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Hydroxycarbonylation of vinyl acetate with formic acid: pathway to lactic acid and lactates

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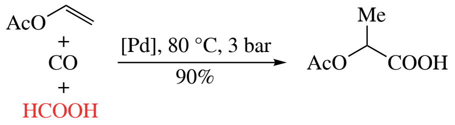
The Pd-catalyzed hydroxycarbonylation of vinyl acetate in the presence of formic acid into 2-acetoxypropionic acid is reported. The reaction proceeds chemo- and regioselectively under very mild conditions of 80 °C and 3–6 bar CO.



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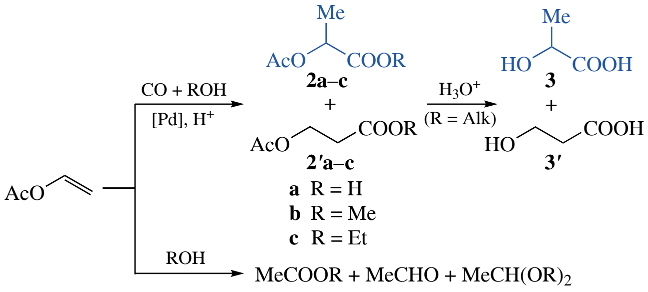
Nowadays, lactic acid (LA) and alkyl lactates find wide application in the food industry and as monomers for ecologically-friendly polylactide. Lactic acid may serve as starting material for the syntheses of acrylic acid, pentane-2,3-dione, pyruvic acid and acetaldehyde.[1–3] Ethyl lactate represents a non-toxic and bio-degradable ‘green’ solvent for various applications including food, perfume industries and pharmacy.[4] Currently, L-lactic acid is produced by fermentation of sugars or sugar-containing biomass.[5] However, the separation and purification of the product from various contaminants such as unreacted sugar, amino acids, carboxylic acids and inorganic salts dissolved in fermenting liquor is tedious and labor-consuming. Moreover, in the course of LA isolation huge amount of calcium sulfate is generated as a waste product.[6] That is why the selective chemical route to LA and lactates would represent an attractive alternative to the biochemical synthesis.

Vinyl acetate (VA) **1** is a bulk chemical which is industrially produced by partial oxidation of ethylene in the presence of acetic acid over supported palladium catalyst.[7] Its cheapness and availability make it attractive for various organic syntheses. In particular, carbonylation and hydroformylation of VA look promising pathways to LA and lactates (Scheme 1).[8,9] Hydroxy- and alkoxycarbonylation of VA **1** in the presence of soluble palladium-phosphine complexes give 2-acetoxypropionic acid **2a** and its alkyl esters **2b**,**c**, respectively. They can be easily converted into racemic LA **3**. Unfortunately, a number of side products are generally formed in the course of carbonylation. First, some amount of linear 3-acetoxypropionic acid **2′a** or its esters **2′b**,**c** are formed depending on phosphine ligand and other additives applied. Second, the acidic components of the catalytic system promote hydrolysis or transesterification of VA yielding acetic acid, alkyl acetate, acetaldehyde, and acetaldehyde dialkylacetals (see Scheme 1).[6,8–10]



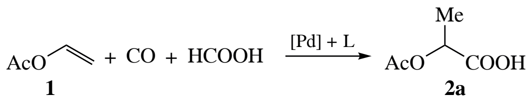
Scheme 1

Alkoxycarbonylation of VA has been studied extensively (see review[8]). Moderate to high yields of alkyl acetoxypropionates have been reported.[6] However, regioselectivity towards target branched esters **2b**,**c** is generally moderate. For example, the most active and chemoselective catalytic system $Pd_2(dba)_3 + 1,2\text{-}(Bu^t_2PCH_2)_2C_6H_4 + MeSO_3H$ provides branched to linear isomer (b/l) ratio as low as 3.6 : 1.[9] As for hydroxycarbonylation of VA, only scarce data can be found in literature.[11,12] The best reported selectivity to **2a** of 67% at 98% VA conversion and 70% at 49% VA conversion was achieved in the presence of $[PdCl(allyl)]_2$ and $Pd(acac)_2$, respectively, under rather harsh reaction conditions (150 °C and 48 bar).[12]

Recently,[13] we proposed a new protocol for Pd-catalyzed regioselective hydroxycarbonylation of olefins using formic acid instead of water as a co-reagent. Its advantages are low CO pressure and temperature as well as no need of strong mineral acids generally required as promoters in the Reppe carbonylation.[14] Formic acid not only reduces the corrosiveness of the reaction mixture but can be useful for the carbonylation of some acid-sensitive substrates. With that in mind, we tested this protocol in the hydroxycarbonylation of VA **1**. To our delight, these gentle reaction conditions provide very high selectivity to target product **2a**, which surpassed all previously reported results. In this communication we report the details of our finding.

In fact, hydroxycarbonylation of VA **1** in the presence of formic acid proceeds smoothly yielding **2a** as a major product (Scheme 2). Acetic acid and acetaldehyde as products of VA side conversion were also detected in the reaction mixture, although their contents were not quantified.

Initial screening of palladium sources and phosphine ligands was performed in toluene at the temperature of 80 °C and 3 bar



Scheme 2

Table 1 Catalyst screening for conversion of vinyl acetate **1** into 2-acetoxypropionic acid **2a**.[a]

Entry	Pd source	Ligand (%)	Conversion of **1** (%)	Yield of **2a** (%)
1	$Pd(OAc)_2$	PPh_3 (3)	67.6	35.3
2	$Pd(dba)_2$	PPh_3 (3)	75.1 (32.4)[b]	43.6 (1.8)[b]
3	Pd black	–	16.3	0
4	$Pd(acac)_2$	PPh_3 (3)	35.1	2.3
5	$PdCl_2(PPh_3)_2$	PPh_3 (2.4)	26.2	0
6	$Pd(dba)_2$	PPh_3 (3) + [bmim]Cl[c]	22.2	0[c]
7	$Pd(OAc)_2$	P(*o*-Tol)$_3$ (3)	22.0	0
8	$Pd(OAc)_2$	PBu_3 (3)	66.5	13.9
9	$Pd(OAc)_2$	P(2-pyridyl)$_3$ (3)	21.7	2.8
10	$Pd(OAc)_2$	$P(OPh)_3$ (3)	20.6	7.8
11	$Pd(OAc)_2$	1,2-$(Bu^t_2PCH_2)_2C_6H_4$ (3)	58.8	17.2 (+9.5% **2′a**)

[a] Reagents and conditions: VA **1** (0.2 ml, 2.17 mmol), CO (3 bar), 0.3% [Pd], HCOOH (0.1 ml, 1.2 equiv.), ligand, toluene (3 ml), 80 °C, 4 h. [b] With 0.6% PPh_3. [c] 0.6% of [bmim]Cl.

CO pressure (Table 1).† In a blank experiment in the absence of the Pd precursor, no carbonylation products were detected. Among Pd precursors tested, $Pd(OAc)_2$ and $Pd(dba)_2$ with PPh_3 showed promising results while Pd black and $Pd(acac)_2/PPh_3$ were inactive (entries 1–4). Surprisingly, $PdCl_2(PPh_3)_2$ which was very active in hydroxycarbonylation of styrene under the same conditions[13] gave no product **2a** (entry 5). We assume that strongly coordinating chloride ion makes Pd complex inactive in VA carbonylation. To test this hypothesis, we added the equal amount of [bmim]Cl as a soluble source of chloride to active $Pd(dba)_2 + PPh_3$ system, which fully decelerated the reaction (entry 6). Ligands such as P(*o*-Tol)$_3$, PBu_3, P(2-pyridyl)$_3$, $P(OPh)_3$ gave no positive results (entries 7–10). Bidentate 1,2-$(Bu^t_2PCH_2)_2C_6H_4$ which is very active in olefin methoxycarbonylation and in promoting formation of linear products[9–11,15,16] in our case gave 17.2% of target product **2a** along with 9.5% isomer **2′a** (entry 11, *cf.* refs. 9–11). Notably, linear acid **2′a** was not detected by GC in any other experiments listed above. As a result, common PPh_3 was a ligand of choice for further optimization. Decreasing the ligand amount from 3 to 0.6% suppresses the yield dramatically (see entry 2).

Screening for solvents was tested with $Pd(OAc)_2/PPh_3$ catalytic system. Aromatics such as toluene, benzene, xylenes as well as chlorobenzene turned to be appropriate reaction media. Other common solvents such as acetonitrile, methyl ethyl ketone, pyridine, tetrahydrofuran, 1,4-dioxane, ethyl acetate, and dichloromethane showed by far worse yield of carbonylation products. Interestingly, using methanol as a solvent did not afford the expected methyl ester **2b** but only acid **2a** in low yield. We also performed the reaction with ligand-free palladium stabilized by molten Bu_4NBr.[17] Unlike previous results, both **2a** (11.7% yield) and **2′a** (1.7% yield) were obtained (see Online Supplementary Materials, Table S1). Further optimization showed that yield of **2a** could be enhanced by increasing palladium loading up to 1 mol%. However, a more economical way is boosting the reaction by increasing formic acid concentration. Also, adding surplus amount of PPh_3 stabilizes Pd complexes in the reaction medium thus enhancing the catalyst performance (Table 2).

Table 2 Optimization of catalytic system for the conversion of vinyl acetate **1** into 2-acetoxypropionic acid **2a**.

Entry	Solvent	$Pd(OAc)_2$ (%)	HCOOH (eqiuv.)	Conversion (%)	Yield of **2a** (%)
1	PhCl	0.1	3.7	73.6	69.6
2	PhCl	0.3	1.2	83.3	64.1
3	PhCl	0.3	3.7	87.6	81.7
4	PhCl	1	1.2	73.6	63.7
5	PhCl	1	2.4	76.3	71.4
6	PhCl	1	3.7	100	89.6
7	PhMe	0.3	3.7	83.3 (100)[b]	77.6 (89.7)[b]

[a] Reagents and conditions: VA **1** (0.2 ml, 2.17 mmol), CO (3 bar), $Pd(OAc)_2$, HCOOH, PPh_3 (3%), solvent (3 ml), 80 °C, 4 h. [b] With 6% PPh_3.

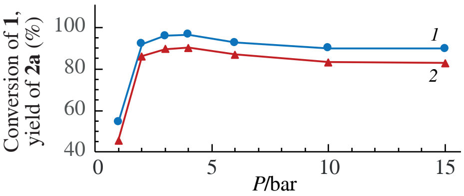


Figure 1 Effect of CO pressure on (*1*) VA **1** conversion and (*2*) yield of **2a**. Conditions: VA **1** (0.2 ml, 2.17 mmol), 0.3% $Pd(OAc)_2$, 6% PPh_3, HCOOH (0.3 ml, 3.7 equiv.), toluene (3 ml), 80 °C, 4 h.

The effect of CO pressure (was indicated by Bourdon pressure gauge) on the catalyst performance is shown in Figure 1. The maximum conversions and yields were observed at 3–4 bar while further raising the pressure slightly suppressed these values. However, decreasing CO pressure to 1 bar caused sharp drop of both the conversion and the yield. Notably, selectivity to product **2a** was almost the same (92–94%) over the entire pressure range, except for 1 bar when the selectivity dropped to 84%. Obviously, the rate of the carbonylation becomes too slow at low pressure and competing routes of VA **1** transformations bring about the selectivity drop.

The mechanism of VA hydroxycarbonylation with CO and formic acid has not been yet clearly rationalized. Nevertheless, the observed deactivation of the catalyst by chloride ions indicates that cationic Pd complexes are likely involved in the catalytic cycle.[18] Decreasing yield of **2a** with CO pressure and susceptibility of the reaction to the phosphine ligand nature demonstrate the challenging nature of catalytically active species.

In conclusion, we elaborated an efficient procedure for hydroxycarbonylation of vinyl acetate **1** into 2-acetoxypropionic acid **2a** under very mild conditions. The product is an intermediate in the alternative synthetic pathway to lactic acid and lactates. To the best of our knowledge, our method is the most selective hydroxycarbonylation of vinyl acetate reported.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7657.

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† Catalytic tests were carried out in a 50 ml electrically heated autoclave equipped with glass lining and magnetic stirrer. The reactor was charged with vinyl acetate **1** (0.2 ml, 2.17 mmol), an appropriate amount of palladium source, ligand, and HCOOH (99.7%, 3 ml) in a solvent (3 ml). The system was purged three times with CO, then pressurized to 3 bar and heated. The reaction was performed under stirring (600 rpm) for 4 h.

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