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Chelation-Assisted Hydroesterification of Alkenes: New Ruthenium Catalyst Systems and Ligand Effects

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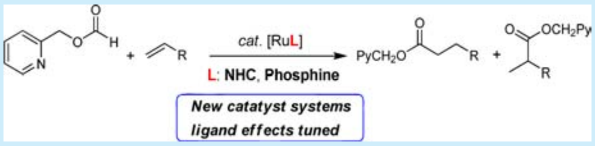
Ⓢ *Supporting Information*

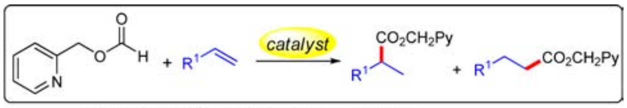
ABSTRACT: New types of ruthenium catalysts were developed for the chelation-assisted intermolecular olefin hydroesterification that employs 2-pyridylmethyl formate as an ester source. Two classes of ligands, NHCs and phosphines, were found to facilitate the reaction delivering isomeric ester products (linear versus branched) with different ratios, thus allowing access to ligand-guided selective hydroesterification.



Transition-metal-catalyzed hydroesterification of alkenes with formates,[1] an alternative route to olefin alkoxycarbonylation using highly pressurized CO gas and alcohols,[2] constitutes one of the most convenient processes for the formation of one-carbon elongated esters. As a result, various catalytic procedures have been developed aiming for high efficiency and selectivity over the past few decades.[3−5] One big issue in the catalytic hydroesterification is in the destructive decarbonylation of an alkoxycarbonyl metal hydride intermediate, *in situ* generated from the reaction of formates with metal species. This side pathway leads to the corresponding alcohols and CO to finish a catalytic cycle.

In this regard, we demonstrated that a chelation-assisted strategy could efficiently be utilized to inhibit the decarbonylation path by using 2-pyridylmethyl formate as a carboxylate reagent in the $Ru_3(CO)_{12}$-catalyzed intermolecular hydroesterification of alkenes and alkynes (Scheme 1, top).[6] While this procedure, as envisioned, does not require an external CO atmosphere, the development of the so-called next generation catalytic systems was not easy mainly due to poor ligand effects.

Scheme 1. Olefin Hydroesterification with 2-Pyridylmethyl Formate



Previous Studies: **$Ru_3(CO)_{12}$** as a catalyst
+ no external CO atmosphere required
- no ligand effects
- poorly-defined catalytic species

This Work: **Ru/NHC** or **Ru/Phosphine** as catalysts
+ New Catalystic Systems
+ Reactivity and Selectivity ***Tuned by Ligands***
+ No External CO Atmosphere Required

This issue becomes more critical especially when a selective transformation is desired with regard to regio- or stereoselectivity. In addition, because the nature and composition of catalytically active species was difficult to determine under the conditions using the $Ru_3(CO)_{12}$ catalyst, a mechanistic understanding of this reaction has been unclear. In this aspect, a recent report of Manabe et al. was notable in that $Ru_3(CO)_{12}$-catalyzed inter- and intramolecular olefin hydroesterification was found to be tuned with the aid of imidazole ligands.[7]

We envisioned that a new catalyst system of hydroesterification could be developed by a proper combination of metal precursors and suitable ligands. Among various potential benefits we can obtain from the well-defined catalytic systems, control of the regioselectivity between two isomeric products (linear versus branched) by tuning the electronic and/or steric properties of ligands employed was especially desired.[8] Described herein are our recent studies on the development of two new catalyst systems for the intermolecular olefin hydroesterification using 2-pyridylmethyl formate as an ester source (Scheme 1, bottom).

At the outset of optimization studies on the catalytic hydroesterification, 3,3-dimethyl-1-butene was chosen as a model substrate to react with 2-pyridylmethyl formate (**1**) using various ruthenium species in combination with a wide range of *N*-heterocyclic (NHC) ligands (Table 1).[9]

Whereas only a negligible amount of product was formed by the action of $Ru(nbd)Cl_2$ alone (entry 1), NHC ligands were found to significantly affect the reaction efficiency. While product yields were moderate to low with NHCs derived from an imidazolium skeleton (entries 2−6), the steric bulkiness of *N*-substituents induced a slightly higher efficiency although the extent was varied depending on the reaction parameters. Interestingly, a saturated NHC derivative having the same *N*-

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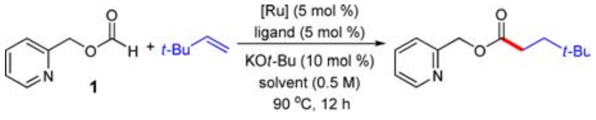
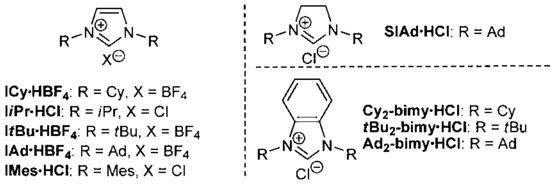
Table 1. Optimization of the Ru/NHC Catalyst System[a]



entry	[Ru]	ligand	solvent	yield (%)[b]
1	Ru(nbd)Cl_2	none	toluene	<5
2	Ru(nbd)Cl_2	ICy·HBF_4	toluene	14
3	Ru(nbd)Cl_2	I*i*Pr·HCl	toluene	7
4	Ru(nbd)Cl_2	I*t*Bu·HBF_4	toluene	21
5	Ru(nbd)Cl_2	IMes·HCl	toluene	17
6	Ru(nbd)Cl_2	IAd·HBF_4	toluene	55
7	Ru(nbd)Cl_2	SIAd·HCl	toluene	27
8	Ru(nbd)Cl_2	Cy_2-bimy·HCl	toluene	50
9	Ru(nbd)Cl_2	Cy_2-bimy·HCl	dioxane	71
10	Ru(nbd)Cl_2	Cy_2-bimy·HCl	MeCN	13
11	Ru(nbd)Cl_2	Cy_2-bimy·HCl	DMF	44
12	Ru(nbd)Cl_2	Cy_2-bimy·HCl	THF	76
13	Ru(nbd)Cl_2	*t*Bu_2-bimy·HCl	THF	78
14	Ru(nbd)Cl_2	Ad_2-bimy·HCl	THF	86
15[c]	Ru(nbd)Cl_2	Ad_2-bimy·HCl	THF	0
16[d]	[Ru(*p*-cymene)Cl_2]$_2$	Ad_2-bimy·HCl	THF	82
17[d]	[Ru(*p*-cymene)Cl_2]$_2$	none	THF	0
18	Ru(cod)Cl_2	Ad_2-bimy·HCl	THF	66
19[d]	(Cp*RuCl_2)$_2$	Ad_2-bimy·HCl	THF	42

[a] **1** (0.2 mmol), alkene (0.4 mmol). [b] Yield determined by ^{1}H NMR (internal standard: 1,1,2,2-tetrachloroethane). [c] Benzyl formate was used instead of **1**. [d] 2.5 Mol % of catalyst was used. Cp* = pentamethylcyclopentadienyl.

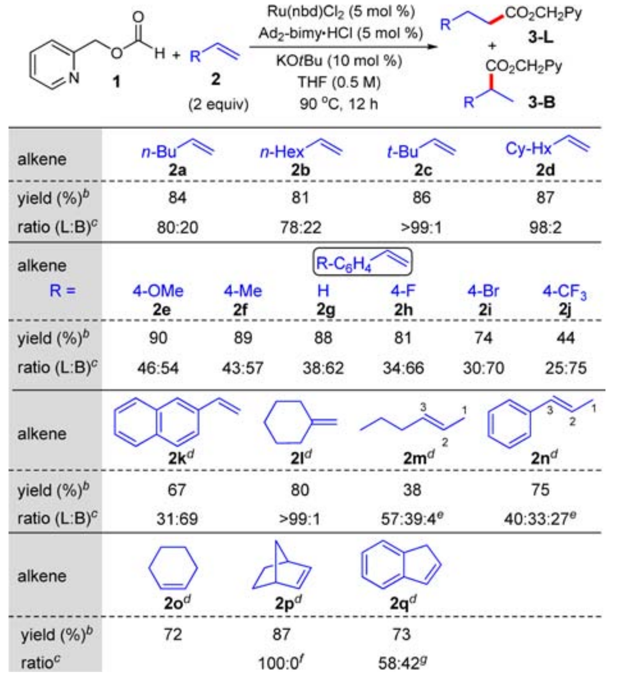


substituent was less effective when compared to unsaturated NHCs (entries 6 and 7). We were pleased to see that NHC ligands of a benzimidazolium skeleton were more effective than the corresponding imidazolyl derivatives (e.g., entries 2 and 8). Moreover, the reaction efficiency turned out to be improved depending on solvents; THF was the most satisfactory (entries 8–12). By combining these variables together, the highest product yield was obtained when an NHC derived from *N*-adamantyl-substituted benzimidazole (Ad_2-bimy) was employed in combination with Ru(nbd)Cl_2 in THF at 90 °C (entry 14).

The present hydroesterification was proved to proceed via a chelation-assisted pathway by observing that a reaction with benzyl formate instead of **1** was totally unsuccessful (entry 15). Other ruthenium species were also examined; while a combination of [Ru(*p*-cymene)Cl_2]$_2$ with Ad_2-bimy gave a similar outcome (entry 16), no conversion was observed in the absence of the NHC ligand (entry 17). On the other hand, Ru(cod)Cl_2 and (Cp*RuCl_2)$_2$ displayed lower catalytic activities under otherwise identical conditions (entries 18 and 19, respectively). To the best of our knowledge, this is the first application of an NHC ligand in the olefin hydroesterification reaction.

Under the optimized conditions, the reaction scope was next investigated by using a range of alkene substrates (Scheme 2).

Scheme 2. Hydroesterification of Various Alkenes Catalyzed by Ru(II)/Ad_2-bimy/KO*t*Bu[a]



alkene	n-Bu **2a**	n-Hex **2b**	t-Bu **2c**	Cy-Hx **2d**
yield (%)[b]	84	81	86	87
ratio (L:B)[c]	80:20	78:22	>99:1	98:2

alkene R =	4-OMe **2e**	4-Me **2f**	H **2g**	4-F **2h**	4-Br **2i**	4-CF_3 **2j**
yield (%)[b]	90	89	88	81	74	44
ratio (L:B)[c]	46:54	43:57	38:62	34:66	30:70	25:75

alkene	**2k**[d]	**2l**[d]	**2m**[d]	**2n**[d]
yield (%)[b]	67	80	38	75
ratio (L:B)[c]	31:69	>99:1	57:39:4[e]	40:33:27[e]

alkene	**2o**[d]	**2p**[d]	**2q**[d]
yield (%)[b]	72	87	73
ratio[c]		100:0[f]	58:42[g]

[a] Reactions in 0.2 mmol scale. [b] Combined isolated yields. [c] Ratio of linear and branched isomers in crude reaction mixture (measured by NMR with 1,1,2,2-tetrachloroethane as an internal standard). [d] At 110 °C. [e] Ratio of 1-, 2-, and 3-isomeric esters. [f] Ratio of *exo*-/*endo*-isomer. [g] Ratio of two regioisomers (1-carboxylate/2-carboxylate).

Both acyclic (**2a**–**2n**) and cyclic (**2o**–**2q**) olefins were readily reacted to afford the corresponding esters in moderate to good yields. As anticipated, the ratio of regioisomers (linear versus branched ester products) was sensitive to the steric environment around the olefinic double bonds. For instance, while linear terminal alkenes (1-hexene, **2a**; and 1-octene, **2b**) were converted to the corresponding esters with an ~4:1 ratio favoring linear isomeric products, hydresterification of 3,3-dimethyl-1-butene (**2c**) and vinylcyclohexane (**2d**) took place almost exclusively to favor linear isomers. On the other hand, styrenes underwent the reaction with a Ru/NHC system to afford branched isomers more favorably, and this preference became more significant with substrates bearing electron-withdrawing substituents. While selectivity in a reaction of 2-vinylnaphthalene (**2k**) was moderate, 1,1,-disubstituted olefin (**2l**) gave a linear product exclusively.

The reaction of linear internal alkenes (e.g., **2m** and **2n**) was nonselective to give terminal esters as the major product in addition to the expected two internal isomers, suggesting that olefin isomerization occurrs during the course of hydroesterification probably initiated by a ruthenium hydride species.[6a,d,10] Cyclic internal olefins (**20**–**2q**) were smoothly reacted to give the corresponding ester products.

It needs to be noted that, in our previous olefin hydroesterification procedure using $Ru_3(CO)_{12}$ as a catalyst,[4] linear esters (anti-Markovnikov products) were obtained always predominantly.[11] In contrast, under the present conditions of using Ru/NHC, not only linear but also branched adducts (Markovnikov products) were formed as major products depending on the substrates employed. As shown above, whereas aliphatic terminal olefins were converted to linear adducts favorably (**2a**−**2d**), branched esters were formed mainly in the reaction of styrenes (**2e**−**2k**).

To see any dependency of the ratio of linear (L) versus branched (B) isomers on the electronic nature of substituents, a Hammett study was performed using various *para*-substituted styrenes. Interestingly, when log(B/L) was plotted against σ_p, a linear relationship was observed with a positive slope (ρ = +0.52, R^2 = 0.97, Figure 1). The positive ρ value suggests that negative charge builds up in the regioselectivity-determining transition state. Thus, the preference for the branched isomers in the hydroesterfication of styrenes with electron-withdrawing substituents might be explained by the stabilization of negative charge in transition states via delocalization onto an aryl ring (compare **A** and **B** in Scheme 3). The regioselectivity should also be affected by the reversibility of the hydrometalation and relative rate for reductive elimination between linear and branched intermediates. It is assumed that the combination of these effects seems to override the steric influence that favors liner isomers.

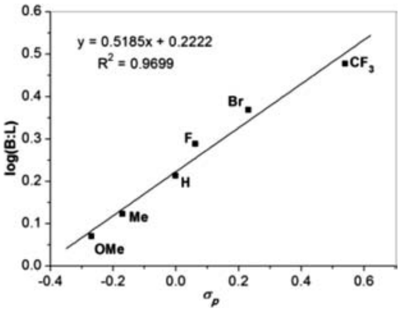
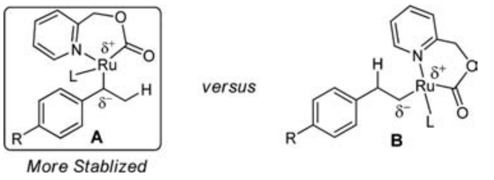


Figure 1. Hammett plot.

Scheme 3. Proposed Intermediates in the Regioselectivity-Determining Step with Ru(II)/NHC (L = NHC)

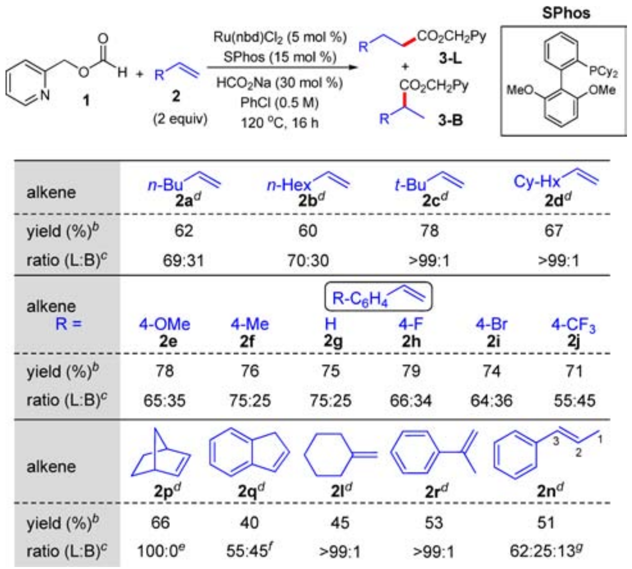


Next, we tried to develop another type of well-defined catalyst system that employs phosphines as a tunable ligand. After extensive optimization studies (see the Supporting Information for details), we found that Ru(II) precursors, representatively Ru(nbd)Cl_2, combined with monodentate SPhos (2-dicyclohexylphosphino-2′,6′-dimethoxy-1,1′-biphenyl) most effectively facilitated the hydroesterification of alkenes with **1** in the presence of HCO_2Na. Chlorobenzene was the solvent of choice regarding reactivity and selectivity. It needs to be mentioned that an analogous catalyst system of [Ru(*p*-cymene)Cl_2]$_2$-phosphines-HCO_2Na was previously applied to the hydroarylation of vinylsilanes and styrenes by Darses and Genet.[11c] They showed that a catalytically active species was *in situ* generated Ru(0) and that HCO_2Na was essential for this process. As anticipated, in our current hydroesterification procedure, [Ru(*p*-cymene)Cl_2]$_2$ displayed similar catalytic activity in the presence of SPhos when compared to the Ru(nbd)Cl_2/SPhos system,[12] thus suggesting that the current catalytic system might also be a similar type of catalytically active species. Again, as in the case of Ru/NHC, olefin hydroesterification with benzyl formate did not occur with Ru(II)/SPhos/HCO_2Na, thus suggesting that the present reaction involves a chelation-assisted pathway.

With a new catalyst system of Ru(nbd)Cl_2−SPhos-HCO_2Na, the scope of alkene substrates was briefly examined (Scheme 4). In general, product yields of resulting esters were lower for the same alkenes when compared to those obtained from the former Ru/NHC catalyst system. Aliphatic terminal alkenes were reacted under the optimized conditions (in chlorobenzene at 120 °C) to afford the corresponding esters although the preference for the linear isomers was slightly lower than that with Ru/NHC (in THF at 90 °C). It was noted that styrenes underwent the hydroesterification to lead to linear products as the major product irrespective of the electronic nature of the substituents. This reversal in regioselectivity is highly interesting in that branched isomers were obtained as major products for all styrenes examined with the Ru/NHC system (Scheme 2). Although it requires further investigation to explain the observed dichotomy, this result may serve as a clue for the future development of highly selective catalytic systems which can control the formation of linear or branched isomers just by tuning ligands. Cyclic olefins (**2p** and **2q**) were also reacted without difficulty although the yields were slightly lower than in the case of the Ru/NHC system. As expected, the hydroesterification of 1,1,-disubstituted olefins, being aliphatic or styrenyl (**2l** or **2r**), was highly selective to afford linear products exclusively in both cases. Again, as in the case of Ru/NHC, isomerization occurred in a reaction of **2n**.

In summary, we have developed two new types of catalyst systems for the intermolecular hydroesterification of alkenes using 2-pyridylmethyl formate as an ester source. With the use of a catalyst system Ru(nbd)Cl_2/NHC, the reaction proceeds more efficiently under milder conditions when compared to

Scheme 4. Olefin Hydroesterification with a Catalyst System of Ru(II)/SPhos/HCO_2Na[a]



alkene	*n*-Bu **2a**[d]	*n*-Hex **2b**[d]	*t*-Bu **2c**[d]	Cy-Hx **2d**[d]
yield (%)[b]	62	60	78	67
ratio (L:B)[c]	69:31	70:30	>99:1	>99:1

alkene R =	4-OMe **2e**	4-Me **2f**	H **2g**	4-F **2h**	4-Br **2i**	4-CF_3 **2j**
yield (%)[b]	78	76	75	79	74	71
ratio (L:B)[c]	65:35	75:25	75:25	66:34	64:36	55:45

alkene	**2p**[d]	**2q**[d]	**2l**[d]	**2r**[d]	**2n**[d]
yield (%)[b]	66	40	45	53	51
ratio (L:B)[c]	100:0[e]	55:45[f]	>99:1	>99:1	62:25:13[g]

[a] Reactions in 0.2 mmol scale. [b] Combined isolated yields. [c] Ratio of linear and branched isomer of crude mixture determined by ^{1}H NMR. [d] Ru(nbd)Cl_2 (7.5 mol %), SPhos (22.5 mol %), HCO_2Na (45 mol %), and 3.0 equiv of alkene. [e] Ratio of *exo*-/*endo*-isomer. [f] Ratio of 1-carboxylate/2-carboxylate. [g] Ratio of 1-, 2-, and 3-isomeric esters.

Ru(nbd)Cl_2/phosphine/HCO_2Na. Importantly, the regioselectivity for the formation of linear versus branched isomeric products was observed to be reversed in certain substrates by the chosen ligands. Although the catalytic activity and selectivity do not yet reach practical standards with these present systems, they represent the first examples of employing NHCs or phosphines for the chelation-assisted hydroesterification reaction. On the basis of the present study, research efforts to develop more efficient and selective catalyst systems are now underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure and characterization of new compounds (^{1}H and ^{13}C NMR spectra). This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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(12) See the Supporting Information for details of the optimization study.