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Palladium-catalyzed Low Pressure Carbonylation of Allylic Alcohols by Catalytic Anhydride Activation

*Mathias Schelwies**, *Rocco Paciello*, *Ralf Pelzer*, *Wolfgang Siegel and Michael Breuer*

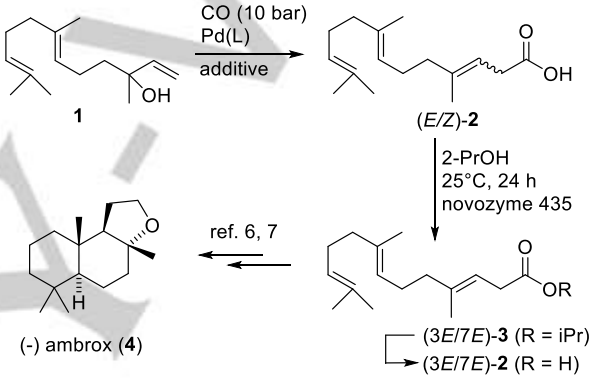
Dedicated to Professor Günter Helmchen on the occasion of his 80th birthday

Abstract: A direct carbonylation of allylic alcohols has been realized for the first time with high catalyst activity at low pressure of CO (10 bar). The procedure is described in detail for the carbonylation of *E*-nerolidol, an important step in a new BASF-route to (-)-ambrox. Key to high activities in the allylic alcohol carbonylation is the finding that catalytic amounts of carboxylic anhydride activate the substrate and are constantly regenerated with carbon monoxide under the reaction conditions. The identified reaction conditions are transferrable to other substrates as well.

The direct carbonylation of allylic alcohols to carboxylic acids is of significant interest, and various possible reaction conditions have been reviewed.[1] In addition, examples from patent literature for this type of carbonylation indicate significant industrial interest in realizing an efficient transformation. Key technological disadvantages of the reported procedures are the high CO-pressures and high catalyst loadings needed. Both are required to compensate low catalyst activity. High catalyst loadings often lead to catalyst precipitation under reaction conditions, making a process less efficient and scaleup often impossible. As compared to alcohols, reported catalyst activities are often higher for related carbonylation type reactions of aryl- or allylhalides (alkoxycarboxylations or aminocarbonylations). Such processes allow reaction at pressures of <10 bar.[2] Although various activating additives (halides or Brønsted acids in most cases) have been reported, no catalytic system for the direct carbonylation of allylic alcohols has been described to date allowing a clean carbonylation at low pressure of <20 bar CO, low temperature of <80°C and additionally at <0.2 mol% of metal catalyst loading .[3], [4] The high pressures required in some of the known procedures cannot be used in multipurpose batch reactors.

Specifically, we have started to develop a process route for the carbonylation of *E*-nerolidol (**1**) to (3*E*/*Z*)-homofarnesylic acid ((*E*/*Z*)-**2**) (Scheme 1),[5] that can serve as key step in a direct and elegant route to (-)-ambrox, a valuable aroma ingredient that is currently produced based on natural sources (i.e. extraction of sclareol). The starting compound *E*-nerolidol (**1**) is an intermediate in the BASF value chain and is produced on large scale from citral. In our new route (*E*/*Z*)-**2** obtained from carbonylation is purified to (3*E*/*7E)*-homofarnesylic acid ((3*E*/*7E)*-**2**), the key precursor to (-)-ambrox (**4**).[3] Thus, the carbonylation of *E*-nerolidol (**1**) is the key step in an attractive interconnection from a synthetic intermediate produced from citral by various suppliers on multi ton scale directly to precursors of valuable sclareolide[6] and finally to (-)-ambrox (**4**) (Scheme 1).[3], [7]

Scheme 1. BASF-route to (-)-ambrox (**4**).



When *E*-nerolidol is subjected to mild Pd-catalyzed carbonylation conditions (Table 1, entry 1, 0.13 mol% $Pd(OAc)_2$, 0.3 mol% PPh_3, 70 °C, 10 bar CO, in NEt_3) no conversion is observed. When acetic anhydride is added and catalytic amounts of DMAP (Table 1, entry 2, 23 mol% Ac_2O and 0.3 mol% DMAP), the carbonylation proceeds to give high yields of *E*/*Z*-homofarnesylic acid with an isomeric ratio of (3*E*/*7E*)-**2**:(3*Z*/*7E*)-**2** = 60:40 (GC/HLPC). Comparison experiments showed that a phosphine ligand needs to be present (table 1, entry 3-4), whereas a high excess of ligand leads to decrease in conversion rate. DMAP leads to even high conversion rates and is not crucial (entry 6 compared to entry 2) for the anhydride effect. Replacement of addition of catalytic Ac_2O by the addition of catalytic amounts of allylic acetate or nerolidol acetate leads to a similar activation effect (entry 8-9). Working without NEt_3 as solvent was found to decrease conversion and yield (entry 11). Various ligands have been tested under the given reaction conditions. However, since we found no significant beneficial influence on selectivity or yield, we decided to continue with triphenylphosphine in this case. High temperatures lead to decreases in yields and selectivity at some point (entry 10). However, we found the optimized protocol to be robust and scalable without alterations. The 3*E*/3*Z*-ratio was found to be similar for all experiments.

Addition of catalytic amounts of anhydride or reagents that are anhydride forming under reaction conditions (allylic acetate or *E*-nerolidol acetate) significantly accelerate the reaction. The fact that catalytic amounts of anhydrides are sufficient to activate the substrate has not been previously described. Anhydride formation

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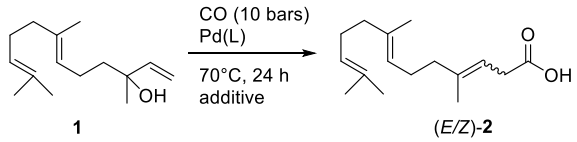
by carbonylation of allylic acetates is known,[8] but has never been used in this manner. In the related transition metal catalyzed allylic substitution reaction[9] of allylic alcohols, acidic additives are used to activate the substrate.[10]

Table 1. Optimization of allylic carbonylation. [a]



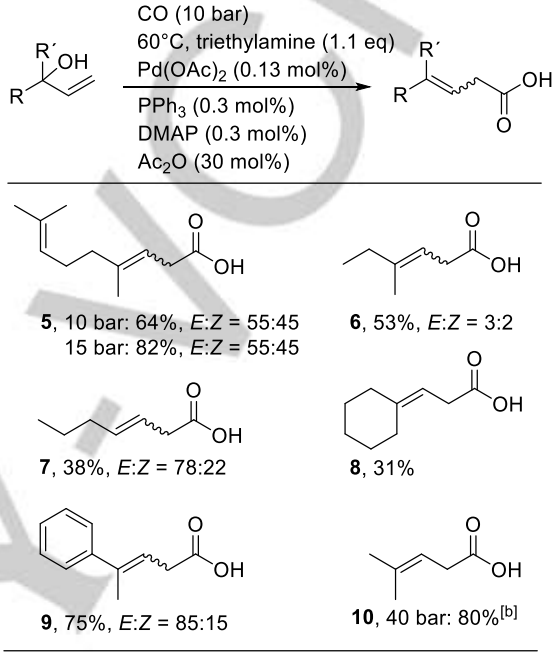
1 (*E*/*Z*)-**2**

entry	$Pd(OAc)_2$ (mol%)	PPh_3 (mol%)	Ac_2O (mol%)	additive (mol%)	conversion[b]	yield[c]
1	0.13	0.3	-	-	-	-
2	0.13	0.3	23	DMAP 0.3	95 (65) [i]	77
3	0.13	1.3	23	DMAP 0.3	50	33
4	0.13	-	23	DMAP 0.3	26	1
5	0.13	0.3	-	DMAP 0.3	-	-
6	0.13	0.3	23	-	94 (54)[i]	77
7[d]	0.13	0.3	23	DMAP 0.3	70	54
8[e]	0.13	0.3	-	DMAP 0.3 / allylic acetate 23	52	32
9[f]	0.13	0.3	-	DMAP 0.3 / E-nerolidol acetate 30	>99	95
10[g]	0.13	0.3	23	DMAP 0.3	34	16
11[h]	0.13	0.3	23	DMAP 0.3	30	18

[a] General procedure: **1** (153 mmol, 1.0 equiv.), NEt_3 (1.1 equiv.), $Pd(OAc)_2$ (0.13 mol%), PPh_3 (0.3 mol%), DMAP (0.3 mol%), and Ac_2O (23 mol%), for details, see experimental section, [b] determined by GC-area %, [c] determined by GC-area %, [d] low amount of NEt_3 (0.65 equiv.) used, [e] allylic acetate (23 mol%) used instead of Ac_2O, [f] E-nerolidylacetate (30 mol%) used instead of Ac_2O, yield relates to the sum of E-nerolidylacetate and **1**, [g] 120°C, [h] THF, no NEt_3, [i] conversion after 6 h reaction time.

Thermodynamically the reaction of an allylic alcohol to the corresponding carboxylic acid is very exergonic (ΔG in the range -85 to -90 kJ/mol, 70°C, DFT-based calculation). The reaction gains even more thermodynamic driving force in the presence of amine as base, because of the subsequent acid base reaction (addition of amine leads to ΔG of ca. -300 kJ/mol, approximation made using Butenol + CO → Pentenic acid). The calculated thermodynamic equilibrium between the two possible product isomers (3*E*/7*E*)-**2** and (3*Z*/7*E*)-**2** is at 79:21. The experimentally observed ratio is at ca. 60:40. Since we find more or less the same isomeric ratio for all performed experiments with the different used conditions (temperatures and catalyst), we interpret this as a hint that the found ratio is thermodynamically controlled.

Scheme 2. Palladium-catalyzed carbonylation of allylic alcohols: Scope. [a]



[a] Carried out according to general procedure **2,** for details, see experimental section, yields determined by GC-area %, [b] in this case reaction was run at 40 bars/70°C, besides **10** (80%) also 4-methyl-2-penteoic acid (14%) was formed as side product.

Different branched allylic alcohols were subjected to carbonylation conditions to explore the scope of the reaction (Scheme 2) and yielded the corresponding carboxylic acids (**5**-**10**). We found that branched allylic alcohols are viable substrates, whereas linear allylic alcohols react much more slowly. Our mechanistic working hypothesis for the carbonylation is shown in Scheme 3. We propose that catalytical amounts of the substrate are converted by acetic anhydride/DMAP in the starting phase to the corresponding nerolidol acetate **11**, which can be monitored *via* GC-reaction control. Intermediate **12** is very likely formed as primary reaction product.[8] However, **12** was not detected by GC, presumably due to low concentration or decomposition during gas chromatography. Under anhydrous reaction conditions one of the intermediary anhydrides, Ac_2O or **12**, should always be present as the substrate activating anhydride. A time conversion plot (Figure 1) shows a strong effect of anhydride addition, as compared to a rather small effect of increasing the CO pressure.

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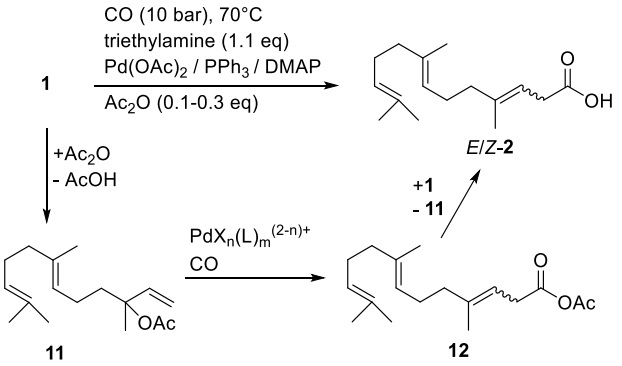
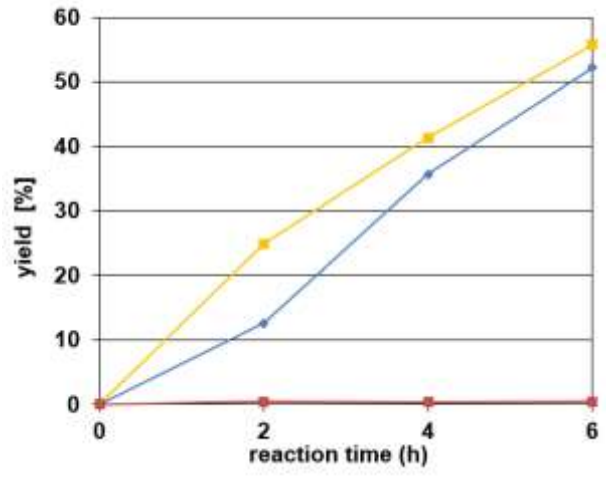
Scheme 3. Palladium-catalyzed carbonylation of allylic alcohols: Mechanistic working hypothesis.



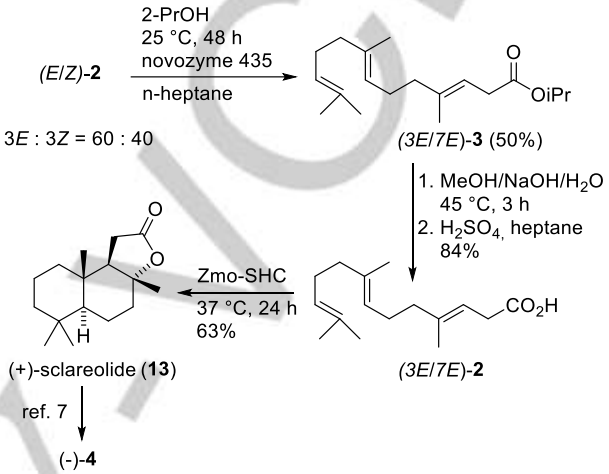
Having an efficient route to (*E*/*Z*)-**2** in hand, we applied it to the preparation of (+)-sclareolide (**13**) (Scheme 4). Pure (3*E*/7*E*)-homofarnesylic acid (3*E*/7*E*)-**2** was obtained by subjecting (*E*/*Z*)-**2** to enzymatic resolution with novozyme 435, which led to ester (3*E*/7*E*)-**3** in 50% yield. Subsequent saponification gave the acid (3*E*/7*E*)-**2**. Pure (3*E*/7*E*)-**2** was converted into enantiopure (+)-sclareolide in 63% isolated yield using recombinant squalene-hopene cyclases (SHC) from *Zymomonas mobilis*.[11] It is known, that squalene-hopene cyclases (SHC) can form ambrox in a one-step cyclization from homofarnesol ((3*E*,7*E*)-4,8,12-trimethyltrideca-3,7,11-trien-1-ol).[12] The bacterial cyclase enzymes are widespread in nature. It is assumed that their function *in vivo* is to provide supply of squalene in order to ensure membrane stability under challenging environmental conditions. Squalene-hopene cyclase accept various substrates for cyclization and additionally catalyze various chemical conversions.[12] Here we show that not only (3*E*/7*E*)-homofarnesol but also (3*E*/7*E*)-homofarnesylic acid can by cyclized.

Figure 1. Yield (%) / reaction time (h) at 10 bar (blue) and 20 bar (yellow) with Ac_2O present (23 mol%) and at 20 bar without Ac_2O (red).



Since the reduction of the obtained (+)-sclareolide (**13**) to (-)-ambrox (**4**) is a known and well described step that can be realized using hydrogenation[7] or reduction with hydride followed by etherification our synthesis of (+)-sclareolide (**13**) completes the formal synthesis of (-)-ambrox (**4**). In the described process, the acid (3*Z*/7*E*)-**2** is a side product in the novozyme resolution. In order to achieve a higher efficiency in the overall process, an isomerization method to recycle (3*Z*/7*E*)-**2** back into the E/Z-mixture is in development.

Scheme 4. BASF-route to (+)-sclareolide.



In conclusion, we have shown here that addition of catalytic amounts of anhydrides or reagents that are anhydride forming under reaction conditions significantly accelerate reaction rates of carbonylation reactions. We think, this finding is both very useful and surprising. Our interpretation is that the reaction system allows the activating anhydride to be constantly regenerated from carbon monoxide. The further application of the catalytic activation using anhydrides to other transformations might be possible, i.e. for insertion reactions where a C-O, C-N or C-X bond needs to be weakened.

Experimental Section

Exemplary procedure (see Table 1, entry 2): Under an atmosphere of argon palladium(II)acetate (46 mg, 0.2 mmol), triphenylphosphine (120 mg, 0.46 mmol), and DMAP (56 mg, 0.46 mmol) are transferred into a steel autoclave. *E*-nerolidol (34 g, 152.6 mmol), triethylamine (17 g, 167 mmol) and acetic anhydride (3.6 g, 35 mmol) are added under a constant argon flow. The autoclave is pressurized with 10 bar CO and heated at 70°C inside temperature. Pressure was kept at 10 bar and after an overall reaction time of 24 h, the reactor was cooled down to room temperature. After release of pressure GC-analysis of the crude product showed a GC-yield of 77% at 95% conversion of *E*-nerolidol. The solution was subjected to Kugelrohr distillation to yield (3*E*/3*Z*)-**2** (23 g, 61%) as a colorless oil with (3*E*/7*E*)-**2**:(3*Z*/7*E*)-**2** = 60:40 (GC/NMR). (3*E*/7*E*)-**2**: ^{13}C NMR (125 MHz, $CDCl_3$): 179.1, 139.8, 135.4, 131.4, 124.4, 123.8, 114.9, 39.8, 39.6, 33.6, 26.8, 25.8, 26.4, 17.8, 16.5, 16.1 ppm; (3*Z*/7*E*)-**2**: ^{13}C NMR (125 MHz, $CDCl_3$): 179.2, 139.7, 135.7, 131.2, 124.5, 123.7, 115.9, 39.8, 33.5, 32.2, 26.8, 26.3, 25.7, 23.4, 17.7, 16.0.

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Keywords: palladium • allylic alcohol • carbonylation • anhydride • carboxylic acid

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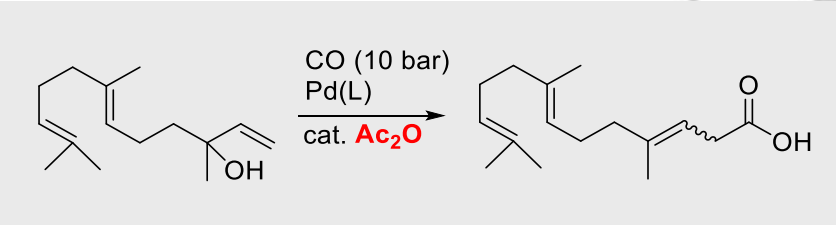

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