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Remarkable Improvement Achieved by Imidazole Derivatives in Ruthenium-Catalyzed Hydroesterification of Alkenes Using Formates

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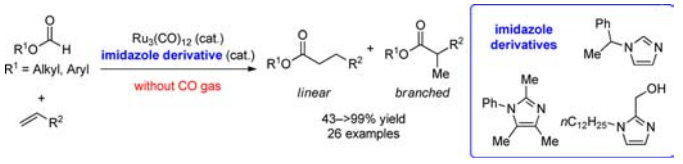
ABSTRACT



Imidazole derivatives are revealed to be effective ligands in the Ru-catalyzed hydroesterification of alkenes using formates, affording one-carbon-elongated esters in high yields. Further, intramolecular hydroesterification was successfully performed to give lactones for the first time. Imidazole derivatives can contribute to promote the reaction as well as to suppress the undesired decarbonylation of formate. Toxic CO gas, a directing group, and large excess alkenes are not required.

Catalytic hydroesterification of alkenes is an important process in synthetic organic chemistry, and hence, considerable efforts are devoted toward enhancing the efficiency of this process.[1] Transition-metal-catalyzed Reppe carbonylation of alkenes by CO gas and alcohols has been commercially used to produce esters with high synthetic versatility.[2] However, the toxicity of CO gas makes handling difficult. Therefore, there is significant interest in the development of alternative processes that do not require CO.[3] Over the past few decades, hydroesterification of alkenes with alkyl or aryl formates has been identified to be a popular one-step route to esters with one-carbon elongation.[4] Formates are considered inexpensive C1 building blocks.[5] They are less toxic and can be handled much more easily than CO. Moreover, the hydroesterification reaction proceeds with complete atom economy.[6]

Previously, hydroesterification with formates was restricted to a few special substrates such as ethylene and

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(2) Kiss, G. *Chem. Rev.* **2001**, *101*, 3435–3456.

(3) (a) Morimoto, T.; Kakiuchi, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 5580–5588. (b) Keim, W. *Pure Appl. Chem.* **1986**, *58*, 825–832.

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(5) For use of methyl formate, see review: (a) Jenner, G. *Appl. Catal., A* **1995**, *121*, 25–44. For a recent example, see: (b) Lee, H. W.; Chan, A. S. C.; Kwong, F. Y. *Chem. Commun.* **2007**, 2633–2635.

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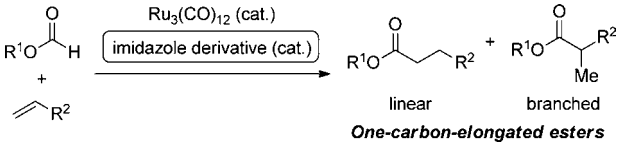
methyl formate.[4a,c] Moreover, high reaction temperatures that exceeded the boiling points of the solvents and the substrates were required, which mandated the use of pressure-resistant apparatus.[4c,j] Further, undesirable side reactions such as decarbonylation of the formates to alcohols resulted in serious complications.[7] In some cases, high-pressure CO gas had to be reluctantly used to suppress the decarbonylation pathway.[8] Recently, significant improvements were reported in the hydroesterification reactions by using either 2-pyridylmethyl formate as a chelating substrate in the presence of Ru catalysts[9] or phenyl formate in the presence of Pd catalysts.[10] However, the limitations of formates have persisted and need to be addressed more effectively. Furthermore, the alkenes or formates must be used in large excess (3−4 equiv) to achieve high yields.

In the course of our investigation of practical methodologies for the synthesis of biologically active compounds, we hypothesized that the use of an appropriate ligand that forms a catalytically active metal complex similar to that formed by Ru and a chelating substrate would aid in efficient hydroesterification with a wider range of substrates. Extensive investigations showed that imidazole derivatives not only accelerate these reactions but also suppress undesired decarbonylation pathways, thereby significantly improving the reaction efficiency. In this paper, we report a general catalytic hydroesterification of alkenes with various alkyl and aryl formates remarkably improved by a novel Ru−imidazole system (Scheme 1). Since the addition of an imidazole derivative could expel the use of either directing groups or any external CO that was previously essential, the reaction is expected to be more economical and practical than those reported previously.

On the basis of the reported hydroesterification using 2-pyridylmethyl formate,[9,11] we hypothesized that a Lewis basic moiety can act as a ligand to alter the catalytic activity. Further, we screened ligands that would coordinate to the metal. $Ru_3(CO)_{12}$-catalyzed hydroesterification of 4-methoxystyrene (**2a**) with benzyl formate (**1a**) in the presence of a catalytic amount of 2-pyridylmethanol (**3a**) as the ligand afforded the desired ester products, linear **4aa** and branched **4ab**, in moderate yields. Benzyl alcohol was observed, which was derived as a byproduct from the decarbonylation of **1a** (Table 1, entry 1). The significance

Scheme 1. Hydroesterification Catalyzed by Ru−Imidazole



of the ligand **3a** was confirmed by a control experiment. No reaction occurred when the reaction was conducted without **3a** (entry 2).

Further, we screened various ligands (Table 1). PPh_3 and 1,2-bis(diphenylphosphino)ethane (DPPE) resulted in significant decarbonylation of **1a**, which was consistent with a precedent literature[12] noting the decarbonylation of formate in the presence of phosphines (entries 3 and 4). *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine (TMEDA) also led to decarbonylation of **1a**, affording no product at all (entry 5). Several nitrogen heterocycles such as pyridine, pyrazole, oxazole, and imidazole were tested. While most of them gave the desired ester in 30−40% yield, a promising result was obtained with imidazole **3d**, with yields up to 55% (entries 6−9). This result prompted us to investigate imidazole derivatives in detail. While other *N*-alkyl imidazoles **3e** were only moderately effective (entry 10), the highly substituted imidazole **3h** and 2-hydroxymethyl imidazole **3i** gave better results (entries 11 and 12, respectively). The length of the carbon chain attached to the hydroxy group seemed to influence the reaction (entries 12 and 13). Further, substitution by a long-chain alkyl group at the N1 position of the imidazole ring contributed to an improvement in the yield (entry 14). However, methyl ether substitution at the C2 position resulted in slightly reduced yield (entry 15). It is worth mentioning that the regioselectivity of the product was reversed only when 2-hydroxymethyl imidazoles **3g** and **3i** were used (entries 12 and 14). Furthermore, through the analysis of catalysts, solvents, and the equivalence of reagents (see Supporting Information for details), we established that the best yield was obtained when using **3i** and a slight excess of **2a** under neat conditions (entry 16). Importantly, complete suppression of decarbonylation was also observed in this case. Thus, we discovered efficient conditions for the Ru-catalyzed hydroesterification of alkenes using formate; *an imidazole ligand could contribute to promote the reaction as well as to suppress undesired decarbonylation of a formate*. A thorough understanding of the reaction mechanism requires further examination. While we assume that the imidazole would facilitate ligand exchange with CO to generate catalytically active triruthenium species, we cannot exclude the possibility that a monomeric Ru species forms in the presence of the ligand.

Having identified the optimal conditions, we investigated the substrate scope of the hydroesterification and found that the reaction was applicable to a wide range of

(7) Both decarbonylation and decarboxylation of alkyl formates have been reported: (a) Kondo, T.; Tantayanon, S.; Tsuji, Y.; Watanabe, Y. *Tetrahedron Lett*. **1989**, *30*, 4137–4140. (b) Jenner, G.; Nahmed, E. M.; Leismann, H. *Tetrahedron Lett*. **1989**, *30*, 6501–6502. (c) Vega, F. R.; Clément, J.-C.; des Abbayes, H. *Tetrahedron Lett*. **1993**, *34*, 8117–8118.

(8) (a) Mlekuz, M.; Joo, F.; Alper, H. *Organometallics* **1987**, *7*, 1591–1593. (b) Kondo, T.; Yoshii, S.; Tsuji, Y.; Watanabe, Y. *J. Mol. Catal.* **1989**, *50*, 31–38. (c) Lin, I. J. B.; Alper, H. *J. Chem. Soc., Chem. Commun.* **1989**, 248–249. (d) Suzuki, Y.; Katoh, H.; Ishii, Y.; Hidai, M. *J. Mol. Catal. A* **1995**, *95*, 129–133.

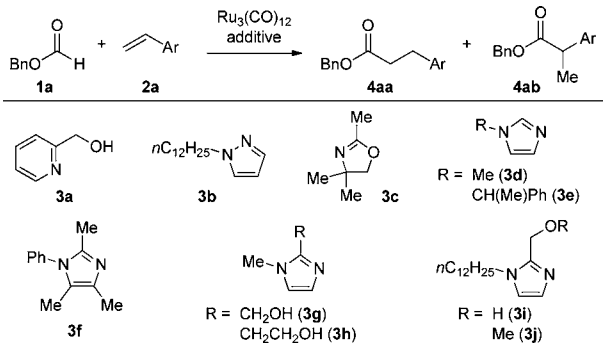
(9) (a) Ko, S.; Na, Y.; Chang, S. *J. Am. Chem. Soc*. **2002**, *124*, 750–751. (b) Na, Y.; Ko, S.; Hwang, L. K.; Chang, S. *Tetrahedron Lett*. **2003**, *44*, 4475–4478.

(10) Katafuchi, Y.; Fujihara, T.; Iwai, T.; Terao, J.; Tsuji, Y. *Adv. Synth. Catal*. **2011**, *353*, 475–482.

(11) Wang, L.; Floreancig, P. E. *Org. Lett*. **2004**, *6*, 4207–4210.

(12) Jenner, G.; Nahmed, E. M.; Leismann, H. *J. Organomet. Chem*. **1990**, *387*, 315–321.

Table 1. Screening of Ligands[a]



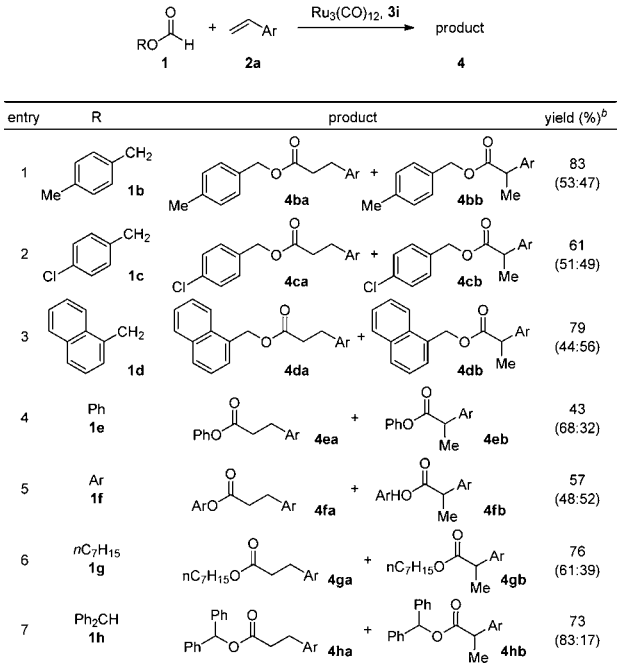
entry	ligand	yield of **4** (%)[b]	**4aa:4ab**[c]	yield of BnOH (%)[d]
1	**3a**	43	73:27	7
2	–	0	–	30
3	PPh_3	22	66:34	88
4	DPPE	0	–	150
5	TMEDA	trace	–	104
6	pyridine	35	75:25	48
7	**3b**	32	76:24	36
8	**3c**	30	69:31	74
9	**3d**	55	68:32	57
10	**3e**	61	69:31	5
11	**3f**	72	72:28	42
12	**3g**	68	35:65	6
13	**3h**	34	78:22	43
14	**3i**	80	38:62	40
15	**3j**	56	76:24	14
16[e]	**3i**	89[f]	54:46	<1

[a] Reactions run with **1a** (1.5 equiv), **2a** (1.0 equiv), $Ru_3(CO)_{12}$ (5 mol %), and ligand (15 mol %) in mesitylene (2.0 M) at 135 °C for 24 h. Ar = 4-methoxyphenyl. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of the isolated mixture of **4aa** and **4ab**. [d] Determined by crude ^{1}H NMR analysis, based on **1a**. [e] **1a** (1.0 equiv) and **2a** (1.5 equiv) were used under neat conditions. [f] Based on **1a**.

formates, including various benzyl, naphthylmethyl, and aryl formates (**1b**–**1f**) (Table 2, entries 1–5). Formates bearing an alkyl group (**1g**) or a sterically bulky benzhydryl group (**1h**) were also well tolerated to afford the desired esters (entries 6 and 7). The wide applicability of formates in our Ru–imidazole system appeared to be highly contrastive to the previous reports that limited usage to only special formates, indicating that a catalytic Ru–**3i** system was unambiguously more versatile for the hydroesterification.

We then investigated the substrate scope of the hydroesterification using a variety of alkenes (Table 3). Styrene **2b** was converted to the desired product in quantitative yield (entry 1). Alkyl-substituted terminal alkene **2c**, geminally disubstituted alkene **2d**, and cyclic alkenes **2e** and **2f** were all found to be suited for the reaction (entries 2–5). In the case of **2d**, only a linear product was obtained, suggesting that steric interaction played an important role in determining the regioselectivity (entry 3). Further, the reaction with β-methylstyrene **2g** yielded three products,

Table 2. Scope of Formates[a]



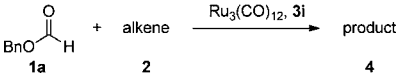
[a] Reactions run with **1** (1.0 equiv), **2a** (1.5 equiv), $Ru_3(CO)_{12}$ (5 mol %), and **3i** (15 mol %) under neat conditions at 135 °C for 24 h. Ar = 4-methoxyphenyl. [b] Isolated yield. The ratio of isomers, determined by ^{1}H NMR analysis of the isolated mixture of products, is shown in parentheses.

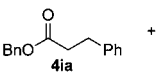
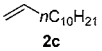
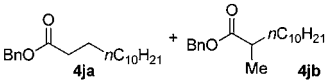
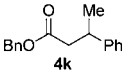
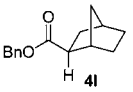
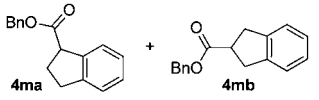
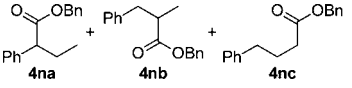
of which **4nc** seemed to be attributed to C=C bond isomerization[13] to form allylbenzene and following hydroesterification (entry 6).

Furthermore, the potential of intramolecular hydroesterification for the direct synthesis of lactones was investigated. Intramolecular hydroesterification with substrates bearing both alkenyl and formyl groups revealed that this is an efficient method to synthesize various lactones in high yields (Table 4). Again, the importance of imidazole derivatives was confirmed, since no product formation was observed when imidazole **3e** was omitted (entry 1). Unlike in the case of the intermolecular version, the use of mesitylene as the solvent and **3e** or **3f** as the ligand contributed to an improvement in the product yield. Terminal alkenes, geminally disubstituted alkenes, and sterically congested trisubstituted alkenes were shown to react intramolecularly with the formyl group. Interestingly, the same products were obtained from different substrates because isomerization of the alkene preceded the hydroesterification under the present reaction conditions (entries 7 and 8). Moreover, spirocycles could be accessed from cyclic alkenes (entries 13 and 14). Thus, these results in Table 4 reveal that our catalytic Ru–imidazole hydroesterification system can be efficiently applied to the direct

(13) (a) Dallmann, K.; Buffon, R. *J. Mol. Catal. A* **2001**, *172*, 81–87. (b) Ammar, H. B.; Nôtre, J. L.; Salem, M.; Kaddachi, M. T.; Toupet, L.; Renaud, J.-L.; Bruneau, C.; Dixneuf, P. H. *Eur. J. Inorg. Chem.* **2003**, 4055–4064.

Table 3. Scope of Alkenes[a]



entry	alkene	product	yield (%)[b]
1	 **2b**	 **4ia** + **4ib**	>99 (55:45)
2	 **2c**	 **4ja** + **4jb**	75 (76:24)
3	 **2d**	 **4k**	50
4	 **2e**	 **4l**	83
5	 **2f**	 **4ma** + **4mb**	88 (76:24)
6	 **2g**	 **4na** + **4nb** + **4nc**	69 (51:20:29)

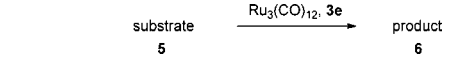
[a] Reactions run with **1a** (1.0 equiv), **2** (1.5 equiv), $Ru_3(CO)_{12}$ (5 mol %), and **3i** (15 mol %) under neat conditions at 135 °C for 24 h. [b] Isolated yield. The ratio of isomers, determined by ^1H NMR analysis of the isolated mixture of products, is shown in parentheses.

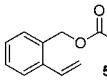
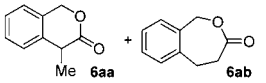
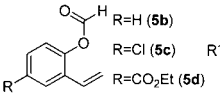
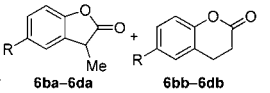
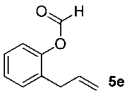
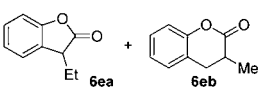
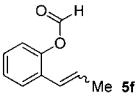
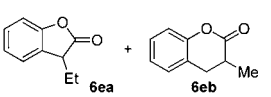
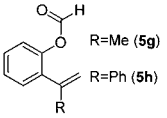
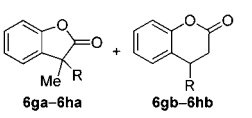
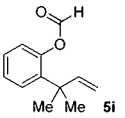
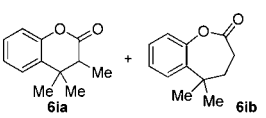
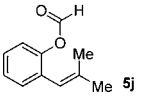
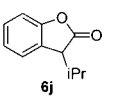
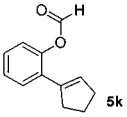
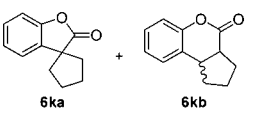
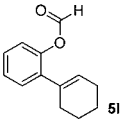
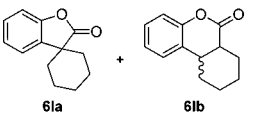
synthesis of structurally diverted lactones. It is noted that these are the first examples of the intramolecular hydroesterification to afford lactones.[14]

In conclusion, imidazole derivatives were discovered to drastically improve the efficiency of the Ru-catalyzed hydroesterification of alkenes with formates. The $Ru_3(CO)_{12}$–**3i** system is the best catalyst for intermolecular reactions, while $Ru_3(CO)_{12}$–**3e** or $Ru_3(CO)_{12}$–**3f** would be suitable for intramolecular reactions. The reaction can be adapted to include a variety of alkenes and formates, which indicates the first achievement of wide substrate generality. Moreover, imidazoles contribute to make the reaction proceed without the use of a directing group, toxic CO gas, or a large excess alkene. As such, the reaction system is safer and more economical than those reported previously. Importantly, the present catalytic system has been applied for the first time and very efficintly to the synthesis of lactones. Investigation of the reaction mechanism, the application of this reaction for the synthesis of biologically active compounds, and development of novel synthetic reactions concerning catalytic Ru–imidazole will be undertaken in due course.

(14) Floreancig et al. reported lactone formation via intermolecular hydroesterification, followed by intramolecular attack of the hydroxy group to the ester carbonyl. See ref 11.

Table 4. Intramolecular Hydroesterification[a]



entry	substrate	product	yield (%)[b]
1[c]	 **5a**	 **6aa** + **6ab**	0
2[d]			56 (91:9)
3			75 (90:10)
4	 R=H (**5b**)	 **6ba–6da** + **6bb–6db**	82 (86:14)
5	R=Cl (**5c**)		79 (84:16)
6	R=CO_2Et (**5d**)		72 (82:18)
7	 **5e**	 **6ea** + **6eb**	>99 (90:10)
8	 **5f**	 **6ea** + **6eb**	94 (87:13)
9[e]	 R=Me (**5g**)	 **6ga–6ha** + **6gb–6hb**	86 (32:68)
10[e]	R=Ph (**5h**)		87 (82:18)
11	 **5i**	 **6ia** + **6ib**	92 (90:10)
12	 **5j**	 **6j**	99
13[e]	 **5k**	 **6ka** + **6kb**	75 (63:37) [60:40][f]
14	 **5l**	 **6la** + **6lb**	>99 (72:28) [81:19][f]

[a] Reaction run with **5**, $Ru_3(CO)_{12}$ (5 mol %), and **3e** (15 mol %) in mesitylene (1.0–2.0 M) at 135 °C for 12–24 h. [b] Isolated yield. The ratio of isomers, determined by ^1H NMR analysis of the isolated mixture of products, is shown in parentheses. [c] **3e** was not used. [d] **3i** (15 mol %) was used instead of **3e**. [e] **3f** (15 mol %) was used instead of **3e**. [f] Ratio of diastereomers (shown in brackets) determined by ^{13}C NMR analysis of the isolated mixture of diastereomers. Relative configuration was not determined.

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Supporting Information Available. Experimental procedures, copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.