Palladium-Catalyzed Reppe Carbonylation

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Contents

I. Introduction

Carboxylic acids and their derivatives (esters, anhydrides, amides, metal salts, etc.) are large volume products and chemical intermediates. Highly branched C_5 and C_{10} acids are made from alkenes by the Koch synthesis reaction.[1] Due to rapid backbone isomerization of alkenes in the presence of the acid catalysts of Koch synthesis, aliphatic acids made by this route are always highly branched

$$R^1R^2C{=}CR^3R^4 + CO + H_2O \rightarrow R^1R^2HC{-}CR^3R^4{-}COOH \quad (1)$$

There are several known routes to carboxylic acids and their derivatives via transition-metal-catalyzed carbonylation.

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(1) Alcohol carbonylation used commercially in Monsanto's acetic acid synthesis[2]

$$CH_3{-}OH + CO \rightarrow CH_3{-}COOH \quad (2)$$

(2) Ester carbonylation, as in Eastman's acetic anhydride synthesis[2]

$$CH_3{-}CO{-}OCH_3 + CO \rightarrow (CH_3{-}CO)_2O \quad (3)$$

(3) Olefin hydroformylation[3] followed by aldehyde oxidation[4]

$$R{-}CH{=}CH_2 + CO + H_2 \rightarrow R{-}CH_2{-}CH_2{-}CHO + R{-}CH(CHO){-}CH_3 \quad (4)$$

$$R{-}CH_2{-}CH_2{-}CHO + {}^1/_2O_2 \rightarrow R{-}CH_2{-}CH_2{-}COOH \quad (5)$$

(5) Oxidative carbonylation of unsaturated hydrocarbons[5]

$$CH_2{=}CH_2 + CH_3{-}OH + CO + O_2 \rightarrow CH_2{=}CH{-}CO{-}OCH_3 + CH_3O{-}OC{-}CH_2{-}CH_2{-}CO{-}OCH_3 + CH_3O{-}CH_2{-}CH_2{-}CO{-}OCH_3 \quad (6)$$

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$$CH_2{=}CH{-}CH{=}CH_2 + CH_3{-}OH + CO + O_2 \rightarrow CH_3O{-}OC{-}CH_2{-}CH{=}CH{-}CH_2{-}CO{-}OCH_3 + CH_3O{-}OC{-}CH{=}CH{-}CH{=}CH_2 \quad (7)$$

(6) Reppe carbonylation[6,7] of alkenes (eq 8), alkynes (eq 9), and conjugated dienes (eq 10)

$$R{-}CH{=}CH_2 + CO + Nu{-}H \rightarrow R{-}CH_2{-}CH_2{-}CO{-}Nu + R{-}CH(CO{-}Nu){-}CH_3 \quad (8)$$

$$R{-}C{\equiv}CH + CO + Nu{-}H \rightarrow R{-}CH{=}CH{-}CO{-}Nu + R{-}C(CO{-}Nu){=}CH_2 \quad (9)$$

$$CH_2{=}CH{-}CH{=}CH_2 + CO + Nu{-}H \rightarrow CH_2{=}CH{-}CH_2{-}CH_2{-}CO{-}Nu + CH_2{=}CH{-}CH(CO{-}Nu){-}CH_3 \quad (10)$$

where Nu = nucleophile, like HO^-, RO^-, $R'{-}COO^-$.

Commercial application of the rhodium-catalyzed carbonylation of primary alcohols is limited to methanol for two reasons: (I) availability of low-cost feedstock and (II) low reactivity of higher-carbon alcohols.[7b]

Higher-carbon linear aliphatic acids are mostly made via the hydroformylation route.[6b] Although it requires two steps to make acids and three steps to make esters, it is still preferred because hydroformylation is a mature technology that affords high linear product selectivity at high productivity. It should also be noted that the carbonyl source in hydroformylation is cheap syngas (a mixture of CO and H_2) rather than the more expensive pure CO required by other carbonylation processes. Clearly, the current benchmark for the petrochemical production of higher-carbon linear aliphatic acids is the hydroformylation route.

$PdCl_2/CuCl_2$-catalyzed oxidative carbonylation of unsaturated hydrocarbons[5] can produce acids and their derivatives in one step (see eqs 6 and 7) but has the disadvantage of generating complex product mixtures, lowering the yield of the desired product, and requiring elaborate separation processes. Despite these drawbacks, Union Oil developed a process for converting ethylene to acrylic acid[5s] and ARCO announced the commercial readiness of their technology to convert butadiene to adipic and sebacic acid.[5i,k,l] To our knowledge, neither of these technologies has been deployed yet.

Recently, Reppe carbonylation has received considerable attention and is the subject of a number of reviews.[6,7] The process is very versatile since it can convert not only olefins but acetylenes and dienes as well. It can also tolerate a wide variety of functional groups, which makes it attractive in organic synthesis.[6a] The co-reagents are CO and a nucleophile, typically water, alcohol, or acid, yielding a wide range of saturated or unsaturated acids, esters, or anhydrides, respectively (eqs 8−10). When the nucleophile is water or alcohol, the process is called hydrocarboxylation or hydroesterification, respectively. Hydroesterification sometimes is also referred to as hydroalkoxycarbonylation or hydrocarbalkoxylation.

Although oxidative carbonylation is sometimes also referred to as hydrocarboxylation or hydroesterification, it is distinctively different in requiring an oxidant, typically air, to reoxidize Pd^0, formed in a stoichiometric amount, into Pd^{2+}. Furthermore, the catalytic system also has a cocatalyst, usually a copper salt, to catalyze the Pd^0/Pd^{2+} transformation, thereby closing the catalytic cycle and stabilizing the Pd catalyst. Therefore, this review will distinguish the two systems and treat Reppe carbonylation only.

Reppe's first catalytic carbonylation process[8] converted acetylene, CO, and water to acrylic acid using $Ni(CO)_4$ as catalyst. It was commercially operated in Germany, Japan, and the United States until the heterogeneously catalyzed oxidation of propene replaced it by relying on a cheaper feedstock. Today, BASF is the only company that applies the nickel catalyst in the production of propionic acid from ethylene.[6b] Since $Ni(CO)_4$ is highly poisonous, its commercial application as a catalyst will likely be limited in the future.

Other Reppe-carbonylation catalysts are mostly based on group VIII transition metals, like Fe, Ru, Co, Rh, Ir, Pd, and Pt, although Eastman also patented a halide-promoted $Mo(CO)_6$ catalyst.[9] Among these, Co and Pd catalysts are the most active and, understandingly, have generated the most interest. Thus, for example, BASF developed and demonstrated on a pilot scale a process that uses pyridine-promoted cobalt carbonyls to convert butadiene to adipic acid.[6c]

BASF[10,11] and Toyo Rayon[7h] researchers reported the first Pd Reppe-carbonylation catalysts in the early 1960s. After a relatively quiet decade, Drent's group at Shell patented a new family of Pd catalysts from the late 1980s. These catalysts are closely related to their CO−alkene copolymerization systems[12] and surpass any known Reppe-carbonylation catalysts in their activity. These Pd catalysts represent the current state of the art. This paper will review the chemistry, composition, performance, and process applications of Pd Reppe-carbonylation catalysts. The cutoff date of the literature search is September 1999.

II. Chemistry and Products

Reppe carbonylation combines three reactants: an unsaturated hydrocarbon substrate, a carbonyl source, and a nucleophile (eqs 8−10). The most frequently studied hydrocarbon substrates are alkenes,[10,13−18] alkynes,[19−21] conjugated dienes (typically butadiene),[22−24] and aryl-substituted alkenes, most often styrene.[25−27] The aryl-substituted alkenes are treated separately from alkenes because of their special application and selectivity pattern (vide infra).

It is well-known that some Pd catalysts can also readily carbonylate halogen−carbon and methoxy−carbon bonds in a chemistry that is similar to hydrocarboxylation.[6a,28] If, in the case of halogenated hydrocarbons, a strong base is used as a stoichiometric reagent, the products are similar to those

Table 1. Alkene Hydroesterification Rates[a] with $(PPh_3)_2PdCl_2-SnCl_2$ Catalyst[13m]

no.	alkene	rate (M/h)	product identity	product %	conv. %
1	propene	0.16	methyl butyrate	84.9	90
2	1-pentene	0.23	methyl hexanoate	89.5	N/A
3	1-heptene	0.24	methyl octanoate	86.5	>95
4	1-undecane	0.11	methyl dodecanoate	88.5	59
5	1-eicosene	0.024	methyl heneicosenate	90.8	20
6	4-methyl-1-pentene	0.16	methyl 5-methylhexanoate	88.8	86
7	3-methyl-1-pentene	0.15	methyl 4-methylhexanoate	98.0	71
8	2-methyl-1-pentene	0.021	methyl 3-methylhexanoate	>99	30
9	cyclooctene	N/A	methyl cyclooctanecarboxylate	>99	36
10	*trans*-2-heptene	0.004	methyl octanoate	10	11
		0.021	methyl 2-methylheptanoate	60	
		0.012	methyl 2-ethylhexanoate	30	
11	*cis*-2-heptene	0.010	methyl octanoate	7	54
		0.120	methyl 2-methylheptanoate	71	
		0.032	methyl 2-ethylhexanoate	22	
12	*cis*-3-heptene	0.018	methyl 2-methylheptanoate	22	N/A
		0.061	methyl 2-ethylhexanoate	78	
13	*trans*-5-decene	N/A	none	N/A	1

[a] Conditions: 70 °C, 136 atm, 180 min, excess methanol. Note: Catalyst composition and concentration for the above data are not reported in the original paper; thus, only relative rates can be derived.

obtained from alkenes. Although this route can be appealing for some fine chemical and pharmaceutical applications, the current review will focus on the conversion of unsaturated hydrocarbon substrates only.

A. Reactivity and Hydroesterification Products of Alkenes

The hydroesterification of 1-alkenes yields esters of aliphatic acids that could be used as solvents. Despite the large economic potential of these products, many academic reports target specialty chemicals. Thus, for example, γ-keto esters were prepared from nonconjugated dienes,[13b] 2-cyclohexen-1-one,[15c] and methyl vinyl ketone,[15h] menthyl isovalerate was synthesized from isobutene and menthol,[13e] cyclohexanecarboxylates were made from cyclohexene,[13l] dicarboxylic acids and their esters were obtained from oleic acid,[13p] etc. Several publications report the hydroesterification of norbornenes and nonconjugated norbornadienes.[6a,13d,r,t] Enolic substrates yield cyclic products containing ester and ether groups in the ring.[16] Ojima addressed the reactivity and selectivity effects of fluoro substitution in fluoroalkenes.[17] Hydroesterification was also used to introduce functionality into polybutadienes in a Ciba-Geigy sponsored project.[18]

Although very few comparative reaction rates are available, qualitative trends for the reactivity and selectivity effects of alkene structure can be deduced. Thus, the reactivity of linear C_3-C_{20} 1-alkenes[13m] shows a maximum plateau in the C_5-C_7 range (Table 1, compare entries 1−5). The lower reaction rate measured with lower-carbon alkenes, like propene, is likely due to their lower concentration in the liquid phase at the same substrate charge due to their higher vapor pressure. A similar reactivity order was observed with $(PPh_3)_2PdCl_2$-10$[NEt_4][SnCl_3]$[13k] and $(PPh_3)_2PdCl_2-PPh_3$[13i] catalysts. Interestingly, norbornene and cyclohexene are often converted at higher reaction rates than linear alkenes and much faster than branched alkenes.[25f] Thus, for example, in the hydroesterification of various alkenes with $[Pd(MeCN)_2(PPh_3)_2](BF_4)_2$ catalyst, the reported reactivity order is norbornene > cyclohexene > octene-1 > cyclopentene > cyclooctene > 3-methyl-pentene-1 ≫ 2-methyl-pentene-2.[25f]

Internal alkenes react approximately an order of magnitude slower than 1-alkenes (compare entries 3 with 10−12 in Table 1). Apparently, the longer the alkyl substituents on the ethylidene group, the lower is its reactivity. Thus, the reactivity orders reflecting this rule are 1-heptene ≫ 2-heptene > 3-heptene ≫ 5-decene (see the third and last four entries in Table 1). This reactivity difference must be due to increasing steric hindrance with increasing substituent size on the ethylidene group. This conclusion is also supported by the higher reactivity of *cis*-2-heptene as compared to that of the closely related *trans*-2-heptene (see Table 1, entries 10 and 11). Similarly, Knifton found[13m] that increasing steric demand around the double bond reduces reactivity in the $PdCl_2$-$(PPh_3)_2$/$SnCl_2$-catalyzed hydroesterification leading to a reactivity order of α-olefin > branched α-olefin > internal olefin. The steric influence of alkenes on the reaction rate can also be observed in the hydrocarboxylation of methylenecyclohexenes to the corresponding acids with the $Pd(OAc)_2$-1,4-bis(diphenylphosphino)butane catalyst.[13h] The reactivity order of the methyl-substituted methylenecyclohexenes follows the expected order: unsubstituted = 4-methyl (para) > 3-methyl (meta) > 2-methyl (ortho). A Russian group also reported the lower reactivity of internal alkenes from their experiments with decene-1 using $Pd(acac)_2$/6PPh_3/3*p*-toluenesulfonic acid catalyst.[13j] They found that the reaction becomes unexpectedly slow as the rapid alkene isomerization converts 1-decene to 2-decene. After consuming the more reactive decene-1, the reaction rate drops an order of magnitude representing the reaction rate of decene-2.

B. Reactivity and Hydroesterification Products of Alkynes

Shell developed and declared commercially ready[19] a process for converting propyne (methyl acetylene) to methyl methacrylate (MMA) in the presence of their Pd^{2+}/2-pyridylphosphine catalysts[19,21a−g]

$$CH_3-C\equiv CH + CO + CH_3-OH \rightarrow CH_2=C(CH_3)-CO-OCH_3 \quad (11)$$

Interestingly, propadiene (allene) acts as a strong inhibitor in the conversion of propyne.[19,21] Thus, 215 weight-ppm propadiene in the propyne feed reduces the conversion of propyne from 83% to 18% at otherwise identical conditions.[19a] The likely reason of the inhibition is the ability of propadiene to form stable π-allyl complexes with transition metals.[6a,29a] Essentially, the active metal catalyst is trapped in this stable π-allyl complex, reducing the overall conversion rate of propyne. The fate of propadiene is not discussed. On the basis of the analogy with our hydroformylation work with mixed feeds,[30] propadiene is likely converted parallel with propyne but at a substantially lower rate due to the stability of the π-allyl intermediate. It is worth mentioning that Wojcicki's group reported the synthesis of a Pd−allenyl complex and its reaction with methanol a few years ago.[29b]

While Shell's published work with the pyridyl phosphines is focused on the conversion of propyne, some of their earlier patents[21e,h] also contain data for different substrates, allowing at least a qualitative comparison of their conversion rates. Thus, in the reaction catalyzed by the Pd^{2+}/P(p-Cl−Ph)$_3$/*p*-toluene sulfonic acid catalyst,[21h] reaction rates of acetylene and propyne are similar, suggesting little, if any, steric hindrance by the methyl group. Data in another Shell patent[21e] suggest that ethene reacts at least an order of magnitude slower than propyne in the presence of bisphenyl(2-pyridyl)phosphine/Pd^{2+} catalyst. Furthermore, it is not clear if this reactivity trend is general or only applies to the pyridylphosphine-modified catalysts. Thus, the alkyne/alkene reactivity order warrants further investigation.

As expected based on the analogy in Rh-catalyzed hydroformylation,[30] acetylenes bind more strongly than alkenes. Thus, if alkenes and alkynes are cofed, the alkene essentially stays unconverted until the alkyne is consumed.[21g,h] Unlike in hydroformylation[30] or in the case of alkyne/cumulated diene pairs in hydroesterification, the overall conversion rate is not affected since the stronger binding alkyne reacts faster than the alkene.[21e] This observation is quite counterintuitive since stable intermediates typically shift the inventory of the catalyst into a slower reacting pool. Nonetheless, the order of metal−substrate binding strengths is well established and is as follows: cumulated dienes ≫ alkynes ≫ alkenes.

α,β-Unsaturated acrylic polymers can be prepared in high yields from poly(2-methylvinylacetylene) (MW = 1600−3060 g/mol) using $Pd(OAc)_2$/dppb/HCOOH (dppb = 1,4-bis(diphenylphosphino)butane) catalyst at 110 °C and 200 psi CO pressure.[20a] The normal/iso-ratio is typically higher than 4.

Some papers[20b−e] report on the reactivity of different aryl- and alkyl-substituted acetylenes. On the basis of these data, it seems that para-substituted aryl acetylenes react nearly at the same rate, regardless of the nature of para substituents. A more pronounced effect can be observed due to steric interference when the aryl ring has a methyl substituent in the ortho position.[20d] The reactivity difference between aryl and alkyl acetylenes is even more substantial, aryl acetylenes showing significantly higher hydroesterification rates.[20b,d,e] Considering that steric effects must be negligible in this case, the electronic effect is the likely cause of the observed reactivity trend.

C. Reactivity and Hydroesterification Products of Conjugated and Cumulated Dienes

Conjugated dienes can undergo a number of different reactions at hydroesterification conditions in the presence of Pd catalysts.[6a,c] The hydroesterification path is favored by catalytic systems with strongly binding ligands that do not allow the formation of the diallylic Pd intermediate, which later is the direct precursor of the products containing multiple diene units.[6a,22d] Thus, for example, $PdCl_2$-derived catalysts tend to favor the formation of pentenoates from butadiene, while catalysts with weakly coordinating anions allow substantial telomerization selectivity.[22d] Due to the telomerization and oligomerization side reactions, reported hydroesterification selectivity values are typically below 90−95% in the conversion of conjugated dienes.[22−24] In fact, sometimes hydroesterification is the minor route.[22c,d,24e,f]

The primary products of the hydroesterification of conjugated and cumulated dienes are the normal- and iso-unsaturated esters, i.e., only one double bond reacts.[22−24] By forming π-allyl intermediates, conjugated and cumulated dienes bind much stronger to Pd than alkenes do. Therefore, the olefin primary product does not react until the diene is completely consumed. For the same reason, butadiene can be reactively separated from C_4 diene−alkene mixtures, forming pentenoates and leaving the C_4-alkenes unreacted.[23a]

Typical reaction temperatures in the hydroesterification of conjugated and cumulated dienes[23] are approximately 50−100 °C higher (around 150 °C) than the temperatures used in alkene or alkyne hydroesterification. This fact also underlines the low reactivity of π-allyl-forming dienes. The reactivities of cumulated and conjugated dienes are similar[23] and clearly much lower than that of simple alkenes and alkynes, which later lack the ability of forming π-allyl intermediates.

The published work is almost exclusively concentrated on butadiene. The target product in the patent literature is often adipic acid, an intermediate in the manufacture of Nylon-6−6.[22b,23,24a−c] It is obtained in a two-step process where the second step is often hydroformylation.[24a−c] Shell has one patent in which hydroesterification is applied in both steps.[23d] The fact that the choice for converting the olefinic intermediate to adipic acid in several patents is hydroformylation is consistent with the conclusion drawn

Table 2. Hydroesterification of Octene-1 in the Presence of H_2[13i]

alcohol	ester yield (%)	n/i-ester ratio
n-butyl	93	5.1
tert-butyl	87	6.0
i-propyl	84	5.7
n-propyl	88	5.1
ethyl	88	4.2
methyl	86	3.1

Conditions: 0.1 mmol $Pd(PPh_3)_2Cl_2$, 1.0 mmol PPh_3, 6.3 mmol octene-1, 1.5 mL alcohol, CO/H_2 = 1.7/0.34 MPa, 110 °C, 12 h.

in the Introduction, namely, that hydroformylation is generally more economic than hydroesterification at the current state of the art.

D. Hydroesterification Products of Aryl-Substituted Alkenes

Hydroesterification of aryl-substituted alkenes[25−27] provides a direct route to 2-arylpropionic acids and their derivatives (profenes, like ibuprofen, naproxen, ketoprofen, etc.), the latter of which are nonsteroidal antiinflammatory agents with a 1992 world market of more than $2.5 billion.[31] The desired 2-arylpropionic product is formed in the iso-addition of the carbonyl group. For this reason, the focus has been on achieving high iso-selectivity. This is in contrast with the objective for chemical intermediates, for which the linear (or normal) carboxylic acids and their derivatives are the preferred, higher value products. Nonetheless, these studies provide valuable insights into the mechanism and the effects of catalyst composition and process conditions on product selectivity and catalyst activity.

E. Reactivity of Nucleophiles

The reactivity order of nucleophiles in Reppe carbonylation has not been studied systematically. On the basis of mostly qualitative observations,[13k,m,21e] the following general reactivity order can be established for the carbonylation of alkenes: aliphatic alcohols ≈ acids > water > phenols. For nucleophiles with oxygen attacking atom, increasing nucleophilicity was suggested[13m] to increase reaction rate. It has to be pointed out, however, that the observed reaction rate differences are typically far smaller than the values reported between alkenes, alkynes, and π-allyl-forming dienes (vide supra).

In the hydroesterification of alkenes, the carbon chain length of C_1-C_6 aliphatic alcohols has little influence on the reaction rate.[13k,m,15c] Increasing bulkiness of the alcohol slightly retards the reaction; thus, the reactivity order is primary > secondary > tertiary alcohols.[13k,m,15h] Interestingly, if the reaction is carried out in the presence of H_2, the steric bulk of the aliphatic alcohol has no effect on the reaction rate, though increasing bulkiness slightly increases n/i-selectivity of the product[13i] (see Table 2).

In the hydroesterification of alkynes, the reactivity orders are slightly different from the ones observed for alkenes. Thus, while the reactivity of water is lower in the Reppe-carbonylation alkenes, reaction rates with water and methanol in the hydroesterification of propyne with Shell's bisphenyl(2-pyridyl)phosphine/Pd^{2+} catalyst are approximately the same,[21g] although water does react more slowly when using the PPh_3/Pd^{2+} catalyst.[21h] Also, in the presence of the pyridyl catalyst system, propyne reacts with methacrylic acid approximately 2 orders of magnitude slower than with methanol[21g] while the reactivity of acids and alcohols seems to be similar in the Reppe carbonylation of alkenes. Similar to the trend for alkenes, phenol and bulky aliphatic alcohols, like glucose, react slower than methanol.[21g,h] It has to be emphasized, however, that these observations are qualitative only. Thus, for example, in contradiction to data from the Shell patents cited above, there are reports showing no clear reactivity differences for primary, secondary, or tertiary aliphatic alcohols in the hydroesterification of alkynes.[20b,d]

F. Hydroesterification with Formates and Oxalates

The carbonyl source is most often carbon monoxide in hydroesterification. However, there are reports of using in part or entirely other carbonyl sources, such as formic acid, formate esters, and oxalic acid.[22a,32] Due to the fact that CO is often used as a co-reactant in these systems, the true source of the carbonyl group is not always clear (and most likely CO). While the chemistry of the latter reaction is interesting, it does not seem to offer advantages in commercial applications or in mechanistic studies and thus will not be covered in detail.

G. Side Reactions in Pd-Catalyzed Hydroesterification

Product yields based on the unsaturated hydrocarbon feed can vary substantially in hydroesterification depending not only on the catalyst and reaction conditions, but also on the nature of the substrate itself. The highest selectivity is reported in the conversion of alkynes, like, for example, for propyne to methyl methacrylate. For the latter reaction, Shell claims reaction yields as high as 99.95%[19,21] based on propyne with an overall process yield of 95%.[19a] On the other end of the spectrum are the conjugated dienes that sometimes yield more telomerization and oligomerization than hydroesterification products.[22−24]

As mentioned earlier, weakly coordinating anions seem to favor both oligomerization and telomerization over hydroesterification by allowing the formation of diallylic Pd intermediates.[22e] Thus, $Pd(OAc)_2$-based catalysts yield as low as 10:1 butadiene-derived oligomer−ester ratios with a wide variety of mono- and bidentate phosphines in quinoline solvents at 110 °C.[22c,24e] The latter catalytic system essentially yields mostly the telomerization product nonadienoate and oligomers, with minor amounts of pentenoates.

$Pd(acac)_2$/bis(dialkyl)phosphine/2,4,6-trimethylbenzoic acid catalysts, published by DSM,[24b] can achieve much higher (around 90%) selectivity to methyl pentenoate. Apparently, changing the pH of the reaction medium from basic to acidic favors hydroesterification over oligomerization and telomerization. Shell obtained similar results by using $Pd(OAc)_2$/

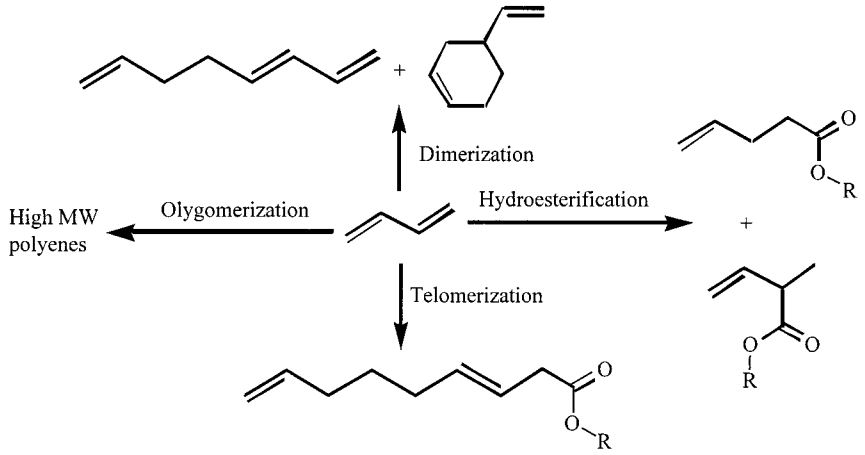


Figure 1. Reaction paths for conjugated dienes at hydroesterification conditions in the presence of Pd catalysts.

bis(diaryl)phosphine/2,4,6-trimethylbenzoic acid catalysts at 150 °C.[23] Apparently, the combination of acidic reaction medium and strongly binding bidentate phosphines can shift the selectivity toward hydroesterification just as well as a strongly coordinating anion.

In the hydroesterification of alkenes, the most significant side reactions of the alkene substrate are the formation of polyketones and double-bond migration. The former reaction is not a serious problem since it can be very effectively suppressed by the proper choice of ligand and reaction conditions.[12] Although very little has been published on alkene isomerization during hydroesterification, it seems to be a more persistent selectivity-reducing factor. Chepaikin et al., for example, observed a sharp decrease in the rate of hydroesterification of 1-decene with *n*-butanol at 25% conversion in the presence of $P(acac)_2/PPh_3$/*p*-toluenesulfonic acid catalyst at 80 °C.[13j] The presence of 2-ethylnonanoate in the product confirms double-bond migration. Similar reaction rate decrease does not occur in the hydroesterification of the nonisomerizing ethene.[13j] Thus, the authors concluded that alkene isomerization happens at a substantial rate during hydroesterification generating the slower-reacting internal olefin isomers.

Most hydroesterification catalysts have an acid component. This acid reacts with the alcohol in the feed[4,24c] producing water and an ester or a halide, depending on the nature of the acid (eq 12). Water can also form via the acid-catalyzed etherification of the feed alcohol, especially in the case of methanol at higher temperature (at or above 100 °C).[33a] The most important consequence of these side reactions is the potential influence of water in every hydroesterification system that has an acid component, even if the reagent and solvent feeds are predried.

$$ROH + HX \rightleftarrows X + H_2O$$

$$X = Cl, R'\text{-}COO, \text{etc.} \qquad (12)$$

Homogeneous catalytic water gas shift reaction (WGSR) is an interesting side reaction in hydroesterification. Considering that the WGSR generates hydrogen (eq 13), its occurrence could impact not only selectivity but activity and stability as well. The latter will be discussed in the sections on mechanism

$$P_2Pd^{2+} + CO \overset{K_1}{\rightleftarrows} [P_2Pd(CO)]^{2+} \qquad (2.1)$$

$$[P_2Pd(CO)]^{2+} + H_2O \overset{K_2}{\rightleftarrows} [P_2Pd(CO)(OH)]^{+} + H^{+} \qquad (2.2)$$

$$[P_2Pd(CO)(OH)]^{+} + P \overset{k_3}{\rightarrow} P_3Pd(COOH)]^{+} \qquad (2.3)$$

$$[P_3Pd(COOH)]^{+} \overset{\text{fast}}{\rightarrow} [P_3PdH]^{+} + CO_2 \qquad (2.4)$$

$$[P_3PdH]^{+} + X^{-} \overset{K_5}{\rightleftarrows} [P_3Pd(H)X] + P \qquad (2.5)$$

$$[P_3Pd(H)X] + H^{+} \overset{k_6}{\rightarrow} P_2Pd^{2+} + H_2 + X^{-} \qquad (2.6)$$

Figure 2. Mechanism of homogeneous water gas shift reaction.[33c]

and catalyst stability (vide infra). WGSR also has process implications, since the CO_2 side product needs to be purged from the reactor.

$$CO + H_2O \rightleftarrows CO_2 + H_2 \qquad (13)$$

Several Pd^{2+}-containing WGSR catalysts have been studied, and potential catalytic intermediates have been proposed.[33] Zudin et al., for example, studied the kinetics and mechanism of WGSR using the $Pd(OAc)_2/PPh_3/CF_3COOH$ hydroesterification catalyst.[33c] They measured 2.0−2.5 mol CO/(mol of Pd h) turnover frequency (TOF) at 70 °C and 1 atm of CO in 80% aqueous CF_3COOH solution. These TOF values are far below the values measured in hydroesterification with the state of the art catalysts. (The best catalysts often yield 10^3 mol of CO/(mol of Pd h) or even higher TOF.) Therefore, the ratio of WGSR and hydroesterification rates, i.e., WGSR selectivity, is low with high activity catalysts as long as the acceleration of hydroesterification is not due to an increase in the concentration of key WGSR catalytic intermediates.

The suggested mechanism of the Pd^{2+}-catalyzed WGSR involves the generation of a Pd−hydride intermediate (see Figure 2). Since the catalytic cycle of hydroesterification can also involve Pd−hydrides,

the hydride formation in the WGSR may have a key role in some unexpected effects, like the acceleration of hydroesterification reported by several groups.[14a,e,15b,25d]

On the basis of the observed first kinetic order in the concentration of the phosphine ligand, the phosphine-induced CO insertion has been proposed to be the rate-determining step in the forward WGSR. The experimental kinetic data can be well described by the kinetic expression derived from the mechanism shown in Figure 2[33c]

$$\text{Forward rate of WGSR} = k_{obs}[Pd][PPh_3][H_2O]p_{CO}/[HX] \quad (14)$$

As expected, the reaction is first order in the concentrations of palladium, water, and CO. Interestingly, excess acid inhibits WGSR according to eq 14.

III. Pd Hydroesterification Catalysts

Known palladium hydroesterification catalyst precursors are summarized in Tables 3−5. As shown in Tables 3−5, palladium precursors can be either Pd^0 (Pd metal and PdL_4 complexes) or Pd^{2+} (PdX_2 and PdX_2L_2) species.

The oxidation state of the active catalyst is not well established. On one hand, it is well-known that without certain stabilizers Pd catalysts tend to decompose to Pd black[10b,12b,13q−s,15h,j,n,26c,45b] or to form dinuclear complexes.[12b] This transformation deactivates the catalyst. Since acid treatment of a deactivated catalyst can restore activity,[13k,q,s] the role of acid promoters is believed to stabilize Pd in an active divalent oxidation state by the following reactions[13k,q,s,20f,49]

$$Pd^0 + HX \rightarrow HPdX \quad (15)$$

$$HPdX + HX \rightarrow PdX_2 + H_2 \quad (16)$$

It is worth mentioning that this reaction sequence not only prevents deactivation by preventing Pd-black formation but also involves the generation of a Pd−hydride intermediate. The hydride intermediate from eq 15 can initiate the catalytic cycle by reacting with the hydrocarbon substrate[6a,7h,13b,c,f,i,l,m,14a,b,e−h,15b,c,g,h,j,16b,c,20b,22h,25a,b,f,26a,c−f,49] (see also section V). It is argued therefore[14g,15c,h,20b,49] that eq 15 leads to an increase in the reaction rate. The rate promotion by acid, therefore, can be caused not only by the preservation of Pd in the divalent oxidation state, but also by an increase in the concentration of the hydride initiator. While the first effect has been clearly demonstrated, the second remains hard to prove. Considering that free protons destabilize the hydride yielding Pd^0 (eq 16),[13q,49] the possibility of kinetic promotion by acids is rightfully a matter of continued debate.

Similar to acids, one of the important roles of phosphine stabilizers is to complex Pd^0, thus inhibiting its agglomeration to Pd black.[13q,15n,q,25e,26c] Interestingly, substrates, like butadiene[22c] and even alkenes,[18b] can also stabilize the catalyst to prevent Pd-black formation. According to this argument, the observed higher rate is due to keeping more of the Pd present in the homogeneous phase where it can be easily activated. Since phosphines can complex both Pd^0 and Pd^{2+}, phosphine stabilization can benefit whether Pd is in the zero or divalent oxidation state.

Table 3. Pd^0 Hydroesterification Catalyst Precursors

Pd precursor	promoter	ref
Pd black or supported Pd^0	HX	15h, 22a,f,g, 43a,b
Pd black or supported Pd^0	L, HX	10a,b, 13p, 18a, 22a, 27a, 34a,b
PdL_4, most often $Pd(PPh_3)_4$	(L, HX)	14g, 20c, 34a,b, 35, 43a

Other results can also support either Pd^0 or Pd^{2+} as the active initiator of catalytic hydroesterification. Thus, $Pd(PPh_3)_4$ and $PdCl_2$[34a] or Pd/C and $Pd(OAc)_2$[43b] give the same conversion and selectivity if all conditions and reagent concentrations are the same.[34a] There are several papers that report $Pd(PPh_3)_4$ as an active catalyst (see Table 3). Furthermore, the often-reported induction period with Pd^{2+} precursors[13l,m,14h,15n,16a,b,26c] suggests that the precursor first needs to undergo a transformation that will lead to the active form. This transformation can be the reduction of Pd^{2+} to Pd^0. This mechanism, in fact, could explain why water reduces the induction period in hydroesterification[14h] if we consider that CO can reduce Pd^{2+} to Pd^0 in the WGSR.[15b] The Pd^0 intermediate then can lead to the catalytically active hydride via eq 15.[15b]

On the other hand, $Pd(PPh_3)_4$ has been shown to reduce the activity of $PdCl_2(PPh_3)_2/10PPh_3$ in the hydroesterification of styrene.[14g] Bittler et al. suggested that Pd^0 complexes have no activity unless HCl is present.[13s] The involvement of Pd^{2+} in the catalytic cycle is also supported by the fact that the nature of the counterion influences both the rate and selectivity of hydroesterification (see next section). The facile Pd^0/Pd^{2+} redox process[7h] makes the elucidation of the issue difficult but also makes it less significant, since the active catalyst can readily form either from Pd^0 or Pd^{2+} precursors.

More recently, several research groups have tested heterogeneous and biphasic Pd hydroesterification systems (Table 5) in an attempt to facilitate catalyst separation from the products. Just as in hydroformylation,[50] the aqueous systems typically have sulfonated phosphines to render the catalyst water-soluble. The two possible drawbacks of the aqueous systems are the increased WGS selectivity[45f] and the reduced reaction rate due to the low solubility of the unsaturated hydrocarbon substrates, especially with carbon numbers above three. Ionic liquids may present a better alternative by offering less reactive solvents. The heterogeneous-supported systems will likely suffer from their well-known liabilities: catalyst leaching and reduced activity.

A. Effect of Counterion on Activity and Selectivity

The vast majority of the reported Pd hydroesterification catalyst precursors have an acid residue

Table 4. Pd^{2+} Hydroesterification Catalyst Precursors[a]

Pd precursor	promoter	ref
PdX_2	none	13r,t, 15h, 20g, 22f, 24g
PdX_2	HX	13u, 16e, 18a, 20g, 22f,g
PdX_2L_2	none	13b,o, 16d, 17, 20c,d, 22c,e,h,i, 25f,i,k,p,r
PdX_2L_2	HX	13d,f−h,n,q,s, 14g, 15h, 18a, 20f, 27a−c,e, 24g, 37
PdX_2L_2	L	13i,l, 14f,h, 15g,i,j,l,n−q, 17, 18c,d, 22d, 24a, 25e,f,g,j,n,o, 26c−f, 34a, 38
PdX_2L_2	HX + L	10b,c, 13e,j,p, 14a, 15c,j, 19, 20a,b, 21, 23, 24b,c, 25c,d,f,l, 27a−d, 36, 40−43
PdX_2L_2	N-base (+L)	13a, 16a−c, 20e, 22c, 24d,e,f
PdX_2L_2	Co- or Fe-based cocatalyst	14a,b,d,e, 26b, 39, 43a
PdX_2L_2	SnX_2 (+ L), X^- is most often Cl^-	13k,m, 14a,i, 15j,k,l,n, 17, 18b,c,d, 25a,b,i, 26a,e,f, 44

[a] X_2 = acid residue anion(s) with a total negative charge of two. L_2 = mono- or bidentate group V ligand(s) with a total number of coordination sites of two.

Table 5. Heterogeneous and Biphasic Pd Hydroesterification Catalyst Precursors

Pd system	promoter	ref
water-soluble PdX_2L_2	HX, L	45, 46
ionic liquid compatible PdX_2L_2	HX, L	47
supported heterogeneous Pd^{2+}	PPh_3, HCl	48b, 48c
supported heterogeneous Pd^0	PPh_3 and Fe, Co, Ni, or Cu chloride	48a

counterion either from the Pd^{2+} salt and/or from the acid promoter (see Tables 3−5). It has been long recognized that the nature of the counterion can significantly affect both activity and selectivity. Tsuji, for example, from his work with butadiene has concluded[22d] that strongly coordinating anions do not allow the formation of diallylic intermediates and thus will favor hydroesterification over oligomerization and telomerization. Hartley and co-workers found[51] that $PdX_2(L_2)$ compounds (L_2 = bidentate phosphine) with "noncoordinating" anions are useful as catalysts while the chloride analogues are inactive, showing examples in hydrogenation and alcoholysis. As will be discussed later, these compounds are also among the most active hydroesterification catalysts.

In the hydroesterification of styrene with $Pd(PPh_3)_2X_2$ catalysts, the activity depends on X as follows: $Cl^- \ll BF_4^- < CF_3SO_3^-$ < *p*-toluenesulfonic acid.[25f] The largest activity boost can be achieved by replacing the strongly coordinating anion with a weakly coordinating one, but there seems to be significant further room for rate improvement by optimizing the weakly coordinating anion. Interestingly, the n/i-selectivity is the same regardless of the coordination strength of the anion.

Drent found that anions significantly influence the rate in the conversion of ethene to methyl propionate with the in-situ-prepared $Pd(PPh_3)_2X_2$ catalysts.[42h] Also, in the hydroesterification of propyne to methyl methacrylate (MMA),[19,21] the observed rates span from 10 to 40 000 mol propyne/(mol of Pd h) TOF values, depending on the acid promoter (see Table 6). Again, the large activity and relatively small selectivity differences depending on the acid are apparent.

Similar trends have been reported in the hydroesterification of alkenes[42h,i] as well. As depicted in Table 7, the reaction with $Pd(OAc)_2$/L catalysts is orders of magnitude slower in the absence of an acid promoter. On the basis of the last three entries for ethene, both the acid and the phosphine need to be present in significant excess to achieve maximum activity. However, no further gain is achieved if the excess exceeds a certain threshold.

Table 6. Effect of Acid Promoter in the Hydroesterification[a] of Propyne[19]

acid		*T*	average rate	MMA
type	mmol	(°C)	(mol propyne/ (mol Pd h))	selectivity (%)
CH_3-SO_3H	2.0	45	40 000	98.9
p-$CH_3-Ph-SO_3H$	2.0	45	20 000	99.1
$Ph-PO(OH)_2$	2.0	50	4 000	98.9
CH_3-COOH	10.0	50	100	99.0
HCl	2.0	50	ca. 10	98.0

[a] Conditions: 30 mL of propyne, 50 mL of methanol, 60 bar CO, 0.025 mmol of $Pd(OAc)_2$, 1.0 mmol of bis(phenyl)-2-pyridylphosphine (2-$PyPPh_2$), batch operation.

Table 7. Hydroesterification Activity of $Pd(OAc)_2$/PPh_3/HA Catalysts.[a] Anion and Phosphine Excess Effects[42i]

PPh_3 (mmol)	acid (mmol)	reaction time (h)	Et−COOMe (g)	average rate (g of ester/ (g of Pd h)
3.0[b]	none	5.00	0.5	10
3.0[b]	pTS (2.0)	0.25	16.0	6400
3.0[b]	CF_3-SO_3H (2.0)	0.25	15.0	6000
0.3[b]	pTS (2.0)	5.00	5.0	100
3.0[b]	pTS (4.0)	0.25	17.0	6800
3.0[b]	pTS (0.5)	0.25	7.8	3100
3.0[c]	none	5.00	trace	N/A
3.0[c]	pTS (2.0)	1.00	14.7	1470
3.0[c]	pTS (2) + H_2O (10)	1.00	17	1700
3.0[c]	$HClO_4$ (2.0)[d]	0.50	16.0	3200
3.0[c]	H_2SO_4 (2.0)	0.50	17.0	3400
3.0[c]	CF_3-SO_3H (2.0)	0.50	16.0	3200
3.0[c]	HCl (2.0)[d]	5.00	4.8	96
3.0[c]	H_3PO_4 (2.0)[d]	5.00	5.1	102
3.0[c]	CF_3COOH	5.00	2.6	52
3.0[c]	CH_3COOH (150)	5.00	trace	N/A
3.0[c]	$Et-PO(OH)_2$ (2)	2.50	2.4	96

[a] Conditions: 135 °C, 20 bar CO, 0.1 mmol $Pd(OAc)_2$, 50 mL of MeOH. Batch experiment. pTS = *p*-toluenesulfonic acid. [b] Ethene: 20 bar. [c] Propene: 8 bar; n/i-ester = 7:3, except for HCl: 56:44. [d] Charged as aqueous solution.

Strong organic and mineral acids of weakly coordinating anions provide similar activity boosts. The promoting effect of the chemically similar sulfonic acids, like *p*-toluenesulfonic acid and trifluoromethanesulfonic acid, is similar although their order is different for ethene and propene. The two best inorganic acid promoters, sulfuric and perchloric acid, are comparable with the best organic acid promoters. The only common feature of the best promoters is

their strong acidity ($p_{Ka} < 2$) and weak coordinating power. These are in fact the features that Shell often claims in its recent hydroesterification patents.[21,23,40−42]

As mentioned before, the promoting effect is most likely due to the replacement of the strongly coordinating acetate anion of the catalyst precursor $Pd(OAc)_2$ via eq 17. Apparently, the removal of the strongly coordinating anion creates coordination sites on the Pd^{2+} central atom that are more accessible to the substrates entering the catalytic cycle.

$$Pd(OAc)_2L_2 + 2HX + 2S \rightleftarrows [PdL_2S_2]^{2+}(X^-)_2 + 2HOAc \quad (17)$$

L = phosphine ligand

HX = strong acid with weakly coordinating anion

S = solvent or other weak ligand present

The rate promoting effect cannot be linked to the presence of protons, since excess acetic acid does not increase the reaction rate at all (see second from last entry in Table 7). Also, several strong acids in Table 7 provide only minor rate enhancement, although they can donate protons as effectively as the strongly promoting acids of weakly coordinating anions do.

The acid strength is likely important only in shifting equilibrium 16 to the right, creating a more accessible Pd center by replacing the strongly coordinating anion of the Pd precursor with a weakly coordinating one. If indeed that is the only role of the acid, preformed or in situ made PdX_2L_2/L catalysts (X = weakly coordinating anion) with nonacidic anion sources in neutral or basic media will be just as active as the acidic systems. In fact, Drent already published some high-activity nonacidic systems that are made by using the latter method.[40b−g]

While weakly coordinating anions do not change selectivity as compared to the strongly coordinating anions (e.g., chloride), $SnCl_2$ dramatically changes n/i-selectivity by forming the π-acceptor $SnCl_3^-$ that effectively acts as a ligand (ref 29a, p 636). Thus, for example, in the hydroesterification of heptene-1, the addition of $SnCl_2$ to $Pd(PPh_3)_2Cl_2$ in a 10:1 ratio increases the selectivity to the linear ester from 58% to 87%.[13m] Noskov and Petrov also reported[26a] a reversal of the n/i-selectivity ratio from 3/7 to 7/3 in the hydroesterification of styrene after the addition of $SnCl_2$ to the $Pd(PPh_3)_2Cl_2$ catalyst. The authors attributed this selectivity change to electronic rather than to steric effects. In a recent report,[25a] a combination of $SnCl_2$ and excess PPh_3 increased the selectivity to the linear ester from 3% to 75% in the hydroesterification of styrene with the $Pd(PPh_3)_2Cl_2$ catalyst at 100 °C. $SnCl_2$ also increases the n/i-ratio in the hydroformylation of alkenes with Pd catalysts.[44c−e,g]

B. Effect of Nonligand Promoters on Activity and Selectivity

Nitrogen bases have been proposed as rate promoters,[21e,22c,24d−f,40c,d] especially in the hydroesterification of dienes.[22c,24d−f] Thus, for example, Tanaka et al. reported[25m] an approximately 3-fold increase of conversion in the hydroesterification of 2-phenylpropene upon addition of nitrogen bases. Bidentate nitrogen bases, such as 2,2′-bipyridyl and 1,10-phenanthroline, were more effective than pyridine. In a Du Pont patent,[24d] both strong acids ($p_{Ka} < 3.5$) and N-bases are used as promoters with $PdCl_2/PPh_3$ catalyst. The role of the N-base in the latter example might be to bind the Cl^- ion released by the strong acid component in the form of an ammonium salt ($R-NH^+Cl^-$). In the case of dienes, however, bases mostly promote telomerization rather than hydroesterification. Although the products in telomerization are also esters, the reaction is distinctively different, since it incorporates two diene substrates, effectively yielding the ester of the diene dimer.

Iron, cobalt, nickel, and copper compounds, like carbonyls and chlorides, have been reported to act as rate promoters and to improve n/i-selectivity (see references in Tables 4 and 5). The source of the promoting effect is not clear. So far, however, no major breakthrough has been achieved by using these cocatalysts.

Several patents and publications mention the rate-promoting and induction period reducing effect of water[6f,14e,15b,25d,43b] and H_2[13i,15j,l,n,36h,40g] in the hydroesterification of alkenes. (Note: A small promoting effect of water, for example, can be seen in Table 7. Compare the second and third entries for the propene series.) The water effect is likely related to hydroesterification via the WGSR.[12b,15b,40g] The observed rate promotion has been proposed[15b,25d,40g] to be caused by an increase in the concentration of the palladium hydride (cf. eq 2.4 in Figure 2), thus allowing a faster rate in the activation of alkene substrates. (Note: The mechanistic aspects of water and H_2 promotion will be discussed in more detail in section V.) Unlike in the hydroesterification of alkenes, H_2 has no promoting effect in the hydroesterification of alkynes. It acts essentially as an inert component in the CO feed.[19a]

It needs to be pointed out that although hydrogen and water can act as rate promoters, they seem to destabilize the catalyst. Drent et al., for example, proposed the use of organic water- and hydride-scavengers to stabilize PdX_2L_2 (X = weakly coordinating anion, L_2 = mono- or bidentate phosphines) catalysts,[12,40c,e,52] especially in the absence of acids that can reoxidize Pd^0 (cf. section III.A). Apparently, Drent's group concluded that the potential gain from the rate-promoting effect of hydrogen is lower than the losses due to catalyst decomposition.

C. Effect of Ligand Structure on Activity and Selectivity

Ligands can not only stabilize Pd hydroesterification catalysts, but also fundamentally change their selectivity and activity. It is well-known, for example, that monodentate phosphines favor hydroesterification of ethene while bidentate phosphines switch selectivity of PdX_2L_2 catalysts (X = weakly coordinating anion, L_2 = mono- or bidentate phosphine ligand) to polyketones.[12,52] Drent's recent hydroesterification research has very successfully capitalized on this

Table 8. Effect of Presence and Position of Pyridyl Group in the Ligand in the Hydroesterification[a] of Propyne[19]

ligand	$Pd(OAC)_2$ (mmol)	T (°C)	average rate (mol of propyne/ (mol of Pd h)	MMA sel. (%)
PPh_3	0.100	115	approximately 10	89.0
4-$PyPPh_2$	0.100	90	approximately 10	90.0
3-$PyPPh_2$	0.100	70	1000	99.2
2-$PyPPh_2$	0.100	45	40 000	98.9
2-$PyPPh_2$	0.012	115	5 000 000[b]	N/A

[a] Conditions: 30 mL of propyne, 50 mL of methanol, 60 bar CO, 3.0 mmol of ligand, 2.0 mmol of CH_3-SO_3H; 2-Py = 2-pyridyl. [b] Note: Calculated by the author from the original data obtained at 45 °C by using an estimated 20 kcal/mol activation energy.

strong ligand effect and achieved orders of magnitude activity improvements over the conventional PPh_3-modified Pd catalyst systems.

The conversion of propyne to MMA (the minor product is the liner ester, methyl crotonate) in the presence of PdX_2L_2 catalysts is well-documented.[19] The introduction of the 2-pyridyl group in the triaryl phosphine ligand has increased catalytic activity by approximately 5 orders of magnitude as compared to the parent PPh_3 system (see Table 8). The enormous activity increase allows low reaction temperatures, leading not only to increased productivity but, indirectly, to improved catalyst stability as well.

Apparently, the pyridyl nitrogen is the most effective in the 2-position allowing optimal interaction with the metal center. Its effectiveness rapidly drops as it is positioned further away. When the nitrogen is in the 4-position, it is completely ineffective. It should be clear, therefore, that the rate enhancement is not a simple pH effect. Rather, the pyridyl nitrogen must be involved in the transformation of a catalytic intermediate.

Interestingly, substituting more than one phenyl group in PPh_3 by a pyridyl group actually reduces activity, although introducing the first pyridyl group resulted in an enormous boost (compare third and last two entries in Table 9). Apparently, while the extra pyridyl nitrogen cannot participate in the rate-enhancing mechanism, it has a secondary, rate-reducing effect. The mechanistic implications of this pyridyl nitrogen promotion will be discussed in more detail in section V.

While the rate is significantly influenced by the pyridyl substitution, it has essentially no impact on selectivity. Trends such as these defy intuition. This is an example of why the emerging new technique of combinatorial chemistry and high-throughput experimentation[53] has great potential in catalysis research.

Pd catalysts of the MMA process can be further fine-tuned by increasing steric demand in the close vicinity of the pyridyl group. Thus, as depicted in Table 9, a methyl substituent in the 6-position of the pyridyl ligand increases the selectivity of the branched ester, MMA, from 98.9% to 99.95%. As expected, if the substituent is further away from the metal center, for example, in the 4-position of the 2-pyridyl group, it does not have any selectivity impact at all. The above selectivity increase may seem small in absolute values but in fact represents a 22-fold rate suppression of the formation of the linear methyl crotonate side product!

While the steric influence on selectivity is quite noticeable, the electronic effects are negligible. Thus, changing the substituent in the 6-position from methyl to methoxy or bromo group yields essentially the same selectivity, although their electronic properties are very different: the methyl group is an electron donor, while the bromo and methoxy groups have an electron-withdrawing effect.

The impact of electronic and steric factors on the reaction rate is just the opposite of what is observed in selectivity. The large electronic effect of substitution in the 6-position on the reaction rate is apparent (compare entries 3, 5, and 6 in Table 9). While selectivity is essentially unchanged by changing the electronic effect of the substituent, electron-withdrawing groups in the 6-position substantially reduce the rate of ester production. On the other hand, introducing the methyl group in the 6-position does not change catalytic activity at all, indicating the lack of steric effect on the rate (see first two entries in Table 9).

There is no best ligand for all hydroesterification reactions. Rather, the ligand should be tailored to the substrate. 2-Pyridyl ligands, for example, work best in alkyne but not in alkene conversion.[19,21,41] For alkenes, bulky bidentate alkyl phosphines are preferred.[40a−d] Another interesting aspect of these recent findings is that steric bulk and/or increased basicity of the aforementioned bidentate ligands changes the selectivity of the Pd catalyst from polyketones to esters. Translating this observation into kinetic terms, the steric bulk and/or increased basicity of the bidentate phosphine fundamentally changes the relative rates of chain propagation vs chain termination,

Table 9. Effect of Substituents in the 6-Position of Pyridyl Group in the Hydroesterification[a] of Propyne[19]

ligand	acid	T (°C)	average rate (mol of propyne/(mol of Pd h))	MMA (%)
2-$PyPPh_2$	p-Me−Ph−SO_3H	60	40 000	98.90
2-(6-Me-Py)PPh_2	p-Me−Ph−SO_3H	60	40 000	99.95
2-(6-Me-Py)PPh_2	Me−SO_3H	60	50 000	99.95
2-(4-Me-Py)PPh_2	Me−SO_3H	70	20 000	98.80
2-(6-OMe-Py)PPh_2	Me−SO_3H	80	4000	99.85
2-(6-Br−Py)PPh_2	Me−SO_3H	90	500	99.65
$(2\text{-}(6\text{-Me-Py}))_2PPh$	Me−SO_3H	80	20 000	99.90
$(2\text{-}(6\text{-Me-Py}))_3P$	Me−SO_3H	80	10 000	99.80

[a] Conditions: 30 mL propyne, 50 mL methanol, 30 mL N-methylpyrrolidone, 60 bar CO, 0.025 mmol $Pd(OAc)_2$, 1.0 mmol ligand, 2.0 mmol acid. Batch operation. 2-Py = 2-pyridyl.

Table 10. Hydroesterification Activity of $Pd(OAc)_2L_2$/L/*p*-Toluenesulfonic Acid Catalysts:[a] Aryl vs Alkyl Phosphines[42i]

phosphine	phosphine (mmol)	reaction time (h)	ester yield (g)	rate (g of ester/ (g of Pd h)	linear ester (%)
PPh_3	3.0	1	14.7	1 470	70
$PEtPh_2$	3.0	5	1.5	30	68
PEt_2Ph	3.0	5	0.5	10	60
$P(^nBu)_3$	3.0	5	0.4	8	68
$P(^nBu)_3$	1.5	5	0.5	10	50
$P(pMeO-Ph)_3$	3.0	1	15	1 500	74

[a] Conditions: 135 °C, 8 bar propene, 20 bar CO, 0.1 mmol of $Pd(OAc)_2$, 2 mmol of pTS = *p*-toluenesulfonic acid, 50 mL of MeOH. Batch experiments.

favoring termination (hydroesterification) over propagation (CO−alkene copolymerization).

Very few studies have been published for ligand structural effects in the hydroesterification of alkenes. Most information available is from patent examples that usually report experiments under different conditions. Fundamental reaction condition data are also often omitted, so direct comparison of the performance of the published systems is not possible. Instead, selected data will be compared for which a reliable direct comparison can be made.

Drent's group at Shell carried out the most extensive ligand screening for the hydroesterification of alkenes with $Pd(OAc)_2L_2$/L catalysts. In most of their systems, the catalyst also has an acid or salt promoter to replace the acetate group of the precursor to a weakly coordinating anion, affording significant activity improvements (see earlier discussions on acid promoters in section III.A and examples in Table 7).

From his early work, Drent concluded that in the hydroesterification of alkenes with $Pd(OAc)_2L_2$/L catalysts, trialkyl phosphines, like $P(^nBu_3)$, are more effective than triaryl phosphines, like PPh_3.[43a] However, this activity order reverses if acid promoter is also present.[42i] As shown in Table 10, the more basic alkyl phosphines yield rates 2 orders of magnitude lower than triaryl phosphines in the presence of *p*-toluenesulfonic acid. Considering the large difference in the basicity of triphenyl- vs tributylphosphines, it is not surprising that moderate (50%) reduction in tributylphosphine concentration cannot compensate for the activity difference between the two ligands (compare entries 4 and 5 in Table 10). This observation unequivocally points to a strong electronic effect on activity.

While basicity of the phosphine ligand strongly influences catalytic activity, it has essentially no impact on the n/i-ester selectivity. These trends are the same as the ones reported for the hydroesterification of alkynes (vide supra), and therefore, they seem to be general in Pd-catalyzed hydroesterification.

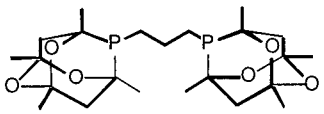
The selectivity effect of increasing steric bulk of the ligand is also the same as in the hydroesterification of alkynes. Du Pont[36b,c] and Atlantic Richfield,[38] for example, claim increased branched ester selectivity in the hydroesterification of propene by using ortho-substituted aryl phosphines. Replacing PPh_3 in the $PdCl_2/PPh_3$/HCl catalyst by, for example, bis(*o*-tolyl)-diphenylphosphine, bis(2,4-dimethylphenyl)phenylphosphine, or bis(*o*-anisoyl)phenylphosphine, the iso-ester selectivity increases from approximately 55% to above 90%.[36b,c] The target product, MMA, is made from the primary hydroesterification product (methyl isobutyrate) by dehydrogenation.

Although (2-pyridyl)diphenylphosphine provides approximately 10 times higher activity in the Pd-catalyzed hydroesterification of alkenes than triphenylphosphine,[41] the highest activity catalysts by Shell contain alkyl diphosphines with bulky end groups.[40] Some representative examples of this ligand family are shown in Figure 3.

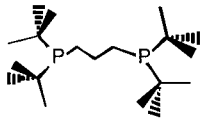
Depending on the reaction conditions, Pd^{2+}−bidentate ligand complexes can catalyze not only ester formation, but also the production of polyketones, ketones, or aldehydes.[40a,g] Thus, with $CO/H_2 = 1:1$ (syngas) feeds, the primary reaction route for alkenes is hydroformylation to aldehydes. With pure CO, either ketones or esters will form. In general, increased phosphine basicity and higher temperature favors hydroesterification over ketone or polyketone formation.

Reaction rates with this new family of phosphines can be rather high (see Table 11). For comparison, the last entry shows the reaction rate with PPh_3, reflecting a 1000-fold rate improvement with the best diphosphine ligands. In ethene hydroesterification, these bidentate ligands afford over 98% methylpropionate selectivity.

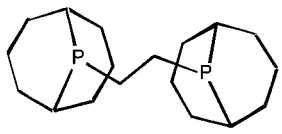
These bidentate ligands not only offer activity advantage, but also allow operation under nonacidic



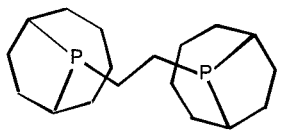
1,3-P,P'-di(phospha-(oxa-adamantyl))propane (DPA3)



1,3-bis(di-t-butylphosphino)propane



1,2-P,P'-Bis(9-phosphabicyclo[3.3.1]nonyl)ethane ([3.3.1]BPNE)



1,2-P,P'-Bis(9-phosphabicyclo[4.2.1]nonyl)ethane ([4.2.1]BPNE)

Figure 3. New Shell ligands for Pd-catalyzed hydroesterification of alkenes.[40]

Table 11. Methyl Propionate Production Rates with Some New Shell $Pd(OAc)_2L_2/L$ Catalysts

phosphine and Pd/L (mmol/mmol)	acid (mmol)	T °C	P_{CO}^0 (bar)	P_{H2}^0 (bar)	average rate (mol of ester/(mol of Pd h))	ref
$(^tBu)_2P-(CH_2)_3-P(^tBu)_2$ (0.1/0.3)	$Me-SO_3H$ (0.25)	100	40	5	13 000	40f
DPA3 (0.1/0.15)	$Me-SO_3H$ (0.20)	90	30	0	8000	40a
BPNE (mixture) (0.25/0.60)	none	125	30	0	490	40c
$P(2\text{-}Py)Ph_2$ (0.1/5.0)	p-tol$-SO_3H$ (2.00)	95	30	0	1000	41a
PPh_3 (0.1/0.3)	$Me-SO_3H$ (0.25)	100	40	0	<10	40f

conditions.[40b−g] The nonacidic catalysts are formulated using $Pd(OAc)_2$, a Ni or Cu salt of the weakly coordinating anion (or the free acid of the anion), and excess nitrogen base (e.g., trihexylamine), creating a basic pH. A water- and hydride-scavenger (e.g., 1,4-naphthoquinone and trimethyl or tributyl orthoformate)[40b−f] is often added as catalyst stabilizer.

Catalysts with strong acid promoters can also convert internal alkenes to esters at reasonable reaction rates.[40a] The observed n/i-selectivity is the same for α and internal olefins. Since internal olefins have relatively low reactivity (cf. section II.A), it is likely that the internal olefins first undergo isomerization and the α olefin intermediate is finally converted to the ester product. It is not clear if the isomerization is catalyzed by the metal or acid component of the catalyst.

DSM and Du Pont patented[36a] a phosphine similar to Shell's new bidentate ligands. The metallocene-bridged bidentate ligand affords a 3700 mol ester/(mol of Pd h) reaction rate in the hydroesterification of methyl 3-pentenoate to dimethyl adipate at 130 °C and 30 bar initial CO pressure. The catalyst composition in the referred experiment is 0.12 mmol each of $Pd(OAc)_2$ and ferrocene diphosphine plus 1.7 mmol of *p*-toluenesulfonic acid. The advantage of the new DSM−Du Pont ligand is claimed to be an increased (approximately 85%) normal-ester selectivity.

The rate-accelerating effect of increased bulkiness of phosphine promoters has also been observed in the hydroesterification of aryl alkenes with $PdCl_2L_2$ catalysts.[25k] Thus, in the reaction of 6-methoxy-2-naphthylethene at 100 °C, the conversion increases from 39% to 100% when the $MePPh_2$ ligand is replaced by (c-Hex)PPh_2. When L is the much bulkier *l*-menthyldiphenylphosphine, 100% conversion is reached at 50 °C.

Effective bidentate phosphines with optimum P−P distance also offer the advantage of increased n/i-ratio over monodentate phosphines.[16d,25p−r] Sugi and Bando, for example, compared the selectivity effect of PPh_3, Ph_2PBu, PBu_3, $P(cHex)_3$, and $Ph_2P-(CH_2)_n-PPh_2$ ($n = 1-6$, 10) in the hydroesterification of styrene with $PdCl_2L_2$ catalysts.[25p] All monodentate phosphines yield essentially identical (approximately 99%) iso-selectivity. The n/i-selectivity with bidentate phosphines is a function of the carbon number of the bridging group. The iso-ester selectivity reaches a minimum at $n = 3$ and 4 (28.1% and 31.6%, respectively). At $n = 6$, the selectivity approaches that of the monodentate phosphines (83.4%), and at $n = 10$, the selectivity is indistinguishable (94.4%) from that of the monodentate ligands. Therefore, the most effective bidentate phosphine forms the most stable—six-membered—metallacycle ring. As the length of the bridging group increases beyond this optimum value, the stability of the metallacycle ring decreases. This destabilization allows more facile arm-off dissociation of the ligand, which in turn brings the catalyst closer to the monodentate systems.

In the hydroesterification of butadiene, Shell typically applies alkyl-bridged bidentate aryl phosphines, like 1,4-bis(diphenylphosphino)butane.[23] DSM claims improved activity if the basicity, and thus the binding strength, of the two arms of the diphosphine ligand is different.[24b] Thus, for example, a factor of 1.75 and 1.5 rate increase is reported with 1-(diisopropylphosphino)-4-(diphenylphosphino)butane and 1-(dibutylphosphino)-4-(diphenylphosphino)butane over 1,4-bis(diphenylphosphino)butane, respectively. Alkyl bidentate phosphines yield lower rates than their aryl derivatives.[24b] Apparently, bidentate phosphines are able to prevent the coordination of two butadienes to the Pd center and therefore can suppress oligomerization and telomerization[23e] without the need for a strongly coordinating anion (cf. section III.A).

IV. Kinetic and Selectivity Response to Reagents and Promoters

Noskov and Petrov published a series of papers[14,26] on their kinetic and mechanistic investigations of hydrocarboxylation with $PdCl_2(PPh_3)_2/PPh_3$. Table 12, for example, summarizes their results for the conversion of heptene-1 to caprylic and α-methylenanthic acids.[14f]

Surprisingly, the measured turnover frequencies with $PdCl_2(PPh_3)_2/PPh_3$ (Table 12) and $Pd(OAc)_2$-$(PPh_3)_2/PPh_3$/Me-SO_3H (Table 10, last entry) are in the same range, although one would expect orders of magnitude difference due to the $Me-SO_3H$ promoter in the latter catalyst (cf. Table 7). The n/i-selectivity, on the other hand, is in agreement with the Shell data, confirming the conclusion that the nature of the anion does not influence regioselectivity (cf. section III.A).

The kinetic response to CO increasing partial pressure is depicted in Figure 5. The overall reaction rate rapidly increases with CO partial pressure, showing a greater than first-order dependence. This indicates that CO adds to catalytic intermediates at least once before or in the rate-limiting step. In fact, the reaction mechanism likely involves a conversion path with two CO additions before the rate-limiting step. The less than second-order response can then be the result of a competition of CO and alkene in which CO suppresses the activation of alkene by shifting the catalyst into a coordinatively saturated, thus inactive, state.

Table 12. Hydrocarboxylation of Heptene-1 (0.65 mol/L in 1,4-dioxane) at 110°C with $PdCl_2L_2$/L (L = PPh_3)[14f]

exp no.	[$PdCl_2L_2$] (mol/L)	p_{CO} (MPa)	excess [L] (mol/L)	p_{CO}/[L] (MPa L/mol)	[H_2O] (mol/L)	rate (normal) (mmol/(L min))	rate (iso) (mmol/(L min))	rate (total) (mmol/(L min))	rate (total) (mol of acid/(mol of Pd h))	selectivity (normal) (%)	n/i acid
1	0.0065	0.60	0.039	15	1.8	3.5	0.7	4.2	38.8	83	4.88
2	0.0065	1.10	0.039	28	1.8	4.1	1.0	5.1	47.1	80	4.00
3	0.0065	1.60	0.039	41	1.8	4.3	1.5	5.8	53.5	74	2.85
4	0.0065	2.10	0.039	54	1.8	6.0	2.6	8.6	79.4	70	2.33
5	0.0065	2.60	0.039	67	1.8	7.2	3.5	10.7	98.8	67	2.03
6	0.0065	2.80	0.039	72	1.8	8.0	3.8	11.8	108.9	68	2.13
7	0.0065	3.10	0.039	79	1.8	8.0	4.5	12.5	115.4	64	1.78
8	0.0065	2.10	0.039	54	1.0	3.5	2.2	5.7	52.6	61	1.56
9	0.0065	2.10	0.039	54	1.6	5.6	2.8	8.4	77.5	67	2.03
10	0.0065	2.10	0.039	54	2.0	6.1	2.8	8.9	82.2	69	2.23
11	0.0065	2.00	0.039	51	3.0	7.1	2.7	9.8	90.5	72	2.57
12	0.0065	1.40	0.039	36	5.0	6.5	1.7	8.2	75.7	79	3.76
13	0.0065	0.97	0.039	25	7.5	4.8	1.0	5.8	53.5	83	4.88
14	0.0065	0.82	0.039	21	10.0	3.7	0.9	4.6	42.5	80	4.00
15	0.0065	2.10	0.007	300	1.6	7.1	6.3	13.4	123.7	53	1.13
16	0.0065	2.10	0.013	162	1.6	6.0	4.9	10.9	100.6	55	1.22
17	0.0065	2.10	0.026	81	1.6	5.5	3.2	8.7	80.3	63	1.70
18	0.0065	2.10	0.052	40	1.6	5.2	2.1	7.3	67.4	71	2.45
19	0.0065	2.10	0.065	32	1.6	5.0	1.8	6.8	62.8	74	2.85
20	0.0065	2.10	0.078	27	1.6	5.3	1.6	6.9	63.7	77	3.35
21	0.0065	2.10	0.104	20	1.6	4.6	1.3	5.9	54.5	78	3.55
22	0.0033	2.10	0.104	20	1.6	2.7	0.7	3.4	61.8	79	3.76
23	0.0130	2.10	0.104	20	1.6	11.2	3.0	14.2	65.5	79	3.76

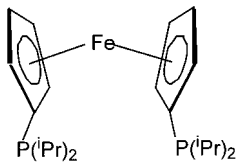


Figure 4. New DSM-Du Pont ligand for Pd-catalyzed hydroesterification of alkenes.[36a]

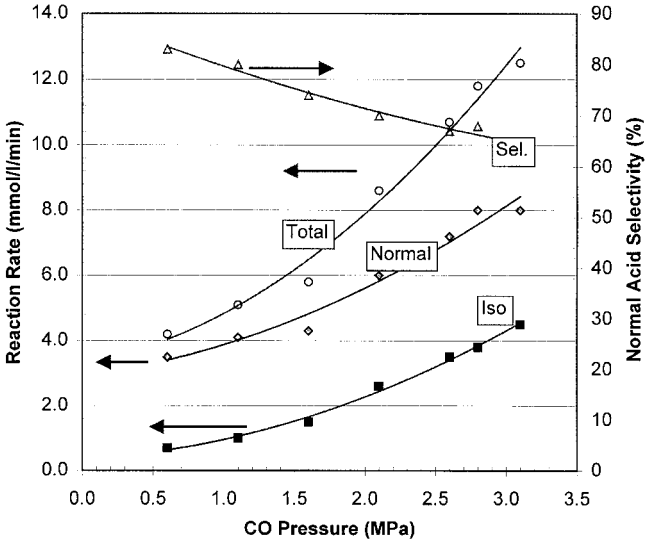


Figure 5. Effect of CO on rate and selectivity in heptene-1 hydrocarboxylation with $PdCl_2L_2$/L (L = PPh_3) catalyst.[14f] Conditions: 110 °C, 0.0033 mol/L $PdCl_2(PPh_3)_2$, 0.039 mol/L PPh_3, 1.8 mol/L H_2O, and 0.65 mol/L 1-heptene in 1,4-dioxane. Initial rates determined as the average rate for the first 20% 1-heptene conversion.

Most reports support[13i,l,m,q,14a,e,15c,25c,d,26a,d] the positive kinetic order for CO in the hydroesterification of alkenes with $PdCl_2(PPh_3)_2$, although there are some that suggest zero.[15p,25f] The reason for this discrepancy is not known. The kinetic order in p_{CO} with the related $PdCl_2(PPh_3)_2/SnCl_2$ catalyst has been found to be 1[13m] and in a more qualitative report greater than 0.[15n]

Since CO boosts both the normal- and iso-acid production rates, normal-acid selectivity is only slightly decreased at higher p_{CO}. Several papers report similar selectivity response to CO[13q,14a,15j,l,n,25c,d,f,26a,d] with only two exceptions.[13i,15q] This selectivity trend suggests at least two parallel catalytic cycles, one of which involves more CO ligand in the transformations toward the product than the other route. The latter route also yields lower selectivity toward normal-acids. The overall effect, therefore, is that increased CO concentration shifts the equilibrium toward the more CO-containing catalytic species and with it toward higher branched product selectivity. Analogous mechanism has been proposed for hydroformylation with $Rh(CO)_2(PPh_3)_2/PPh_3$ (ref 30b and references therein).

Just as in hydroformylation,[30] the kinetic and selectivity effect of excess PPh_3 is the opposite of CO (see Figure 6). Thus, the overall rate is inhibited by the excess phosphine, but increasing phosphine concentration increases the selectivity to the linear acid. Most publications support the inhibiting[13i,q,14a,e,g,15c,26a,c] and positive n/i-selectivity[13i,q,14e,g,15j,l,p−q,25c,26a,c,d] effect of the phosphine. Again, this selectivity trend can be explained by the existence of at least two parallel catalytic cycles with different CO/PPh_3 ratio within the ligand sphere of the Pd catalyst.

This competition in the ligand sphere is also strongly supported by the fact that the normal/iso-selectivity can be described as a function of the p_{CO}/[PPh_3] ratio for a wide range of catalyst compositions (Figure 7). It needs to be pointed out, however, that the correlation shown in Figure 7 will only hold at constant water concentration since, unlike other substrates, water has an influence not only on the rate but also on the regioselectivity of the reaction, as well (see Figure 8).

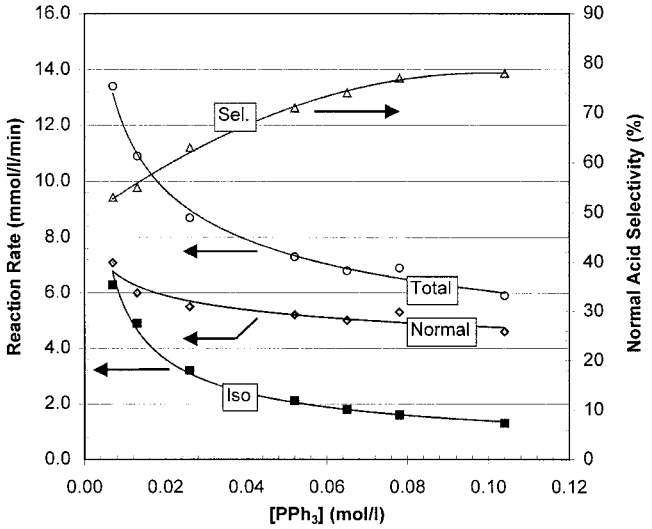


Figure 6. Effect of [PPh_3] on rate and selectivity in heptene-1 hydrocarboxylation with $PdCl_2L_2$/L (L = PPh_3) catalyst.[14f] Conditions: 110 °C, 2.1 MPa CO, 0.0033 mol/L $PdCl_2(PPh_3)_2$, 1.6 mol/L H_2O, and 0.65 mol/L 1-heptene in 1,4-dioxane. Initial rates determined as the average rate for the first 20% 1-heptene conversion.

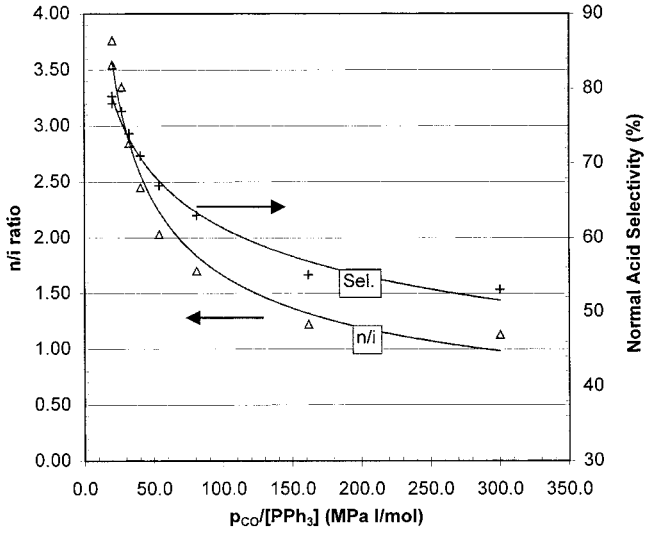


Figure 7. Effect of p_{CO}/[PPh_3] ratio on normal/iso-ester selectivity in heptene-1 hydrocarboxylation with $PdCl_2L_2$/L (L = PPh_3) catalyst.[14f] Conditions: 110 °C, 0.0033 mol/L $PdCl_2(PPh_3)_2$, 0.007−0.104 mol/L PPh_3, 0.6-3.1 MPa CO, and 0.65 mol/L 1-heptene in 1,4-dioxane. Initial rates determined as the average rate for the first 20% 1-heptene conversion.

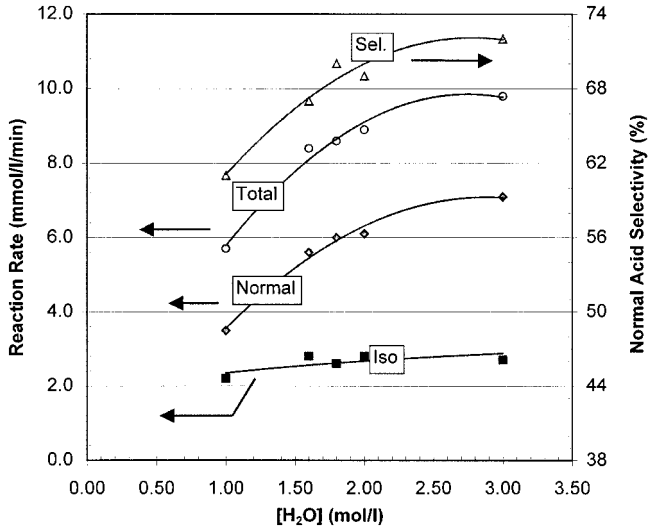


Figure 8. Effect of [H_2O] on rate and normal/iso-ester selectivity in heptene-1 hydrocarboxylation with $PdCl_2L_2$/L (L = PPh_3) catalyst.[14f] Conditions: 110 °C, 0.0033 mol/L $PdCl_2(PPh_3)_2$, 0.039 mol/L PPh_3, 2.1 MPa CO, and 0.65 mol/L 1-heptene in 1,4-dioxane. Initial rates determined as the average rate for the first 20% 1-heptene conversion.

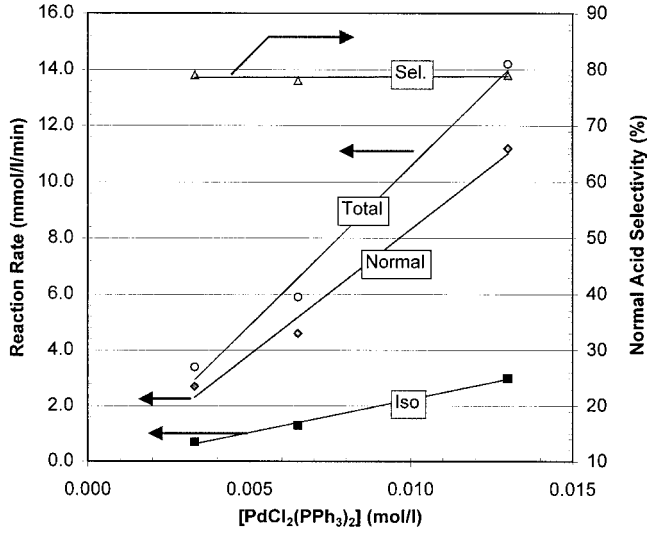


Figure 9. Effect of [$PdCl_2L_2$] on rate and normal/iso-ester selectivity in heptene-1 hydrocarboxylation with $PdCl_2L_2$/L (L = PPh_3) catalyst.[14f] Conditions: 110 °C, 0.104 mol/L PPh_3, 2.1 MPa CO, 1.6 mol/L H_2O, and 0.65 mol/L 1-heptene in 1,4-dioxane. Initial rates determined as the average rate for the first 20% 1-heptene conversion.

The kinetic effect of water is special among the nucleophiles participating in the Reppe-carbonylation reaction. As mentioned before (cf. section III.B), it is often described as a rate promoter in hydroesterification. Interestingly, water increases the formation rate of the linear acid far more than it does for the branched acid (Figure 8). The overall kinetic response in Figure 8, therefore, results both from its promoting effect and from its participation as a substrate. The selectivity change as a function of water concentration is more likely linked to the promoting rather than to the substrate role, since similar behavior has not been reported for any other nucleophile substrate.

There is relatively little known about the kinetic effect of other nucleophiles. They are often used in large excess as solvents, especially in hydroesterification. One publication[19a] reports a zero kinetic order for the concentration of alcohol in the hydroesterification of cyclohexene.

As expected, the reaction is first order in the concentration of palladium.[13l,m,q,14a,e,g,15c,25d,26a,c,d] As depicted in Figure 9, changing the concentration of the precursor palladium complex does not influence regioselectivity if all other concentrations are kept constant. In this regard, it needs to be pointed out that the latter condition can only be met in the presence of substantial ligand excess that ensures constant phosphine concentration. In the absence of ligand excess, the position of ligand exchange equilibrium of the PdX_2L_2 metal complex is influenced

by the concentration of the precursor, which in turn will affect rate and selectivity.[15q]

The reported kinetic response to alkenes varies between first[13l,q,15c,n] and zero[15n,26a] order. Zero-order kinetics seems to be characteristic for the $SnCl_2$-modified systems.[15n,26a] There are also reports that suggest a variable kinetic response to the concentration of the alkene.[14a,e,25d,26c] Furthermore, in the hydrocarboxylation of styrene, Noskov and Petrov found a zero kinetic order in the production of the normal but a first kinetic order in the production of the branched acid. Consequently, increasing substrate concentration results in a reduced n/i-product ratio.

Unlike in hydroformylation,[30] increasing temperature typically leads to higher n/i-ratios.[13q,25d,f,26e,f] The apparent activation energy for the normal-product is higher than that for the iso-route. In fact, the published activation energies in the hydrocarboxylation of styrene to 3- and 2-phenylpropionic acid are 105 and 30 kJ/mol, respectively.[26f] This large difference in the activation energies is the result of the n/i-selectivity shift when the reaction temperature changed. For the same reaction, catalyzed by $Pd(OAc)_2/PPh_3$, another paper[25d] gives an overall activation energy of 65.5 kJ/mol, which seems to be in a reasonable agreement with the combined values in 26f (the overall activation energy is the selectivity-weighed average of the activation energies of the normal- and iso-routes).

The large difference between the activation energies of the normal- and iso-routes is reduced to 18 kJ/mol (119 vs 101 kJ/mol) in the presence of $SnCl_2$, resulting in high activation energy for the overall reaction.[26f] In the hydroesterification of heptene-1 with $PdCl_2(PPh_3)_2/SnCl_2$ catalyst, the reported[13m] activation energy is also rather high, 130 kJ/mol. Clearly, higher reaction temperatures afford substantial rate benefits with the $SnCl_2$-promoted palladium catalysts.

In the hydroesterification of propyne to methyl methacrylate, the reaction is first order for the catalyst and both for the alkyne and methanol substrates.[19a,b] As in the case for alkenes, increasing CO concentration results in a faster conversion rate to MMA.[19a,b] The (2-pyridyl)-bis(triphenyl)phosphine component of Shell's MMA catalyst apparently has a rate-promoting property and is used in large excess. The large excess is also required to make up for the ligand losses. The third component of the catalyst, the excess acid, has a nearly zero-order kinetic response if the acid/Pd ratio exceeds 2.[19a,b]

V. Catalytic Intermediates and the Mechanism of Hydroesterification

Hydroesterification and CO−alkene copolymerization are two closely related reactions. Hydroesterification can be described as a CO−alkene copolymerization with a very high termination/propagation rate ratio, yielding a product with only a single incorporation of the two comonomers (i.e., $n = 1$ in eq 18)

$$n\mathrm{R^1CH{=}CHR^2} + n\mathrm{CO} + \mathrm{H{-}OR^3} \rightarrow \mathrm{H{-}(R^1CH{=}CHR^2\text{-}CO)_n{-}OR^3} \quad (18)$$

The relation between the two reactions can also be described as hydroesterification encompassing initiation and termination with a single propagation event. For this reason, the mechanistic results and conclusions obtained in CO−alkene copolymerization directly relate to hydroesterification. On the basis of the analysis of end groups in CO−ethylene copolymers, two different initiation−termination mechanisms have been established for copolymerization.[12] Not surprisingly, the same two mechanisms have been proposed for hydroesterification as well.[6c]

According to the "hydride" mechanism (Figure 10), a palladium hydride intermediate initiates the catalytic cycle by reacting with the alkene substrate. The reaction then proceeds via the palladium alkyl and acyl intermediates. The most accepted[12] termination step in the catalytic cycle is the nucleophilic attack on the acyl intermediate by the alkoxy group. However, other routes, like the formation of a ketene intermediate from the Pd−acyl complex via β-hydride elimination[16b] and its rapid reaction with the alcohol, yielding the ester product have also been proposed. Either termination step will also recover the hydride initiator, thereby closing the catalytic cycle.

In the second mechanism (Figure 11), the catalytic cycle is initiated by the formation of a Pd−alkoxy complex that reacts with CO, yielding the palladium alkoxycarbonyl intermediate. The catalytic cycle then propagates through the reaction of the alkoxycarbonyl complex with the alkene, forming an alkyl intermediate that has the ester group of the final product in the ω position. In the termination step, protonolysis of the alkyl intermediate releases the ester product and the alkoxy catalytic initiator, which later initiates the next catalytic turnover.

It should be noted that the termination step involves the alcohol in both mechanisms. In the hydride mechanism, the alkoxy group combines with the organic radical, yielding the ester product, while the hydrogen from the alcohol goes to the Pd, yielding the hydride. The alcohol splits just the opposite way in the termination step of the alkoxy mechanism. Either way, however, the hydrogen in the ester originates from the alcohol, which has been experimentally confirmed by following the deuterium label from alcohols (R−OD, R = Me, Et).[13m,25a,b]

The dominating end-group configuration of CO−ethene copolymers consists of an ester and a keto group.[12] However, all other possible combinations, i.e., ester−ester and keto−keto configurations, also occur. On the basis of these data, both the hydride and alkoxy mechanisms seem to significantly contribute to the initiation of CO−ethene copolymerization. The polymers with identical end groups may then originate from "crossover" reactions, when the termination step creates the catalytic initiator of a different catalytic cycle. Unfortunately, end-group analysis of CO−alkene copolymers cannot discriminate between the two mechanisms even in the absence of "crossover" because the both routes yield identical end-group configurations. It can only help

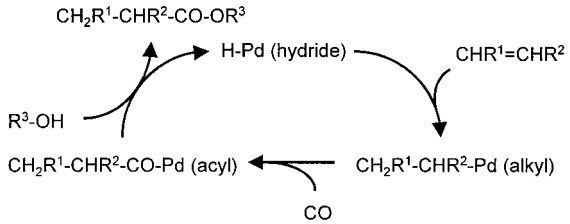


Figure 10. "Hydride" mechanism of hydroesterification.

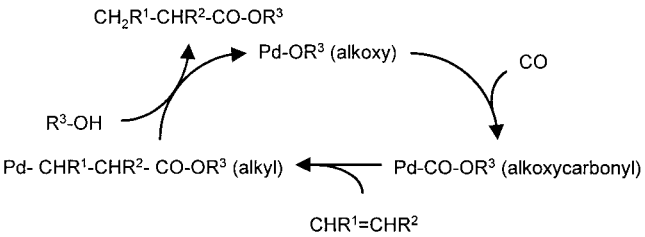


Figure 11. "Alkoxy" mechanism of hydroesterification.

to understand their basic steps and suggests that they both can happen in copolymerization.

Although neither mechanism can be excluded based on the above arguments, the hydride route seems to gain more acceptance in recent publications for hydroesterification.[25a,b] For example, Noskov and Petrov concluded from their kinetic and spectroscopic studies that the catalytic cycle is initiated by H−Pd^+ in the hydroesterification of heptene-1[14] and styrene[26] with $PdCl_2/PPh_3$ or $PdCl_2/PPh_3/SnCl_2$ catalysts. Their rather complex schemes also involve a Pd^0/Pd^{2+} redox cycle with a Pd^0 entry point. According to this mechanism, the initial reduction of the Pd^{2+} precursor is essentially due to stoichiometric WGSR (cf. section II.G) and happens during the induction period.[14a,h,26c] It is worth mentioning that WGSR has also been proposed to increase the concentration of H−Pd, thus promoting the rate of hydroesterification.[15b,25d]

Solutions of the catalyst precursor $PdCl_2(PPh_3)_2$ have two IR bands in the ν_{CO} region at 1980 and 2020 cm^{-1}.[14e,h] These two bands have been assigned to $Pd(CO)(PPh_3)_2$ and $Pd(CO)_2(PPh_3)_2$, respectively. These bands are retained even after introducing ethene, but now two new peaks also appear in the spectrum at 1680 and 1725 cm^{-1}, assigned to EtCO−$PdCl(PPh_3)_2$ and the product ester, respectively. It should be noted that the $Pd(CO^nPr)Cl(PPh_3)$ complex has been isolated and its molecular structure determined by X-ray.[15m,o] The latter complex has an IR band in the ν_{CO} region at 1690 cm^{-1},[15o] confirming the above assignment. The presence of the acyl intermediate in hydroesterification, therefore, provides strong evidence for the hydride route. The hydride mechanism is also supported by the fact that deuterium from D_2O incorporates into styrene during hydrocarboxylation, presumably after β-hydride elimination from the alkyl intermediate.[26e]

Although the presence of acyl intermediates strongly supports the hydride route, some kinetic effects are yet to be accounted for. Thus, for example, the rate-promoting effect of H_2 has been mostly linked to the formation H−Pd.[13i,15j,g,l,n,40g] However, H_2 can also promote the reaction by reducing the Pd^{2+} precursor to Pd^0 if the catalytic cycle involves Pd^0 intermediates. Unlike hydride formation from H_2, the latter route can be reconciled with the experimental data showing no significant incorporation of tritium from $^3H_2$ into the ester product.[13m]

As pointed out (see section III.A), the rate-promoting effect of excess free acid cannot be ascribed to the presence of protons, although in some proposed mechanisms the excess free acid makes the hydride to start the catalytic reaction.[14g,25d] Furthermore, it is known[49] that free acid reduces the concentration of H−Pd^+ by the following reaction

$$H-Pd^+ + H^+ \rightarrow Pd^{2+} + H_2 \qquad (19)$$

It needs to be pointed out that H_2 from eq 19 can reduce Pd^{2+} into Pd^0. The promoting effect of excess acid, therefore, may also be due to activating the catalyst by making Pd^0 intermediates. Interestingly, water promotion might have the same mechanism, since WGSR also produces H_2.

Excess acid has also been suggested to promote the reaction by cleaving the acyl intermediate to produce acyl chloride, which in turn would quickly convert into the ester product by reacting with the alcohol.[11,14g,15j] In this scenario, the acid would act as a kinetic promoter in the rate-determining nucleophilic attack on the acyl intermediate. However, if that were the promoting mechanism, the kinetic order of free acid should not be zero as reported.[19b,c] Furthermore, the kinetic order for the alcohol would also be nonzero in the absence of acid promoter, but in fact, it is often zero (cf. section IV). It seems therefore more reasonable that the role of excess acid is to prevent catalyst decomposition and perhaps to aid the formation of Pd^0 intermediates, as discussed above.

On the basis of indirect evidence, the alkoxy mechanism was first proposed by Kalia[20f] and Fenton.[13q] This route offers an alternative to explain why Pd hydroesterification catalysts do not yield hydroformylation products even in the presence of H_2. Also, the alkoxy route does not contradict with the promoting effect of free acids that can destroy H−Pd (vide supra). However, Cavinato and Toniolo later showed[15g] that while the $PdCl(COR)(PPh_3)_2$ (R = Et, ^{n}Hex) acyl complexes yield esters both in catalytic and stoichiometric reactions, $PdCl(CO-OR)(PPh_3)_2$ (R = Et, ^{n}Hex, $\nu_{CO} \approx 1650$ cm^{-1}) complexes do not form methyl ester with alkenes at the same temperature. (Note: For detailed IR and NMR data of alkoxycarbonyl and related complexes, see ref 15f.) It has thus been concluded that the hydride route is the true catalytic cycle and the alkoxy and carbalkoxy species are only spectators in the hydroesterification of alkenes. A recent ab initio molecular orbital study has come to the same conclusion.[13c]

Interestingly, the reactivity of methyl and methoxy groups in $MePd(OMe)(L_2)$ (L_2 = bidentate phosphine) is the opposite of the results obtained by Cavinato and Toniolo. Toth and Elsevier recently published their NMR and IR studies[54] of the above methyl−methoxy complex. They found that CO not only readily exchanges with the methoxy group at −70−80 °C, but also inserts into the Pd−OMe bond while

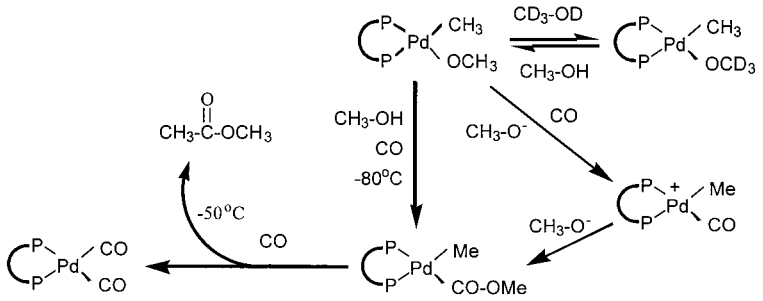


Figure 12. Carbonylation and methoxy-exchange reactions of $MePd(OMe)(L_2)$ (L_2 = bidentate phosphine).[54b]

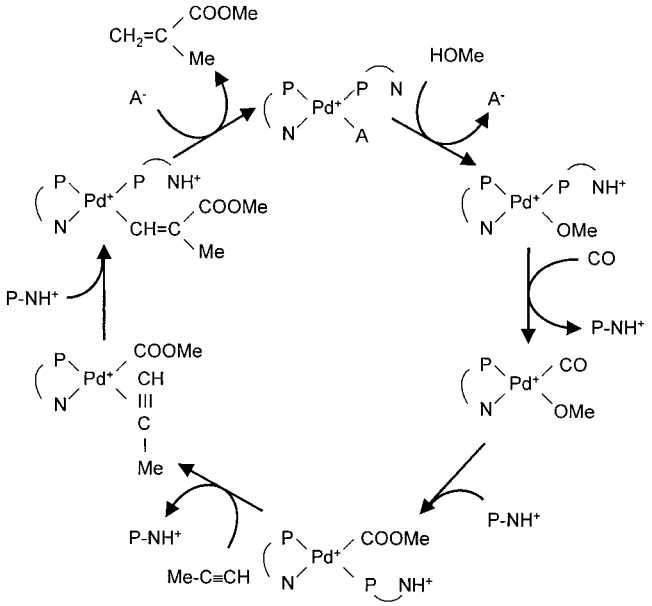


Figure 13. Ligand-assisted alkoxy mechanism of propyne hydroesterification with $Pd(OAc)_2$/PN/HA (PN = (2-pyridyl)diphenylphosphine, HA = methanesulfonic acid).[6d,19b,c]

no insertion occurs into the Pd−Me bond. They also showed that after CO insertion, methyl acetate eliminates yielding $Pd(L_2)(CO)_2$:[54b]

The facile formation of $Pd(CO-OMe)(OAc)(PPh_3)_2$ from $Pd(OAc)_2(PPh_3)_2$, CO, and methanol has also been reported.[55] Apparently, CO inserts readily into the Pd−OMe bond of the methoxy intermediate. These results suggest that (a) both the hydride and alkoxy routes are feasible and (b) the catalytic cycle may involve the Pd^{2+}/Pd^0 redox cycle as discussed above.

Drent suggested the alkoxy mechanism (see Figure 13) as the main reaction path in the conversion of propyne to MMA with $Pd(OAc)_2$/PN/HA (PN = (2-pyridyl)diphenylphosphine, HA = strong acid of a weakly coordinating anion, like methanesulfonic acid).[6d,19b,c] As discussed earlier, the substitution of a phenyl group of the PPh_3 ligand of the $Pd(OAc)_2$/PPh_3/HA catalyst with the 2-pyridyl group resulted in a several orders of magnitude rate enhancement. This enormous kinetic effect has been attributed to the nitrogen base that is closely associated with the metal, which in turn enables the ligand to assist the chemical transformation. Considering the ligand-assisted nature of the catalytic process, it is possible that the alkoxy route is preferentially accelerated and that is why the dominating catalytic cycle is different from that of the hydroesterification of alkenes. This conclusion is also supported by the fact that unlike with alkenes, the hydroesterification of propyne with the Shell catalyst is first order in the concentration of methanol.[19b,c]

Another interesting—and likely special—aspect of the mechanism of the 2-pyridyl system is the strong steric effect of the substituent of the pyridyl group on the n/i-selectivity.[19b,c] It has been found (cf. section III.C) that a substituent in the 3-position significantly increases the selectivity for the iso-product MMA in the hydroesterification of propyne. The PN bidentate ligand with a substituent in the 3-position seems to favor the approach of propyne in an orientation that leads to MMA because of the steric repulsion between the substituent of the ligand and the methyl group of propyne.

The observed shifts of regioselectivity of the typical Pd catalysts with monodentate ligands (cf. section IV) is generally attributed to the existence of parallel catalytic cycles, in which the number of CO ligands in the coordination sphere of Pd is different.[14a,b,f,h,25d,26a,c,d] The possibility of phosphine substitution by CO and therefore the formation of Pd complexes with different number of CO and phosphine ligands has been established when Pd is in the zero oxidation state. Thus, an IR investigation of PPh_3 substitution by CO in $Pd(PPh_3)_4$ found an equilibrium mixture of $Pd(PPh_3)_n(CO)_{4-n}$ (n = 1−4) complexes.[56] However, a similar ligand exchange equilibrium has not been observed for Pd^{2+}. In fact, Davies found[57] that CO cannot replace even acetone or the weakly coordinating ClO_4^- anion in $[Pd(dppe)L_2]^{2+}$. Therefore, shifting regioselectivity by changing the phosphine/CO ratio may be more feasible by a path that involves Pd^0 intermediates in the catalytic cycle. Although a similar selectivity effect in hydroformylation with phosphine-modified Rh catalysts is well- established,[3] the mechanism of the Pd-catalyzed hydroesterification clearly warrants further investigation.

VI. Hydroesterification Processes and Catalyst Stability

Although there is no current commercial hydroesterification plant that utilizes Pd catalysts, Shell patented a large number of catalysts and processes.[21,23,34,40−43,46] Shell's patenting activity was particularly strong during the decade from 1985 to 1994 (Figure 14). While the number of Shell's patents has significantly declined from their peak between 1985 and 1989, the contributions from other compa-

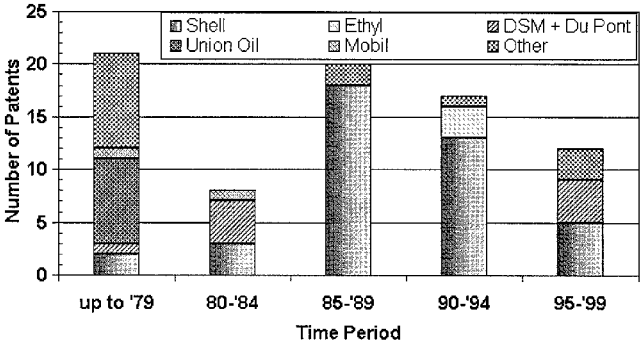


Figure 14. Patenting activities in Pd-catalyzed hydroesterification.

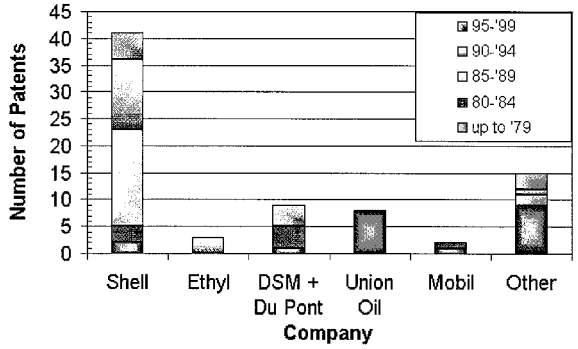


Figure 15. Break-up of Pd hydroesterification patent assets by corporations.

nies, like Ethyl, DSM, and Du Pont, have significantly increased during the same period.

Despite this new trend in hydroesterification patenting, Shell is still the single most important player in Pd-catalyzed hydroesterification technology. As shown in Figure 15, Shell owns 41 of the 78 patents identified by this review. The nearest competitors with current patent assets are Ethyl (three patents) and the DSM−Du Pont alliance (nine, of which five are old Du Pont patents). Union Oil's patents are old, all published before 1979.

Shell's patents cluster around two major technologies. As mentioned before, one of them, the conversion of propyne to MMA,[19,21] has been declared commercially ready.[19] The other major technology component of their portfolio is the conversion of olefins to esters and acids.[40−43] It is not clear if the latter is commercially ready, but the process has

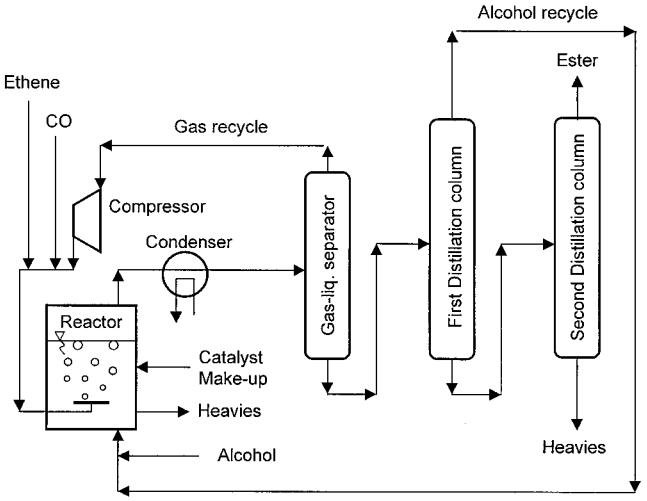


Figure 16. Shell's ethene hydroesterification process.[42a,b]

apparently been tested in pilot plant by using more than one catalyst formulation (see next, in section VI.A).

A. Alkene Hydroesterification Processes

Two identical Shell patents issued in the United States[42a] and Europe[42b] describe a continuous process for making propionate esters by using $Pd(OAc)_2/PPh_3$/Me-SO_3H catalyst (Figure 16). The reactor is a 600 mL CSTR with a sparger. The ester product is removed overhead in the vapor phase. Since methyl propionate forms an azeotropic mixture with methanol, the latter is recycled in the form of this mixture. According to an earlier patent,[42e] the phosphine and acid makeup is necessary because they are consumed by a side reaction, making inactive phosphonium salts. Process conditions, feeds, and productivity values are summarized in Table 13. The claimed preferred ranges of reaction temperature and pressure are 90−100 °C and 8−12 bar, respectively.

Later patents use the same process flow as depicted in Figure 16; however, they claim reduced catalyst makeup rate. This process credit is mostly due to higher catalytic activity achieved by using bulky bidentate alkyl phosphines.[40] Thus, for example, the reported phosphine consumption rate is as low as 0.04−0.08 kg/metric ton of *n*-butyl propionate with the 1,2-*P*,*P*′-bis(9-phosphabicyclo[3.3.1 or 4.2.1]non-

Table 13. Ethene Hydroesterification Process Data for the Pd/PPh_3/Me-SO_3H Catalyst[42a,b]

alcohol	methanol	2-propanol	1-butanol
run length (h)	500	75	75
temperature, (°C)	100	115−120	110−115
pressure (bar)	11	11	7
CO: ethene = 1:1 flow (Nl/h)	110	25−30	40
gas conversion per pass (%)	10−15	N/A	N/A
alcohol concentration (w%)	18	20	20
alcohol conversion per pass (%)	25−30	N/A	N/A
ester production rate (mol/(mol Pd h))	N/A	350	initial: 500 after 20 h: 100
stripping efficiency (%)	100	95	93
initial $Pd(OAc)_2$ concentration (mmol/l)	2.2	1.0	2.0
initial PPh_3 concentration (mmol/l)	45	50	50
initial Me-SO_3H concentration (mmol/l)	13	20	20
PPh_3 consumption (kg/metric ton ester)	1.6	5.5	initial: 3.3 after 20 h: 6.8

yl)ethane ligand.[40b] The highest production rate with this ligand is 683 mol of ester/(mol of Pd h) as compared to the 100 mol of ester/(mol of Pd h) value in Table 13 (1-butanol column). The newest oxa-adamantane ligand likely offers further improvements since reported reaction rates with this phosphine are several thousands mol of ester/(mol of Pd h).[40a]

B. Propyne Hydroesterification to MMA

Shell developed a process for the manufacturing of MMA from naphtha-cracker feeds.[19,21] The strongly inhibiting propadiene is converted in the first step of the process by isomerization to propyne on a K_2O/Al_2O_3 catalyst. The hydroesterification catalyst consists of $Pd(OAc)_2$, (2-pyridyl)diphenylphosphine, and methanesulfonic acid. 4-Methoxyphenol is also added to the reaction mixture as MMA stabilizer. Because of the high activity of the catalyst, the concentration of palladium is low and the process conditions are mild. Thus, for example, 81−95% conversion has been achieved by using only 18 wppm Pd in the methanol feed at 45 °C, 11 bar CO pressure, and a phosphine/acid/Pd ratio of 20:20:1.[19b] The corresponding turnover frequency in these runs is approximately 20 000−50 000 mol of ester/(mol of Pd h). Although ligand degradation is mentioned as a problem,[19] phosphine consumption data have not been found in the literature. It is likely low because of the low concentration of the catalyst and mild process conditions. A comparison with current MMA technologies suggests an approximately 20% advantage over the production cost from isobutene.[19a] The cost advantage is somewhat higher, 30%, in comparison with the acetone−cyanohydrin route that accounts for approximately 80% of the current MMA output.

C. Catalyst Stability

It has been early recognized that Pd-hydroesterification catalysts can decompose by transforming into Pd black.[13q−s,22c] Pd^{2+} can be reduced to Pd^0 by several components of the hydroesterification reaction mixture.

(1) Stoichiometric WGSR[13q,14a,15b,20f,33,45f]

$$Pd^{2+} + CO + H_2O \rightarrow Pd(solid) + CO_2 + 2H^+ \quad (20)$$

As it discussed earlier (cf. sections II.G, III.B, and V), water also has beneficial effects by reducing the induction period and accelerating the reaction. It is possible that the same process that boosts catalyst performance also leads to Pd-black formation.

(2) Oxidation of alkene to aldehyde[15b]

$$Pd^{2+} + C_2H_4 + H_2O \rightarrow Pd(solid) + Me\text{-}CHO + 2H^+ \quad (21)$$

This reaction, in fact, is part of the well-known Wacker process.[6a] High water concentration, as in the case of aqueous hydroesterification or hydrocarboxylation to acids, will certainly facilitate WGSR and therefore may be problematic (see the effect of WGS on catalyst stability above).

(3) Oxidation of the phosphine ligand to phosphine oxide[15b]

$$Pd^{2+} + PR_3 + H_2O \rightarrow Pd(solid) + O{=}PR_3 + 2H^+ \quad (22)$$

Equation 22 not only decomposes the catalyst by precipitating the active metal, but also converts the phosphine into inactive oxide, thus leading to ligand loss. Drent also mentioned ligand oxidation[19a] as one of the sources of ligand degradation.

(4) Alcohol oxidation[15b,55]

$$Pd^{2+} + CH_3{-}OH \rightarrow Pd(solid) + H{-}CHO + H_2 \quad (23)$$

$$Pd^{2+} + 2CH_3{-}OH + CO \rightarrow Pd(solid) + (CH_3O)_2CO + H_2 \quad (24)$$

Since ligands can keep palladium in the homogeneous phase by forming stable Pd^0 complexes, eqs 20−24 can explain the stabilizing effect of phosphines.[10b,12b,13r,15b,q,25e] It is likely that increased catalyst stability in the presence of unsaturated hydrocarbon substrates[18b,22c] is also a result of this mechanism. It is also known that strong acids can convert Pd black to soluble Pd^{2+} complexes in the presence of phosphines.[13q,s] This process may explain the stabilizing and rate enhancing effect of excess acid,[10b,13s,15h,19a,24c,42c,45b] often applied as promoter (see section III.A). Also, organic oxidizers and water scavengers presumably promote the reaction by keeping palladium in the (2+) oxidation state.[12b,40e] They are also believed to break up $[L_2Pd]_2^{2+}$ dimers that can form by the combination of Pd^0 and Pd^{2+} complexes.[12b]

Although high phosphine concentration retards the rate of hydroesterification, the phosphine is always used in excess to stabilize the catalyst. Excess phosphine is also necessary to make up for the unavoidable losses due to ligand degradation. The ligand can be transformed into inactive oxide form not only by eq 22, but also by the O_2 contaminant in the feed streams.[13q,19a] Pd is known to catalyze the reaction of phosphines with O_2.[19a,58] This reaction yields an orange Pd dimer if no excess phosphine is present[58b]

$$2Pd(OAc)_2(PPh_3)_2 + O_2 \rightarrow [Pd(OAc)_2(PPh_3)]_2 + 2O{=}PPh_3 \quad (25)$$

Another phosphine degradation route is the reaction of the excess acid promoter with the phosphine-forming phosphonium salts.[19a,42c,e] This reaction has been suggested to be the major contributor to ligand and acid losses in hydroesterification.[19a,42e]

Last, a DSM−Du Pont patent mentions ester formation with the alcohol reagent as a source of acid promoter loss.[24c] It is not clear how significant this acid loss is or if the side product can cause complications in product separation.

VII. Summary

$PdX_2L_2/L/HA$ (A = weakly coordinating anion, L = phosphine) complexes are active catalysts in the

hydroesterification of alkenes, alkynes, and conjugated dienes. Shell, the only major corporate player in the field, recently developed two very active catalyst systems tailored to the hydroesterification of either alkenes[40] or alkynes.[19] The hydroesterification of propyne with their $Pd(OAc)_2$/PN/HA (PN = (2-pyridyl)diphenylphosphine, HA = strong acid with weakly coordinating anion, like methanesulfonic acid) catalyst has been declared commercially ready.[19]

However, despite the significant progress in the activity of Pd-hydroesterification catalysts, further improvements are warranted. Thus, for example, activity maintenance still seems to be an issue. Homogeneous Pd catalysts are prone to a number of deactivation reactions. Activity and stability promoters are often corrosive and add to the complexity of the system, making it less attractive. Nonetheless, the versatility of the process and its tolerance toward the functional groups of substrates should appeal especially to the makers of specialty products.

Although hydroesterification yields esters from alkenes, alkynes, and dienes in fewer steps than hydroformylation does, the latter has some advantages at the current state of the art.

(1) Hydroformylation catalysts, particularly some recently published phosphine-modified Rh systems, can achieve very high regioselectivity for the linear product[3a] that hydroesterification catalysts cannot match yet. By analogy with hydroformylation, bulkier ligands ought to be tested in hydroesterification to increase normal-ester selectivity.

(2) Hydroformylation is proven, commercial. Hydroesterification can only replace it if it can provide significant economic incentives. Similar or just marginally better performance could not justify the cost of development of a new technology.

(3) Hydroesterification requires pure CO while hydroformylation uses syngas, a mixture of CO and H_2. The latter is typically more available and less expensive (for industrial applications CO is most often separated from syngas).

(4) The acid component of the hydroesterification catalyst makes the process corrosive. It would be desirable to develop new hydroesterification catalysts that do not require acid stabilizer/activity booster.

Clearly, any new hydroesterification technology will directly compete with the hydroformylation route. This is especially true for olefin feeds, since both processes add one CO to the olefin, yielding oxygenates that can be converted into identical products. For some niche applications, like the production of MMA from propyne, hydroesterification seems to have an advantage as compared to hydroformylation due to the high activity and selectivity of the $Pd(OAc)_2$/(2-pyridyl)diphenylphosphine catalyst. Since hydroesterification is an emerging technology, it is reasonable to assume that the potential for improvement is greater than in the mature hydroformylation. It is therefore possible that hydroesterification will become competitive in the future; thus, continued effort in the field is warranted.

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