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Imidazole Derivatives as Accelerators for Ruthenium-Catalyzed Hydroesterification and Hydrocarbamoylation of Alkenes: Extensive Ligand Screening and Mechanistic Study

Hideyuki Konishi,[a] Takashi Muto,[a] Tsuyoshi Ueda,[a, b] Yayoi Yamada,[a] Miyuki Yamaguchi,[a] and Kei Manabe*[a]

Imidazole derivatives are effective ligands for promoting the $[Ru_3(CO)_{12}]$-catalyzed hydroesterification of alkenes using formates. Extensive ligand screening was performed to identify 2-hydroxymethylated imidazole as the optimal ligand. Neither carbon monoxide gas nor a directing group was required, and the reaction also showed a wide substrate generality. The Ru–imidazole catalyst system also promoted intramolecular hydrocarbamoylation to afford lactams. A Ru–imidazole complex was unambiguously analyzed by X-ray crystallography, and it had a trinuclear structure derived from one $[Ru_3(CO)_{12}]$ and two ligands. This complex was also successfully used for hydroesterification. The mechanism was examined in detail by using D- and ^{13}C-labeled formates, indicating that the hydroesterification reaction proceeds by a decarbonylation–recarbonylation pathway.

Introduction

Esters are simple functional groups ubiquitously found in both natural and synthesized compounds. As nature uses enzymes to synthesize esters, chemists can use acid catalysts or condensation reagents to obtain esters from the corresponding carboxylic acids and alcohols.[1] New synthetic methods for inserting ester groups at the desired position in a target molecule are needed. Alkenes, an important class of compounds, are substrates for metal-catalyzed alkoxycarbonylation using carbon monoxide (CO) and alcohols to synthesize esters.[2] Since its discovery by Reppe,[3] this method has been tremendously improved, enabling the synthesis of esters from alkenes on an industrial scale. Later, metal-catalyzed hydroesterification of alkenes using formates was developed.[4–8] This modification of Reppe's method allows the direct construction of esters without using the toxic CO gas.[9] This method utilizes the preexisting ester group of formate instead of CO and an alcohol to afford esters that are one-carbon-homologated products of the original alkene. This method is especially useful if the product is difficult to synthesize from a carboxylic acid and an alcohol because of, for example, acid lability or safety and preparation cost. Alkenes are readily available through various functional group manipulations, and formate esters are inexpensive, less toxic, and stable compounds. Several formate esters are commercially available with an acceptable cost. Moreover, catalytic hydroesterification is atom economical[10] and matches the current trend to reduce waste production in synthetic protocols.

Pioneering work on metal-catalyzed hydroesterification using formates was reported by Sneeden et al. in 1983.[4] However, this reaction was not practical because of the harsh conditions employed and the use of methyl formate as a solvent. Strict limitation of the substrate scope was also a major issue, because only methyl formate and ethylene could be applied. Although scattered examples[5] have appeared since the original report, a general method for metal-catalyzed hydroesterification was not published until 2002. Chang et al. demonstrated that formate substituted with a 2-pyridylmethyl group was effective for the Ru-catalyzed hydroesterification of alkenes.[6] This method was broadly applicable to alkenes; however, the formate scope was limited to 2-pyridylmethyl formate. Recently, a Pd-catalyst was reported to be effective for hydroesterification, but the formate scope was rather limited.[7] Although hydroesterification with formates is an attractive method to synthesize esters, development of a general method for both alkenes and formates remains challenging.

In the process of developing practical synthetic reactions for biologically active compounds, we recognized the potential of catalytic hydroesterification. Despite its lack of generality, sys-

[a] Dr. H. Konishi, T. Muto, Dr. T. Ueda, Y. Yamada, Dr. M. Yamaguchi, Prof. Dr. K. Manabe
School of Pharmaceutical Sciences
University of Shizuoka
52-1 Yada, Suruga-ku, Shizuoka 422-8526 (Japan)
Fax: (+81)54-264-5586
E-mail: manabe@u-shizuoka-ken.ac.jp

[b] Dr. T. Ueda
Process Technology Research Laboratories
Pharmaceutical Technology Division
Daiichi Sankyo Co. Ltd.
1-12-1 Shinomiya
Hiratsuka, Kanagawa 254-0014 (Japan)

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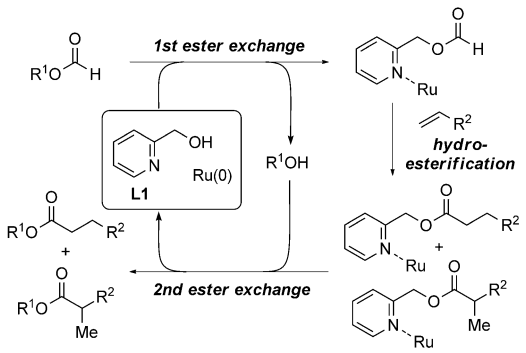
tematic screening of additives led us to the development of highly effective imidazole derivatives for the reaction. Herein, we report the development of a Ru-catalyzed hydroesterification of alkenes using formates by adding imidazole derivatives as accelerators.[8] The reaction has a wide substrate generality in both alkenes and formates. Further application of these findings led to the development of a Ru-catalyzed hydrocarbamoylation of alkenes using formamides. Furthermore, mechanistic studies for the catalytic hydroesterification reaction imply that the reaction involves both decarbonylation and recarbonylation pathways.

Results and Discussion

Effect of ligands in Ru-catalyzed hydroesterification

Our investigations began by considering the intermediate of Chang's Ru-catalyzed hydroesterification using 2-pyridylmethyl formate.[6] The stability of this intermediate, generated after oxidative addition of the formyl C–H bond to Ru metal, presumably results from the coordination of the pendant pyridine nitrogen of the formate to Ru. At this point, we hypothesized that an alcohol exchange of a simple formate with 2-pyridylmethanol (**L1**)[11] would form 2-pyridylmethyl formate (Scheme 1), which was known as the active substrate for

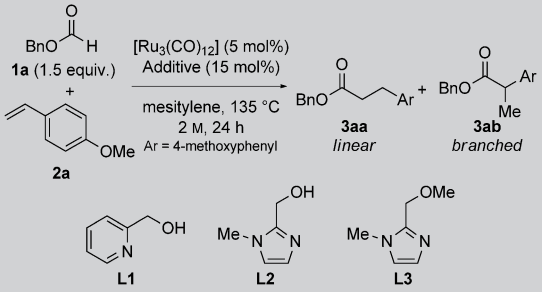


Scheme 1. Initial working hypothesis for Ru-catalyzed hydroesterification.

Chang's hydroesterification. After the hydroesterification step, a second alcohol exchange with the alcohol generated from the first ester exchange would give the desired product and regenerate **L1**. This reaction should require only a catalytic amount of **L1** and utilize, in principle, any formate ester if the exchange occurs. Based on this working hypothesis, we investigated the effects of catalytic amounts of additives such as **L1** for the Ru-catalyzed hydroesterification reaction.

Then, we briefly tested the capability of **L1** and similar compounds as catalytic promoters using $[Ru_3(CO)_{12}]$ as the catalyst for the hydroesterification of 4-methoxystyrene (**2a**) with benzyl formate (**1a**) in mesitylene (Table 1). Without additive, the reaction did not proceed at all (Table 1, entry 1). However, a catalytic amount of **L1** indeed afforded the desired product as a mixture of the linear and branched isomers (entry 2). Furthermore, imidazole **L2** bearing a hydroxymethyl moiety was more effective (entry 3).[12] Surprisingly, imidazole **L3**, which lacked a hydroxy group, also afforded the product (entry 4). These results indicate that an ester exchange is not necessary for the reaction. These additives might function as ligands to form an active Ru complex.

Table 1. Catalytic use of additives for hydroesterification.



Entry	Additive	Yield [%][a]	3aa:3ab[b]
1	–	0	–
2	**L1**	43	73:27
3	**L2**	68	35:65
4	**L3**	47	75:25

[a] Combined isolated yields of **3aa** and **3ab**. [b] Determined by ^{1}H NMR spectroscopy.

These initial studies led us to investigate the effect of ligands in greater detail. We screened various ligands shown in Figure 1 for the hydroesterification. The ligands are categorized into four classes: imidazoles with alkyl and aryl groups, imidazoles with a hydroxy group, imidazoles with functional groups, and other ligands.

The results of the screening are shown in Figure 2. Imidazoles with alkyl and aryl groups (**L4**–**L18**) generally afforded the desired product in moderate yields, except for N-unsubstituted imidazole **L4**. For imidazoles with a hydroxy group (**L2**, **L19**–**L30**), the yields largely depended on the ligand structures. Among them, **L21** gave the best combined yield (80% yield). Uses of imidazoles with functional groups (**L3**, **L31**–**L37**) and other ligands (**L1**, **L38**–**L56**) resulted in poor to modest yields that did not exceed 60%. In the case of **L53**–**L55**, significant amounts of benzyl alcohol were generated as a byproduct (59–100% based on **1a**).[13]

In most cases of the ligand screening, linear isomer **3aa** was preferentially obtained over branched isomer **3ab**. However, interesting reversal of regioselectivity was observed for N-substituted, hydroxymethylated imidazoles **L2**, **L20**, and **L21**, and **3ab** was obtained as the major isomer. Increasing the steric bulk at the hydroxymethyl carbon (**L22**–**L26**) or introduction of substituents at C4 and C5 positions (**L28**, **L29**) resulted in higher linear selectivity. Although the reason for the change in regioselectivity is unclear, these results suggest that the regioselectivity of the catalytic hydroesterification reaction can be controlled by the choice of ligand.

We optimized the reaction conditions using the best ligand (**L21**), and finally found that the reaction using a slight excess

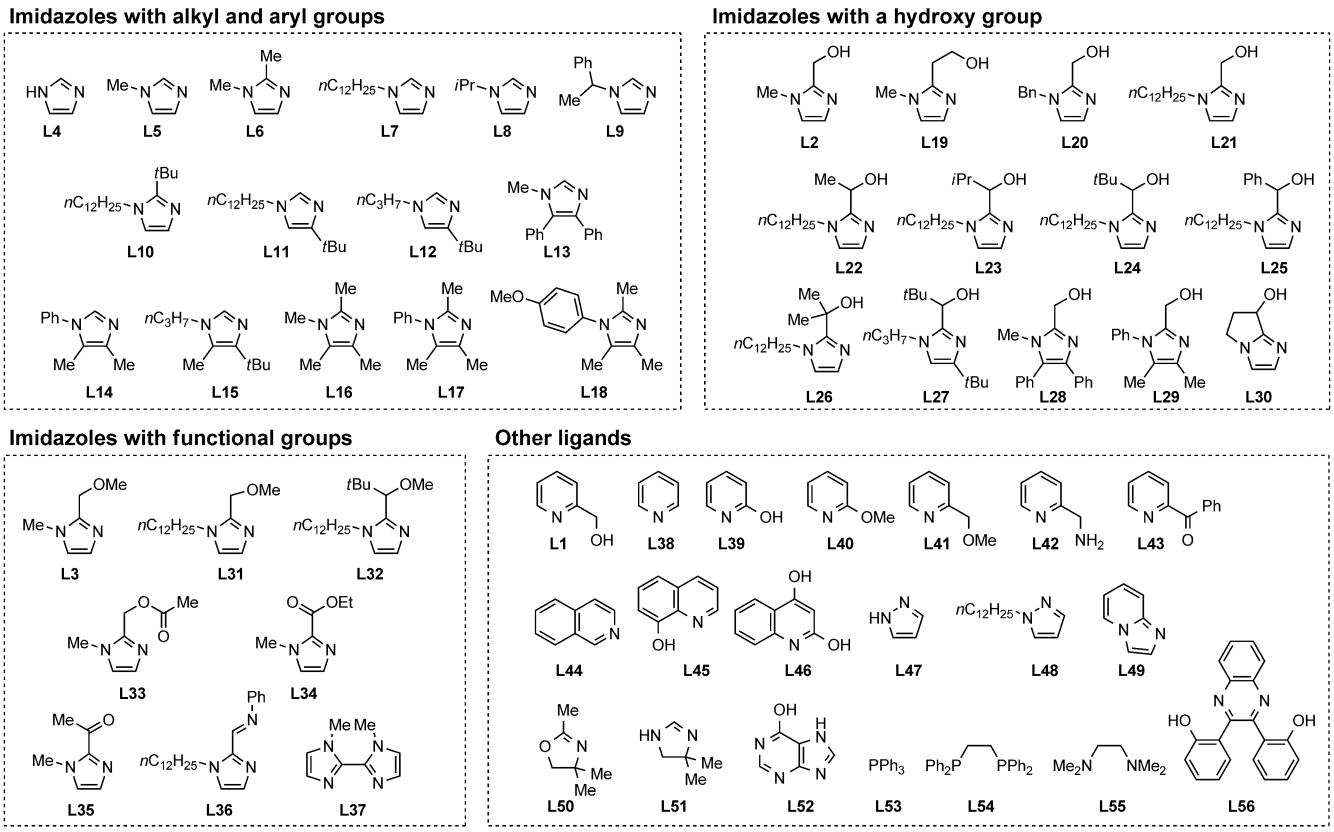


Figure 1. Ligands screened for hydroesterification.

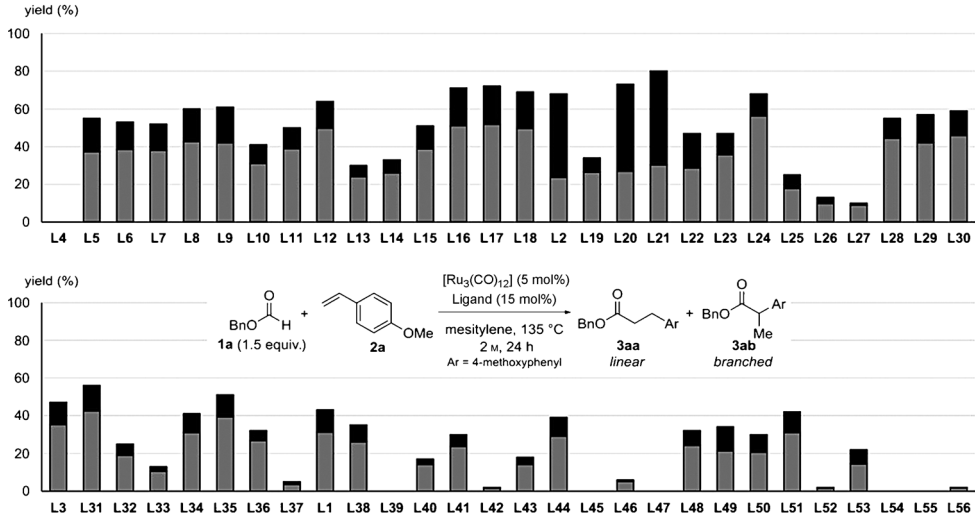
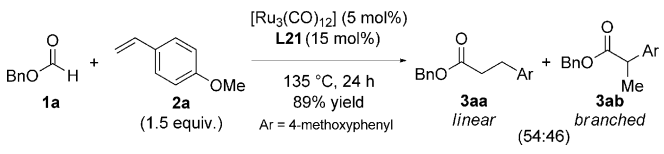


Figure 2. Screening of ligands for hydroesterification of **2a** with **1a**. *y* axis: combined isolated yield of **3aa** and **3ab**. Gray: yield of **3aa**. Black: yield of **3ab**.



Scheme 2. Hydroesterification using **L21** under solvent-free conditions.

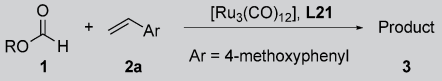
of alkene **2a** under solvent-free conditions afforded the desired product in 89% yield (Scheme 2). Interestingly, formation of the linear isomer was slightly preferred.

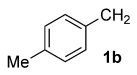
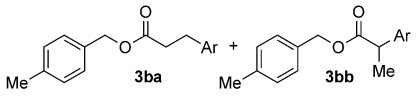
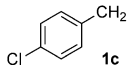
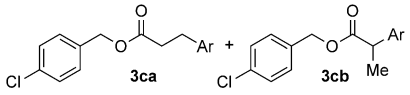
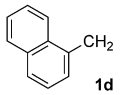
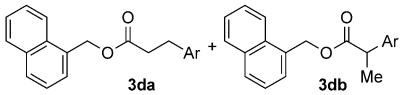
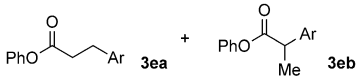
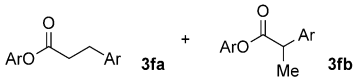
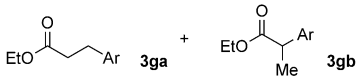
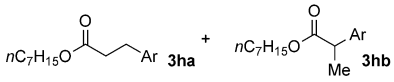
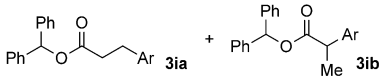
Substrate scope for hydroesterification

An extensive study of the ligand effects for the Ru-catalyzed hydroesterification of alkenes using formates revealed that **L21** was optimal in terms of the desired product yield. Therefore, **L21** was used to investigate the substrate scope of the reaction.

First, the substrate scope of formates was investigated (Table 2). Benzyl formates with substitution on the benzene ring afforded products in moderate to high yield (Table 2, entries 1 and 2). 1-Naphthylmethyl formate (**1d**) gave the product in high yields (entry 3). Aryl formates afforded lower yields, and the formation of phenols was observed (entries 4 and 5). An excess of ethyl formate (**1g**) and a higher temperature were required to obtain the ethyl ester

Table 2. Substrate scope of formates.[a]



Entry	R	Product	Yield [%][b]
1	 **1b**	 **3ba** + **3bb**	83 (53:47)
2	 **1c**	 **3ca** + **3cb**	61 (51:49)
3	 **1d**	 **3da** + **3db**	79 (44:56)
4	Ph **1e**	 **3ea** + **3eb**	43 (68:32)
5	Ar[c] **1f**	 **3fa** + **3fb**	57 (48:52)
6[d]	Et **1g**	 **3ga** + **3gb**	48 (51:49)
7	nC_7H_{15} **1h**	 **3ha** + **3hb**	76 (61:39)
8	Ph_2CH **1i**	 **3ia** + **3ib**	73 (83:17)
9	H		0

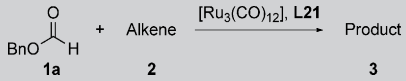
[a] Reactions were conducted with **1** (0.40 mmol), **2a** (1.5 equiv.), $[Ru_3(CO)_{12}]$ (5 mol%), and **L21** (15 mol%) under solvent-free conditions at 135 °C for 24 h. [b] Combined isolated yields of the linear and branched isomers. The ratio of isomers (determined by ^{1}H NMR spectroscopy) is shown in parentheses. [c] Ar = 4-methoxyphenyl. [d] The reaction was conducted on a 1.0 mmol scale at 155 °C. 3.0 equiv. of **1g** were used.

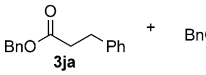
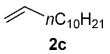
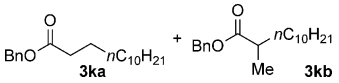
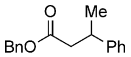
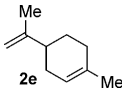
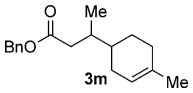
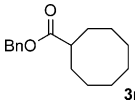
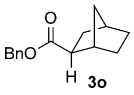
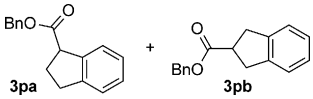
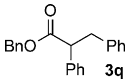
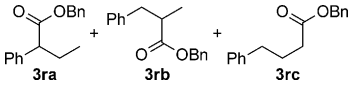
product (entry 6). Also, formates with a long alkyl chain **1h** or a bulky benzhydryl group **1i** were applicable in this reaction (entries 7 and 8). These results clearly indicate that hydroesterifications using a Ru–imidazole catalyst have a wide substrate generality for formates. The use of formic acid instead of formates did not give the desired carboxylic acid at all (entry 9).

Next, the alkene scope was examined (Table 3). Monosubstituted terminal alkenes were good substrates for the reaction (Table 3, entries 1 and 2). Geminally disubstituted alkene **2d** afforded a single regioisomer in moderate yield (entry 3). The reactivity and regioselectivity were affected by steric hindrance, as observed in the reaction of limonene (**2e**), which afforded the least sterically hindered isomer (entry 4). The reactivity of cyclic alkenes depended on their structure. Although cyclooctene (**2f**) afforded the desired product in moderate conversion, both norbornene (**2g**) and indene (**2h**) gave the corresponding products in high yields (entries 5–7). An acyclic internal alkene, *trans*-stilbene (**2i**), required a higher temperature to form the product, probably because of the steric hindrance. On the other hand, β-methylstyrene (**2j**) reacted at 135 °C, but gave three products (entry 9). This was ascribed to alkene isomerization by the Ru catalyst[14] to form allylbenzene (**2k**) followed by hydroesterification of both **2j** and **2k**. The same products were obtained for the reaction of **2k** because it could also isomerize to the thermodynamically more stable **2j** (entry 10). This result is consistent with a report by Carreira et al., who recently demonstrated the tandem Ru-catalyzed isomerization and hydroesterification of alkenes using allylamines as substrates.[15] Overall, both reactivity and regioselectivity in the Ru-catalyzed hydroesterification were strongly influenced by the steric environment of alkenes, with aromatic alkenes being slightly more reactive than the aliphatic ones. Nevertheless, enhancement of the catalytic ability of Ru by the imidazole ligand was prominent.

Hydroesterification catalyzed by a Ru–imidazole catalyst was further applied to intramolecular reactions (Table 4). Catalytic intramolecular hydroesterification may be one of the most efficient methods to obtain lactones, although this process had not been demonstrated until our initial report.[8a,16] Several substrates bearing both formyl and alkenyl groups were readily synthesized and applied to this reaction. As with intermolecular hydroesterification, imidazole ligands were necessary to promote catalytic intramolecular hydroesterification (Table 4, entry 1). Ligand **L9**, which lacks the hydroxymethyl group, produced better results than **L21**, which enabled the formation of six- and seven-membered lactones from benzyl formate derivatives (entries 2 and 3). Phenyl formate derivatives were successfully applied by using **L9**. No electronic effects were observed for different substituents on the benzene ring (entries 4–6). Substrates **4e** and **4f** gave the same products. This result indicates that rapid Ru-catalyzed isomerization of the terminal alkene in **4e** led to more energetically stable internal alkene **4f** prior to hydroesterification (entries 7 and 8). Substrates **4g** and **4h**, both bearing an *exo*-alkene moiety, reacted smoothly, whereas steric effects of substituents adjacent to the

Table 3. Substrate scope of alkenes.[a]



Entry	R	Product	Yield [%][b]
1	 2b	 3ja + 3jb	>99 (55:45)
2	 2c	 3ka + 3kb	75 (76:24)
3	 2d	 3l	50
4[c]	 2e	 3m	39[d]
5	 2f	 3n	46
6	 2g	 3o	83
7	 2h	 3pa + 3pb	88 (76:24)
8[c]	 2i	 3q	24
9	 2j	 3ra + 3rb + 3rc	69 (51:20:29)
10	 2k		66 (39:19:42)

[a] Reactions were conducted with **1a** (0.40 mmol), **2** (1.5 equiv.), $[Ru_3(CO)_{12}]$ (5 mol%), and **L21** (15 mol%) under solvent-free conditions at 135 °C for 24 h. [b] Combined isolated yields of the linear and branched isomers. The ratio of isomers (determined by ^{1}H NMR spectroscopy) is shown in parentheses. [c] The reaction was conducted on a 1.0 mmol scale at 155 °C. [d] Mixture of two diastereomers (58:42).

alkenes were clearly observed in the product distribution (entries 9 and 10). Despite steric hindrance, gem-dimethyl-substituted **4i** and trisubstituted alkene **4j** afforded products in high yields (entries 11 and 12). Finally, the Ru–imidazole catalyst was amenable to the construction of spirocyclic lactones when cyclic alkenes were used (entries 13 and 14). Use of **L17** resulted in a better combined yield of **5ka** and **5kb** (entry 13).

Application to Ru-catalyzed hydrocarbamoylation

Discovery of ligand acceleration in the Ru-catalyzed hydroesterification reaction prompted us to investigate catalytic hydrocarbamoylation reactions of alkenes using formamides. Metal-catalyzed hydrocarbamoylation using formamides is an attractive method for constructing amides from alkenes because of its synthetic utility and atom economy.[17,18]

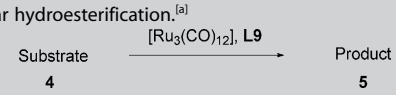
Catalytic hydrocarbamoylation was investigated by using the Ru–imidazole catalyst. Unfortunately, reaction of 4-methoxystyrene with *N*-benzylformamide gave only a trace amount of the desired product. Benzylamine was detected in the crude mixture by ^{1}H NMR analysis, which indicated that only decarbonylation of *N*-benzylformamide occurred. Despite the optimization of the reaction conditions, the hydrocarbamoylated product was obtained in only low yields.

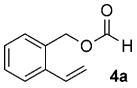
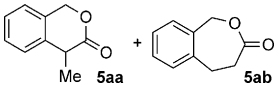
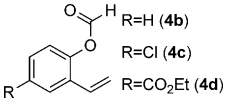
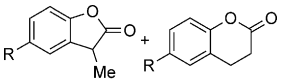
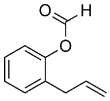
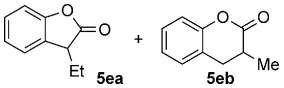
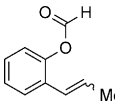
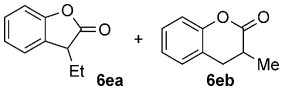
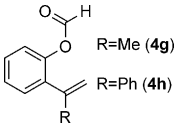
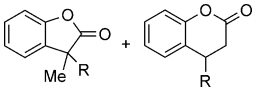
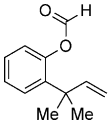
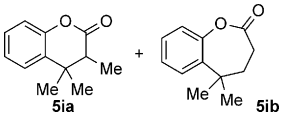
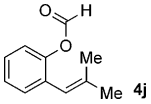
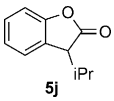
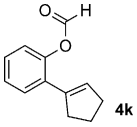
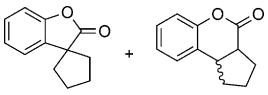
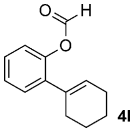
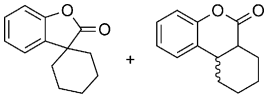
Next, intramolecular hydrocarbamoylation was tested. Catalytic hydrocarbamoylation using $[Ru_3(CO)_{12}]$ and **L21** afforded the desired lactams in high yields (Scheme 3). Compound **6b** predominantly gave the six-membered lactam, but other substrates including N-alkyls favored the formation of the five-membered lactams. Similarly to hydroesterification, these results indicated that the regioselectivity was strongly substrate-dependent. As the starting materials were easily obtained by the formylation of anilines, Ru-catalyzed hydrocarbamoylation is an attractive method to synthesize many oxindole derivatives.

Characterization of the Ru–imidazole complex

The combination of Ru and imidazoles was efficient for the catalytic hydroesterification and hydrocarbamoylation of alkenes using formates and formamides, respectively. The fact that both hydroesterification and hydrocarbamoylation did not proceed without a ligand strongly indicated that the in situ generated Ru-ligand complex was involved in catalytic cycles. We tried to identify and characterize an intermediate Ru complex by mixing $[Ru_3(CO)_{12}]$ and 1–3 equivalents of **L21** in mesitylene at 135 °C for several hours. However, all attempts resulted in the formation of an unidentified oily black mixture, and none of the solid crystallized out of the solution. The long alkyl chain on the N1 in **L21** may have prevented crystallization. Therefore, **L2**, in which the dodecyl group of **L21** was replaced by a methyl group, was used for preparation of the Ru complex. After mixing **L2** with $[Ru_3(CO)_{12}]$ at 135 °C, a brown solid was obtained, which decomposed within 1 day under ambient conditions and could not be fully characterized. When **L20** bearing a benzyl group on the N1 of the imidazole ring was used, yellow needle-like crystals suitable for X-ray crystallographic analysis were obtained. The crystallized complex was unambiguously composed of three Ru atoms and two **L20** li-

Table 4. Catalytic intramolecular hydroesterification.[a]



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

[a] Reactions were conducted with **4** (100 mg), $[Ru_3(CO)_{12}]$ (5 mol%), and **L9** (15 mol%) in mesitylene (1.0–2.0 M) at 135 °C for 12–24 h. [b] Combined isolated yields of two regioisomers. The ratio of isomers (determined by ^{1}H NMR spectroscopy) is shown in parentheses. [c] **L9** was not used. [d] **L21** was used instead of **L9**. [e] **L17** was used instead of **L9**. [f] Ratio of diastereomers (shown in brackets) determined by ^{13}C NMR analysis of the isolated mixture of diastereomers. The relative configuration was not determined.

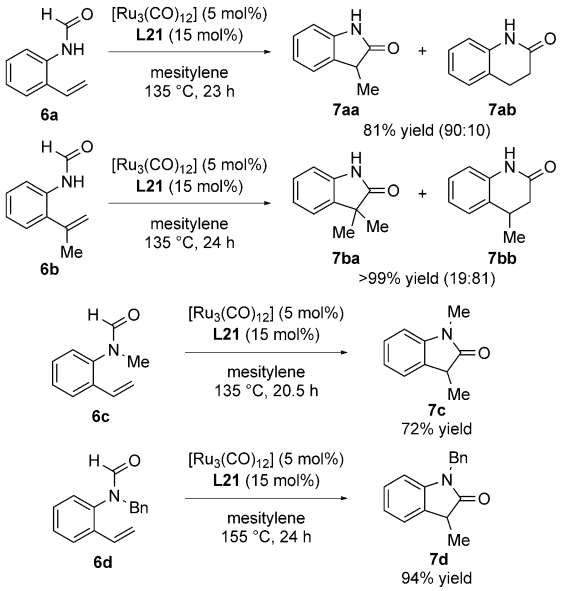
gands (Figure 3), and was similar to the complex previously reported for 2-pyridylmethanol.[19] Each ligand coordinated to a different Ru atom from imidazole N3 and oxygen in a bidentate manner, with oxygen bridging two of the three Ru atoms. Furthermore, ^{1}H NMR analysis of a $CDCl_3$ solution of the crystals revealed that the peak for the CH_2 protons adjacent to the bridging oxygen atom were split into two doublets, supporting the presence of the ring structure. ^{13}C NMR spectroscopy revealed four carbonyl peaks, also supporting a C_2 symmetric structure. Surprisingly, this crystal was stable under ambient conditions for more than 1 year. Although we also tried to obtain crystals composed of Ru and imidazole ligands without the hydroxy group such as **L9**, we did not succeed in obtaining crystals suitable for structural studies.

The ESI–MS spectrum of the Ru–**L20** complex displayed a characteristic peak for $[Ru_3(CO)_6(C_{11}H_{11}N_2O_1)_2+H]^+$, and $C_{11}H_{11}N_2O_1$ seemed to be generated by the loss of one hydrogen atom from **L20** (Figure 4). The isotopic pattern of Ru–**L20** was in good agreement with the calculated one. The same pattern was observed from the reaction mixture of $[Ru_3(CO)_{12}]$ and **L20**, which supported retaining the trinuclear structure in solution.

The Ru–**L20** complex was examined for its catalytic ability in the hydroesterification reaction (Table 5). Combination of $[Ru_3(CO)_{12}]$ (5 mol%) and **L20** (10 mol%) furnished the product in almost the same yield as the addition of 15 mol% of **L20** (Table 5, entries 1 and 2). This decrease in the loading of ligand **L20** resulted in an increase in the linear/branched ratio. The Ru–**L20** complex also promoted the reaction to afford the desired product in slightly lower yields. In addition, the preformed catalyst showed a higher preference for the linear product. This result suggests that the Ru–ligand complex itself or a species derived from it catalyzes the reaction with a linear preference, but its catalytic activity is less than the main catalytic species derived from the in situ formation of $[Ru_3(CO)_{12}]$ and **L20**. At this juncture, it is unclear whether the real catalytic species has a mononuclear[8c] or a trinuclear Ru structure.

Mechanistic studies for catalytic hydroesterification

Although we initially hypothesized the ester exchange mechanism (Scheme 1), we later determined that even imidazoles without a hydroxy group accelerated Ru-catalyzed hydroesterification. Therefore, a mechanism other than the ester exchange



Scheme 3. Catalytic intramolecular hydrocarbamoylation. The ratio of regioisomers (determined by ^{1}H NMR spectroscopy) is shown in parentheses.

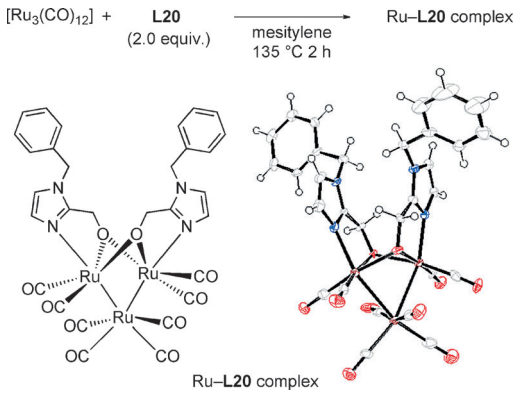


Figure 3. Molecular structure of the Ru–**L20** complex with thermal ellipsoids set at 50% probability.

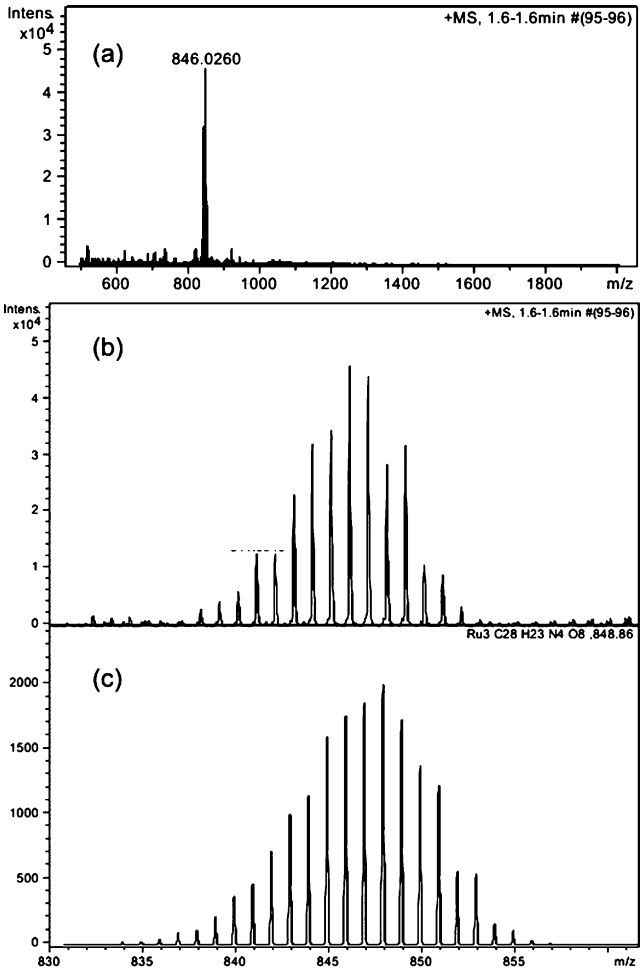
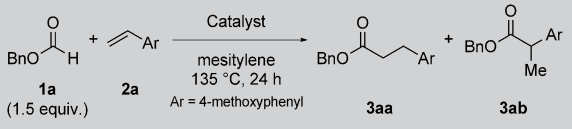


Figure 4. ESI–MS spectra of the Ru–**L20** complex. a) The complete spectrum; b) the magnified region containing peaks of $[Ru_3(CO)_6(C_{11}H_{11}N_2O_1)_2+H]^+$; c) the calculated isotopic pattern of $[Ru_3(CO)_6(C_{11}H_{11}N_2O_1)_2+H]^+$.

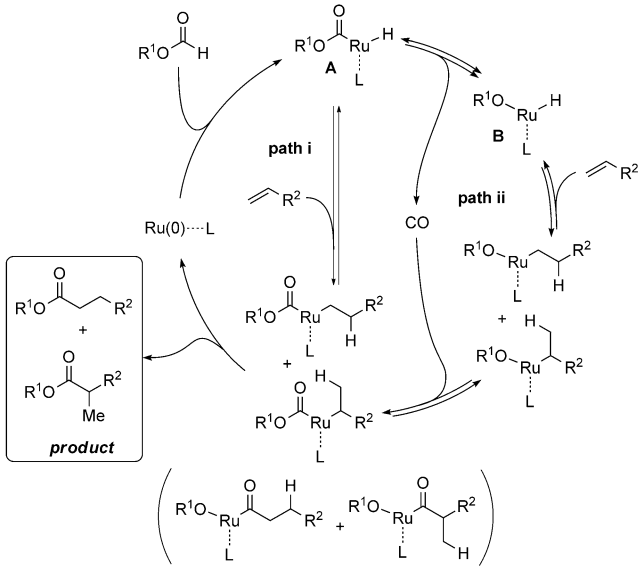
Table 5. Catalytic hydroesterification using Ru–**L20** complex.



Entry	Catalyst [(mol%)]	Yield [%][a]	**3aa**:**3ab**[b]
1	$[Ru_3(CO)_{12}]$ (5) + **L20** (15)	73	37:63
2	$[Ru_3(CO)_{12}]$ (5) + **L20** (10)	72	58:42
3	Ru–**L20** (5)	58	71:29

[a] Combined isolated yields of **3aa** and **3ab**. [b] Determined by ^{1}H NMR spectroscopy.

mechanism must be operative. On the basis of our results and the literature precedent,[6,7a,8c,16a] we propose the mechanism shown in Scheme 4. In this mechanism, the catalytic activity of Ru is enhanced by the imidazole ligands. In path i, ruthenium

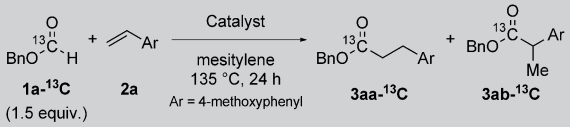


Scheme 4. Proposed reaction mechanism. L = ligand.

hydride **A** undergoes alkene insertion. In path ii, initial decarbonylation of **A** forms ruthenium hydride **B**, which undergoes alkene insertion followed by recarbonylation. Similar decarbonylation–recarbonylation processes were proposed for hydroesterification reactions using formate.[7a,8b,c] Because CO insertion could occur at the metal–O[20] or metal–C bond, reductive elimination finally gives the product.

Experimental differentiation between paths i and ii in Scheme 4 was difficult, but we could confirm the presence of the decarbonylation–recarbonylation pathway through labeling experiments. Benzyl [^{13}C]formate (**1a-^{13}C**) was prepared from [^{13}C]formic acid and used in the hydroesterification reaction to verify ^{13}C incorporation in the product (Table 6). The reaction using **1a-^{13}C** proceeded similarly to the reaction using unlabeled **1a** (Table 6, entries 1 and 2). The ^{13}C incorporation in products **3aa** and **3ab** was approximately 50–60%. Partial incorporation of ^{13}C indicated the existence of an alternative recarbonylation pathway for the incorporation of unlabeled carbonyl groups originating from [$Ru_3(CO)_{12}$]. This result suggests that the labeled formate undergoes initial decarbonylation and the ^{13}CO formed competes with CO from [$Ru_3(CO)_{12}$] in the recarbonylation step. As ^{13}CO from **1a-^{13}C** corresponds to 1.5 equivalents and CO from [$Ru_3(CO)_{12}$] corresponds to 0.60 equivalents, less than a statistical amount of ^{13}C resulted in incorporation (entry 2). Therefore, it can be assumed that ^{13}CO from **1a-^{13}C** did not well accumulate at the beginning of the reaction and thus CO from [$Ru_3(CO)_{12}$] was preferentially incorporated into the products. Conducting the reaction with the isolated Ru–imidazole complex, a theoretical source of 0.40 equivalents of ^{12}C carbonyl groups demonstrated a reasonable increase in ^{13}C incorporation (entry 3). In this case, the regioselectivity was reversed with a strong preference for the linear product.

Table 6. Ru-catalyzed hydroesterification using **1a-^{13}C**.



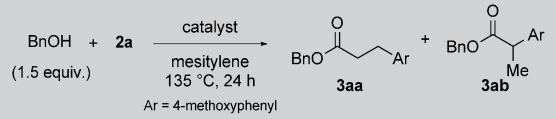
1a-^{13}C (1.5 equiv.) **2a** **3aa-^{13}C** **3ab-^{13}C**

Entry	Catalyst [(mol%)]	Yield [%][a]	**3aa-^{13}C**:**3ab-^{13}C**[b]	^{13}C incorporation [%][c] **3aa-^{13}C**/**3ab-^{13}C**
1[d]	$[Ru_3(CO)_{12}]$ (5) **L20** (15)	80	38:62	–
2	$[Ru_3(CO)_{12}]$ (5) **L20** (15)	72	38:62	53/57
3	Ru-**L20** (5)	56	72:28	61/70

[a] Combined isolated yields of **3aa-^{13}C** to **3ab-^{13}C**. [b] Determined by ^{1}H NMR spectroscopy. [c] Calculated by ^{13}C NMR spectroscopy. [d] **1a** (not ^{13}C-labeled) was used instead of **1a-^{13}C**.

The decarbonylation–recarbonylation pathway was further confirmed by the reaction using benzyl alcohol instead of benzyl formate (Table 7). This reaction afforded the desired product in 34% yield using 10 mol% of $[Ru_3(CO)_{12}]$, i.e., 1.2 equivalents of the CO source (Table 7, entry 1). If the reaction was conducted using 10 mol% of the Ru–**L20** complex (0.80 equiv. of CO source), the product was obtained in 24% yield. This decrease in yield was reasonable for the reduction in the total amount of CO source (entry 2). These results clearly indicate the presence of decarbonylation and recarbonylation steps in the catalytic cycle.

Table 7. Ru-catalyzed hydroesterification using BnOH.

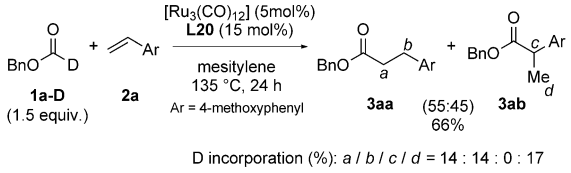


3aa **3ab**

Entry	Catalyst [(mol%)]	Yield [%][a]	**3aa**:**3ab**[b]
1	$[Ru_3(CO)_{12}]$ (10) + **L20** (20)	34	64:36
2	Ru–**L20** (10)	24	81:19

[a] Combined isolated yield of **3aa** and **3ab**. [b] Determined by ^{1}H NMR spectroscopy.

Next, a labeling study using benzyl formate-d_1 (**1a-D**) in the Ru-catalyzed hydroesterification was conducted. Deuterium-labeled formate would be effective for obtaining mechanistic insight into the rate-determining step and reversibility of the alkene insertion step. A similar mechanistic study using deuterium-labeled formate was conducted by Floreancig and Wang for the Ru-catalyzed tandem hydroesterification and lactonization reaction.[16] Therefore, **1a-D** was prepared according to the literature precedent[21] and used for deuterium-labeling study (Scheme 5). The yield of the product obtained using **1a-D** was similar to that for unlabeled **1a** (Scheme 5 vs. Table 5, entry 1). Deuterium incorporation at carbons *a*, *b*, and *d* but not at *c* suggests that alkene insertion for the branched isomer is reversible through β-elimination, and alkene insertion for the linear isomer is irreversible. It should be noted that the deuterium incorporation for each regioisomer is low, suggesting that the species having Ru–H, which was generated by the β-elimination process, would undergo alkene insertion preferentially over the species having Ru–D because of isotope effect. Hydrogen derived from sources other than the formyl C–H might have also been incorporated, although these sources have not been identified so far.[22]

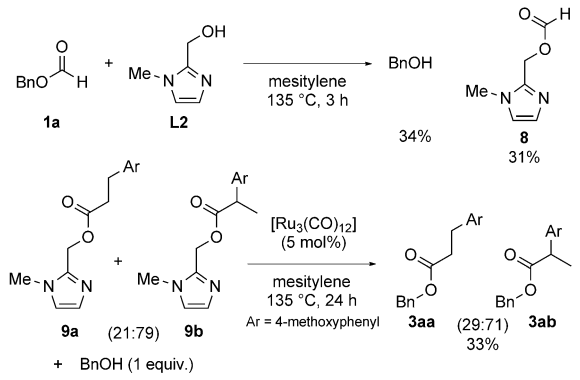


1a-D (1.5 equiv.) **2a** **3aa** (55:45) 66% **3ab**

D incorporation (%): *a* / *b* / *c* / *d* = 14 : 14 : 0 : 17

Scheme 5. Ru-catalyzed hydroesterification using **1a-D**.

Although the mechanism shown in Scheme 4 does not invoke the initially hypothesized ester exchange mechanism for imidazoles with a hydroxy group, this process cannot be conclusively ruled out. In fact, ester exchange of **1a** with **L2** in



Scheme 6. Reactions used to confirm the ester exchange steps.

mesitylene at 135 °C occurred in 3 h to produce ester **8** (Scheme 6). In addition, the reaction of a mixture of **9a** and **9b** with BnOH in the presence of $[Ru_3(CO)_{12}]$ gave the corresponding benzyl esters. Thus, the two ester exchange steps shown in Scheme 1 occur under the hydroesterification conditions. As further investigations are needed to conclusively identify the mechanism for hydroesterification, at this juncture, we cannot exclude the presence of the ester exchange mechanism if ligands bearing a hydroxy group are used.

Conclusions

Imidazole derivatives were identified as highly efficient ligands for drastically accelerating the $[Ru_3(CO)_{12}]$-catalyzed hydroesterification of alkenes with formates. 2-Hydroxymethylimidazoles were especially effective for intermolecular hydroesterification, whereas simpler alkylimidazoles were suitable for intramolecular hydroesterification. This novel Ru-imidazole catalyst system promotes the hydroesterification of various formates and alkenes to afford a series of one-carbon homologated esters. Modification of the ligand structure improved the regioselectivity. Moreover, Ru-catalyzed intramolecular hydrocarbamoylation was effective for the construction of lactams. A complex obtained from $[Ru_3(CO)_{12}]$ and 2-hydroxymethylimidazole was unambiguously characterized by NMR, ESI–MS, and X-ray crystallographic analyses, and was successfully used for the hydroesterification reaction. The reactions promoted by the Ru–imidazole catalyst system proceed by a decarbonylation–recarbonylation pathway, which was confirmed for the first time by a series of mechanistic studies. Further applications of this novel Ru–imidazole catalyst are underway in our laboratory.

Experimental Section

General procedure for intermolecular hydroesterification (Tables 2 and 3)

Formate (0.40 mmol), **L21** (16.0 mg, 0.060 mmol, 15 mol%), and $[Ru_3(CO)_{12}]$ (12.8 mg, 0.020 mmol, 5 mol%) were added to a 2 mL vial equipped with a silicon septum cap under a flow of Ar. The alkene (0.60 mmol, 1.5 equiv.) was added to the vial and then sealed by a new silicon septum cap. The mixture was warmed to 135 °C (bath temperature) and stirred for 24 h. The reaction mixture was cooled to RT and diluted with EtOAc, washed with H_2O three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel (hexane/EtOAc 5:1) to afford a mixture of the desired linear and branched product.

Representative procedure for intramolecular hydroesterification (Table 4, entry 3)

Compounds **4a** (100 mg, 0.62 mmol), **L9** (15.9 mg, 0.093 mmol, 15 mol%), and mesitylene (0.30 mL) were added to a 2 mL vial equipped with a silicon septum cap under a flow of Ar. $[Ru_3(CO)_{12}]$ (19.8 mg, 0.031 mmol, 5 mol%) was added to the vial and then sealed by a new silicon septum cap. The mixture was warmed to 135 °C (bath temperature) and stirred for 24 h. The reaction mixture was cooled to RT and directly purified by preparative TLC on silica gel (hexanes/EtOAc 4:1) to afford six-membered lactone **5aa** (67.5 mg, 0.42 mmol, 68%) as a colorless oil and seven-membered lactone **5ab** (7.8 mg, 0.048 mmol, 8%) as a colorless oil.

Representative procedure for intramolecular hydrocarbamoylation (Scheme 3, first reaction)

Compounds **6a** (100 mg, 0.68 mmol), **L21** (27.1 mg, 0.10 mmol, 15 mol%), and mesitylene (0.30 mL) were added to a 2 mL vial equipped with a silicon septum cap under a flow of Ar. $[Ru_3(CO)_{12}]$ (21.7 mg, 0.034 mmol, 5 mol%) was added to the vial and then sealed by a new silicon septum cap. The mixture was warmed to 135 °C (bath temperature) and stirred for 23 h. The reaction mixture was cooled to RT and directly purified by column chromatography on silica gel (10 g, hexanes/EtOAc 4:1) to afford five-membered lactam **7aa** (72.4 mg, 0.49 mmol, 72%) as a white solid and six-membered lactam **7ab** (8.1 mg, 0.055 mmol, 8%) as a white needle-like solid.

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Keywords: alkenes · carbonylation · ligand design · reaction mechanisms · ruthenium

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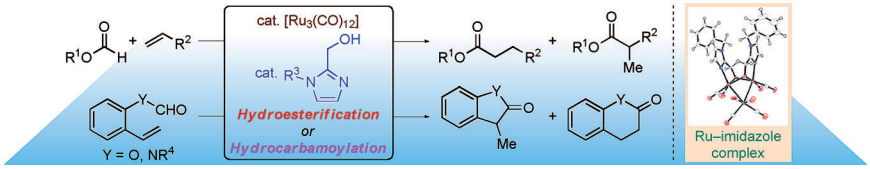

Effective imidazole assistant: $[Ru_3(CO)_{12}]$-catalyzed hydroesterification of alkenes by using formates is drastically accelerated by imidazole derivatives and exhibits a broad substrate scope for both alkenes and formates. The Ru–imidazole complex also catalyzes the intramolecular hydrocarbamoylation of alkenes.

*H. Konishi, T. Muto, T. Ueda, Y. Yamada, M. Yamaguchi, K. Manabe**

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Imidazole Derivatives as Accelerators for Ruthenium-Catalyzed Hydroesterification and Hydrocarbamoylation of Alkenes: Extensive Ligand Screening and Mechanistic Study