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Carbonylation at sp^3 C–H Bonds Adjacent to a Nitrogen Atom in Alkylamines Catalyzed by Rhodium Complexes

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The development of catalytic reactions which involve the cleavage of C–H bonds is one of the most challenging projects in organic synthesis.^{1,2} In the past decade, a number of reactions, which involve the cleavage of sp^2 C–H bonds, have been reported.¹ In contrast, catalytic reactions involving sp^3 C–H bonds are still rare.² On the basis of a recent literature survey, an sp^3 C–H bond which is adjacent to a heteroatom is more reactive than one surrounded by carbon atoms. A few reactions which are catalyzed by transition metal complexes and which involve the cleavage of sp^3 C–H bonds adjacent to heteroatoms have been reported. The addition of a C–H bond adjacent to an oxygen atom in dimethoxyethane across alkenes was achieved via an Ir-catalyzed reaction.³ The tungsten-catalyzed addition of a C–H bond α to a nitrogen in secondary amines has been reported.⁴ Catalytic alkyl exchange reactions of primary and secondary amines, in the presence of Pd, has been reported by Murahashi.⁵ Recently, Jun found that $Ru_3(CO)_{12}$ is effective in catalyzing addition of benzylic C–H bonds adjacent to a nitrogen across alkenes.⁶ In this laboratory, we also found the $Ru_3(CO)_{12}$ -catalyzed carbonylation occurs at an sp^3 C–H bond in a piperidine ring.⁷ However, our finding led us to conclude that carbonylation does not take place directly at an sp^3 C–H bond but, rather, at sp^2 C–H bonds which are formed as a result of the initial dehydrogenation.⁷ The results obtained from the above examples suggest that an sp^3 C–H bond adjacent to a heteroatom can be easily cleaved. Our ultimate goal is to develop catalytic carbonylation reactions at an sp^3 C–H bond. To achieve this process, we utilized substrates which contain a directing group, in addition to a heteroatom sufficiently close to the C–H bond. The directing group-promoted cleavage of unreactive bonds has proved to be an effective method for the development of catalytic reactions involving the cleavage of unreactive bonds, such as C–H.^{7–9}

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(2) For a recent review on the cleavage of sp^3 C–H bonds, see: Arndsten, B. A.; Bergman, R. G.; Mobley, T. A.; Peterson, T. *Acc. Chem. Res.* **1995**, 28, 154. For a recent paper, see: Chen, H.; Schlecht, S.; Semple, T. C.; Hartwig, J. F. *Science* **2000**, 287, 1995.

(3) Lin, Y.; Ma, D.; Lu, X. *Tetrahedron Lett.* **1987**, 28, 3249.

(4) Nugent, W. A.; Ovenall, D. W.; Holmes, S. J. *Organometallics* **1983**, 2, 161.

(5) Murahashi, S.-I.; Yoshimura, N.; Tsumiyama, T.; Kojima, T. *J. Am. Chem. Soc.* **1983**, 105, 5002 and references therein.

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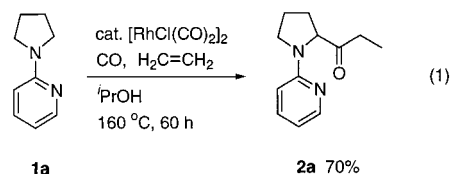
(7) Ishii, Y.; Chatani, N.; Kakiuchi, F.; Murai, S. *Organometallics* **1997**, 16, 3615.

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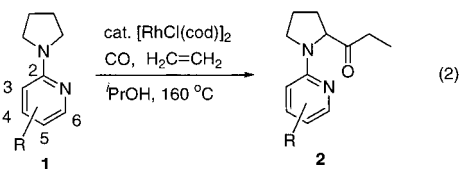
(9) Kakiuchi, F.; Sonoda, M.; Tsujimoto, T.; Chatani, N.; Murai, S. *Chem. Lett.* **1999**, 1083 and references therein.

C–C,¹⁰ and C–F bonds.¹¹ The photomediated Rh-catalyzed carbonylation of simple alkanes to isomeric alkanals has been achieved,¹² although the efficiency is low. We report herein the first effective example of a carbonylation at the sp^3 C–H bonds in alkylamines in the presence of a rhodium catalyst.

Although an intensive screening of a variety of types of substrates and reaction variables was undertaken, we were unable to achieve carbonylation at an sp^3 C–H bond when ruthenium complexes were used as the catalyst. Finally, we found that the use of cyclic amine **1a** as the substrate in conjunction with a rhodium complex as the catalyst and 2-propanol as the solvent provided the most successful results. The reaction of **1a** (1 mmol) with CO (15 atm) and ethylene (10 atm) in 2-propanol (3 mL) in the presence of $[RhCl(CO)_2]_2$ (0.04 mmol) at 160 °C for 60 h gave 1-[1-(2-pyridinyl)-2-pyrrolidinyl]-1-propanone (**2a**)¹³ in 70% yield (eq 1).



Of interest is the fact that a saturated ketone was obtained, in contrast to the reaction of *N*-2-pyridylpiperidine reported previously by us.⁷ Carbonylation took place at a C–H bond α to the pyrrolidine nitrogen, with no other regioisomeric products being observed. A trace amount of the bis-carbonylation products, which arise from further reaction of the second α C–H bond, were obtained. Among the solvents examined, 2-propanol was the solvent of choice (toluene 4%, THF 7%, CH_3CN 23%). The rhodium complex $[RhCl(cod)]_2$ was found to be superior to $[RhCl(CO)_2]_2$ and $Rh_4(CO)_{12}$ as the catalyst. After optimization of the reaction conditions, we found that **1a** (1 mmol) with CO (10 atm) and ethylene (5 atm) in 2-propanol (3 mL) in the presence of $[RhCl(cod)]_2$ (0.04 mmol) at 160 °C for 40 h gave **2a** in 68% yield (eq 2).



R = H (1a)	40 h	68%
3-Me (1b)	60 h	73%
4-Me (1c)	60 h	73%
5-Me (1d)	40 h	84%
6-Me (1e)	60 h	12%
5-CF ₃ (1f)	60 h	15%

It is noteworthy that the nature of the substituents on the pyridine ring had a significant effect on the product yields (eq 2). The presence of an electron-donating group at the 5-position on the pyridine ring, as in **1d**, resulted in an increased product yield. Steric hindrance around the pyridine nitrogen and electron-

(10) Jun, C.-H.; Lee, H. *J. Am. Chem. Soc.* **1999**, 121, 880. Chatani, N.; Ie, Y.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **1999**, 121, 8645.

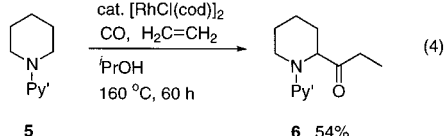
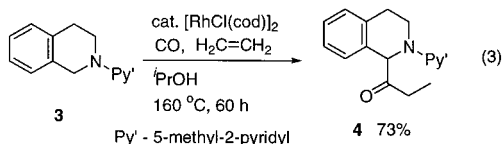
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(12) Sakakura, T.; Sodeyama, K.; Sasaki, K.; Wada, K.; Tanaka, M. *J. Am. Chem. Soc.* **1990**, 112, 7221.

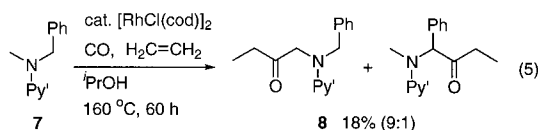
(13) All new compounds were characterized by NMR, IR, mass spectral data, and by elemental analyses or high-resolution mass spectra. See Supporting Information.

deficient pyridine dramatically decreased the product yields, as in the case of **1e** and **1f**.

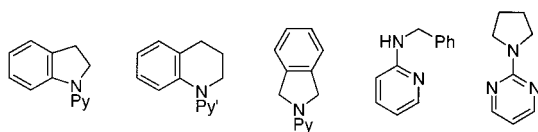
The reaction of **3** resulted in the regioselective carbonylation at the benzylic position to give **4** in 73% yield, along with 16% of unreacted **3** being recovered (eq 3). The reaction of **5** gave **6** in 54% yield, while the corresponding pyridine derivative gave a small amount of the product, again showing the usefulness of the 5-methylpyridine ring as a directing group (eq 4).



The carbonylation of acyclic amines also proceeded to give the corresponding ketones, albeit with low efficiency. The reaction of **7** gave regioisomeric mixtures of α -aminobutanones **8** in a 9:1 ratio, along with 63% of unreacted **7** being recovered. (eq 5). In contrast to reaction of **3**, the carbonylation took place at the methyl, instead of benzylic, C–H bond, presumably because of steric factors.



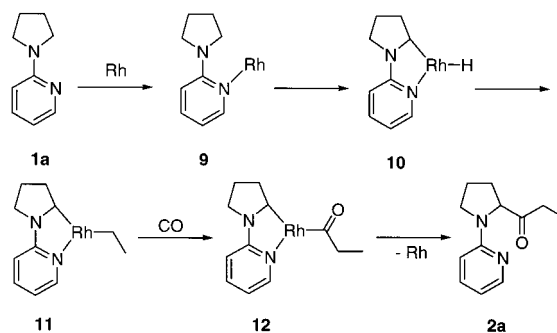
The presence of a pyridine ring is essential for the present carbonylation to proceed. Thus, the reaction of *N*-alkyl- and *N*-phenyl-substrates failed to take place. In addition, the substrates shown below were not appropriate for the present carbonylation.



A proposed reaction mechanism is shown in Scheme 1. In this mechanism, coordination of the nitrogen on **1a** to rhodium provides complex **9**, in which the C–H bond undergoes cleavage to give the alkyl Rh complex **10**. The insertion of ethylene into a H–Rh bond in **10** followed by CO insertion gives the acyl Rh

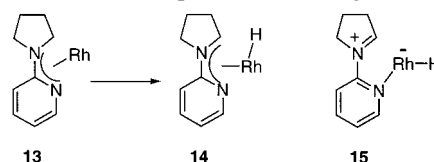
complex **12**, from which reductive elimination gives the final product **2a** and the starting Rh complex.

Scheme 1. Proposed Reaction Mechanism



Besides the conventional, direct oxidative addition,¹⁴ two possible steps for C–H bond cleavage exist (Scheme 2). One involves a hydride elimination from 1,3-diaza- π -allyl Rh complex **13** to **14**. The second involves the participation of an iminium intermediate.¹⁵ We cannot, at present, determine which mechanism is operating.

Scheme 2. Alternative Steps for the Cleavage of C–H Bond



In summary, we report on a new carbonylation reaction at sp^3 C–H bonds, which is catalyzed by rhodium complexes. While the scope of substrate and olefin is rather limited at present,¹⁶ the reaction is the first effective example of carbonylation at sp^3 C–H bonds which are adjacent to the nitrogen in alkylamines.¹⁷ The presence of the pyridine ring is essential for the reaction to proceed.

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Supporting Information Available: Full experimental details (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(14) The direct oxidative addition of an sp^3 C–H bond adjacent to a nitrogen atom to ruthenium was proposed by Jun in the Ru-catalyzed addition of the benzylic C–H bond across alkenes. See ref 6.

(15) Related iminium intermediates or imine intermediates have been proposed as key species in the transition metal-catalyzed alkyl exchange reaction of amines. See ref 5.

(16) The reaction of **1a** with 1-hexene did not give the expected carbonylation product. The use of *tert*-butylethylene gave 9% of the corresponding product.

(17) Quite recently, Sames reported the pyridine-directed cleavage of saturated C–H bond. Johnson, J. A.; Sames D. *J. Am. Chem. Soc.* **2000**, *122*, 6321.