

Halide Ions as a Highly Efficient Promoter in the Ru-Catalyzed Hydroesterification of Alkenes and Alkynes

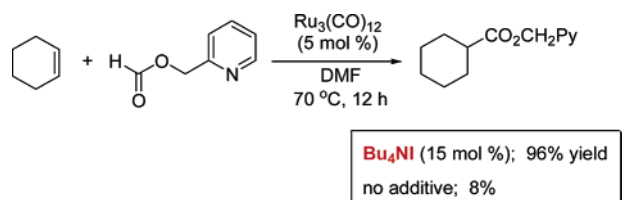
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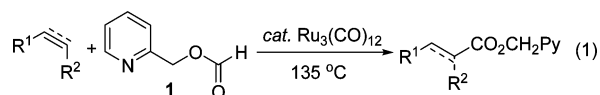
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ABSTRACT



The presence of catalytic amounts of halide salts was found to enhance dramatically the reaction efficiency in the Ru-catalyzed hydroesterification of alkenes and alkynes using a chelating 2-pyridylmethyl formate by lowering the reaction temperature. On the basis of IR and NMR studies, the halide effect on the reaction is mainly attributed to the facile dissociation of the trirutheniumcarbonyl precursor into the presumed active metal species. With this milder condition, the substrate scope has been significantly broadened.

Functionalization of unsaturated compounds into carbonyl-containing molecules is an area of great interest.¹ We recently reported one notable example of those functionalizations by virtue of $\text{Ru}_3(\text{CO})_{12}$ catalyst in the hydroesterification and hydroamidation of double and triple bonds using 2-pyridylmethyl formate (**1**, eq 1).²



The reaction is believed to proceed via a chelation-assisted pathway,³ and it exhibits excellent efficiency and selectivity

with a range of substrates. Additionally, the reaction does not require external CO atmosphere and it can be run even in solvent-free conditions. The chelating auxiliary, 2-pyridine-methanol, can be quantitatively recovered after hydrolysis of the produced esters, thus offering additional merits.

Despite these advantages, the reaction usually requires relatively high temperatures and a large excess of substrates, which provide difficulties for making this one-carbon homologating protocol more practical. Although several aspects may be considered to improve the reaction conditions,⁴ we envisioned that the generation of catalytically more active

(1) For selected examples of hydroacylation of alkenes, see: (a) Lochow, C. F.; Miller, R. G. *J. Am. Chem. Soc.* **1976**, *98*, 1281–1283. (b) Marder, T. B.; Roe, D. C.; Milstein, D. *Organometallics* **1988**, *7*, 1451–1453. (c) Bosnich, B. *Acc. Chem. Res.* **1998**, *31*, 667–674. (d) Tanaka, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 11492–11493. (e) Sato, Y.; Oonishi, Y.; Mori, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 1218–1221. (f) Tanaka, M.; Sakai, K.; Suemune, H. *Curr. Org. Chem.* **2003**, *7*, 353–367. (g) Kakiuchi, F.; Chatani, N. *Top. Organomet. Chem.* **2004**, *11*, 45–79.

(2) (a) Ko, S.; Na, Y.; Chang, S. *J. Am. Chem. Soc.* **2002**, *124*, 750–751. (b) Na, Y.; Ko, S.; Hwang, L. K.; Chang, S. *Tetrahedron Lett.* **2003**, *44*, 4475–4478. (c) Ko, S.; Lee, C.; Choi, M.-G.; Na, Y.; Chang, S. *J. Org. Chem.* **2003**, *68*, 1607–1610. (d) Ko, S.; Han, H.; Chang, S. *Org. Lett.* **2003**, *5*, 2687–2690.

(3) For some selected examples, see: (a) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529–531. (b) Itami, K.; Koike, T.; Yoshida, J.-i. *J. Am. Chem. Soc.* **2001**, *123*, 6957–6958. (c) Han, H.; Bae, I.; Yoo, E. J.; Lee, J.; Do, Y.; Chang, S. *Org. Lett.* **2004**, *6*, 4109–4112. (d) Ko, S.; Kang, B.; Chang, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 455–457.

species via the facile dissociation of the trirutheniumcarbonyl cluster might be a key to overcome the present drawback. Herein, we report our findings that certain halide additives greatly improve the reaction conditions, thereby enabling the hydroesterification to be carried out under much milder conditions with a more diverse range of substrates.⁵

We embarked on the study of additive effects⁶ in a test reaction of 3,3-dimethyl-1-butene (1.2 equiv) with 2-pyridylmethyl formate (**1**) by the action of $\text{Ru}_3(\text{CO})_{12}$ catalyst in DMF at 70 °C (Table 1).⁷ Addition of amine bases or acids

Table 1. Additive Effects in the Hydroesterification Reaction^a

entry	additive	conv ^b (%)	yield ^b (%)
1		12	10
2	Et_3N	<5	<5
3	2,6-lutidine	10	<5
4	$\text{CH}_3\text{CO}_2\text{H}$	13	<5
5	NMO	25	15
6	NH_4PF_6	16	10
7	<i>t</i> -BuOH	10	<5
8	PPh_3	<5	<5
9	Ph_3PO	10	6
10	LiCl	40	20
11	LiBr	90	85
12	LiI	>98	95
13	Bu_4NCl	13	12
14	Bu_4NBr	30	30
15	Bu_4NI	>98	95
16	Bu_4NI (50 °C)	10	8

^a Alkene (0.48 mmol), **1** (0.4 mmol), $\text{Ru}_3(\text{CO})_{12}$ (5 mol %), and additive (15 mol %) in DMF (0.2 mL). ^b Conversion and yield were determined by ¹H NMR relative to an internal standard.

(15 mol %) showed rather inhibitory effects (entries 2–4). While Floreancig et al. showed that the addition of *N*-methylmorpholine *N*-oxide (NMO) resulted in a rate enhancement in the hydroesterification using **1**,⁴ it did not greatly improve the reaction efficiency under our conditions (entry 5). In addition, the employment of various other

(4) For an intuitive mechanistic work on the hydroesterification of olefins using **1**, see: (a) Wang, L.; Floreancig, P. E. *Org. Lett.* **2004**, *6*, 569–572. (b) Wang, L.; Floreancig, P. E. *Org. Lett.* **2004**, *6*, 4207–4210.

(5) For selected examples of halide additive effects in catalytic reactions, see: (a) Lavigne, G.; Kaesz, H. D. *J. Am. Chem. Soc.* **1984**, *106*, 4647–4648. (b) Dombek, B. D. *Organometallics*, **1985**, *4*, 1707–1712. (c) Kiso, Y.; Tanaka, M.; Nakamura, H.; Yamasaki, T.; Saeki, K. *J. Organomet. Chem.* **1986**, *312*, 357–364. (d) Yoshida, S.-I.; Mori, S.; Kinoshita, H.; Watanabe, Y. *J. Mol. Catal.* **1987**, *42*, 215–227. (e) Lautens, M.; Fagnou, K.; Yang, D. *J. Am. Chem. Soc.* **2003**, *125*, 14884–14892. (f) Dahlén, A.; Hilmersson, G. *Eur. J. Inorg. Chem.* **2004**, 3393–3403. (g) Ruck, R. T.; Zuckerman, R. L.; Krsko, S. W.; Bergman, R. G. *Angew. Chem., Int. Ed.* **2004**, *43*, 5375–5377.

(6) For selected examples showing that the addition of certain salts to a solution of rutheniumcarbonyl complexes results in catalytically more active species, see: (a) Dombek, B. D. *J. Am. Chem. Soc.* **1981**, *103*, 6508–6510. (b) Knifton, J. F. *J. Am. Chem. Soc.* **1981**, *103*, 3959–3961. (c) Dombek, B. D. *J. Organomet. Chem.* **1983**, *250*, 467–483. (d) Dombek, B. D. *J. Organomet. Chem.* **1989**, *372*, 151–161. (e) Lavigne, G. *Eur. J. Inorg. Chem.* **1999**, 917–930. (f) Fagnou, K.; Lautens, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 26–47.

additives such as NH_4PF_6 ,⁸ *t*-BuOH, Ph_3P , or Ph_3PO displayed deteriorative effects (entries 6–9).

On the other hand, certain halide salts dramatically improved the efficiency of the hydroesterification, the extent of which was varied depending on the counteranions. While the lithium salt of chloride displayed a marginal improvement, the use of bromide or iodide salts resulted in notable activation effects (entries 10–12). Interestingly, in the case of organic ammonium salts, the halide effect was most significant with iodide anion (entries 13–15). The additive effects turned out to be less effective below 70 °C (entry 16).

There are several precedents in which a series of new interexchangeable ruthenium species are generated when a solution of $\text{Ru}_3(\text{CO})_{12}$ is treated with halide ions. For example, it is known that $\text{Ru}_3(\text{CO})_{12}$ reacts readily with iodide ion to form initially $[\text{Ru}_3(\text{CO})_{11}(\text{I})]^-$, which is next converted to a bridging species $[\text{Ru}_3(\text{CO})_{10}(\mu_2\text{-I})]^-$ and then to $[\text{Ru}_3(\text{CO})_9(\mu_3\text{-I})]^-$ having a triply bridged iodide ligand.⁹ Interestingly, Dombek reported that iodide reacts with $\text{Ru}_3(\text{CO})_{12}$ under normal H_2 or H_2/CO atmosphere to afford two main ruthenium species, $[\text{HRu}_3(\text{CO})_{11}]^-$ and $[\text{Ru}(\text{CO})_3\text{I}_3]^-$.⁶ He further demonstrated that a combination of these two adducts is required for achieving an optimal activity in the hydrogenation of CO to produce ethylene glycol with the $\text{Ru}_3(\text{CO})_{12}/\text{I}^-$ catalyst precursor system. Since $\text{Ru}_3(\text{CO})_{12}$ is in equilibrium with its monomeric $\text{Ru}(\text{CO})_5$ species only under high CO pressure,¹⁰ it is reasonable, in our case, to rule out a possibility that the added halide ions directly dissociate the trinuclear cluster into monomeric species under the present hydroesterification conditions.

When we treated a solution of $\text{Ru}_3(\text{CO})_{12}$ in THF with LiI at 60 °C, IR spectroscopy showed that the original carbonyl peaks of $\text{Ru}_3(\text{CO})_{12}$ were gradually replaced with a series of new vibrational bands at 2043, 1991, and 1950 cm^{-1} (Figure 1). In contrast, no spectroscopic change was

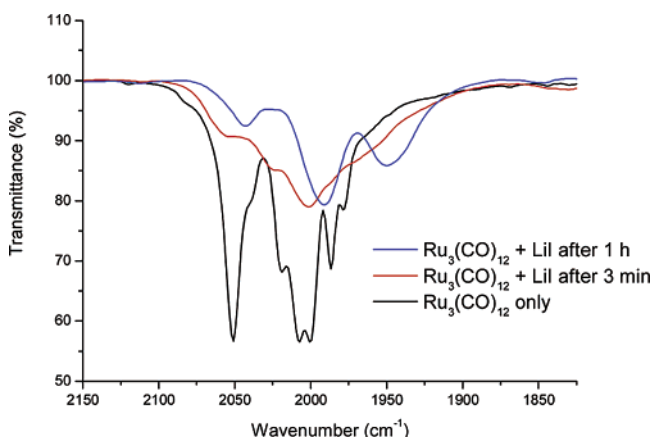


Figure 1. IR spectra of a mixture of $\text{Ru}_3(\text{CO})_{12}$ and LiI (3 equiv) in THF at 60 °C.

detected when a $\text{Ru}_3(\text{CO})_{12}$ solution was treated with additives possessing no promoting effects such as NH_4PF_6 .¹¹ Interestingly, several characteristic IR peaks obtained from

the presently employed system of $\text{Ru}_3(\text{CO})_{12}/\text{LiI}$ are well matched with those of the reported complex $[\text{Ru}_3(\text{CO})_9-(\mu_3\text{-I})][\text{N}(\text{PPh}_3)_2]$, albeit missing a bridging carbonyl peak near 1793 cm^{-1} .⁹ The IR studies imply that all of the CO's from the present combination of $\text{Ru}_3(\text{CO})_{12}$ and LiI are terminal. Although further studies remain to elucidate the exact structure of the catalytically active species in our case,¹² this observation suggests that the main reason for the present improvement of the reaction conditions by virtue of additives is probably due to the facile CO ligand dissociation of the rutheniumcarbonyl cluster upon the addition of halide ions.

In addition, when we treated a solution of $\text{Ru}_3(\text{CO})_{12}$ and 2-pyridylmethyl formate (**1**) in $\text{DMF-}d_7$ with tetrabutylammonium iodide (**2**) at 70°C , it was observed by ^1H NMR that two peaks appeared gradually at -12.5 and -15.7 ppm, which are assignable to ruthenium hydride presumably generated by an oxidative addition of formyl C–H bond of **1** with ruthenium metal.¹³ Interestingly, the intensity of the peaks was maintained without much diminution even after 12 h, suggesting that the presence of halides may also help increase the half-life of the emerging rutheniumcarbonyl hydride species, which subsequently insert into the unsaturated C–C bonds.⁴

The halide additive effects turned out to be general, and a wide range of alkenes were efficiently converted to the corresponding one-carbon elongated esters under the optimized conditions (Table 2). The additive effects are often moderate with highly reactive alkenes such as terminal or strained internal olefins. With those olefins, excellent product yields could be obtained even when only 1.2 equiv of substrates were employed by virtue of Bu_4NI salt (**2**) (entries 1–10).

(7) Lavigne and co-workers showed that preformed ruthenium carbonyl halide species $[\text{N}(\text{PPh}_3)_2]_2[\text{Ru}_3(\mu\text{-Cl})_2(\text{CO})_{11}]$ could be used as a good catalyst precursor in the hydroesterification of ethylene using methyl formate at 160°C : (a) Lavigne, G.; Lugan, N.; Kalck, P.; Soulié, J. M.; Lerouge, O.; Saillard, J. Y.; Halet, J. F. *J. Am. Chem. Soc.* **1992**, *114*, 10669–10670. (b) Lugan, N.; Lavigne, G.; Soulié, J. M.; Fabre, S.; Kalck, P.; Saillard, J. Y.; Halet, J. F. *Organometallics* **1995**, *14*, 1712–1731.

(8) For selected examples of NH_4PF_6 additive effects in $\text{Ru}_3(\text{CO})_{12}$ catalysis, see: (a) Tokunaga, M.; Eckert, M.; Wakatsuki, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 3222–3225. (b) Shimada, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 6646–6647. (c) Yi, C. S.; Yun, S. Y.; Guzei, I. A. *J. Am. Chem. Soc.* **2005**, *127*, 5782–5783.

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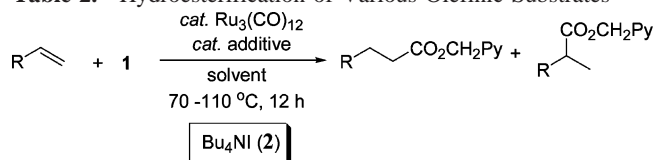
(10) (a) Bor, G. *Pure Appl. Chem.* **1986**, *58*, 543–552. (b) Koelliker, R.; Bor, G. *J. Organomet. Chem.* **1991**, *417*, 439–451.




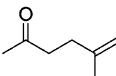




(11) See the Supporting Information for details.

(12) Several additional examples have been reported on the halide promotion effects in $\text{Ru}_3(\text{CO})_{12}$ -catalyzed reactions. Hydrogenation of carbon dioxide: (a) Tominaga, K.-i.; Sasaki, Y. *J. Mol. Catal. A: Chem.* **2004**, *220*, 159–165. Oxonation of olefins: (b) Knifton, J. F. *J. Mol. Catal.* **1988**, *47*, 99–116. Alkoxy carbonylation: (c) Hidai, M.; Koyasu, Y.; Chikanari, K.; Uchida, Y. *J. Mol. Catal.* **1987**, *40*, 243–254. Hydroformylation of olefins with CO_2 : (d) Keister, J. B.; Gentile, R. *J. Organomet. Chem.* **1981**, *222*, 143–153. Homologation of methyl formate: (e) Ragaini, F.; Cenini, S. *J. Mol. Catal. A: Chem.* **2000**, *161*, 31–38. Reductive carbonylation of aromatic nitro compounds: (f) Pizzotti, M.; Cenini, S.; Quici, S.; Tollari, S. *J. Chem. Soc., Perkin Trans. 2.* **1994**, 913–917.

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Table 2. Hydroesterification of Various Olefinic Substrates^a



entry	alkene	temp ($^\circ\text{C}$, solvent)	additive	yield (%) ^b
1	<i>t</i> -Bu	70 (DMF)	–	30 (>98:2)
2		70 (DMF)	2	99 (>98:2)
3	<i>n</i> -Bu	70 (DMF)	–	9 (80:20)
4		70 (DMF)	2	86 (81:19)
5		70 (DMF)	–	18 (>98:2)
6		70 (DMF)	2	96 (>98:2)
7	TMS	70 (DMF)	–	50 (88:12)
8		70 (DMF)	2	95 (89:11)
9		70 (DMF)	–	70 ^c
10		70 (DMF)	2	84 ^c
11		70 (DMF)	–	8
12		70 (DMF)	2	96
13		70 (DMF)	–	8 (>98:2)
14		70 (DMF)	2	88 (>98:2)
15		110 (THF)	–	<5
16		110 (THF)	2	78 ^d
17		110 (THF)	–	<5
18		110 (THF)	2	91 (>98:2)
19		110 (THF)	–	<5
20		110 (THF)	2	74 (82:18) ^e
21		110 (THF)	–	<5
22		110 (THF)	2	91 (15:85) ^f

^a Olefin (0.48 mmol in entries 1–10 and 1.2 mmol in entries 11–22), **1** (0.4 mmol), and **2** (15 mol %) in the indicated solvent (0.2 mL). ^b Isolated yield and ratio of linear/branched isomer of crude mixture. ^c Only *exo*-product was generated. ^d An equal mixture of two diastereomers. ^e Ratio of α - to β -ester. ^f Ratio of 1- to 2-carboxylate.

The regioselectivity for the formation of linear to branched isomeric ester was not noticeably changed by the presence of halide additives (entries 3, 4 and 7, 8), suggesting that the main catalytic cycle is not altered by the promoter.⁴ Moreover, the nature of halide ions does not seem to have much influence on the regioselectivity of the reaction. For example, when less effective LiCl or LiBr was employed as an additive in the reaction of 1-hexene, the regioselectivity of the linear/branched products was observed to be 3.7:1 and

Table 3. Hydroesterification of Dienes and Alkynes^a

$ \begin{array}{c} \text{R}^1\text{---}\text{C}=\text{C}\text{---}\text{R}^2 + \text{1} \xrightarrow[\text{solvent, 12 h}]{\text{Ru}_3(\text{CO})_{12} (5 \text{ mol } \%), \text{ additive}} \text{R}^1\text{---}\text{CH}(\text{R}^2)\text{---}\text{CH}_2\text{CO}_2\text{CH}_2\text{Py} \\ \text{(R} = \text{---CO}_2\text{CH}_2\text{Py)} \end{array} $					
entry	substrate	product	temp (°C, solvent)	additive	yield(%) ^b
1			70 (DMF)	—	25
2			70 (DMF)	2	98
3			90 (DMF)	—	<5
4			90 (DMF)	2	99 ^c
5			90 (THF)	—	<5
6			90 (THF)	2	85
7	<i>n</i> -Pr—C≡C— <i>n</i> -Pr		110 (DMSO)	—	20
8	<i>n</i> -Pr—C≡C— <i>n</i> -Pr		110 (DMSO)	2	83
9	<i>n</i> -Pr—C≡C—Me		110 (DMSO)	—	<5
10	<i>n</i> -Pr—C≡C—Me		110 (DMSO)	2	85 (2.7:1) ^d

^a Substrate (1.2 mmol), **1** (0.4 mmol), Ru₃(CO)₁₂ (5 mol %), **2** (15 mol %) in the indicated solvent (0.2 mL). ^b Isolated yield. ^c Two diastereomers were produced almost as an equal mixture. ^d Ratio of two regioisomers **A/B** determined by ¹H NMR of crude mixture.

4.0:1, respectively, which are in a similar range compared to that with the LiI additive (4.0:1). As anticipated, the halide effect was more dramatically exerted with less reactive olefin substrates. For example, while only negligible conversion was observed with cyclohexene or 5-methyl-5-hexen-2-one without additives, excellent yields were obtained in the presence of Bu₄NI (entries 11–14). In addition, hydroesterification of β-pinene and α-methylstyrene took place smoothly only in the presence of the halide additive leading to good to excellent yields of the corresponding esters (entries

15–18). When 3,4-dihydro-2*H*-pyran was employed, tetrahydropyran carboxylates were produced in a satisfactory yield as a mixture of 2- and 3-regioisomer (α-/β-ester, 82:18) only in the presence of **2** at 110 °C (entries 19 and 20). Likewise, the similar promotion effect of **2** was observed in the reaction of 1,2-dihydronaphthalene (entries 21 and 22). Interestingly, 2-carboxylate was generated as a major isomer relative to 1-carboxylate (α-/β-ester, 15:85).

The halide additive effect was next investigated in the Ru-catalyzed hydroesterification of dienes and alkynes with 2-pyridylmethyl formate (**1**). It was found that the reaction of those compounds efficiently proceeded only in the presence of ammonium iodide salt in aprotic polar solvents (Table 3). For example, a regioselective hydroesterification of 4-vinylcyclohexene took place more smoothly by the combined action of Ru₃(CO)₁₂ and Bu₄NI catalyst at 70 °C (entries 1 and 2). The promotion effects were exerted more dramatically on bulkier diolefinic substrates (entries 3–6). When alkynes were examined, a similar additive effect of iodide ion was also observed as demonstrated by entries 7–10.

In summary, we have demonstrated that certain halides induce dramatic enhancement effects in the Ru₃(CO)₁₂-catalyzed hydroesterification of alkenes and alkynes using 2-pyridylmethyl formate, thus enabling the reaction to be carried out under milder conditions with a much broader substrate scope. The promotion effect is mainly attributed to the facile dissociation of CO ligand from the ruthenium-carbonyl precursor catalyst initiated by the added halides. It is anticipated that this study can lead to more diverse synthetic applications using the developed milder procedure as an one-carbon homologation approach.

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Supporting Information Available: General procedures, data, and spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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