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# A Unique Palladium Catalyst for Efficient and Selective Alkoxycarbonylation of Olefins with Formates

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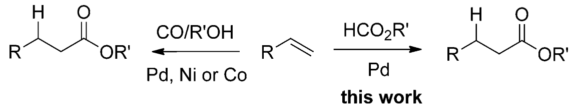
In terms of scale, carbonylations are among the most important homogeneously catalyzed processes in industry.[1] Within this class of reactions, alkoxycarbonylations, also called hydroesterifications, represent a straightforward method for the conversion of olefins, CO, and alcohols to the corresponding esters.[2] Nickel-based catalysts were originally employed, as described in the seminal work by Reppe and Vetter.[3] However, nowadays palladium catalysts are generally used for this transformation because they work under milder conditions and allow for a broader substrate scope. As a result, these reactions currently are a valuable tool in organic synthesis,[4] and they are also used in industrial bulk production.[5]

So far, the vast majority of catalytic alkoxycarbonylations employ CO as source of the carbonyl group (Scheme 1). Clearly, CO is a versatile and inexpensive C1 building block; however, its toxicity and physical properties (gaseous form, flammability) make it less convenient to handle in most academic laboratories. Hence, there is significant interest in easier-to-handle, less toxic synthetic equivalents of carbon monoxide. Formic acid derivatives are especially promising alternatives in this regard, because of their low price and availability.



**Scheme 1.** Alkoxycarbonylation of olefins using CO/alcohols versus formates.

Unlike the extensive research conducted on CO-based chemistry, carbonylations with formates have only been scarcely studied.[6] The first hydroesterifications of olefins with formates were reported in 1983 by Sneeden and co-workers.[7] They used a ruthenium complex for the conversion of ethylene to methyl propionate at 190 °C. Since then only few catalyst modifications, using ruthenium,[8] iridium,[9] or palladium,[10] have been developed. However, the reported reactions require harsh conditions, such as high temperatures ($T > 150\,^{\circ}\mathrm{C}$), high catalyst loadings (typically 1–5 mol%), and/or additional CO pressure. Furthermore, the obtained chemo- and regioselectivities are poor and the reported substrate scopes are narrow, very often limited solely to ethylene.

Based on our interest in the synthesis and use of formates for organic synthesis and energy applications,[11] we present herein an efficient and general protocol for the catalytic alkoxycarbonylation of olefins with aliphatic and aromatic formates without using CO.

First, we investigated the activity of different in situ generated palladium phosphine complexes towards a model reaction between 1-octene and methyl formate. Here, several ligands, known to be successful in the analogous methoxycarbonylation with CO, were tested by using air-stable palladium(II) acetyl acetonate as catalyst precursor. In view of practical relevance we used only low catalyst loadings (0.038 mol% Pd). Surprisingly, of all the ligands studied (Figure 1), only one catalyst system gave significant amounts (>5%) of the corresponding alkoxycarbonylation product. The successful ligand, α,α′-bis-[di-*tert*-butylphosphino]-*o*-xylene (**1**), was originally described by Moulton and Shaw[12] and previously utilized in palladium-catalyzed methoxycarbonylation of ethylene by Tooze and co-workers[13] and more recently by Cole-Hamilton and co-workers.[5b, 14]

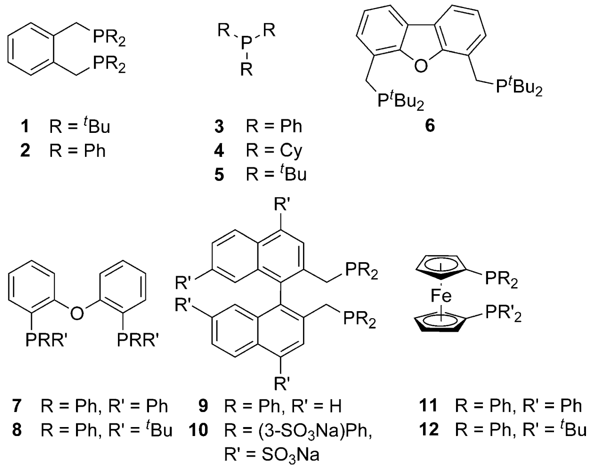


**Figure 1.** Ligands tested for methoxycarbonylation of 1-octene with methyl formate.

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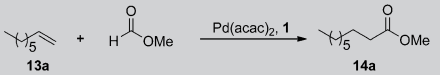
In agreement with the work of Drent,[15] Bianchini,[16] and others,[17] who reported that cationic P-ligated Pd–H complexes represent the catalytically active species in alkoxycarbonylations, we observed the same effect in the case of methoxycarbonylation with methyl formate. As shown in Table 1 (entries 1–4), adding an acidic co-catalyst with weakly coordinating anion is crucial to achieve conversion of the olefin. The optimal reaction temperature was found to be 100 °C and methanol as solvent proved to be essential (entries 6–8). Only low yield of ester **14a** was obtained when the reaction was performed with equimolar amount of methyl formate (entry 9).

**Table 1.** Pd-catalyzed alkoxycarbonylation of 1-octene: influence of reaction parameters.[a]



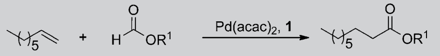
**13a** **14a**

| Entry | Acid | $T$ [°C] | MeOH/MF [mL] | Yield [%][b] | $n$-Sel. [%][b] |
|---|---|---|---|---|---|
| 1 | $MeSO_3H$ | 100 | 10:10 | 46[c] | 95 |
| 2 | $p$-TsOH | 100 | 10:10 | 36[c] | 95 |
| 3 | HOAc | 100 | 10:10 | 0 | – |
| 4 | – | 100 | 10:10 | 0 | – |
| 5 | $MeSO_3H$ | 80 | 10:10 | 34 | 94 |
| 6 | $MeSO_3H$ | 100 | 10:10 | 97 | 94 |
| 7 | $MeSO_3H$ | 120 | 10:10 | 74 | 94 |
| 8 | $MeSO_3H$ | 100 | 0:10 | 28 | 95 |
| 9[d] | $MeSO_3H$ | 100 | 4:4 | 2 | – |

[a] Unless otherwise stated, reactions were carried out for 20 h at 100 °C with 0.038 mol% $Pd(acac)_2$, **1**/Pd = 4, acid/**1** = 4, 10 mL methyl formate (MF), 10 mL methanol, 54 mmol of 1-octene. [b] Determined by GC using an internal standard. [c] Yields are given after 5.5 h. [d] Performed in 12 mL THF as a solvent.

Next, we validated the possibility of using other formates in the reaction with 1-octene (Table 2). In fact, ethyl formate reacted well, and benzyl and phenyl nonanoate were formed in moderate yields. In the latter two examples ether formation was observed as a side reaction. All esters were produced with high regioselectivity. Interestingly, only in the case of phenyl formate, the pressure increased to 40 bar, requiring the use of an autoclave. The pressure in reactions with alkyl formates did not exceed 5 bar, allowing the use of sealable glas pressure tubes.

**Table 2.** Pd-catalyzed alkoxycarbonylations with different formates.[a]

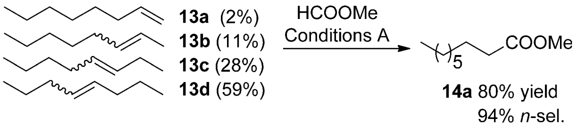


**13a** **14**

| Entry | $R^1$ | Product | Conditions | Yield[b,c] [%] | $n$-Sel.[b] [%] |
|---|---|---|---|---|---|
| 1 | Me | **14a** | A | 97 [78] | 94 |
| 2 | Et | **14b** | B | 84 [82] | 95 |
| 3 | Bn | **14c** | B | 31 | 92 |
| 4 | Ph | **14d** | B | 32 [29] | 93 |

[a] Conditions A: Reactions were carried out for 20 h at 100 °C with 1-octene (54 mmol), $Pd(acac)_2$ (6.3 mg, 21 µmol, 0.038 mol%), **1** (32.7 mg, 82.8 µmol, 0,15 mol%), methanesulfonic acid (20 µL, 30 mg, 0.31 mmol), formate (10 mL), MeOH (10 mL); B: performed with 1-octene (27 mmol), $Pd(acac)_2$ (9.1 mg, 30 µmol, 0.11 mol%), **1** (49.1 mg, 124 µmol), $MeSO_3H$ (28 µL, 42 mg, 0.44 mmol), formate (10 mL), alcohol (10 mL, corresponding alcohol to the formate used). [b] Determined by GC using an internal standard. [c] Isolated yields are given in brackets.

Mixtures of internal and terminal olefins are usually preferred as raw materials for bulk carbonylation processes, as they are less expensive compared to pure starting materials. Hence, isomerization combined with selective functionalization is of major industrial interest.[18] To test whether the alkoxycarbonylation of olefins with formates allows for simultaneous isomerization, we subjected a mixture of octenes to the standard reaction conditions (Scheme 2). To our delight, the present system was able to transform the seven different octene isomers into the corresponding linear methyl nonanoate with a yield of 80% and with 94% $n$-selectivity.

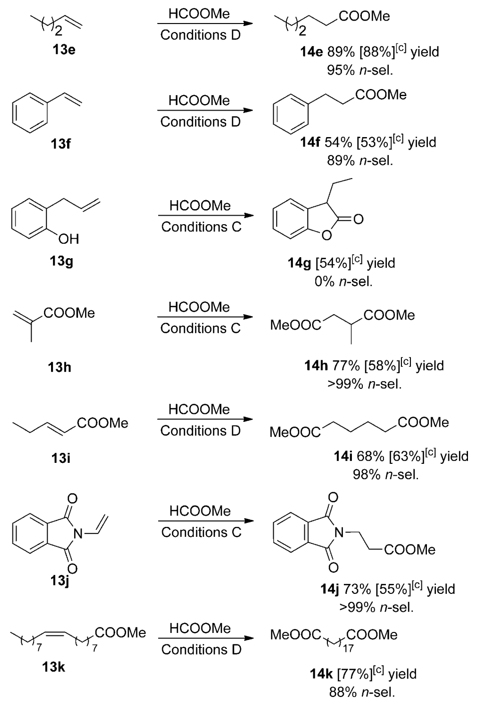


**Scheme 2.** Palladium-catalyzed alkoxycarbonylation of octene mixture.

Furthermore, we wanted to demonstrate the practicability and effectiveness of this methodology using various, also functionalized substrates. The transformation of 1-pentene (**13e**) proceeded efficiently and with high regioselectivity (Table 3). Styrene, as an example of an aromatic olefin, is usually carbonylated with most complexes at the iso-position due to the benzylic stabilization of the metal center. However, Pd/**1**-catalyst again enabled a highly $n$-selective transformation. On the other hand, reaction of 2-allylphenol proceeded via isomerisation of the double bond, subsequent carbonylation at the benzylic position, and partial formation of cyclic ester **14g**. GC–MS analysis of the crude reaction mixture revealed the formation of methyl 2-(2-hy-droxyphenyl)butanoate as the main product. Finally, transesterification took place during the isolation and lactone **14g** was obtained in 54% yield.

In addition, two conjugated esters were examined as substrates. In the case of methyl methacrylate (**13h**), the linear product **14h** was obtained exclusively at a yield of 77% (Table 3). Using a somewhat higher catalyst loading (0.41 mol% Pd) we were also able to convert methyl 2-pentenoate (**13i**) to the industrially important dimethyl adipate (**14i**), which is produced on multimillion-tonne scale for the synthesis of polymers such as nylon. It should be noted that in this case even a conjugated double bond was isomerized to the terminal position. Then, $N$-vinylphthalimide was tested as a nitrogen-substituted olefin. In general, this substrate is difficult to carbonylate with high regioselectivity. Once more, the presented catalyst system transformed this substrate into the corresponding linear product **14j** with excellent regioselectivity. Finally, naturally occurring methyl oleate (**13k**) was carbonylated to the linear diester **14k** in 77% isolated yield. Here, the catalyst system was able to isomerize the double bond over 7 carbon atoms and selectively (88%) provided functionalization

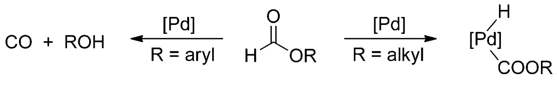
**Table 3.** Pd-catalyzed alkoxycarbonylations with formates: Substrate scope.[a,b]



[a] Conditions C: Reactions were carried out for 20 h at 100 °C with alkene (27 mmol), $Pd(acac)_2$ (6.3 mg, 21 μmol, 0.078 mol%), **1** (32.7 mg, 82.8 μmol), $MeSO_3H$ (20 μL, 30 mg, 0.31 mmol), HCOOMe (10 mL), MeOH (10 mL); D: performed with alkene (10 mmol), $Pd(acac)_2$ (12.6 mg, 41.4 μmol, 0.41 mol%), **1** (65.4 mg, 166 μmol), $MeSO_3H$ (43 μL, 63 mg, 0.66 mmol), HCOOMe (10 mL), MeOH (10 mL). [b] Yields and selectivities determined by GC using an internal standard. [c] Isolated yields are given in brackets.

at the terminal position. This reaction demonstrates the potential of CO-free alkoxycarbonylations for the refinement of renewable resources, which is of current interest.

From a mechanistic point of view, in principle two pathways for the activation of methyl formate are possible: (1) Thermal, acidic, or metal-catalyzed decomposition of the formate to produce CO and methanol with subsequent traditional methoxycarbonylation; or (2) C–H activation of the formate by a metal hydride complex and transfer of the alkoxycarbonyl group through reductive elimination (Scheme 3). Under catalytic conditions the pressure of the reaction mixture was almost constant (5 bar) over the whole time using alkyl formates. On the other hand, for carbonylation with phenyl formate a pressure increase up to 40 bar was observed.



**Scheme 3.** Activation of aryl and alkyl formates.

Thus, we suggest a C–H activation pathway for alkyl formates and a decompositition pathway for phenyl formate. The latter is in agreement with the work of Tsuji and co-workers,[10f] who observed decomposition of aryl formates to CO in the hydroesterification of alkynes. Interestingly, alkyl formates did not react under these conditions. As additional proof, no carbon monoxide was found in the gas phase of the reaction with methyl formate. Palladium-catalyzed H–(C=O) bond activation of aldehydes and formamides was recently described.[19] However, the formation of [Pd]–H species was not observed under catalytic and stoichiometric conditions. Furthermore, no reaction was observed when complexes [Pd(**1**)(dba)], [Pd(**1**)($\eta^2$-$MeSO_3$)]($MeSO_3$),[17c] and in situ catalyst system $Pd(OAc)_2$/**1**/$MeSO_3H$ were treated with a stoichiometric amount of HCOOMe. Further mechanistic studies are ongoing.

In conclusion, we describe a specific palladium catalyst system for the alkoxycarbonylation of alkenes with alkyl and phenyl formates. Terminal and internal aliphatic as well as aromatic substrates produce the corresponding linear esters in the presence of low loadings of a palladium/**1** system with very good regioselectivity. Most of the olefins used and the resulting esters are of considerable industrial interest. The key aspect of our work is the convenient alkoxycarbonylation without using toxic gaseous carbon monoxide. Using alkyl formates, our methodology provides a carbonylation method which does not need high-pressure equipment, only a sealable 5 bar stable vessel or tube.

## Experimental Section

Experimental details are given in the Supporting Information.

## *Acknowledgements*

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**Keywords:** carbonylations · formates · homogeneous catalysis · olefins · palladium

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