Ru-Catalyzed Hydroamidation of Alkenes and Cooperative Aminocarboxylation Procedure with Chelating Formamide

Sangwon Ko, Hoon Han, and Sukbok Chang*

Center for Molecular Design and Synthesis (CMDS), Department of Chemistry and School of Molecular Science (BK21), Korea Advanced Institute of Science and Technology (KAIST), Daejeon 305-701, Korea

sbchang@mail.kaist.ac.kr

Received May 18, 2003

ABSTRACT



A strategy of chelation-assisted activation of formamide was employed to achieve hydroamidation of alkenes to generate one-carbon-elongated amides in moderate to good selectivity and yields. Also reported is the two-metal-catalyzed cooperative aminocarboxylation of aryl iodides, in which Ru is presumed to catalyze decarbonylation of formamide to release carbon monoxide and amine for the subsequent Pd-catalyzed aminocarboxylation routes, thus enabling the net transformation to be performed in the absence of external CO pressure.

Metal-catalyzed C–H bond activation and subsequent addition of the activated species to unsaturated compounds constitute one of the most economical and efficient methods in organic synthesis.¹ Among them, the method for insertion of alkene or alkyne into the activated C–H bond of aldehyde, resulting in the corresponding ketone moiety, is considered highly useful.² However, the use of hydroacylation in organic synthesis is rather limited mainly due to facile decarbonylation of the activated hydroacyl intermediate under the normally used conditions.³ Chelation strategy has been elegantly utilized in transition metal-catalyzed organic transformations to direct reaction pathways by virtue of forming tight transition states.⁴ During the course of studies on transition metal catalysis,⁵ we have recently demonstrated that the chelation strategy could be employed to effectively activate pyridyl group-containing formates to achieve efficient hydroesterification of alkenes.⁶ In this protocol, the pyridyl moiety of formats serves as a directing group and facilitates the formation of chelating species, thus effectively suppressing decarbonylation of ruthenium acyl hydride intermediates. It is surprising that whereas hydroesterification

Vol. 5, No. 15

2687-2690

⁽¹⁾ For recent examples of catalytic C-H bond activation, see: (a) Arndtsen, B. A.; Bergman, R. G.; Mobley, T. A.; Peterson, T. H. Acc. Chem. Res. **1995**, 28, 154. (b) Shilov, A. E.; Shul'pin, G. B. Chem. Rev. **1997**, 97, 2879. (c) Dyker, G. Angew. Chem., Int. Ed. **1999**, 38, 1698. (d) Jia, C.; Kitamura, T.; Fujiwara, Y. Acc. Chem. Res. **2001**, 34, 633. (e) Kakiuchi, F.; Murai, S. Acc. Chem. Res. **2002**, 35, 826. (f) Ritleng, V.; Sirlin, C.; Pfeffer, M. Chem. Rev. **2002**, 102, 1731.

⁽²⁾ For selected examples of metal-catalyzed hydroacylation, see: (a) Lochow, C. F.; Miller, R. G. J. Am. Chem. Soc. **1976**, 98, 1281. (b) Marder, T. B.; Roe, D. C.; Milstein, D. Organometallics **1988**, 7, 1451. (c) Bosnich, B. Acc. Chem. Res. **1998**, 31, 667. (d) Tanaka, K.; Fu, G. C. J. Am. Chem. Soc. **2001**, 123, 11492. (e) Jun, C.-H.; Lee, H.; Hong, J.-B.; Kwon, B.-I. Angew. Chem., Int. Ed. **2002**, 41, 2146. (f) Sato, Y.; Oonishi, Y.; Mori, M. Angew. Chem., Int. Ed. **2002**, 41, 1218.

⁽³⁾ Bates, R. W. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, UK, 1995; Vol. 12, pp 373–378.

⁽⁴⁾ For some selected recent examples, see: (a) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529. (b) Gozin, M.; Weisman, A.; Ben-David, Y.; Milstein, D. *Nature* **1993**, *364*, 699. (c) Jun, C.-H.; Lee, H. *J. Am. Chem. Soc.* **1999**, *121*, 880. (d) Itami, K.; Koike, T.; Yoshida, J.-i. J. Am. Chem. Soc. **2001**, *123*, 6957 and references therein.

^{(5) (}a) Na, Y.; Chang, S. Org. Lett. **2000**, 2, 1887. (b) Lee, M.; Chang, S. Tetrahedron Lett. **2000**, 41, 7507. (c) Lee, M.; Ko, S.; Chang, S. J. Am. Chem. Soc. **2000**, 122, 12011. (d) Chang, S.; Na, Y.; Choi, E.; Kim, S. Org. Lett. **2001**, 3, 2089. (e) Chang, S.; Yang, S. H.; Lee, P. H. Tetrahedron Lett. **2001**, 42, 4833. (f) Choi, E.; Lee, C.; Na, Y.; Chang, S. Org. Lett. **2002**, 4, 2369.

^{(6) (}a) Ko, S.; Na, Y.; Chang, S. J. Am. Chem. Soc. **2002**, 124, 750. (b) Ko, S.; Lee, C.; Choi, M.; Na, Y.; Chang, S. J. Org. Chem. **2003**, 68, 1607. (c) Na, Y.; Ko, S.; Hwang, L. K.; Chang, S. Tetrahedron Lett. **2003**, 44, 4475.

has been well studied previously,⁷ only a few examples of hydroamidation, in which formamides are directly added to alkenes, have been reported.⁸ Considering the high potential utility of hydroamidation in organic synthesis, an efficient and preparative method for the reaction is highly desirable. Herein, we report our studies on the chelation-assisted hydroamidation of alkenes via ruthenium catalysis and its application in an aminocarboxylation of aryl halides by a cooperative catalysis with two metal catalysts, ruthenium and palladium.

As shown in our previous reports that low-valent ruthenium carbonyl species can effectively activate formyl C–H bond,⁶ hydroamidation of alkenes was initially scrutinized with $Ru_3(CO)_{12}$ catalyst with various formamides, which were readily prepared from the corresponding amines (Table 1).⁹

Table 1. Hydroamidation of 3,3-Dimethyl-1-butene with
 Various Formamides a

R N R	0 ⊣ + ∽t-E	3u — <i>cat.</i> Ru solv 135 °C	u ₃ (CO) ₁₂ ➤ rent R [⊂] C, 5 h	R' N O t-Bu
entry	R	R′	solvent	conversion (%) ^b
1	2-PyCH ₂	H (1a)	CH ₃ CN	10 (<5)
2	2-Py	H (1b)	CH ₃ CN	>99 (80)
3	2-Py	H (1b)	DMF	>99 (23)
4	2-Py	Н (1b)	2-propanol	>99 (9)
5	2-Py	Me (1c)	CH ₃ CN	13 (<5)
6	(6-Me)-2-Py	H (1d)	CH ₃ CN	79 (10)
7	Ph	Н (1е)	CH ₃ CN	<5 (<5)

^{*a*} All reactions were carried out with formamide (1.0 mmol), alkene (3.0 mmol), and ruthenium catalyst (0.05 mmol) in the indicated solvent (1 mL). ^{*b*} Conversion and product yields were calculated by ¹H NMR using an internal standard (anisole).

Contrary to the results of hydroesterification studies,⁶ in which 2-pyridylmethy formate was the most efficient acyl donor based on the reaction rates and selectivity, the corresponding amide, N-(2-pyridylmethyl)formamide (**1a**), reacted very slowly with alkene and almost no desired product was obtained under the employed conditions (entry 1). In contrast, N-(2-pyridyl)formamide (**1b**) reacted much more readily with alkene (entry 2), giving the one-carbonelongated amide in good yield in acetonitrile along with the decarbonylated moiety (2-aminopyridine) in small portion

(15%).¹⁰ Among the various solvents examined, acetonitrile was the most suitable for the reaction under the catalytic system. For example, in DMF or 2-propanol, decarbonylation became significant and only a low yield of the desired amide could be obtained (entries 3 and 4). N-Methylated formamide (**1c**) was almost inert to the transformation (entry 5). Substituents near the pyridyl nitrogen of formamides turned out to accelerate decarbonylation, thereby giving poor yields of hydroamidation (entry 6). Reaction of formanilide (**1e**) did not proceed under the conditions, clearly demonstrating the crucial role of chelation on the reactivity (entry 7).

The chelation-assisted hydroamidation protocol could be extended to a range of alkenes, and the corresponding onecarbon-homologated amides could be obtained in moderate to good yields (Table 2).¹¹ The preference for the formation

Table 2.	Ru-Catalyzed	Hydroamidation o	f Alkenes	with
N-(2-Pyrid	lyl)formamide	(1b) ^{<i>a</i>}		

1b +		D) ₁₂	PyHNOC R	CONHPy + ↓_R
entry	alkene	time (h)	conv (%) ^b	yield (%, ratio) ^c
1	n-Bu	6	99	67 (80:20)
2	cyHex	10	95	75 (93:7)
3	t-Bu	6	99	73 (>99:1)
4	C ₆ H ₅	6	99	72 (76:24)
5	C ₆ H ₂ Me ₃ (2,4,	6) 8	95	53 (99:1)
6	SiMe ₃	7	99	53 (82:18)
7	SiMe ₃	6	99	69 (>99:1)
8	al t	13	95	76 (87:13) ^d

^{*a*} Formamide (**1b**, 0.5 mmol), alkene (1.5 mmol), and Ru₃(CO)₁₂ (0.025 mmol) in CH₃CN (1 mL). ^{*b*} Conversion was calculated by ¹H NMR integration using anisole as a standard. ^{*c*} Isolated yield after chromatography and ratio of linear/branched isomer (parenthesis). ^{*d*} Ratio of exo/endo isomer obtained by comparison to the literature.¹²

of linear formamide over branched isomer was observed for all substrates examined, and the extent of the ratio turned out to be dependent on the steric bulkiness of olefins. For example, whereas a 4:1 ratio of linear/branched amide product was observed with 1-hexene by the reaction of *N*-(2pyridyl)formamide (**1b**), the ratio was increased to 93:7 with vinylcyclohexane and then up to >99:1 with 3,3-dimethyl-1-butene (entries 1–3). Hydroamidation of aromatic olefins with **1b** proceeded with similar tendency compared to aliphatic alkenes (entries 4–5). Allylsilane was also reacted to afford *N*-(2-pyridyl)-4-trimethylsilyl butanamide, albeit in

⁽⁷⁾ For selected examples of hydroesterification of alkenes using alkyl formates, see: (a) Kondo, T.; Yoshii, S.; Tsuji, Y.; Watanabe, Y. J. Mol. Catal. **1989**, *50*, 31. (b) Lugan, N.; Lavigne, G.; Soulić, J. M.; Fabre, S.; Kalck, P.; Saillard, J. Y.; Halet, J. F. Organometallics **1995**, *14*, 1712. (c) Legrand, C.; Castanet, Y.; Mortreux, A.; Petit, F. J. Chem. Soc., Chem. Commun. **1994**, 1173. (d) Grevin, J.; Kalck, P. J. Organomet. Chem. **1994**, 476, C23.

^{(8) (}a) Tsuji, Y.; Yoshii, S.; Oshumi, T.; Kondo, T.; Watanabe, Y. J. Organomet. Chem. **1987**, *331*, 379. (b) Kondo, T.; Okada, T.; Mitudo, T.-a. Organometallics **1999**, *18*, 4123.

⁽⁹⁾ Formamides (1a-e) were prepared by the reaction of acetic formic anhydride with the corresponding amines in 86–95% yields up to a 10 g scale. For a reference, see: Strazzolini, P.; Giumanini, A. G.; Cauci, S. *Tetrahedron* **1990**, *46*, 1081.

⁽¹⁰⁾ For ruthenium-catalyzed hydroamidation of olefins with primary amines under high-pressure CO, see: Tsuji, Y.; Ohsumi, T.; Kondo, T.; Watanabe, Y. *J. Organomet. Chem.* **1986**, *309*, 333.

⁽¹¹⁾ For experimental details, see Supporting Information.

moderate yield and selectivity (entry 6). However, reaction of vinylsilane with **1b** showed almost exclusive formation of the linear product in satisfactory yield, presumably due to steric reasons (entry 7). Reaction of norbornylene resulted in preferential formation of *exo*-isomeric product in good yield (entry 8).¹² Although the ruthenium catalyst was used in 5 mol % in this study, the amount of the catalyst could be reduced to as low as 2 mol % without a significant decrease in the efficiency. For example, when 3,3-dimethyl-1-butene was allowed to react with **1b** in the presence of 2 mol % Ru₃(CO)₁₂ under otherwise identical conditions, 71% yield of the desired amide was obtained with the same selectivity (6 h, linear/branched isomer, >99:1, compare entry 3 of Table 2).

On the basis of previous studies, including a crystal structure analysis of a chelated Ru-pyridyl species,⁶ we propose the following mechanism for the hydroamidation of alkenes using **1b** (Scheme 1, only a major isomeric

Scheme 1. Proposed Mechanism of the Ru-Catalyzed Hydroamidation of Alkenes with N-(2-Pyridyl)formamide (1b)^{*a*}



^{*a*} Only one plausible pathway for the formation of the linear isomer is shown.

pathway is shown). Although it is not clear at the present stage whether ruthenium acts as a mononuclear or as a cluster,¹³ it is presumed that the coordination of ruthenium to the pyridyl nitrogen should facilitate the activation of the formyl C–H bond, leading to a five-membered chelation intermediate. The observation that formanilide (**1e**) does not react under the identical conditions (Table 1, entry 7) may support our assumption. In addition, such a chelation is believed to be a driving force for the significant suppression of the decarbonylation pathway during the catalytic hydroamidation cycles using **1b**. Although more extensive inves-

tigations have to be carried to get a precise mechanism of the present reaction, an alternative pathway, rutheniumcatalyzed decarbonylation of **1b** and subsequent aminocarboxylation of alkenes with the released CO and 2-aminopyridine, could be ruled out on the basis of the following result. The aminocarboxylation of alkenes with CO and 2aminopyridine instead of **1b** gave very low yields (<10%) with the use of Ru₃(CO)₁₂ catalyst under identical conditions.

In the course of our studies on the hydroamidation of alkenes, we found that with certain olefin substrates, decarbonylation of formamide **1b** occurred much faster than addition of the formamide to alkenes, which is especially conspicuous with sterically bulky olefins. In fact, in the absence of alkenes, decarbonylation of **1b** was complete in 2 h at temperatures above 130 °C with $Ru_3(CO)_{12}$ catalyst (3 mol %) in acetonitrile to give 2-aminopyridine quantitatively. The fact that palladium is known to be an excellent catalyst for aminocarboxylation of aryl halides with CO and amines led us to examine a cooperative coupling of formamide **1b** with aryl halides by the use of both ruthenium and palladium catalysts (Table 3).¹⁴ Two sequential catalytic

Table 3. Cooperative Catalytic Aminocarbonylation of Aryl

 Iodides by the Combined Use of Pd and Ru Catalysts^a

Ar—I +		(CO) ₁₂ (5 mol%) dCl ₂ (5 mol%) HCO ₃ (1.5 equiv) H ₃ CN, 135 ^o C	► Ar-CONHPy
entry	Ar	t (h)	yield (%) ^b
1	C ₆ H ₅	4	58
2	$(3-Br)C_6H_4$	8	50
3	$(4-Me)C_6H_4$	8	76
4	$(4-MeO)C_6H_4$	8	62
5	$(4-Ac)C_6H_4$	10	83
6	(6-HO)C ₆ H ₄	8	57
7	1-naphthyl	10	54

^{*a*} Formamide (**1b**, 0.4 mmol), aryl iodides (0.8 mmol), and the indicated ratio of NaHCO₃, Pd, and Ru species in CH₃CN (0.8 mL). ^{*b*} Isolated yields after column chromatography.

routes were intended to combine, Ru-catalyzed decarbonylation of **1b** to generate CO and 2-aminopyridine and subsequent aminocarboxylation of aryl halides using the released CO and amine in the presence of Pd catalyst. Among several solvents examined, acetonitrile turned out to be most suitable for the transformation in combination with sodium bicarbonate. For example, from the reaction of **1b** with iodobenzene, the desired amide was isolated in 58, 20, and 50% yields in CH₃CN (entry 1), toluene, and DMF, respectively, under otherwise identical conditions.¹⁵ It should be mentioned that *N*-(2-pyridyl)benzamide was produced

⁽¹²⁾ Regioselectivity of *exo/endo* isomer was determined unambiguously by comparison to the literature after hydrolysis of the obtained amide to the corresponding carboxylic acid; see: Eda, M.; Takemoto, T.; Ono, S.-i.; Okada, T.; Kosaka, K.; Gohda, M.; Matzno, S.; Nakamura, N.; Fukaya, C. *J. Med. Chem.* **1994**, *37*, 1983.

⁽¹³⁾ We isolated a triruthenium cluster bound to 2-pyridylmethanol from the previous studies and showed that it was a stoichiometric reagent for the hydroesterification of alkenes. For a reference, see ref 6b.

⁽¹⁴⁾ For some recent examples of sequential catalytic reactions, see: (a) Jeong, N.; Seo, S. D.; Shin, J. Y. J. Am. Chem. Soc. 2000, 122, 10220. (b) Park, K. H.; Son, S. U.; Chung, Y. K. Org. Lett. 2002, 4, 4361.

⁽¹⁵⁾ On the basis of this result, the possibility that DMF acts as a CO source through decomposition of the solvent can be ruled out. For a reference of a related example, see: Wan, Y.; Altermann, M.; Larhed, M.; Hallberg, A. J. Org. Chem. **2002**, 67, 6232.

only by the combined use of both Ru and Pd catalysts, and that no desired product was obtained with any single metal catalytic species examined under the present reaction conditions. Whereas aryl chlorides and bromides were inert to the coupling with 1b under the conditions, various aryl iodides having different electronic properties were readily reacted to afford benzamide derivatives in moderate to good yields. Electron variation in aryl halides had little effect on the reaction efficiency, and moderate to good yields were obtained from the couplings (entries 2-5). Free hydroxyl group was tolerant to the employed reaction conditions (entry 6). 1-Iodonaphthalene was also coupled with 1b, although in moderate yield (entry 7). Although further studies have to be carried out to elucidate detailed mechanistic pathways of the present cooperative reaction, by the analogy of our previous report on sequential alkoxycarboxylation protocol,^{6b} the reaction is believed to proceed via ruthenium-catalyzed initial decarbonylation of formamide 1b to afford CO and 2-aminopyridine and then palladium-catalyzed subsequent aminocarboxylation of aryl iodides with the released moieties.16,17

Hydrolysis of the obtained N-(2-pyridyl) amides, represented by N-(2-pyridyl)-4,4-dimethyl pentanamide (**2**), could be readily carried out under mild conditions to generate the corresponding carboxylic acid (**3**) in almost quantitative yield (eq 1). On the other hand, reduction of the pyridyl amide **2** with LAH afforded in high yield a pyridylamine (**4**) that bears



one more carbon compared to the starting material. It should be noted that the present hydroamidation and reduction approach is highly comparable to the known Pd-catalyzed hydroamination of alkenes,¹⁸ by which amines are produced with the same number of carbons as in the olefinic starting materials.

In summary, we have demonstrated that hydroamidation of alkenes can be developed into a useful catalytic transformation by the assistance of chelation strategy with the use of a readily prepared and hydrolyzable formamide. In addition, in the absence of an external CO atmosphere, a cooperative catalytic coupling of pyridyl formamide and aryl iodides was realized by the combined use of ruthenium and palladium catalyst in one pot to afford aminocarboxylation adducts.

Acknowledgment. This research was supported by Korea Science & Engineering Foundation (Grant No. R02-2002-000-00140-0) through the Basic Research Program.

Supporting Information Available: Detailed experimental procedures and spectroscopic data for all new compounds obtained in this study. This material is available free of charge via the Internet at http://pubs.acs.org.

OL034862R

⁽¹⁶⁾ Recent example of aminocarbonylation of aryl iodides using DMF as an amide source: Hosoi, K.; Nozaki, K.; Hiyama, T. *Org. Lett.* **2002**, *4*, 2849.

⁽¹⁷⁾ Use of aldehyde as a CO source in catalytic Pauson-Khand reaction has been reported recently; see: (a) Morimoto, T.; Fuji, K.; Tsutsumi, K.; Kakiuchi, K. J. Am. Chem. Soc. **2002**, 124, 3806. (b) Shibata, T.; Toshida, N.; Takagi, K. Org. Lett. **2002**, 4, 1619.

⁽¹⁸⁾ For recent reviews of hydroamination, see: (a) Gasc, M. B.; Lattes, A.; Perie, J. J. *Tetrahedron* **1983**, *39*, 703. (b) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675. (c) Nobis, M.; Driessen-Holscher, B. *Angew. Chem., Int. Ed.* **2001**, *40*, 3983. (d) Müller, T. E.; Beller, M. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, Germany, 1998; Vol. 2, p 316.