JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

COMMUNICATION

pubs.acs.org/JACS

# Highly Regioselective Carbonylation of Unactivated C($sp^3$)−H Bonds by Ruthenium Carbonyl

Nao Hasegawa, Valentine Charra, Satoshi Inoue, Yoshiya Fukumoto, and Naoto Chatani*

Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565-0871, Japan

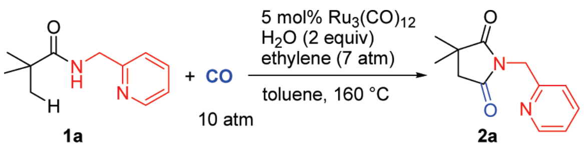
Supporting Information

**ABSTRACT:** The regioselective carbonylation of unactivated C($sp^3$)−H bonds of aliphatic amides was achieved using $Ru_3(CO)_{12}$ as a catalyst. The presence of a 2-pyridinylmethylamine moiety in the amide is crucial for a successful reaction. The reaction shows a preference for C−H bonds of methyl groups as opposed to methylene C−H bonds and tolerates a variety of functional groups. The stoichiometric reaction of an amide with $Ru_3(CO)_{12}$ gave a dinuclear ruthenium complex in which the 2-pyridinylmethylamino moiety was coordinated to the ruthenium center in an N,N manner.

The direct utilization of C−H bonds, which are ubiquitous in organic molecules, is a straightforward method in organic synthesis that avoids the need for prefunctionalization of the starting materials.[1] The utilization of C−H bonds involving the activation of C($sp^2$)−H bonds by transition-metal complexes is now a commonly used method in organic synthesis, and a wide variety of catalytic transformations of arenes, heteroarenes, and alkenes have been reported to date. In contrast, functionalization involving the activation of *C($sp^3$)−H bonds* continues to be a challenge in organic synthesis. The catalytic functionalization of unactivated C($sp^3$)−H bonds, in particular by Pd catalysis, has been extensively investigated in recent years,[2] and include reported reactions include intramolecular arylation,[3] intermolecular arylation,[4] vinylation,[5] alkylation,[4c,e,6] dehydrogenation,[3a,b,7] carbonylation,[8] amination,[9] and oxidation.[10] In the reactions involving activation of unactivated C($sp^3$)−H bonds reported to date, soft, electrophilic, late transition metals such as Pd(II), Pt(II), Hg(II), and Au(III) have frequently been used because C−H bonds are capable of interacting with the electrophilic metal.[11] In contrast, only a few examples of the functionalization of unactivated C($sp^3$)−H bonds by low-valent late transition metals are known, including dehydrogenation[12] and borylation.[13] There are many systems that support stoichiometric C($sp^3$)−H activation reactions by low-valent transition-metal complexes,[14] but only a few of these can be incorporated into useful catalytic cycles that generate organic products. If complexes of low-valent late transition metals could be used as catalysts, it would open new possibilities for exploring new catalytic reactions of *unactivated C($sp^3$)−H bonds.*

The catalytic carbonylation of C−H bonds is an attractive method for the direct preparation of carbonyl compounds from alkanes, but no effective examples of the carbonylation of C($sp^3$)−H bonds have been reported. Tanaka reported the Rh-catalyzed carbonylation of alkanes to produce aliphatic aldehydes under photoirradiation conditions.[15] Because of its endothermic nature, the reaction requires continuous photoirradiation and the use of the alkane as the solvent. In addition, no regioselectivity was observed. We previously reported the Rh-catalyzed carbonylation of C($sp^3$)−H bonds adjacent to the nitrogen in an amine. In this case, the presence of the adjacent nitrogen was required for the carbonylation of C($sp^3$)−H bonds to proceed.[16] More recently, we reported the development of a 2-pyridinylmethylamino chelation system for the carbonylation of C($sp^2$)−H bonds.[17] To broaden the scope of this concept and examine its potential for the exploration of new reactions that have not yet been achieved by a conventional chelation-assisted system, we tested the system for possible use in various types of catalytic reactions. We report herein the Ru-catalyzed cyclocarbonylation of aliphatic amides through the regioselective carbonylation of *unactivated C($sp^3$)−H bonds.*

**Scheme 1. Carbonylation of Unactivated C($sp^3$)−H Bonds in Amides**




| | | |
|---|---|---|
| 1 d | | 22% |
| 3 d | | 55% |
| 3 d | no ethylene | 0% |
| 3 d | no $H_2O$ | 16% |
| 5 d | | 79% |

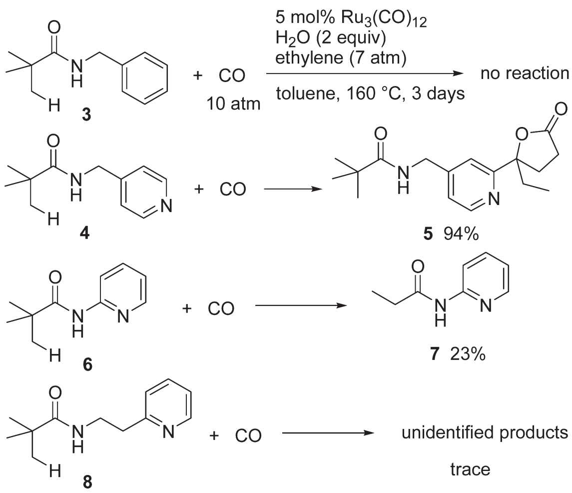
The reaction of amide **1a** with CO and ethylene in the presence of $Ru_3(CO)_{12}$ in toluene at 160 °C for 24 h gave succinimide **2a** in 22% yield with 60% recovery of **1a** (Scheme 1). Importantly, the carbonylation of an unactivated C($sp^3$)−H bond was achieved. Running the reaction for 3 days resulted in an increase in the product yield to 55%. In the absence of ethylene, no carbonylation product was detected. The absence of $H_2O$ decreased the efficiency of the reaction. After optimization of the reaction conditions, the following conditions were selected as the standard reaction conditions: amide (1 mmol), CO (10 atm), ethylene (7 atm), $H_2O$ (2 mmol), and $Ru_3(CO)_{12}$ (0.05 mmol) in toluene (3 mL) at 160 °C for 5 days.

We next examined the effect of directing groups (Scheme 2). No reaction occurred when the corresponding benzylamide **3**

**Received:** January 7, 2011
**Published:** May 04, 2011

**Scheme 2. Effect of Directing Groups**

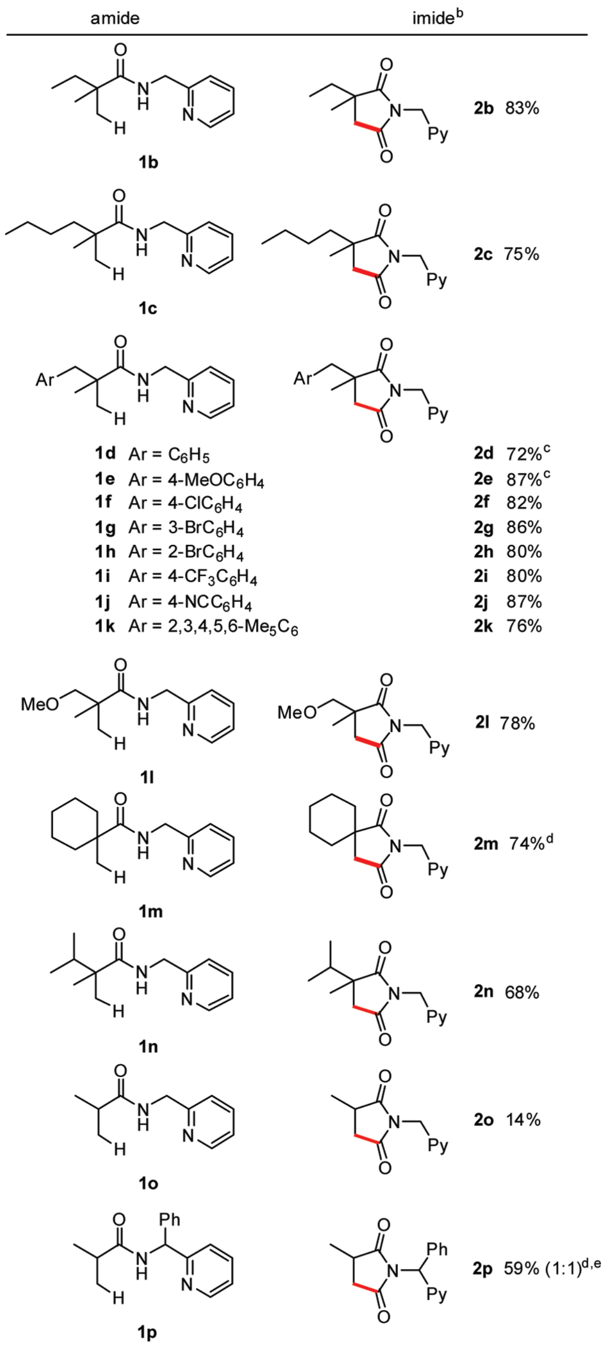



was used as the substrate in place of **1a**, indicating that coordination of the pyridine nitrogen to the catalyst is a key step for the reaction to proceed. In addition, the reaction of amide **4** did not result in the formation of a C−H bond carbonylation product but instead gave **5** in high yield.[18] Amides having shorter and longer carbon chains, such as **6** and **8**, also did not give the corresponding imides.[19]

Table 1 shows representative results for some reactions of aliphatic amides under the standard reaction conditions. The reactions were highly regioselective, exclusively producing carbonylation products at methyl C−H bonds in preference to methylene C−H bonds, as shown in the reactions of **1b** and **1c**. Five-membered-ring closure occurred preferentially over six-membered-ring formation in substrates containing multiple methyl substituents.[10b] Thus, the reaction of **1b** gave an 83% yield of **2b**, a derivative of the succinimide anticonvulsant ethosuximide, which is used mainly in the treatment of absence seizures. Even when a methylene group was activated by the presence of a phenyl group (**1d**−**k**) or a methoxy group (**1l**), methyl C−H bonds were selectively carbonylated. This selectivity can be attributed to steric factors. The reaction tolerated certain functional groups such as MeO, Cl, $CF_3$, CN, and even Br under the reaction conditions. Electron-withdrawing substituents gave better yields. A sterically bulky aryl group, such as the pentamethylphenyl group, as in **1k** had no effect on the efficiency of the reaction. While various α,α-disubstituted aliphatic amides were carbonylated in good yields under the current reaction conditions, an α-monosubstituted aliphatic amide, namely, isobutylic amide **1o**, gave the corresponding imide **2o** in low yield as a result of hydrolysis of **1o** under the reaction conditions. To avoid hydrolysis, isobutylic amide **1p** having a sterically bulky directing group was used as the substrate. As expected, the carbonylation took place to give **2p** in 59% yield.

The reaction of **9** gave **10** in 90% yield through C(sp$^2$)−H bond activation, along with a small amount (<5%) of succinimide formed through C(sp$^3$)−H bond activation. This result indicates that carbonylation took place preferentially at the C(sp$^2$)−H bond rather than the C(sp$^3$)−H bond,[10b] even though a six-membered product was formed (Scheme 3A). It is known that the reactivity of cyclopropyl C−H bonds is similar to that of C(sp$^2$)−H bonds. However, activation of a methyl C(sp$^3$)−H bond competed with that of the cyclopropyl

**Table 1. Substrate Scope for Carbonylation of Unactivated C(sp$^3$)−H Bonds[a]**

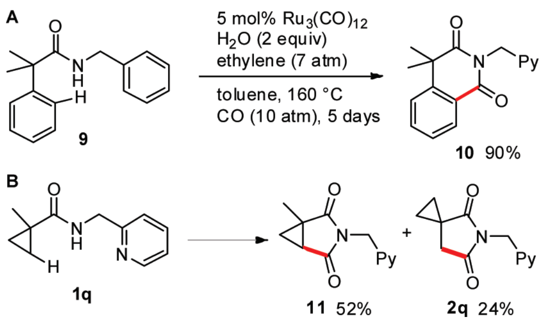



[a] Reaction conditions: amide (1 mmol), CO (10 atm), ethylene (7 atm), $H_2O$ (2 mmol), and $Ru_3(CO)_{12}$ (0.05 mmol) in toluene (3 mL) at 160 °C for 5 days. [b] Isolated yields are shown. [c] Toluene (4 mL). [d] $Ru_3(CO)_{12}$ (0.1 mmol) was used. [e] Diastereomeric ratio.

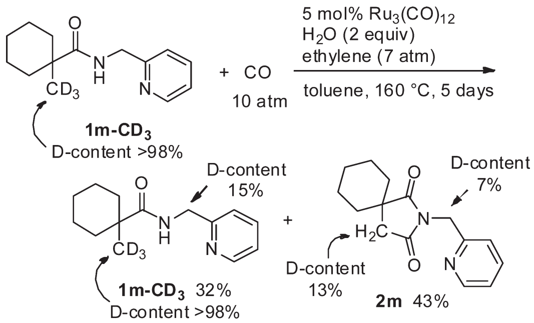
C−H bond, leading to a nearly 2:1 mixture of **11** and **2q** (Scheme 3B).

To investigate the mechanism of the reaction, deuterated **1m-CD$_3$** was subjected to the reaction conditions with a low catalyst loading of 5 mol % (Scheme 4). Even at 68% conversion, no H/D exchange in the methyl group was observed in the recovered starting amide, indicating that cleavage of the C−H bond is irreversible.

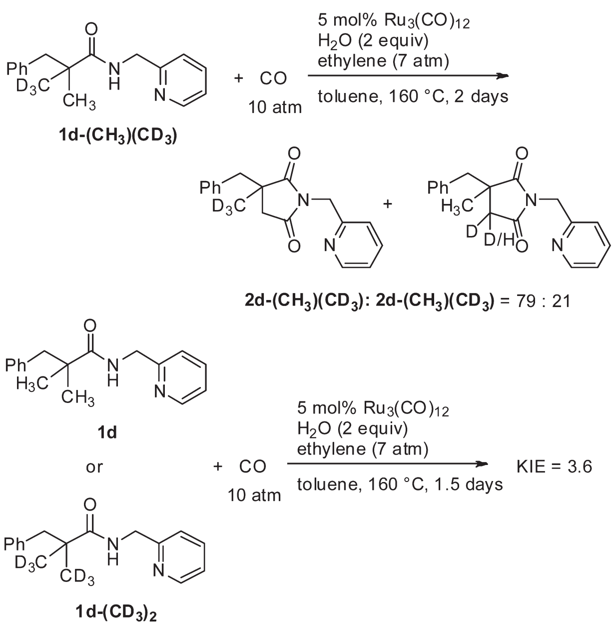
**Scheme 3. Intramolecular Competition for Preferential Carbonylation: (A) C($sp^3$)−H versus C($sp^2$)−H; (B) Methyl C($sp^3$)−H versus Cyclopropyl Methylene C($sp^3$)−H**




**Scheme 4. Deuterium Labeling Experiment**




**Scheme 5. Competition Experiments**




In contrast, a significant amount of H/D exchange at the methylene group α to the carbonyl group was observed in product **2m** because of the acidity of the proton.[20] We then performed kinetic isotope effect (KIE) experiments using **1m** and **1m-CD$_3$**. The value of the KIE was 1.8.

We next carried out an intramolecular competition experiment using **1d-(CH$_3$)(CD$_3$)** and obtained a KIE of 3.8 (Scheme 5).[21] It was also found that that **1d** was more reactive than **1d-(CD$_3$)$_2$** in the intermolecular competition experiment, which resulted in an intermolecular KIE of 3.6. These results apparently suggest that the cleavage of C−H bonds is the rate-determining step in this new carbonylation reaction.

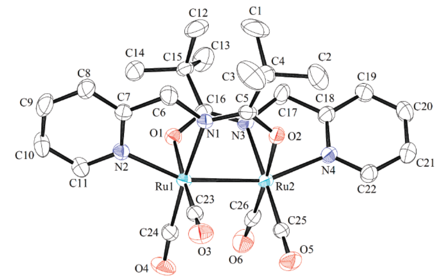
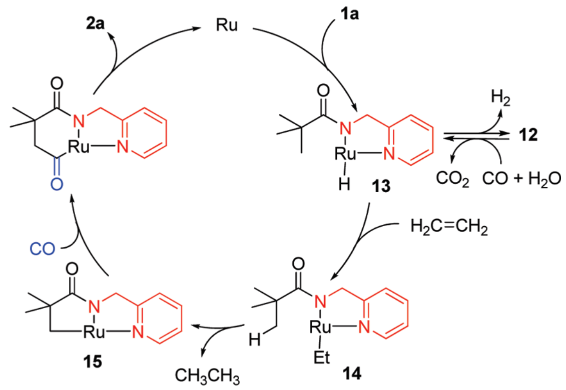


**Figure 1.** ORTEP drawing of **12**.

**Scheme 6. Proposed Mechanism**




In order to isolate the active catalytic species, the stoichiometric reaction of amide **1a** with $Ru_3(CO)_{12}$ was carried out in toluene at 160 °C under $N_2$. The reaction formed dinuclear ruthenium complex **12**, the structure of which was confirmed by X-ray crystallography (Figure 1). As expected, the 2-pyridinylmethylamine moiety coordinates to the ruthenium center in an N,N fashion and the carbonyl oxygen coordinates to the other ruthenium center.

Although the mechanistic details are unclear at the present time, a proposed mechanism for the reaction is shown in Scheme 6. Coordination of the amide followed by N−H bond activation gives the ruthenium hydride complex **13**. The insertion of ethylene followed by irreversible C−H bond activation gives metallacycle **15** with the concomitant generation of ethane. The insertion of CO and subsequent reductive elimination affords the final product with regeneration of the ruthenium catalyst. The fact that no carbonylation product was formed in the absence of ethylene suggests that no direct cleavage of a C−H bond takes place in complex **13** and that ethylene functions as a hydrogen acceptor. Complex **12** does not participate in the main catalytic cycle but rather exists in a resting state.[17] The presence of $H_2O$ is also important for increasing of efficiency of the reaction. The role of $H_2O$ is to allow the resting complex **12** to enter the catalytic cycle.

In summary, we have reported the development of a new method for the carbonylation of unactivated C($sp^3$)−H bonds.[8,22]

The reaction proceeds selectively at a methyl C−H bond over a methylene C−H bond. The reaction tolerates a variety of functional groups.

## ■ ASSOCIATED CONTENT

**S Supporting Information.** Experimental procedures, characterization data for all new compounds, and crystallographic data for **12** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION

**Corresponding Author**
chatani@chem.eng.osaka-u.ac.jp

## ■ ACKNOWLEDGMENT

This work was supported in part by a Grant-in-Aid for Scientific Research on Innovative Areas "Molecular Activation Directed toward Straightforward Synthesis" from The Ministry of Education, Culture, Sports, Science, and Technology.

## ■ REFERENCES

(1) For recent reviews of C−H bond functionalization, see: (a) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013. (b) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (c) Sehnal, P.; Taylor, R. J. K.; Fairlamb, I. J. S. *Chem. Rev.* **2010**, *110*, 824. (d) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (e) Xu, L.-M.; Li, B.-J.; Yang, Z.; Shi, Z.-J. *Chem. Soc. Rev.* **2010**, *39*, 712. (f) Ackermann, L. *Chem. Commun.* **2010**, *46*, 4866.

(2) For a recent review of C($sp^3$)−H bond functionalization, see: Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem.—Eur. J.* **2010**, *16*, 2654.

(3) (a) Baudoin, O.; Herrbach, A.; Guéritte, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 5736. (b) Hitce, J.; Retailleau, P.; Baudoin, O. *Chem.—Eur. J.* **2007**, *13*, 792. (c) Lafrance, M.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 14570. (d) Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2008**, *10*, 1759. (e) Liégault, B.; Fagnou, K. *Organometallics* **2008**, *27*, 4841. (f) Chaumontet, M.; Piccardi, R.; Audic, N.; Hitce, J.; Peglion, J.-L.; Clot, E.; Baudoin, O. *J. Am. Chem. Soc.* **2008**, *130*, 15157. (g) Chaumontet, M.; Piccardi, R.; Baudoin, O. *Angew. Chem., Int. Ed.* **2009**, *48*, 179. (h) Feng, Y.; Wang, Y.; Landgraf, B.; Liu, S.; Chen, G. *Org. Lett.* **2010**, *12*, 3414. (i) Rousseaux, S.; Davi, M.; Sofack-Kreutzer, J.; Pierre, C.; Kefalidis, C. E.; Clot, E.; Fagnou, K.; Baudoin, O. *J. Am. Chem. Soc.* **2010**, *132*, 10706. (j) Pierre, C.; Baudoin, O. *Org. Lett.* **2011**, *13*, 1816.

(4) (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (b) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510. (c) Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 7190. (d) Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 9886. (e) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965. (f) Renaudat, A.; Jean-Gérard, L.; Jazzar, R.; Kefalidis, C. E.; Clot, E.; Baudoin, O. *Angew. Chem., Int. Ed.* **2010**, *49*, 7261.

(5) (a) Dangel, B. D.; Godula, K.; Youn, S. W.; Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 11856. (b) Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 3680.

(6) (a) Chen, X.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 12634. (b) Shi, B.-F.; Maugel, N.; Zhang, Y.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 4882.

(7) (a) Hitce, J.; Baudoin, O. *Adv. Synth. Catal.* **2007**, *349*, 2054. (b) Johnson, J. A.; Li, N.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 6900. (c) Giri, R.; Maugel, N.; Foxman, B. M.; Yu, J.-Q. *Organometallics* **2008**, *27*, 1667.

(8) During the preparation of this manuscript, a similar carbonylation of unactivated C($sp^3$)−H bonds catalyzed by Pd(II) was reported. See: Yoo, E. J.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 17378.

(9) Neumann, J. J.; Rakshit, S.; Dröge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2009**, *48*, 6892.

(10) (a) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542. (b) Giri, R.; Chen, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 2112.

(11) For recent reviews, see: (a) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633. (b) Bhalla, G.; Mironov, O.; Jones, C. J.; Tenn, W. J., III; Nakamura, S.; Periena, R. A. In *Handbook of C−H Transformations*; Dyker, G., Ed. Wiley-VCH, Weinheim, Germany, 2005; pp 529−542.

(12) (a) Burk, M. J.; Crabtree, R. H.; Parnell, C. P.; Urlarte, R. J. *Organometallics* **1984**, *3*, 816. (b) Burk, M. J.; Crabtree, R. H. *J. Am. Chem. Soc.* **1987**, *109*, 8025. (c) Nomura, K.; Saito, Y. *J. Chem. Soc., Chem. Commun.* **1988**, 161. (d) Sakakura, T.; Sodeyama, T.; Tokunaga, Y.; Tanaka, M. *Chem. Lett.* **1988**, 263. (e) Maguire, J. A.; Boese, W. T.; Goldman, A. S. *J. Am. Chem. Soc.* **1989**, *111*, 7088. (f) Fujii, T.; Saito, Y. *J. Chem. Soc., Chem. Commun.* **1990**, 757. (g) Aoki, T.; Crabtree, R. H. *Organometallics* **1993**, *12*, 294. (h) Xu, W.-w.; Rosini, G. P.; Gupta, M.; Jensen, C. M.; Kaska, W. C.; Krogh-Jespersen, K.; Goldman, A. S. *Chem. Commun.* **1997**, 2273.

(13) (a) Chen, H.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **1999**, *38*, 3391. (b) Chen, H.; Schlecht, S.; Semple, T. C.; Hartwig, J. F. *Science* **2000**, *287*, 1995. (c) Kondo, Y.; García-Cuadrado, D.; Hartwig, J. F.; Boaen, N. K.; Wagner, N. L.; Hillmyer, M. A. *J. Am. Chem. Soc.* **2002**, *124*, 1164. (d) Webster, C. E.; Fan, Y.; Hall, M. B.; Kunz, D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 858. (e) Lawrence, J. D.; Takahashi, M.; Bae, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 15334. (f) Hartwig, J. F.; Cook, K. S.; Hapke, M.; Incarvito, C. D.; Fan, Y.; Webster, C. E.; Hall, M. B. *J. Am. Chem. Soc.* **2005**, *127*, 2538. (g) Murphy, J. M.; Lawrence, J. D.; Kawamura, K.; Incarvito, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 13684. Also see: (h) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890.

(14) For a review of C($sp^3$)−H bond activation, see: Crabtree, R. H. *J. Organomet. Chem.* **2004**, *689*, 4083.

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

(16) Chatani, N.; Asaumi, T.; Ikeda, T.; Yorimitsu, S.; Ishii, Y.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc.* **2000**, *122*, 12882.

(17) Inoue, S.; Shiota, H.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2009**, *131*, 6898.

(18) The reaction proceeds via two successive reactions. The first is Ru-catalyzed C−H bond carbonylation at the 2-position of pyridine (see: Moore, E. J.; Pretzer, W. R.; O'Connell, T. J.; Harris, J.; LaBounty, L.; Chou, L.; Grimmer, S. S. *J. Am. Chem. Soc.* **1992**, *114*, 5888). This is followed by Ru-catalyzed cyclocarbonylation of the resulting pyridinyl ketone (see:Tobisu, M.; Chatani, N.; Asaumi, T.; Amako, K.; Ie, Y.; Fukumoto, Y.; Murai, S. *J. Am. Chem. Soc.* **2000**, *122*, 12663).

(19) Product **7** would be formed by the hydrolysis of **6**, leading to the production of a 2-aminopyridine that would undergo the hydroamidation with ethylene under the reaction conditions.

(20) The mechanism of H/D exchange at the methylene C−H bond in the 2-pyridinylmethyl group is not clear at the present time. For a recent review of the activation of C($sp^3$)−H bonds adjacent to nitrogen, see: Campos, K. R. *Chem. Soc. Rev.* **2007**, *36*, 1069.

(21) Similar to the case of **2m**, H/D exchange at the $CH_2$ group α to the carbonyl group and at the $CH_2$ group in the 2-pyridinylmethyl group rather than at the methyl group was also observed in product **2d-($CD_3$)**.

(22) Quite recently, photocatalyzed alkane carbonylation was reported. See: Ryu, I.; Tani, A.; Fukuyama, T.; Ravelli, D.; Fagnoni, M.; Albini, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 1869.