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Chelation-assisted carbonylation reactions catalyzed by Rh and Ru complexes*

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Abstract: This account reviews chelation-assisted carbonylation reactions catalyzed by late transition metals. New carbonylation reactions are achieved with these catalysts in the presence of pyridin-2-ylmethanol and pyridin-2-ylmethylamine. The reactions involve activation of O–H and N–H bonds, coordination of the pyridine nitrogen to Rh being essential for the reaction to proceed. In addition, a new type of carbonylation of the *ortho* C–H bonds in aromatic amides in which the pyridin-2-ylmethylamino moiety functions as a bidentate directing group, is demonstrated. In this reaction, a dinuclear ruthenium complex was isolated from a stoichiometric reaction of amide and $Ru_3(CO)_{12}$, in which amide binds to one Ru atom in the expected *N,N* fashion and the carbonyl oxygen binds to the other Ru atom as an O-donor. These studies indicate that chelation methodology is useful for new types of carbonylation reaction, which cannot be achieved by non-chelation systems.

Keywords: bidentate directing group; carbon monoxide; carbonylation; chelation assistance; transition-metal catalysis.

INTRODUCTION

The control of regio- and stereoselectivity constitutes an important development in organic synthesis, and directed reactions offer powerful methodology to achieve such control [1]. Amongst the earliest examples of selectivity through intramolecular direction are Henbest epoxidation [2] and Simmons–Smith cyclopropanation [3] of 2-cyclohexe-1-ol [3]. In these reactions, the hydroxyl group in an allylic alcohol promotes stereoselective addition to the neighboring olefinic bond. Since the publication of these reports, many additional reactions have been achieved using directed methodology. One of the recent advances of directed transformation involves regioselective transformations of C–H bonds. The pioneering work related to regioselective C–H bond transformation, the catalytic deuteration and ethylation at the *ortho* position of phenol, was reported by Lewis and Smith [4]. In 1993, Murai et al. reported on the catalytic alkylation of *ortho* C–H bonds of aromatic ketones with olefins [5]. This was the first example of the highly efficient, regioselective functionalization of C–H bonds in aromatic ketones. In this reaction, coordination of a heteroatom, such as an oxygen atom to a metal center, is critical for success. Since this report, chelation-assisted transformations have proven to be amongst the most reliable methodologies for regioselective transformation of C–H bonds in arenes and alkanes [6]. These reactions allow for the highly site-selective transformation of a C–H bond into a new C–X bond (X = C,

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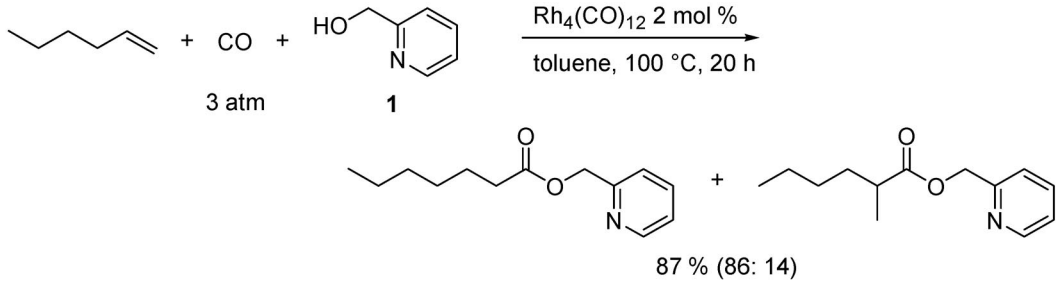
O, N, F, Cl, Br, I, Si). A wide variety of functionality, such as ketone, ester, amide, pyridine, oxazoline, imine, and cyano groups, have been reported to perform as directing groups. We have also successfully developed a series of catalytic reactions involving cleavage of unreactive bonds other than C–H bonds, including C–F [7], C–C [8], C–O [9], and C–N bonds [10], by utilizing chelation-assistance strategy. These results indicate that chelation methodology is useful not only for controlling regio- and stereoselectivity but is also applicable to new types of catalytic reactions. Herein, we report some new types of chelation-assisted carbonylation reactions of O–H, N–H, and C–H bonds.

RHODIUM-CATALYZED HYDROESTERIFICATION OF ALKENES

We have previously reported on chelation-assisted carbonylation reactions at the *ortho* C–H bond in aromatic compounds [11]. In all cases, coordination of the sp^2 nitrogen to a metal center is responsible for both the high efficiency and high regioselectivity of these reactions. This prompted us to examine carbonylation reactions using alcohols, which also contain an sp^2 nitrogen. Carbonylation of alkenes with alcohols is an important process, both industrially and in the laboratory. Although it is well known that a variety of late transition-metal complexes can be used in these reactions, cobalt and palladium complexes are the most frequently used catalysts. Moreover, 1,1- and 1,2-disubstituted alkenes give hydroesterification products in relatively lower yields than monosubstituted alkenes. The reaction of pyridin-2-ylmethanol (**1**) with 1-hexene in the presence of $Rh_4(CO)_{12}$ under 3 atm of CO for 20 h gave the hydroesterification products in an 87 % isolated yield in a 86:14 ratio of linear and branched esters (Scheme 1) [12].



Scheme 1 $Rh_4(CO)_{12}$-catalyzed hydroesterification of 1-hexene with pyridin-2-ylmethanol (**1**).

In contrast, when benzyl alcohol and pyridin-4-ylmethanol are used in place of **1**, hydroesterification products are produced in 13 % isolated yield. This indicates that the presence of the nitrogen at the appropriate position in the alcohol apparently accelerated the reaction. Representative examples of some $Rh_4(CO)_{12}$-catalyzed hydroesterification reactions are shown in Fig. 1. Not only monosubstituted alkenes but 1,1- and 1,2-disubstituted alkenes also give hydroesterification products in good yields.

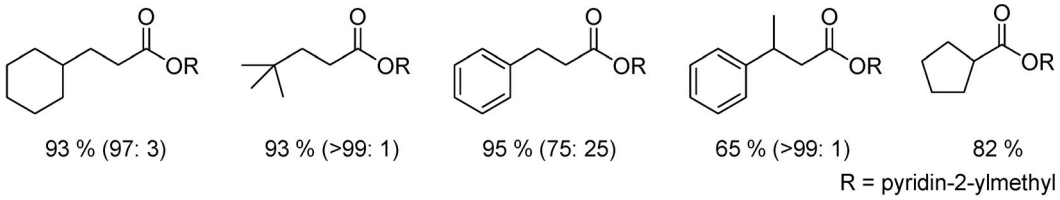
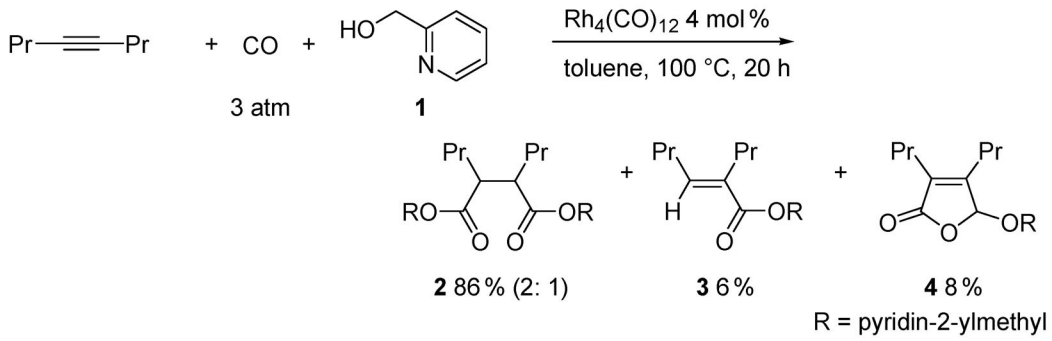


Fig. 1 Representative examples for $Rh_4(CO)_{12}$-catalyzed hydroesterification of alkenes.

RHODIUM-CATALYZED DOUBLE-HYDROESTERIFICATION OF INTERNAL ALKYNES

We next examined the hydroesterification of alkynes. The hydroesterification of alkynes has also been extensively studied because synthetically useful α,β-unsaturated esters can be obtained from these reactions. The hydroesterification of alkynes are well-known reactions that proceed in the presence of nickel-, cobalt-, iron-, ruthenium-, platinum-, or palladium-based catalyst systems [13]. An intramolecular version of hydroesterification has also been reported. For example, the reaction of acetylenic alcohols gives the unsaturated lactones [14].

When the reaction of pyridin-2-ylmethanol (**1**) with 4-octyne was carried out under 3 atm of CO in the presence of $Rh_4(CO)_{12}$ in toluene at 100 °C, the corresponding 1,4-dicarboxylate esters (**2**) were produced in 86 % isolated yield in a 2:1 ratio of *meso* and *dl* isomers (Scheme 2). Two by-products (**3** and **4**) were also formed [15].



Scheme 2 $Rh_4(CO)_{12}$-catalyzed double-hydroesterification of 4-octyne with pyridin-2-ylmethanol (**1**).

The reaction of benzyl alcohol or benzyl alcohol with pyridine as base in place of **1** failed to proceed. Therefore, the presence of a 2-pyridinylmethyl moiety in the alcohol is important for a successful reaction. Figure 2 shows the scope of reaction involving alkynes. A terminal alkyne, such as 1-octyne, or diethyl acetylenedicarboxylate gave complex mixtures.

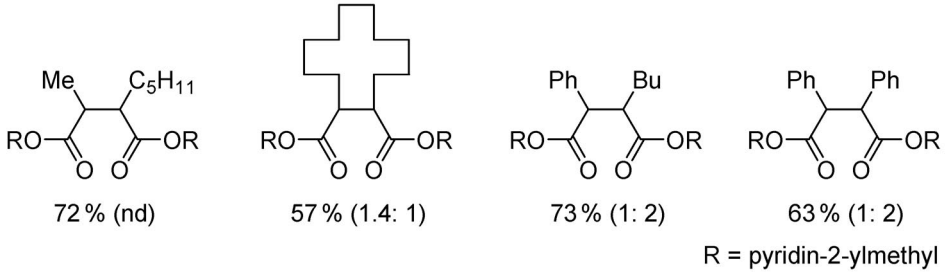
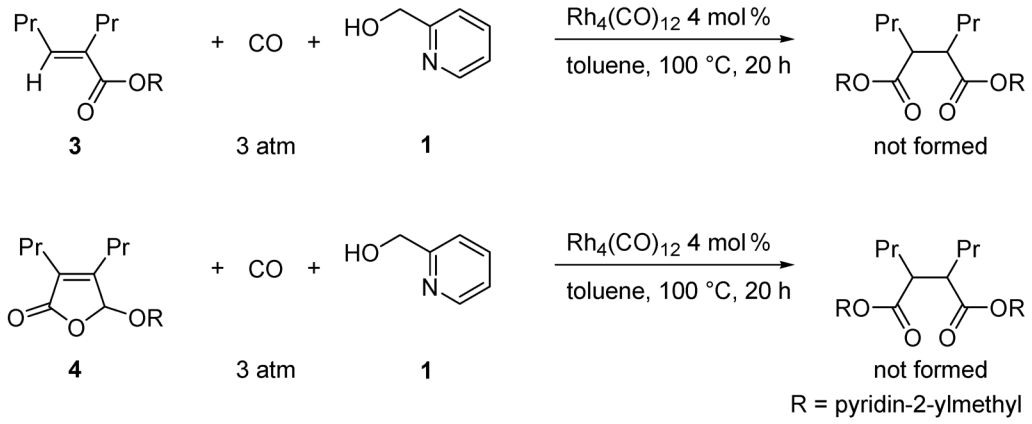


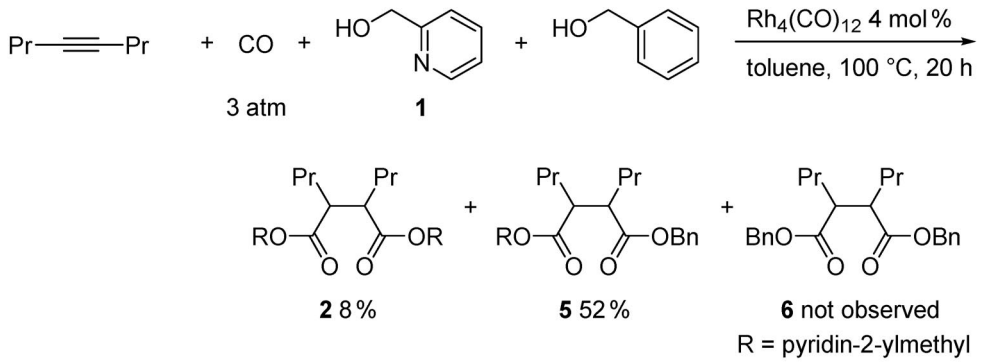
Fig. 2 Representative examples of 1,4-dicarboxylate esters.

Some control experiments were performed, in an attempt to examine the reaction mechanism in more detail. The reaction of **3** or **4** with **1** in the presence of $Rh_4(CO)_{12}$ under otherwise identical conditions did not result in the formation of the corresponding 1,4-dicarboxylate ester, and the starting materials **3** and **4** were recovered in 96 and 94 % yield, respectively (Scheme 3). These results show that the formation of the main product **2** does not proceed via by-products **3** and **4**.



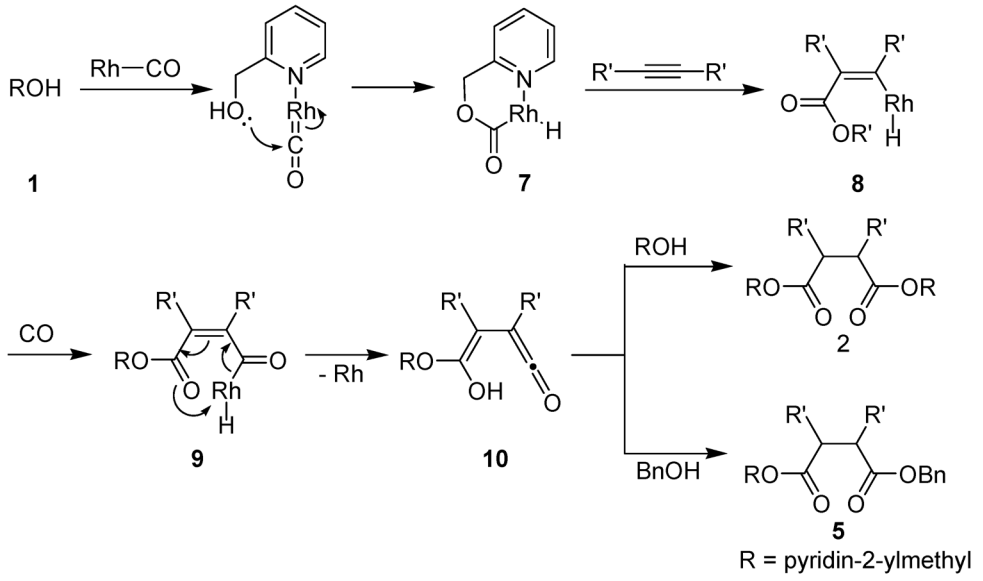
Scheme 3 Attempted reactions of **3** or **4** with pyridin-2-ylmethanol (**1**).

The reaction of 4-octyne with **1** and benzyl alcohol (the ratio = 1:1) gave **2** in 8 % and **5** in 52 % yields (Scheme 4). It should be noted that the formation of **6**, which contains two benzyl esters, was not observed. This indicates that alcohol, with an sp^2 nitrogen, is required in the first step and that the subsequent step does not require a directing group in the alcohol for the reaction to proceed.



Scheme 4 Reaction of 4-octyne with **1** and benzyl alcohol under standard conditions.

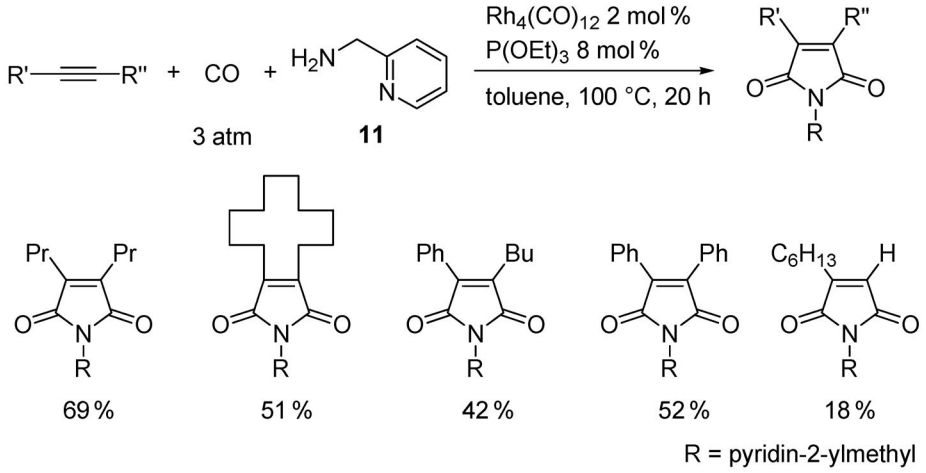
A proposed reaction mechanism is shown in Scheme 5. The coordination of the pyridine nitrogen in **1** to the rhodium center, followed by an intramolecular attack of the alcohol on the coordinated carbon monoxide gives the rhodium hydride species **7**. The insertion of an alkyne into the acyl–Rh bond in **7** then gives **8**. The successive insertion of CO results in the formation of the acyl complex **9**, and the complex **9** is then converted into the ketene intermediate **10**. Pyridin-2-ylmethanol or benzyl alcohol may both attack the ketene carbon to give **2** and **5**, respectively. The formation of a mixture of **2** and **5**, with **5** being favored, can be rationalized by the intermediacy of **10** and by an excess of benzyl alcohol remaining in the reaction system because the generation of **10** requires **1**. Coordination of **1** to rhodium is required to form an active species such as **7**, showing that at least one molecule of **1** is incorporated into the product.



Scheme 5 Proposed mechanism for double-hydroesterification of alkynes.

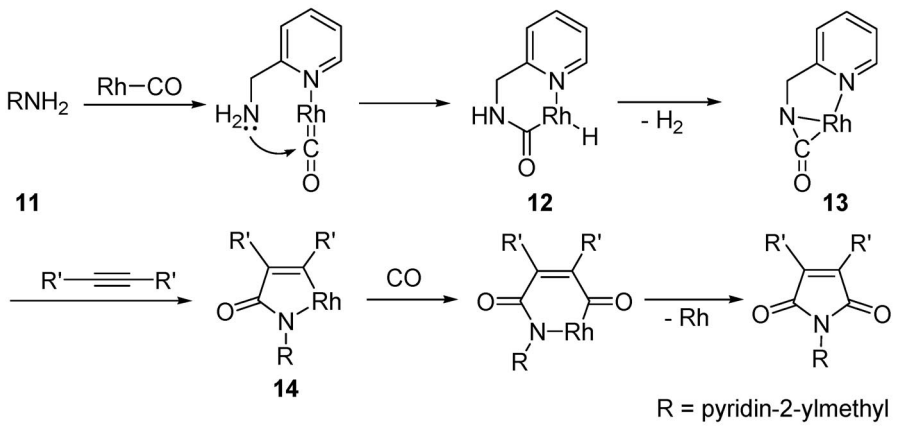
CARBONYLATIVE CYCLIZATION OF ALKYNES WITH AMINE

We successfully developed some carbonylation reactions using pyridin-2-ylmethanol (**1**). In these reactions, the presence of a pyridine ring is a key factor for the reaction to proceed. We concluded that it would be possible to achieve new reactions using the corresponding amine. During the development of these new chelation-assisted catalytic reactions, it was found that the reaction of alkynes with CO and pyridin-2-ylmethylamine (**11**) in the presence of $Rh_4(CO)_{12}$/$P(OEt)_3$ results in carbonylative cyclization to give maleimides [16]. Representative examples are shown in Scheme 6. Both aliphatic and aromatic internal alkynes gave the corresponding maleimides in good yields. On the other hand, a terminal alkyne, such as 1-octyne, gave the corresponding maleimide in low yield.



Scheme 6 Synthesis of maleimides by $Rh_4(CO)_{12}$-catalyzed carbonylation reaction.

A proposed reaction mechanism is shown in Scheme 7. Coordination of the pyridine nitrogen in **11** to the rhodium center facilitates the intramolecular attack of the amine on the coordinated carbon monoxide to give the rhodium hydride species **12**, analogous to the case of pyridine-2-methanol (**1**). The elimination of H_2 gives η^2-isocyanate–rhodium complex **13** [17]. The rhodacycle **14** is formed by oxidative cyclization of complex **13** and an alkyne. The insertion of CO in **14** is followed by reductive elimination to afford maleimide and the rhodium catalyst is regenerated. The coordination of **11** to the rhodium center appears to be required to form the formation an active species such as **12** and **13**, although there is no experimental evidence for this. Kondo et al. reported that the $Ru_3(CO)_{12}$-catalyzed carbonylation of alkynes with isocyanates affords maleimides and a complex related to **14**, which is proposed as a key intermediate [18,19].



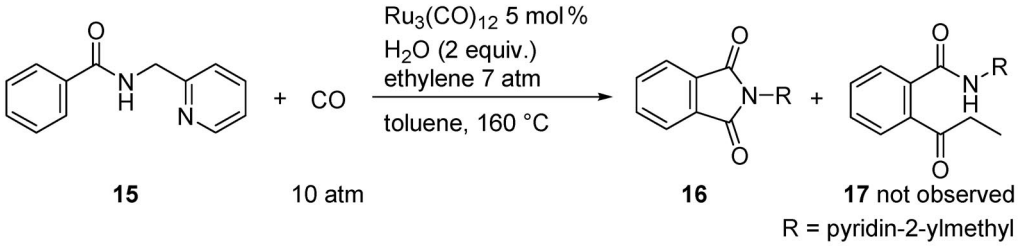
Scheme 7 Proposed mechanism for the carbonylative cyclization of alkynes and pyridin-2-ylmethylamine (**11**).

RUTHENIUM-CATALYZED CARBONYLATION REACTION AT *ORTHO* C–H BONDS IN AROMATIC AMIDES

We previously reported on a series of direct carbonylation of C–H bonds. All substrates applicable to the direct C–H bond carbonylation reactions include an sp^2 nitrogen atom [11]. The coordination of the sp^2 nitrogen to the catalyst is responsible for both the high efficiency and regioselectivity of these reactions. In sharp contrast, carbonyl compounds, such as aldehydes, ketones, esters, and amides, have never been used as directing groups in the Ru-catalyzed carbonylation of C–H bonds reported thus far, because the coordination of a carbonyl group, which has a relatively poor coordination ability, must compete with the higher pressure (20 atm) of CO employed in Ru-catalyzed reactions. We designed a new directing group for the carbonylation of C–H bonds in aromatic carbonyl compounds. We expected that a bidentate ligand, such as a pyridin-2-ylmethylamine moiety, would bind tightly to catalysts as an *N*,*N*-donor, even under higher CO pressures, thereby allowing the catalyst to come into close proximity with a C–H bond, which can then be cleaved. Daugulis et al. reported a C–H bond transformation by a bidentate system, picoline amide [20]. We expected that a bidentate system would have the potential to lead to new catalytic reactions that cannot be achieved using a conventional monodentate system.

On the basis of this working hypothesis, we prepare the amide **15** with *N*-pyridine-2-ylmethyl moiety as a test substrate. When the reaction was carried out under 20 atm of CO and 7 atm of ethylene in the presence of $Ru_3(CO)_{12}$ in toluene at 160 °C, the expected product **17** was not formed; instead, the phthalimide **16** was formed in 25 % yield. In the absence of ethylene, even **16** was not formed. Ethylene functions as a hydrogen accepter. Other alkenes, such as norbornene and methyl acrylate or aldehydes, which are also known to serve as hydrogen acceptors, did not result in a successful reaction. Some oxidants were also ineffective. We found that the carbonylation of **16** in the presence of ethylene

as a hydrogen acceptor and H_2O (2 equiv), which probably functions to generate a catalytically active species, resulted in an effective catalytic system (Scheme 8) [21].



Scheme 8 Catalytic carbonylation reaction at the *ortho* C–H bond in aromatic amide.

No reaction occurred when the corresponding *N*-benzyl amide or *N*-pyridin-4-ylmethyl amide was used in place of **15** as the substrate. These results indicate that coordination in a *N*,*N* fashion is a key step for the reaction to proceed. Futhermore, the corresponding phthalimides were not formed from amides having shorter and longer carbon chains. The catalytic process tolerates a number of functional groups, including methoxy, dimethylamino, ester, ketone, cyano, and even bromo groups. In all cases, 4-substituted phthalimides were obtained in good to high yields (Fig. 3).

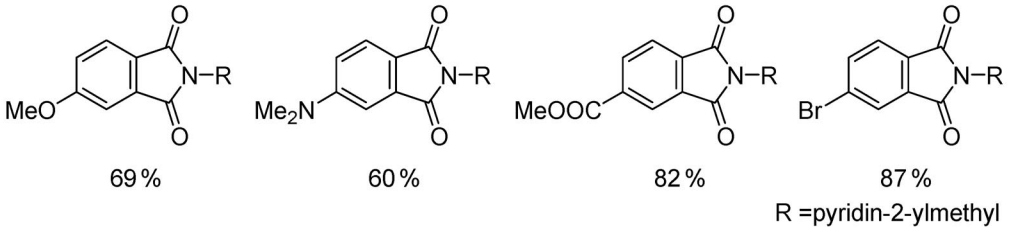


Fig. 3 Representative examples of $Ru_3(CO)_{12}$-catalyzed carbonylation reaction.

To better understand the reaction mechanism, reactions using stoichiometric amounts of reactants were performed. When $Ru_3(CO)_{12}$ was reacted with 3 equiv of an amide in toluene-d_8 at 130 °C in a sealed tube, the amide was consumed completely within 20 h. A new ruthenium complex was formed as a single organometallic product. The molecular structure of **18** was confirmed by X-ray crystallography (Fig. 4). The complex we isolated is a dinuclear Ru(II) complex. The amide binds to one Ru atom in the expected *N*,*N*-fashion and the carbonyl oxygen binds to the other Ru atom as an O donor. The others amide coordinates to one Ru atom in an *N*,*N*-donor fashion and the carbonyl oxygen coordinates to the other Ru atom.

The complex **18** remained intact even when heated at 130 or 160 °C for an extended period of time. We next examined the catalytic activity of the isolated complex. The reaction of an amide in the presence of **18** as the catalyst in place of $Ru_3(CO)_{12}$ under standard reaction conditions gave phthalimide in 82 % isolated yield. In contrast, no reaction occurred for the reaction of an amide in the presence of **18** *without* H_2O under otherwise identical conditions. This result shows that the presence of H_2O is required for the conversion of **18** into an active catalytic species.

The di-nuclear Ru complex **18** itself does not show any catalytic activity, but is activated in the presence of H_2O under the reaction conditions described above. This result can be explained as follows. The complex is not included in the main catalytic cycle. Rather, it exists in a resting state and is reduced to the mono-nuclear Ru species by a water–gas shift reaction. At this point, the complex becomes an

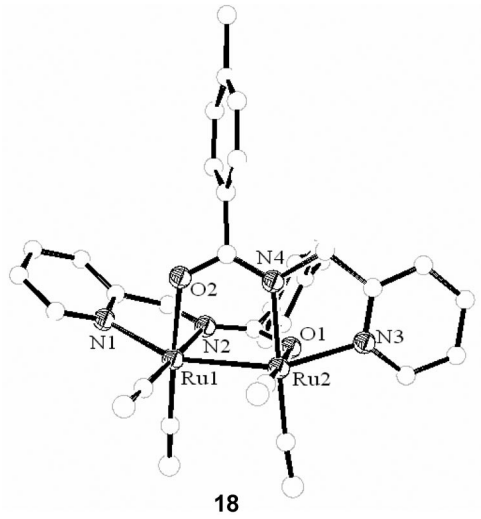


Fig. 4 ORTEP drawing of Ru complex.

active participant in the catalytic cycle. Although the role of H_2O is not clear, it is probably to allow the resting complex to participate in the main catalytic cycle by reduction. A detailed mechanistic study including stoichiometric reactions using the complex **18** is underway.

CONCLUSIONS

Our recent progress on the development of new types of catalytic carbonylation reactions with Rh and Ru complex is described. Chelation methodology is able to transmute the reactivity of O–H and N–H bonds and allow for the regioselective transformation of C–H bonds. We believed that the chelation methodology promises to become a powerful system that will lead to new types of reactions that are not possible using currently available methods.

Activation of C–H bonds has been extensively studied, but most of the reactions involve cleavage of sp^2 C–H bonds. We are currently in the process of exploring carbonylation of sp^3 C–H bonds by using the newly developed bidentate directing group. We have already obtained successful preliminary results.

ACKNOWLEDGMENTS

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REFERENCES

1. Reviews, see: (a) M. T. Reetz. *Angew. Chem., Int. Ed.* **23**, 556 (1984); (b) A. H. Hoveyda, D. A. Evans, G. C. Fu. *Chem. Rev.* **93**, 1307 (1993).
2. H. B. Henbest, R. A. L. Wilson. *J. Chem. Soc*. 1958 (1959).
3. W. G. Dauben, G. H. Berezin. *J. Am. Chem. Soc.* **85**, 468 (1963).
4. L. N. Lewis, J. F. Smith. *J. Am. Chem. Soc.* **108**, 2728 (1986).

5. S. Murai, F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda, N. Chatani. *Nature* **366**, 529 (1993).
6. For recent reviews on chelation-assisted transformation, see: (a) F. Kakiuchi, N. Chatani. *Adv. Synth. Catal.* **345**, 1077 (2003); (b) A. R. Dick, M. S. Sanford. *Tetrahedron* **62**, 2439 (2006); (c) K. Godula, D. Sames. *Science* **312**, 67 (2006); (d) D. Alberico, M. E. Scott, M. Lautens. *Chem. Rev.* **107**, 174 (2007); (e) L.-C. Campeau, D. R. Stuart, K. Fagnou. *Aldrichim. Acta* **40**, 35 (2007); (f) N. Chatani (Ed.). *Directed Metallation: Topics in Organometallic Chemistry*, Vol. 24, Springer, Berlin (2007); (g) F. Kakiuchi, T. Kochi. *Synthesis* 3013 (2008); (h) W. Lyons, M. S. Sanford. *Chem. Rev.* **110**, 1147 (2010).
7. Y. Ishii, N. Chatani, S. Yorimitsu, S. Murai. *Chem. Lett.* 157 (1998).
8. N. Chatani, Y. Ie, F. Kakiuchi, S. Murai. *J. Am. Chem. Soc.* **121**, 8645 (1999).
9. (a) F. Kakiuchi, M. Usui, S. Ueno, N. Chatani, S. Murai. *J. Am. Chem. Soc.* **126**, 2706 (2004); (b) H. Tatamidani, K. Yokota, F. Kakiuchi, N. Chatani. *J. Org. Chem.* **69**, 5615 (2004); (c) Y. Harada, Y. Fukumoto, N. Chatani. *Org. Lett.* **7**, 4385 (2005); (d) J. Nakanishi, H. Tatamidani, Y. Fukumoto, N. Chatani. *Synlett* 869 (2006).
10. (a) S. Ueno, N. Chatani, F. Kakiuchi. *J. Am. Chem. Soc.* **129**, 6098 (2007); (b) T. Koreeda, T. Kochi, F. Kakiuchi. *J. Am. Chem. Soc.* **131**, 7238 (2009).
11. S. Imoto, T. Uemura, F. Kakiuchi, N. Chatani. *Synlett* 170 (2007) and refs. cited therein.
12. K. Yokota, H. Tatamidani, Y. Fukumoto, N. Chatani. *Org. Lett*. **5**, 4329 (2003).
13. (a) J. F. Knifton. *J. Mol. Catal*. **2**, 293 (1977); (b) Y. Tsuji, T. Kondo, Y. Watanabe. *J. Mol. Catal.* **40**, 295 (1987); (c) B. E. Ali, H. Alper. *J. Mol. Catal.* **67**, 29 (1991); (d) E. I. Drent, P. Arnoldy, P. H. M. Budzelaar. *J. Organomet. Chem.* **455**, 247 (1993); (e) B. E. Ali, J. Tijani, A. M. El-Ghanam. *Tetrahedron Lett*. **42**, 2385 (2001); (f) Y. Na, S. Ko, L. Hwang, S. Chang. *Tetrahedron Lett*. **44**, 4475 (2003).
14. For a review, see: (a) B. El Ali, H. Alper. *Synlett* 161 (2000); (b) T. F. Murray, J. R. Norton. *J. Am. Chem. Soc*. **101**, 4107 (1979); (c) T. F. Murray, E. G. Samsel, V. Varma, J. R. Norton. *J. Am. Chem. Soc*. **103**, 7520 (1981); (d) W. Y. Yu, H. Alper. *J. Org. Chem*. **62**, 5684 (1997); (e) C. S. Consorti, G. Ebeling, J. Dupont. *Tetrahedron Lett*. **43**, 753 (2002).
15. S. Inoue, K. Yokota, H. Tatamidani, Y. Fukumoto, N. Chatani. *Org. Lett*. **8**, 2519 (2006).
16. S. Inoue, Y. Fukumoto, N. Chatani. *J. Org. Chem*. **72**, 6558 (2007).
17. For papers on η^2-isocyanate complexes, see: (a) G. La Monica, S. Cenini, M. Freni. *J. Organomet. Chem*. **76**, 355 (1974); (b) J. Drapier, M. T. Hoornaerts, A. J. Hubert, P. Teyssie. *J. Mol. Catal.* **11**, 53 (1981); Isocyanates are well known to participate in cycloaddition reactions as two-atom components. For recent papers, see: (c) Y. Yamamoto, K. Kinpara, T. Saigoku, H. Takagishi, S. Okuda, H. Nishiyama, K. Itoh. *J. Am. Chem. Soc*. **127**, 605 (2005); (d) L. V. R. Boñaga, H.-C. Zhang, A. F. Moretto, H. Ye, D. A. Li, J. Gauthier, G. C. Leo, B. E. Maryanoff. *J. Am. Chem. Soc*. **127**, 3473 (2005); (e) K. Tanaka, Y. Hagimura, M. Hirano. *Angew. Chem., Int. Ed*. **45**, 2734 (2006); (f) R. T. Yu, T. Rovis. *J. Am. Chem. Soc.* **128**, 14816 (2006).
18. T. Kondo, M. Momura, Y. Ura, K. Wada, T. Mitsudo. *J. Am. Chem. Soc*. **128**, 14816 (2006).
19. For recent examples of carbonylation of alkynes with amines, see: (a) Y. Li, H. Alper, Z. Yu. *Org. Lett*. **8**, 5199 (2006); (b) J. H. Park, S. Y. Kim, S. M. Kim, Y. K. Chung. *Org. Lett*. **9**, 2465 (2007).
20. V. G. Zaitsev, D. Shabashov, O. Daugulis. *J. Am. Chem. Soc.* **127**, 13154 (2005).
21. S. Inoue, H. Shiota, Y. Fukumoto, N. Chatani. *J. Am. Chem. Soc.* **131**, 6898 (2009).

