Ru/C-Catalyzed Carbonylation at *ortho*-C–H Bonds in 2-Phenylpyridines

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Received 21 September 2006

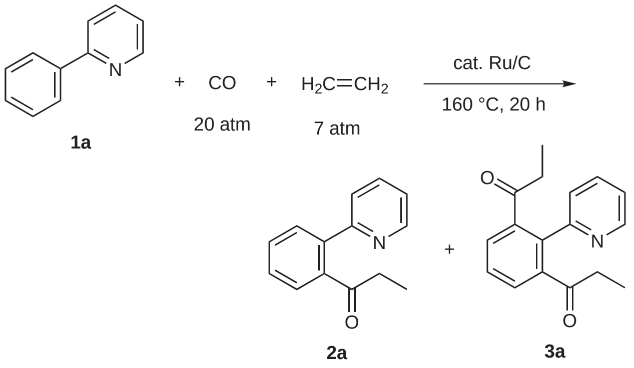
Abstract: Ru/C also exhibits catalytic activity for carbonylation at *ortho*-C–H bonds in 2-phenylpyridines.

Key words: acylations, carbonylations, catalysis, heterocycles, ruthenium

In the course of our studies on the development of catalytic reactions, involving the cleavage of C–H bonds,[1] we previously reported on a series of direct carbonylations at C–H bonds catalyzed by rhodium or ruthenium carbonyl complexes.[2–6] A variety of sp^2-nitrogen-containing substrates were found to undergo regioselective carbonylation with CO and olefins to give ketone derivatives. Although the regioselectivity at the position where the carbonylation takes place is dependent on the structure of substrates used, selectivity is exclusive in all cases reported, thus far, no other regioisomers have been detected. When chelation could not be utilized, no reaction occurred, indicating that coordination of the sp^2 nitrogen to the catalyst is required for the reaction to proceed.

Heterogeneous catalysts, such as Pd/C[7] and Ru/C[8] have recently been used as the catalyst because of its many salient advantages, (1) an inexpensive source, (2) ease of separation from the reaction mixture by simple filtration, (3) it can sometimes be recycled, and (4) it can be used without ligands. This prompted us to examine Ru/C as a catalyst for direct carbonylation of C–H bonds. We wish to report here that Ru/C can be used in the carbonylation at *ortho*-C–H bonds in 2-phenylpyridine derivatives.

The reaction of 2-phenylpyridine (**1a**, 2 mmol) with carbon monoxide (20 atm at r.t.) and ethylene (7 atm) in the presence of 5 wt% Ru/C (101 mg, corresponding to 0.05 mmol of Ru atom) in toluene (6 mL) at 160 °C for 20 hours gave 1-[2-(2-pyridinylphenyl)]-1-propanone (**2a**) in 62% yield (Scheme 1). We recently reported that DMA (*N*,*N*-dimethylacetamide) is the solvent of choice for the carbonylation of C–H bonds.[4e,f] The use of DMA significantly improved the yield of **2a** to 81% yield, along with 1% of the dicarbonylation product **3a**. The use of $Ru_3(CO)_{12}$ (0.017 mmol) as the catalyst gave comparable yields of **2a** (86% yield) and biscarbonylation product **3a** (8% yield). After the reaction, the black solids were removed by filtration and reused as the catalyst; however, no reaction took place, indicating that the recovered black solids did not possess any catalytic activity. We anticipated that the active ruthenium species do not remain on the carbon, but leaches into the solvent under the reaction conditions employed. In fact, the color of the reaction mixture was orange, the color similar to that of $Ru_3(CO)_{12}$ in DMA. After exposure of Ru/C under the reaction conditions in the absence of **1a**, the black solids were removed. The recovered black solids again showed no catalytic activity. In contrast, the orange-colored filtrate showed comparable catalytic activity (**2a**: 90% yield), clearly indicating that the active ruthenium species leaches from the Ru/C into the solvent under the reaction conditions employed. While the structure of the leached ruthenium complexes could not be identified, the reaction mechanism of the Ru/C-catalyzed reaction is essentially the same as that of the $Ru_3(CO)_{12}$-catalyzed reaction.[4a]



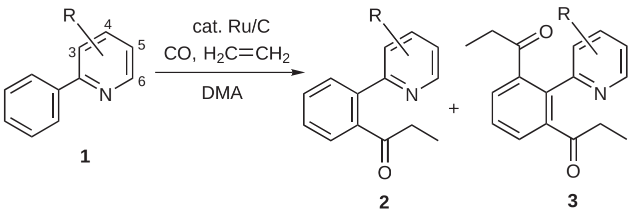
	2a	3a
toluene	62%	0%
DMA	81%	1%

Scheme 1

The effects of a methyl group on the pyridine ring were next examined, as shown in Scheme 2. Similar to the $Ru_3(CO)_{12}$-catalyzed reaction of 2-phenylpyridines,[4a] the presence of a methyl group at the 6-position retarded the reaction because of steric hindrance to the coordination of the nitrogen to ruthenium. The presence of a methyl group at the 4- and 5-positions had no significant effects on the reactivity of the substrates.

The results for the reactions of some 2-arylpyridines are shown in Table 1. The reaction of *para*-substituted 2-phenylpyridines selectively gave monocarbonylation products **4**–**6**. In the case of *meta*-substituted 2-phenylpyridines, carbonylation occurred exclusively at the less hindered C–H bonds to give the corresponding ketones

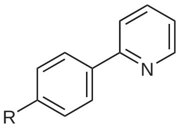
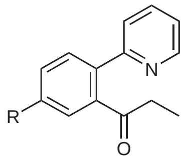
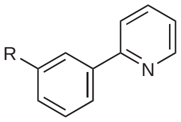
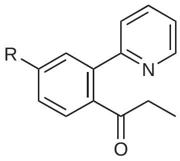
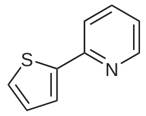
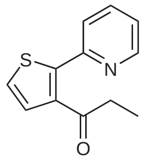
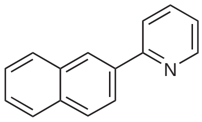
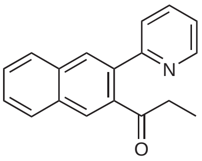
SYNLETT 2007, No. 1, pp 0170–0172
Advanced online publication: 20.12.2006
DOI: 10.1055/s-2006-958451; Art ID: U11106ST



R =	2	3
H (**1a**)	81%	1%
3-Me (**1b**)	29%	0%
4-Me (**1c**)	78%	19%
5-Me (**1d**)	81%	6%
6-Me (**1e**)	19%	0%

Scheme 2

Table 1 Ru/C-Catalyzed Reaction of 2-Arylpyridines with CO and Ethylene[a]

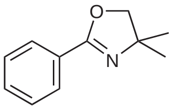
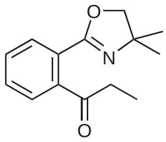
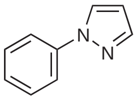
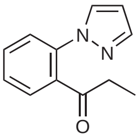
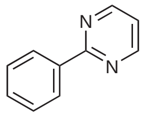
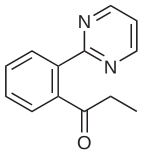
2-Arylpyridine	Product		Yield[b,c]
			
	R = OMe	**4**	77%
	R = Me	**5**	79% (4%)
	R = CF_3	**6**	34%
			
	R = OMe	**7**	82%
	R = Me	**8**	70%
	R = CF_3	**9**	22%
 **1h**		**10**	70%
 **1i**		**11**	96%

[a] Reaction conditions: 2-arylpyridine (2 mmol), ethylene (7 atm), CO (20 atm), Ru/C (101 mg) in DMA (6 mL) for 20 h.

[b] Yields are isolated yields based on 2-arylpyridine.

[c] The number in parentheses is the yield of biscarbonylation product.

Table 2 Ru/C-Catalyzed *ortho*-Carbonylation of C–H Bonds in a Benzene Ring[a]

Substrate	Product		Yield[b,c]
		**12**	54% (23%)
		**13**	27%
		**14**	30% (2%)

[a] Reaction conditions: substrate (2 mmol), ethylene (7 atm), CO (20 atm), Ru/C (101 mg) in DMA (6 mL) for 20 h.

[b] Yields are isolated yields based on substrate.

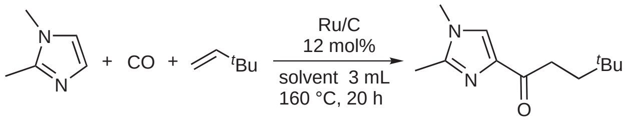
[c] The number in parentheses is the yield of biscarbonylation product.

7–**9**, irrespective of the nature of the substituent, as similar to the case of the $Ru_3(CO)_{12}$-catalyzed reaction.[4a]

Some other nitrogen-containing compounds also underwent regioselective carbonylation of C–H bonds to give the corresponding ketones, as shown in Table 2.

In contrast to γ-carbonylation, as shown in Table 1 and Table 2, Ru/C was not effective for the α- and β-carbonylation of C–H bonds, although it is likely that the active ruthenium species leaches from the Ru/C into the DMA solution. While no reaction took place, even when a 10-fold excess of catalyst was loaded in the reaction of *N*-methylimidazole in DMA, the use of toluene as the solvent gave the corresponding kentone in 39% yield (Scheme 3). *N*-Methylbenzimidazole was unreactive in both solvent systems.

In summary, we demonstrate that Ru/C also exhibit catalytic activity for carbonylation at *ortho*-C–H bonds.[9] Because of the catalyst leaching from the Ru/C into DMA solution under the reaction conditions employed, Ru/C cannot be recycled. However, it is an advantage to use Ru/C as a catalyst, because Ru/C is cheap and easily handled compared to $Ru_3(CO)_{12}$.



1 mmol	20 atm	4 mmol	DMA	0%
			toluene	39%

Scheme 3

Acknowledgment

This work was supported, in part, by grants from Ministry of Education, Culture, Sports, Science and Technology, Japan. N.C. wishes to acknowledge The Sumitomo Foundation and The General Oil Foundation for financial support.

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(9) **General Procedure for the Ru/C-Catalyzed Reactions of 2-Arylpyridines with Ethylene and CO.**
In a 50-mL stainless-steel autoclave were placed 5 wt% Ru/C (101 mg, corresponding to 0.05 mmol of Ru atom), 2-phenylpyridine (**1a**, 310 mg, 2 mmol), and DMA (6 mL). After flushing the system with 10 atm of ethylene three times, it was pressurized with ethylene to 7 atm and then with CO to an additional 20 atm. The autoclave was then immersed in an oil bath at 160 °C. After 20 h had elapsed, it was removed from the oil bath, allowed to cool and the gases were then released. The contents were transferred to a round-bottomed flask with EtOAc. After evaporation, the resulting residue was subjected to column chromatography on silica gel with hexane–EtOAc as the eluent to give 1-{2-[2-(pyridinyl)phenyl]}-1-propanone (**2a**, 346 mg, 81% yield) and 1-[2-(3-propionyl-2-pyridinyl)phenyl]-1-propanone (**3a**, 6 mg, 1% yield).