J. Am. Chem. Soc. **2000,** *122,* 12882−12883

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

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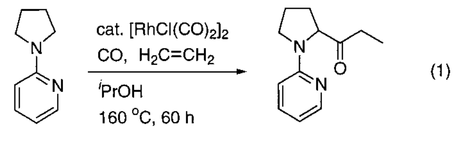
Received July 13, 2000

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 occurrs at an sp^3 C−H bond in a piperadine 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] 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.

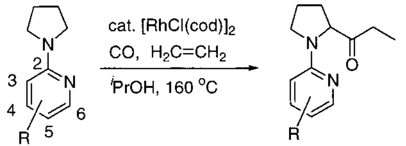
Although an intensive screening of a variety of types of substrates and reaction variables was undertaken, we were unable to achieve carbonylation at an sp^3 C−H bond when ruthenium complexes were used as the catalyst. Finally, we found that the use of cyclic amine **1a** as the substrate in conjunction 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).



(1)

1a **2a** 70%

Of interest is the fact that a saturated ketone was obtained, in contrast to the reaction of *N*-2-pyridylpiperadine 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).



(2)

1 **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-

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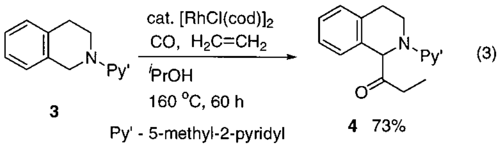
[13] All new compounds were characterized by NMR, IR, mass spectral data, and by elemental analyses or high-resolution mass spectra. See Supporting Information.

10.1021/ja002561w CCC: $19.00

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).

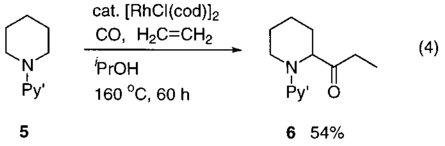


3

Py' - 5-methyl-2-pyridyl

4 73%

(3)

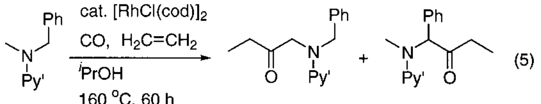


5

6 54%

(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.

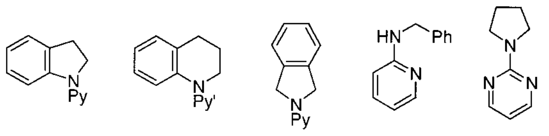


7

8 18% (9:1)

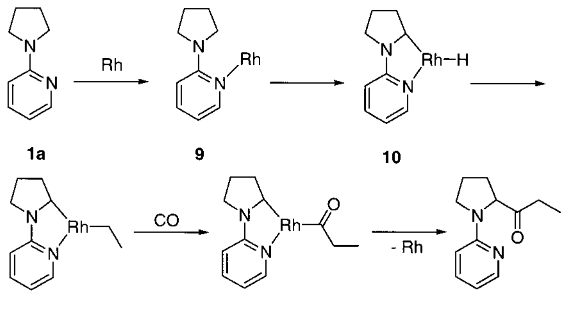
(5)

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

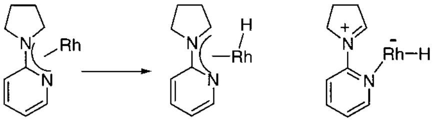


1a **9** **10**

11 **12** **2a**

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



13 **14** **15**

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.

Acknowledgment. Thanks are given to the Instrumental Analysis Center, Faculty of Engineering, Osaka University, for assistance in obtaining MS, HRMS, 600-MHz NMR, and elemental analyses.

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

JA002561W

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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.