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Ru$_3$(CO)$_{12}$-Catalyzed Site-Selective Carbonylation Reactions at a C−H Bond in Aza-Heterocycles

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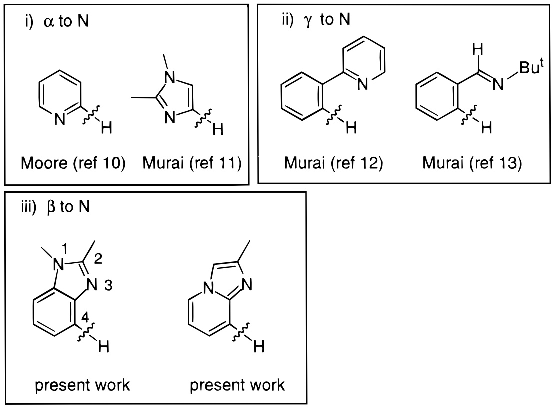
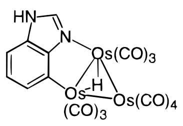
Transition-metal-catalyzed reactions which involve the formation of a C−C bond from a C−H bond provide a new, useful synthetic tool.[1] Recently, ruthenium and rhodium complexes have been found to be efficient catalysts for the addition of sp^2 C−H bonds in a benzene ring to olefins[2−7] and acetylenes.[8,9] It is interesting to note, however, that direct carbonylation at a C−H bond, catalyzed by transition metal complexes, has not yet been extensively studied. Based on reports to date, the catalytic carbonylation at a C−H bond can be classified into two types, based on the position where the C−H bond is carbonylated, as shown in Chart 1: (i) carbonylation at a C−H bond α to the ring nitrogen[10,11] and (ii) carbonylation at a C−H bond γ to the ring nitrogen.[12−14] In both cases, the coordination of the nitrogen to the ruthenium complex is essential for the site-selective cleavage of a C−H bond. The absence of a directing group leads to much lower efficiency and site-selectivity.[15]

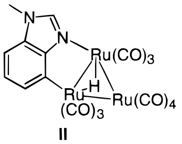
Chart 1



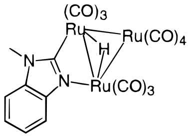
The goal of this study was to develop a method for carbonylation at a C−H bond β to the nitrogen. The β relation is, electronically, a difficult system compared to the α and γ relationships, which are conjugated. A literature survey led us to conclude that the stoichiometric reaction of Os$_3$(CO)$_{10}$(CH$_3$CN)$_2$ with benzimidazole undergoes cleavage of the C−H bond at the 4-position to give the ortho-metalated trinuclear complex **I**.[16] It would appear that a related ruthenium complex **II** might be generated in situ as an intermediate with the potential to react with CO and olefins. Thus, a Ru$_3$(CO)$_{12}$-catalyzed reaction of benzimidazole might well give 4-acylbenzimidazoles. This attempt did not result in carbonylation at the β position but gave products arising from carbonylation at the carbon between the two nitrogen atoms (vide infra). We then examined the Ru$_3$(CO)$_{12}$-catalyzed reaction of 1,2-dimethylbenzimidazole and found a high level of carbonylation at the C−H bonds β to the ring nitrogen.



I

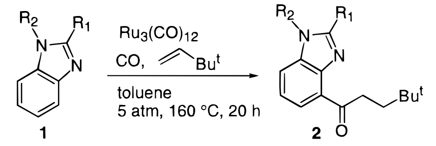


II



III

The reaction of 1,2-dimethylbenzimidazole (1 mmol, **1a**) with *tert*-butylethylene (4 mmol) under 5 atm of CO in toluene (3 mL) at 160 °C for 20 h in the presence of Ru$_3$(CO)$_{12}$ (0.04 mmol) gave 1-(1,2-dimethylbenzimidazol-4-yl)-4,4-dimethyl-1-pentanone (**2a**)[17] in 77% yield along with 21% of unreacted **1a** (eq 1).



(1)

a:	R$_1$ = Me	R$_2$ = Me	77% (21%)*
b:	R$_1$ = Me	R$_2$ = CH$_2$Ph	69% (28%)
c:	R$_1$ = Me	R$_2$ = Ac	no reaction
d:	R$_1$ = Et	R$_2$ = Me	42% (55%)
e:	R$_1$ = *i*-Pr	R$_2$ = Me	8% (87%)

* Numbers in parenthesis are recovery of **1a**.

Interestingly, the carbonylation occurred highly site-selectively at the 4-position. A longer reaction time (40 h) resulted in no increase in the product yield (81% yield), and **1a** was recovered in 17%. A lower reaction temperature (140 °C) decreased the yield to 49%, along with a 47% recovery of **1a**. Higher CO pressure decreased the reaction rate (20 atm, 26% yield **2a** with 62% recovered **1a**; 40 atm, 10% **2a** and 76% **1a**). Higher CO pressure suppresses the coordination of **1a** to the ruthenium center, which is essential for the metal to cleave the C−H bond.

The effects of substituents (R$_1$ and R$_2$) on the reaction was examined. Replacement of *N*-methyl with *N*-benzyl (**1b**) had no effect on the reaction. However, an *N*-acyl substrate such as **1c** is not reactive because of its weak coordination character. The bulkiness of R$_1$ appears to be an important factor. The yields

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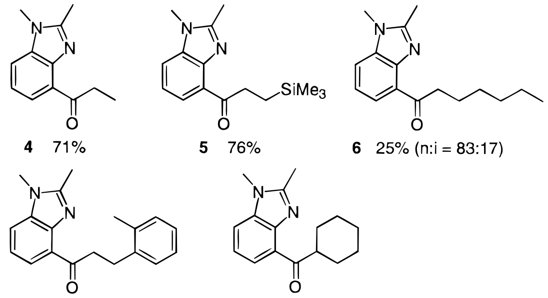
Chart 2

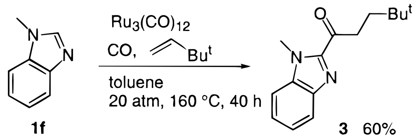


4 71% **5** 76% **6** 25% (n:i = 83:17)

7 78% (n:i = 88:12) **8** 25%

decrease as the size of R_1 increases: Me (77%) > Et (42%) > ^{i}Pr (8%). Steric hindrance around the 3-nitrogen atom makes the coordination of the nitrogen to the metal difficult.

As mentioned above, the carbonylation of **1f**, which has no substituent at the 2-position, took place at the 2-position with high site-selectivity to give **3** (eq 2). The reaction of **1f** (0.1 mmol of catalyst, 20 atm of CO at 160 °C for 40 h) gave **3** in 60% yield. Competitive carbonylation between the α-position (i.e., at 2-position) and the β-position (i.e., at 4-position) favors the α-position exclusively. The intermediacy of the complex **III** would be invoked in the reaction.[18]

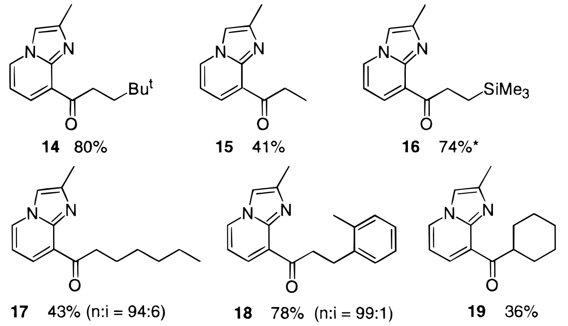


1f **3** 60% (2)

The results for the reaction of **1a** with some olefins are summarized in Chart 2. The reaction conditions were the same as those indicated in eq 1 except for ethylene, for which they were **1a** (2 mmol), ethylene (7 atm at room temperature in a 50-mL stainless steel autoclave), CO (5 atm), and $Ru_3(CO)_{12}$ (0.08 mmol) in toluene (6 mL) at 160 °C for 20 h. The use of hexene gave a mixture of linear and branched isomers, in favor of the linear isomer. The type of products obtained here are difficult to prepare using conventional methods reported thus far. A Friedel−Crafts acylation cannot be applied because of the deactivation that occurs on complexation of the substrate with the Lewis acid.[19]

A variety of heterocyclic compounds, such as 2-methylbenzoxazole (**9**), 2-methylbenzothiazole (**10**), 2,2,3-trimethyl-3*H*-indole (**11**), and 1-methylbenzotriazole (**12**), were also examined with respect to reaction with *tert*-butylethylene. In the case of **9**, no reaction was observed. The reaction of **10** (20 atm of CO, 0.1 mmol of the catalyst at 180 °C for 3 d) gave 7% of the coupling product. When **11** was treated with 0.1 mmol of catalyst at 160 °C for 40 h, the corresponding ketone was obtained in 15% yield. Compound **12** gave (at 160 °C for 20 h) the corresponding ketone in 46% yield. In all cases, carbonylation took place at a C−H bond β to the ring nitrogen, showing the same site-selectivity as observed for as imidazoles. We found that the reactivity of **1a**, **9**, **10**, and **12** corresponds to the pK_a values of the conjugated acids:[20] **1a** (p$K_a = 6.19$)[20b] $\gg$ **12** (p$K_a = 1.60$)[21] > **10** (p$K_a = 1.20$)[22] > **9** (p$K_a = 0.99$).[23] Hence, the higher the pK_a of the substrate, the higher is the reactivity. This result suggests that the coordination of the substrates to a ruthenium complex is a necessary prerequisite for the carbonylation to proceed.

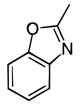
Chart 3



14 80% **15** 41% **16** 74%*

17 43% (n:i = 94:6) **18** 78% (n:i = 99:1) **19** 36%

* The corresponding ethylketone was also obtained in 2% yield.



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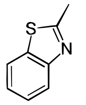

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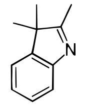
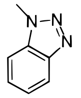
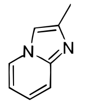


11



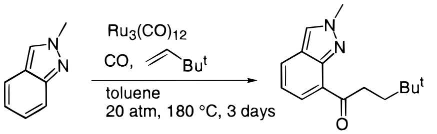
12



13

We next chose 2-methylimidazo[1,2-*a*]pyridine (**13**) as the substrate because of its high pK_a (6.79).[24] As expected, the reaction of **13** with CO and *tert*-butylethylene under the same reaction conditions as in eq 1 proceeded smoothly, and 1-(2-methylimidazo[1,2-*a*]pyridin-8-yl)-4,4-dimethylpentanone (**14**) was obtained in 56% yield. In contrast to the case of **1a**, a higher CO pressure (20 atm) increased the product yield to 80%, with 9% of unreacted **13** being recovered. The results for the reaction of **13** with some olefins are summarized in Chart 3. All of the reactions are carried out under 20 atm of CO. The results obtained were nearly the same for **1a** shown in Chart 2.

The reaction of **20**[25] (0.1 mmol of $Ru_3(CO)_{12}$, CO 20 atm at 180 °C for 3 days) with *tert*-butylethylene gave the corresponding ketone in 34% yield, along with 63% of unreacted **20** (eq 3).



20 **21** 34% (3)

In summary, we provide the first example of a direct carbonylation at a C−H bond β to a directing nitrogen atom.[26]

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Supporting Information Available: Lists of special data and elemental analyses for the products (10 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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[18] It was reported that the complex **III** is obtained by the stoichiometric reaction of benzimidazole with $Ru_3(CO)_{12}$. Cabeza, J. A.; Oro, L. A.; Tiripicchio, A.; Tiripicchio-Camellini, M. *J. Chem. Soc., Dalton Trans.* **1988**, 1437. A contrasting result was obtained in the reaction of benzimidazole with $Os_3(CO)_{12}$. See ref 16.

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[26] We have no evidence that triruthenium cluster, such as **II**, works as a real active catalyst.