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$\mathrm{Ru_3(CO)_{12}}$-Catalyzed Coupling of Heteroaromatic C−H/CO/Olefins. Regioselective Acylation of the Imidazole Ring

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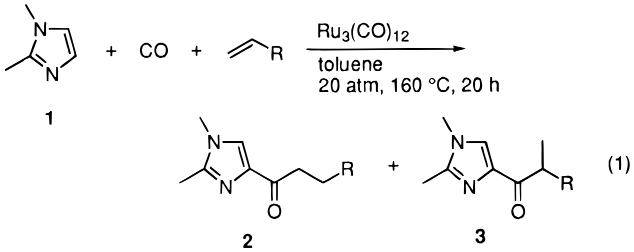
Development of transition metal catalyzed reactions involving formation of C−C bonds with cleavage of C−H bonds has been one of the most attractive and challenging projects.[1] Cleavage of C−H bonds in a catalytic manner has been demonstrated by H−D exchange reaction,[2] silyl coupling,[3] isonitrile insertion,[4] and C−C multiple bond insertion.[5,6] Recently, we have reported efficient catalytic addition of sp² C−H bonds to C−C unsaturated bonds.[7−11] On the other hand, carbonylation with cleavage of aromatic C−H bonds is still relatively rare. In 1979 Hong and Yamazaki reported that the reaction of benzene with ethylene under CO pressure in the presence of $\mathrm{Rh_4(CO)_{12}}$ gave a small amount of propiophenone, along with styrene and 3-pentanone as the major products.[12] Eisenberg found that $\mathrm{IrH_3(CO)(dppe)}$ and $\mathrm{RhCl(CO)(PPh_3)_2}$ catalyzed the photochemical carbonylation of benzene to benzaldehyde.[13] Later, Tanaka[14] found that $\mathrm{RhCl(CO)(PMe_3)_2}$ is more active for carbonylation of benzene although the reaction required photoirradiation. In 1992, Moore found a direct method for acylation of pyridine with CO and olefins using a ruthenium catalyst.[15] Although the reaction exhibits a high regioselectivity and high catalyst turnover frequencies, pyridine or a pyridine derivative was used as the solvent in most cases, and therefore the yields based on the pyridine were not high. We report a new catalytic reaction which enables high-yield carbonylation at C−H bonds. Regioselective coupling of an imidazole C−H bond with CO and an olefin proceeded in a very efficient way (eq 1).



a:	R = Bu	68% (94:6)	**e**:	R = $\mathrm{SiMe_3}$	66% (>99:1)
b:	R = Ph	74% (75:25)	**f**:	R = $\mathrm{CH_2SiMe_3}$	61% (94:6)
c:	R = 2-$\mathrm{MeC_6H_4}$	77% (93:7)	**g**:	R = $\mathrm{CH_2CN}$	42% (87:13)
d:	R = ^{t}Bu	88% (>99:1)			

The reaction of 1,2-dimethylimidazole (**1**) (1 mmol) with 1-hexene (4 mmol) under 20 atm of CO in toluene (3 mL) at 160 °C for 20 h in the presence of $\mathrm{Ru_3(CO)_{12}}$ (0.04 mmol) gave 1-(1,2-dimethyl-1*H*-imidazol-4-yl)-1-heptanone (**2a**)[16] and its isomer **3a** in 68% total yield with a linear to branched ratio of 94:6. The coupling occurred highly regioselectively at the 4-position, no 5-heptanoylation isomer being detected by ¹H and ¹³C NMR spectroscopies or GCMS. The assignment of the regiochemistry was based on the comparison of the ¹H NMR chemical shifts of $\mathrm{CH_3N}$ protons of **2a** with those of the known 4-acetyl-1,2-dimethylimidazoles.[17] Although a variety of transition metal complexes were examined for their ability to catalyze the coupling reaction of **1**, CO, and 1-hexene, complexes such as $\mathrm{H_2Ru(CO)(PPh_3)_3}$, $\mathrm{RuCl(CO)_2(PPh_3)_2}$, $\mathrm{[RuCl_2(CO)_3]_2}$, $\mathrm{Ru(acac)_3}$, $\mathrm{Rh_6(CO)_{16}}$, $\mathrm{Ir_4(CO)_{12}}$, and $\mathrm{Os_3(CO)_{12}}$ were not effective. The reaction of 2-hexene (cis/trans mixture) also gave a mixture of **2a** and **3a** in 41% yield with exactly the same linear to branched ratio as that in the reaction of 1-hexene.

Olefins that can be used include alkyl-, aryl-, and trialkylsilyl-substituted alkenes (eq 1). The linear to branched ratio was affected by the steric factor. The ratio became 93:7 in the case of *o*-methylstyrene, while styrene gave a low linear to branched ratio. The more bulky groups *tert*-butyl and trimethylsilyl led exclusively to linear isomers **2d** and **2e**, respectively. The reaction of electron deficient olefins such as acrylonitrile and ethyl acrylate did not proceed; however, allyl cyanide underwent a coupling reaction to give **2g** preferentially.

As indicated in Table 1, the reaction is both highly efficient and selective. A cyclic olefin was applicable to the present reaction (entry 1). The reaction of α-methylstyrene gave a somewhat lower yield, but led to a single isomer (entry 2). It is noteworthy that the present reaction was compatible with N-protecting groups such as methoxymethyl and benzyl (entries 4 and 5). These protecting groups are removable under a variety conditions, so that the procedure represents a general method for the preparation of 4(5)-acyl NH-imidazoles. Unsaturated ketals underwent coupling reactions to produce the monoprotected 1,6-diketones, which have been shown to be synthetically useful. 1,2-Fused bicyclic imidazole **12** also underwent coupling regioselectively to give **13** (entry 6).

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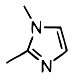
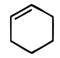
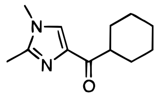
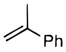
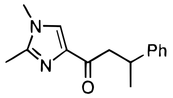
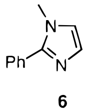
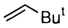
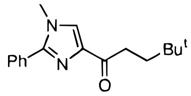
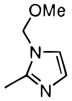
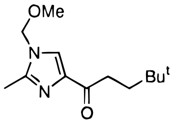
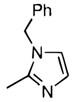
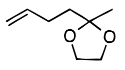
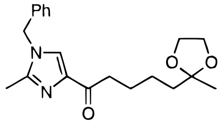
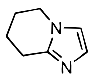
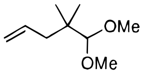
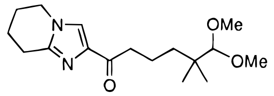
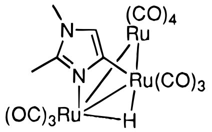
Table 1. $Ru_3(CO)_{12}$-Catalyzed Coupling of Imidazole CH/CO/Olefins[a]

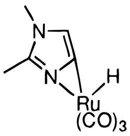
entry	imidazole	olefin	product[b]
1	 **1**		 **4** 50%
2	**1**		 **5** 42% (>99:1)
3	 **6**		 **7** 79% (>99:1)
4	 **8**		 **9** 95% (>99:1)
5	 **10**		 **11** 72% (97:3)
6	 **12**		 **13** 90% (>99:1)

[a] Reaction conditions: imidazole (1 mmol), olefin (4 mmol), CO (20 atm), $Ru_3(CO)_{12}$ (0.04 mmol), toluene (3 mL), 160 °C, 20 h. [b] Isolated yields. The ratio of linear to branched is in parentheses.

Although stoichiometric reactions of $Ru_3(CO)_{12}$ with nitrogen-containing heterocycles have been studied extensively,[18] few complexes derived from imidazoles have been reported, no 1,2-disubstituted imidazole complexes being described. Rosenberg reported that the reaction of $Os_3(CO)_{10}(CH_3CN)_2$ with 1-vinylimidazole gave a (μ-H)triosmium cluster with the C(4)−H bond cleaved as the main product.[18] This observation may suggest that a complex such as **A** is the key species in the present coupling reaction. Actually, the corresponding pyridine triruthenium cluster (similar to **A**) has been proposed to be involved in $Ru_3(CO)_{12}$-catalyzed acylation of pyridine,[15] without any experimental evidence. Another possible species, a mononuclear complex such as **B**, cannot be excluded. Jordan reported zirconium-catalyzed coupling of 2-picoline and propene where C−C bond formation occurred at the 6-position.[5] As a key species, a η^2-piconyl Zr complex (analogous to **B**) is suggested. The structure of the real key species aside, high regioselectivity in the present reaction is due to the initial coordination through the imino nitrogen atom to ruthenium, which leads to cleavage of the adjacent C−H bond (4-position) giving a postulated complex such as **A** or **B**. Insertion of an olefin into a H−Ru bond and successive CO insertion followed by reductive elimination gives the final product.[19]



A



B

In summary, acylation of imidazoles is accomplished by the $Ru_3(CO)_{12}$-catalyzed coupling reaction of imidazoles, CO, and olefins. While a number of methods have already been well documented for the elaboration of this important nucleus,[20] there appear to be few practical procedures available for the synthesis of 1,2-disubstituted 4-acyl imidazoles.[17] Friedel−Crafts acylation of 1,2-disubstituted imidazoles does not give the corresponding ketones because of the deactivation that occurs on complexation of the imidazole with the Lewis acid.[20] The present method has several advantages over existing methods, including high yield, impressive catalytic efficiency, functional group compatibility, and simple operation. In addition, this reaction is a new catalytic carbonylation reaction involving cleavage of an aromatic C−H bond.

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Supporting Information Available: Lists of special data and elemental analyses for the products (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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