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Ruthenium-Catalyzed Carbonylation at Ortho C−H Bonds in Aromatic Amides Leading to Phthalimides: C−H Bond Activation Utilizing a Bidentate System

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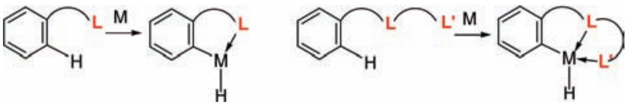
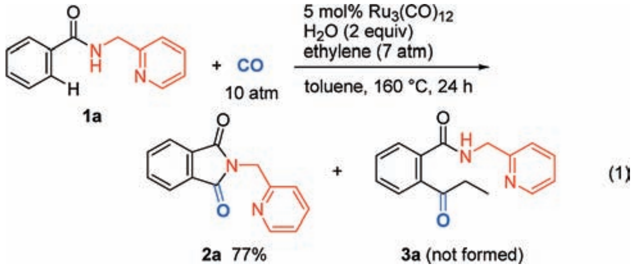
Chelation-assisted transformation has emerged as a powerful alternative method for the direct conversion of arenes and alkanes into new products.[1] These reactions allow for the highly site-selective transformation of a C−H bond proximal to a coordinating functional group into a new C−X bond (X = C, O, N, F, Cl, Br, I, Si). A wide variety of functional groups, such as ketone, ester, amide, pyridine, oxazoline, imine, and cyano groups, have been reported to function as directing groups. In most cases reported to date, a monodentate system has been utilized. In contrast, a bidentate system has rarely been used for the catalytic activation of C−H bonds,[2] although such a system has the potential to lead to new catalytic reactions that cannot be achieved using a conventional monodentate system (Scheme 1).

Scheme 1. Monodentate and Bidentate Systems



Carbonyl groups have rarely been used as directing groups in the carbonylation of C−H bonds reported to date[3−7] because the coordination of a carbonyl group, which has a relatively poor coordination ability, must compete with the higher pressure of CO. We expected that the bidentate system would bind tightly to catalysts even under higher CO pressure, thereby bringing the catalyst into close proximity to a C−H bond, which may then cleave. To evaluate the feasibility of this methodology, amide **1a**, in which the pyridin-2-ylmethylamine moiety would strongly coordinate to the catalyst as a N,N donor even under higher CO pressure, was chosen as a test substrate. In addition, the directing group can be easily converted into another functional group, which is potentially useful in terms of organic synthesis. Herein we report on the Ru-catalyzed cyclocarbonylation of aromatic amides leading to phthalimides through C−H bond activation.

The reaction of amide **1a** with CO and ethylene in the presence of $Ru_3(CO)_{12}$ in toluene at 160 °C under the same reaction conditions as used in the monodentate system[4a,b] did not give the expected product **3a**; instead, the phthalimide **2a** was formed in 25% yield. Curiously, the formation of **2a** involves the carbonylation of a C−H bond. Encouraged by this promising result, we then optimized the reaction conditions to maximize the yield of **2a**. The conversion of **1a** to **2a** requires the release of two hydrogen atoms, suggesting that the reaction requires a hydrogen acceptor for high conversion to be achieved. In fact, in the absence of ethylene, **2a** was not formed. Other alkenes, such as norbornene and methyl acrylate or aldehydes, which are also known to serve as hydrogen acceptors, were also ineffective. Finally, we found that the carbonylation of **1a** in the presence of ethylene as a H_2 acceptor and H_2O (2 equiv) resulted in an effective catalytic system (eq 1).[8]



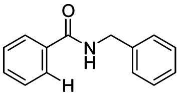
1a

2a 77%

3a (not formed)

(1)

No reaction occurred when the corresponding benzyl amide **4** or amide **5** was used in place of **1a** as the substrate, indicating that the coordination in a N,N fashion is a key step for the reaction to proceed. Furthermore, the reaction of *N*-methyl amide **6** did not result in any carbonylation products. Amides having shorter and longer carbon chains, as in **7** and **8**, also did not give the corresponding phthalimides.



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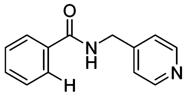

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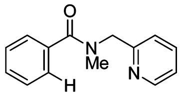

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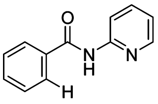

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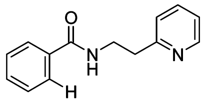

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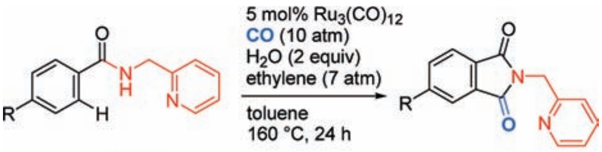
Scheme 2 shows the results of the reaction of para-substituted aromatic amides under standard reaction conditions: amide (1 mmol), CO (10 atm), ethylene (7 atm), H_2O (2 mmol), and $Ru_3(CO)_{12}$ (0.05 mmol) in toluene (3 mL) at 160 °C for 24 h. A wide variety of functional groups, including methoxy, amino, ester, ketone, cyano, chloro, and even bromo substituents, could be substituted for aromatic amides. In all cases, substituted phthalimides were obtained in high yields.

Scheme 2. Carbonylation of Para-Substituted Aromatic Amides



R = H (**1a**)	**2a**	77%
Me (**1b**)	**2b**	79%
OMe (**1c**)	**2c**	69%
NMe_2 (**1d**)	**2d**	60%
COOMe (**1e**)	**2e**	82%
$C(O)CH_3$ (**1f**)	**2f**	78%
CN (**1g**)	**2g**	84%
Cl (**1h**)	**2h**	89%
Br (**1i**)	**2i**	87%

10.1021/ja900046z CCC: $40.75

We next examined the regioselectivity of the carbonylation using meta-substituted aromatic amides (Scheme 3). The reaction of meta methyl-substituted aromatic amide **1j** gave a nearly 1:1 regioisomeric mixture of imide.[9] However, the use of **1k** bearing a methoxy group led to the selective formation of **2c**, in which the less hindered C−H bond selectively underwent carbonylation. The same selectivity was observed in the case of the CF_3O, Me_2N, and keto-substituted amides. These results suggest that electronic effects are not a dominant factor but that the steric nature of the substituents has a significant effect on the regioselectivity of the reaction. As shown in the case of **1o**, a methoxy group has a more significant effect on the regioselectivity than a methyl group.

Scheme 3. Carbonylation of Meta-Substituted Aromatic Amides

R = Me	R' = H (**1j**)	**2j**	68% (1 : 1)
R = OMe	R' = H (**1k**)	**2c**	84% (14 : 1)
R = OCF_3	R = H (**1l**)	**2l**	80% (9 : 1)
R = NMe_2	R = H (**1m**)	**2d**	86% (>20 : 1)
R = $C(O)CH_3$	R = H (**1n**)	**2f**	82% (20 : 1)
R = OMe	R = Me (**1o**)	**2o**	73% (11:1)
R = OMe	R = OMe (**1p**)	**2p**	92%

For information on the reaction mechanism, ^1H NMR experiments on a stoichiometric reaction were performed. When **1b** (0.02 mmol) was treated with $Ru_3(CO)_{12}$ (0.008 mmol) in toluene-d_8 at 130 °C under N_2 in a sealed tube, **1b** was completely consumed within 15 h, and a new ruthenium complex **9** was formed as a single organometallic product. Electrospray ionization mass spectrometry showed that the complex consisted of two Ru atoms, two molecules of **1b**, and four molecules of CO.[10] The structure of **9** was confirmed by X-ray crystallography, which showed that **1b** 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 (Figure 1).[10,11]

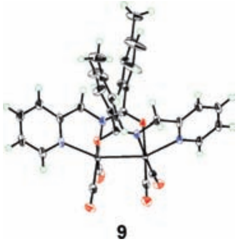


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Figure 1. ORTEP drawing of **9**.

The dinuclear Ru(I) complex **9** remained intact even when it was heated at 130 °C for an extended period of time. However, it was found to show a high catalytic activity. The reaction of **1b** in the presence of **9** as the catalyst in place of $Ru_3(CO)_{12}$ under the standard reaction conditions gave **2b** in 88% isolated yield. In sharp contrast, no reaction occurred for the reaction of **1b** in the presence of **9** as a catalyst under the standard reaction conditions but *without H_2O*. This result shows that the presence of H_2O is required for the conversion of **9** into an active catalytic species.[12] On the basis of these results, we speculate that **9** is not included in the main catalytic cycle but that an active catalytic species is probably generated from **9** by reduction under water-gas-shift reaction conditions (H_2O and CO).[13] This explains why the addition of H_2O is necessary for the carbonylation to proceed (77% yield in the presence of H_2O, 25% yield in the absence of H_2O).

In summary, the findings herein demonstrate that aromatic amides having a pyridin-2-ylmethylamine moiety undergo ortho carbonylation of C−H bonds, leading to phthalimides.[14,15] The bidentate system has the potential for the exploration of new reactions that have not been achieved by conventional monodentate-assisted systems. In order to rationalize the reaction mechanism of the new carbonylation of C−H bonds, studies of stoichiometric reactions intended to permit the isolation of key intermediates are now underway.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org/.

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(8) The yield of **2a** was 25% when the reaction was carried out in the absence of H_2O.

(9) This result is in sharp contrast to those obtained using monodentate systems such as 2-arylpyridines and 2-aryloxazolines, in which the less hindered C−H bonds exclusively underwent carbonylation in the case of meta Me-substituted substrates (see ref 4a, b).

(10) See the Supporting Information.

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(12) A mononuclear Ru(0) species is proposed as a key catalytic species that is also generated directly from $Ru_3(CO)_{12}$ under these reaction conditions.

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(15) Product **2a** can be easily converted to phthalic acid in 96% isolated yield by hydrolysis with KOH in EtOH/H_2O. Treatment of **2a** with KOH in EtOH/H_2O followed by the reaction with *p*-toluenesulfonyl chloride and benzylamine gave *N*-benzyl phthalimide in 55% yield.

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