, low reactivity for other alkenes such as **2a** and producing undesired dehydrogenated products.[4f] In the case of using $RhCl(PPh_3)_3$, the ketimines show a high reactivity with alkenes, but the aldimines do not react with alkenes without a co-catalyst.[10] We have already reported that in the alkylation of 2-phenylpyridines, exchange of ligands from PPh_3 to Cy_3P on rhodium metal led to high conversion yields and short reaction times. Thus, we decided to apply this rhodium catalytic system to the alkylation of aromatic aldimines and ketimines with alkenes. To investigate the effects of substituent substrates, we also carried out the alkylation of substrates having electron-donating and electron-withdrawing groups on the benzene ring. Herein, we report the alkylation of aromatic aldimines and ketimines with alkenes by a rhodium catalytic system, $[RhCl(coe)_2]_2$ and Cy_3P, proceeded without a need for additives (see Scheme 1).

Aldimine **1a** reacted with **2a** (5 equiv.) under $[RhCl(coe)_2]_2$ (5 mol%) and Cy_3P (30 mol%) in THF at 140°C for 24 h with stirring to give the *anti*-Markovnikov *ortho*-alkylated benzaldehydes in 93% isolated yields (**4a**:**5a** = 11:89) after hydrolysis and chromatographic isolation (Table 1, run 1). This rhodium catalytic system showed higher reactivity than that[4f] of $Ru_3(CO)_{12}$ for **2a**. The ligand-exchange step for formation of $RhCl(Cy_3P)_3$ from $[RhCl(coe)_2]_2$ and Cy_3P is essential for this alkylation before the addition of substrate and alkene. When the alkylation was carried out



Scheme 1.

Keywords: alkylation; C–C bond formation; rhodium catalyst; aldimines; ketimines.
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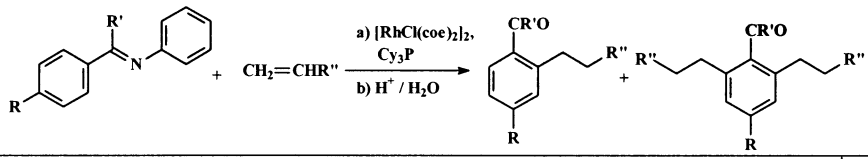
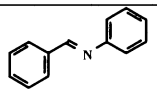
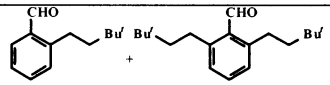
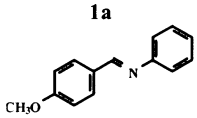
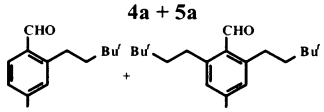
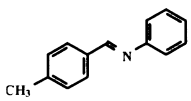
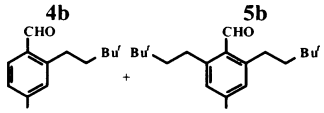
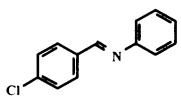
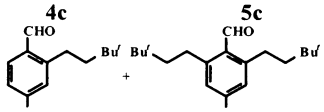
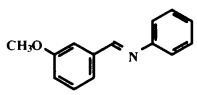
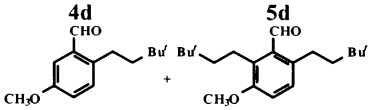
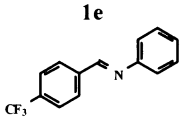
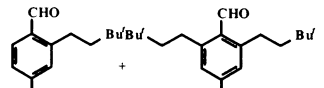
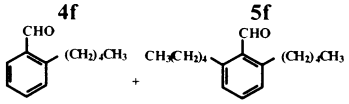
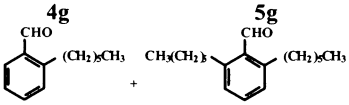
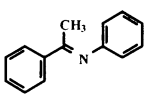
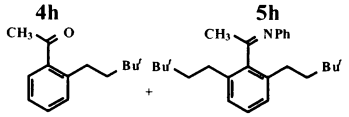
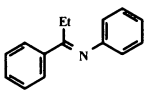
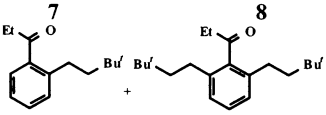
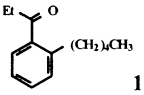
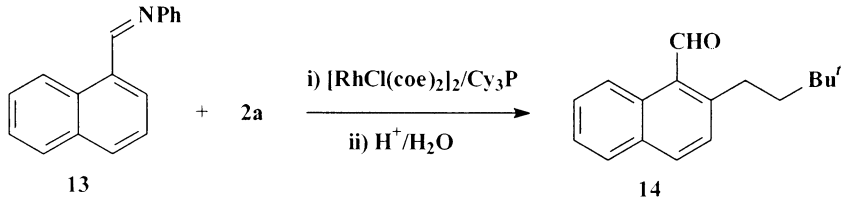
without a ligand-exchange step, the yield of the alkylated product was low (20–30%). However, 2-phenylpyridines do not require this ligand-exchange step.[3c] In an attempt to obtain the mono alkylated product **4a** as a major product, 1 equiv. of **2a** was used. However, **5a** was still the major product (run 2). Even though 0.7 equiv. of **2a** was used, this alkylation preferred double alkylation (run 3). This result indicates that after mono alkylation, the next catalytic cycle takes place without dissociation of the nitrogen of the imine on the rhodium metal center. The Wilkinson's complex $RhCl(Ph_3P)_3$, $(Ph_3P)_2Rh(CO)Cl$ and

Table 1. Results of the alkylation of aromatic aldimines and ketimines[a]



Run	Substrate	Alkene (equiv.)	Product	Yield[b]	Ratio of mono : double[c]
1	 **1a**	**2a** R"=Bu^t (5)	 **4a** **5a**	93	11 : 89
2	**1a**	(1)	**4a + 5a**	53	23 : 77
3	**1a**	(0.7)	**4a + 5a**	20[d]	36 : 64
4	 **1b**	**2a** (5)	 **4b** **5b**	90	1 : 99
5	 **1c**	**2a** (5)	 **4c** **5c**	87	5 : 95
6	 **1d**	**2a** (5)	 **4d** **5d**	88	3 : 97
7	 **1e**	**2a** (5)	 **4e** **5e**	50	97 : 3
8	 **1f**	**2a** (5)	 **4f** **5f**	90	2 : 98
9	**1a**	1-pentene **2b** (5)	 **4g** **5g**	44	20 : 80
10	**1a**	1-hexene **2c** (5)	 **4h** **5h**	19	34 : 66
11	 **6**	**2a** (5)	 **7** **8**	99	28 : 72
12	 **9**	**2a** (5)	 **10** **11**	86	97 : 3
13	**9**	**2b** (5)	 **12**	65	100 : 0

[a]Substrate : $[RhCl(coe)_2]_2$: Cy_3P = 1 : 0.05 : 0.3, THF, 140°C, 24h. [b]Isolated yield. [c]The ratio was determined by ^1H NMR or GC.
[d] Yield based on alkene used.



Scheme 2.

$(Ph_3P)_2Ir(CO)Cl$ were inactive under similar reaction conditions. The results of the alkylation are listed in Table 1. To investigate the effect of substituted groups on the benzene ring, aldimines bearing electron-donating and electron-withdrawing groups were examined under the same reaction conditions. The *p*-methoxy group, an electron-donating group, accelerated the alkylation and gave quantitative yields of the alkylated products (run 4). Another electron-donating group, the *p*-methyl group, also showed high reactivity (run 5). On the other hand, the aldimine-bearing electron-withdrawing group, *p*-NO_2, reacted slowly with alkene (6%; mono:double = 88:12). However, another aldimine-bearing electron-withdrawing group, *p*-CF_3, shows an unexpectedly high reactivity (run 8). The reason for this exceptional reactivity is not clear at the present time. However, the exceptional reactivity of the *p*-CF_3 group can be found in Murai's results of the alkylation of aromatic esters.[4e] Another electron-withdrawing group, *m*-CH_3O, reacted slowly (run 7). *m*-Methoxy substituted aldimine has two different sites (positions 2 and 6) for alkylation. This alkylation only gave the 6-position alkylated product **4e** together with small amount of double alkylated product **5e**. The product alkylated at the 2-position was not detected in the reaction mixture. This may be due to steric effects. The *meta*-substituent interferes with the approach of rhodium metal for C–H bond activation. Thus, the double alkylated product **5e** must come from **4e**. Unlike the case of 2-phenylpyridines, all aldimines preferred the double alkylated products.

Linear terminal alkenes, such as 1-pentene **2b** and 1-hexene **2c**, gave moderate yields (runs 9 and 10). The alkenes are isomerized to the internal alkene during the reaction. This isomerization competes with the alkylation between alkene and aldimine.

To elucidate the distribution of mono and double alkylated products of ketimines compared with aldimines, ketimines such as **6** and **9** were alkylated under the same reaction conditions. Substrate **6** gave the alkylated product with a 28:72 mono:double ratio (yield 99%, run 11). Interestingly, the double alkylated product **8** was not hydrolyzed in 1N HCl aqueous solution. On the other hand, **9** gave the mono alkylated product **10** predominantly (mono:double = 97:3, 86% isolated yield, run 12) because of the interference of rotation of the C–N bond between the phenyl ring and the imine group in the alkylated ketimine by steric hindrance of the ethyl group in the imine group and the alkyl in the phenyl group. Moreover, **9** reacted with **2b** to give **12** solely (run 13).

Another substrate, naphthalene derivative **13**, reacted with **2a** (5 equiv.) to give the alkylated 1-naphthaldehyde **14** in 99% yield after hydrolysis and chromatographic isolation (see Scheme 2).

In conclusion, we have found that aldimines and ketimines reacted with alkenes under a rhodium catalyst without additives to give mainly the double alkylated products with moderate to high yields. The aldimines bearing H, *p*-CH_3O, *p*-CH_3, *p*-Cl and *p*-CF_3 groups have high reactivities, but *m*-CH_3O and *p*-NO_2 exhibit low reactivities. The ketimine **9** gave the mono alkylated products predominantly.

Acknowledgements

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