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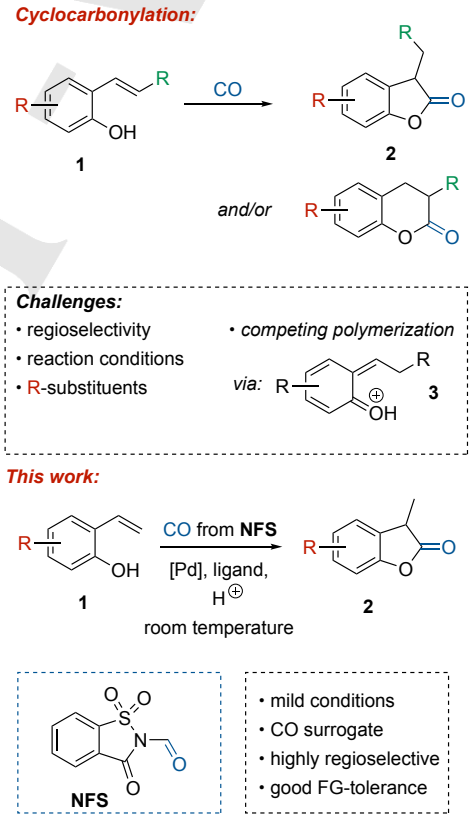
Synthesis of Benzofuranones *via* Palladium-Catalyzed Intramolecular Alkoxycarbonylation of Alkenylphenols

Vera Hirschbeck,[b] and Ivana Fleischer*[a]

Abstract: Herein, a new catalytic system to synthesize benzofuranones is reported. A palladium-catalyzed intramolecular alkoxycarbonylation is employed to generate 3-substituted-benzofuran-2(3H)-ones from alkenylphenols under mild reaction conditions, linked to an *ex situ* formation of CO from N-formylsaccharin. The carefully chosen catalytic system enables an efficient reaction with a novel functional group tolerance, despite the high polymerization tendency of the starting material.

Benzofuran-2(3*H*)-ones, which can often be found in natural products, constitute interesting structural motives with unique pharmaceutical importance.[1] Moreover, substituted derivatives play an important role in polymer chemistry, where they are used as antioxidants, in order to inhibit oxidative degradation of polymers. Due to the weak benzylic C–H bond, benzofuranyl radicals can easily be formed, which are able to trap oxygen and therefore prevent autoxidation.[2] Many different synthetic strategies to synthesize benzofuran-2(3*H*)-ones are known in the literature.[3] A convenient and atom economic way to generate benzo-fused 5-, 6- or 7-membered lactones is the intramolecular Reppe-type carbonylation of alkenyl- or allylphenols.[4] The control of regioselectivity is one of the challenges of this transformation. Several approaches to the synthesis of 6-membered lactones were reported.[5] A general method for the synthesis of benzofuran-2(3*H*)-ones (**2**) from alkenylphenols (**1**) proved more difficult (Scheme 1). Alper employed a catalyst system based on a Pd(0) precursor and bidentate ligand dppb (1,4-bis(diphenylphosphino)butane) in a ionic liquid to obtain a series of 5-membered lactones with no or moderate regioselectivity.[6] Better results were achieved by Manabe *et al.*, who developed a cyclization of 2-vinyl aryl formates using $Ru_3(CO)_{12}$ under forcing reaction conditions (135 °C, 15 mol% of [Ru]).[7] In 2014, Shi and co-workers reported a hydroesterification of alkenylphenols with phenyl formate as CO surrogate generating benzofuran-2(3*H*)-ones.[8] They described a catalytic system consisting of $Pd(OAc)_2$ (5 mol%) and PPh_3 (20 mol%), which showed a good functional group tolerance for α-, β- or non-substituted alkenylphenols.

However, only one example with substituent on aryl ring was shown, probably because of the high polymerization tendency of some substrates and the employed high temperature (90 °C) in combination with an acid. Protonation of the substrate leads to the protonated quinone methide intermediate **3**, which undergoes cationic polymerization. Herein we report the first cyclocarbonylation of 2-vinylphenols proceeding at room temperature, which allows for the expansion of the substrate scope to vinyl phenols with substituted aryl ring. In order to avoid working with gaseous carbon monoxide, *N*-formylsaccharin (NFS) - originally described by Manabe and co-workers[9] - was used as a CO surrogate, in combination with a two-chamber pressure tube developed by Skrydstrup[10] (Scheme 1, bottom).



Scheme 1. Regioselectivity of cyclocarbonylation and our new system.

Based on our earlier reports on the alkoxy- and the thiocarbonylation of alkenes at ambient temperature, a modified Pd(0)-based catalytic system for lactonization was identified.[11] We found that the combination of $Pd(dba)_2$, ligand **L1** (dppdtbpf; 1-diphenylphosphino-1´-(di-tertbutylphosphino)-ferrocene)[12] and diphenylphosphoric acid (DPPA) that was previously used in the thiocarbonylation led to 81% of **2a** (Table 1, entry 1). Whereas, the original alkoxycarbonylation conditions (**L2**, (dtbpx; bis(di-tert-butylphosphinomethyl)benzene)[13]/BNPA (1,1´-bi-2-naphthol

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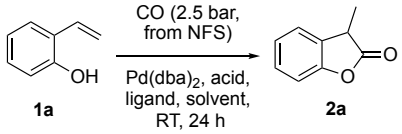
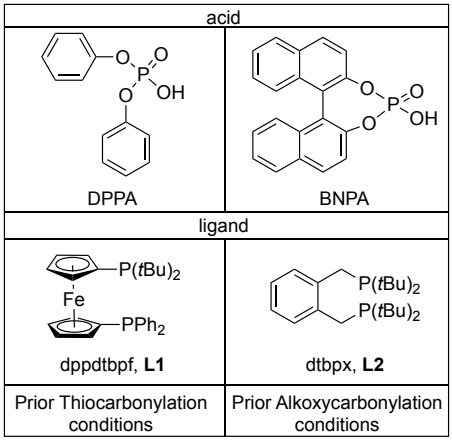
phosphoric acid)) generated only 73% yield (entry 2). A transpose of the respective ligand/acid pair led to decreased activity, which is in accordance to our earlier report (entries 3,4).[11b] A slightly increased yield was observed by using TFA (entry 5), but because of its volatility and in order to circumvent possible reproducibility issues in the two-chamber pressure tube, we decided to use DPPA in further studies. The acid is essential for the generation of the catalytically active Pd-hydride, as confirmed by the corresponding control experiment without any acid (entry 6).[13c, 14]

Table 1. Initial optimizations.[a]





Entry	ligand	acid	solvent	additive	Yield [%][c]
1	**L1**	DPPA	CH_2Cl_2	-	81
2	**L2**	BNPA	CH_2Cl_2	-	73
3	**L2**	DPPA	CH_2Cl_2	-	75
4	**L1**	BNPA	CH_2Cl_2	-	69
5	**L1**	TFA	CH_2Cl_2	-	83
6	**L1**	-	CH_2Cl_2	-	0
7	**L1**	DPPA	CH_2Cl_2[d]	$^nC_7H_{15}SH$ [d]	70
8	**L1**	DPPA	CH_2Cl_2[e]	MeOH[e]	27[f]
9	**L1**	DPPA	MeOH	-	9[g]
10	**L1**	DPPA	CH_2Cl_2	LiCl[h]	0

[a] reaction conditions: The reaction was carried out in a 2-chamber system. Chamber A: CO generation (2.5 bar): NFS (2.13 mmol, 450 mg), Na_2CO_3 (3.20 mmol, 339 mg) in DMF (1 mL); Chamber B: 2-vinylphenol (115 µL, 1.0 mmol), $Pd(dba)_2$ (5.8 mg, 10 µmol, 1 mol%), ligand (40 µmol, 4 mol%), acid (150 µmol, 15 mol%), solvent (1 mL), RT, 24 h. [c] determined by quant. NMR using $OHCNPh_2$ as an internal standard; [d] CH_2Cl_2 (790 µL), $^nC_7H_{15}SH$ (210 µL, 177 mg, 1.3 mmol). [e] CH_2Cl_2 (790 µL), MeOH (210 µL, 166 mg, 5.2 mmol). [f] Further 47% of branched methylester (determined by GC-FID). [g] Further 62% of branched methylester (determined by NMR). [h] LiCl (200 µmol, 8.5 mg, 0.2 eq).

Also, few additives were tested. In the thiocarbonylation project we suggested that the used thiol forms the Pd-H *via* oxidative addition, therefore the same amount of $^nC_7H_{15}SH$ was added. In addition, it also may form the reactive thioester first and this would undergo fast transesterification.[15] However, this led to a reduction of catalytic activity in case of intramolecular alkoxycarbonylation resulting in 70% yield (entry 7). Then, we examined if there may be a positive influence by the addition of methanol (entries 8, 9). Beside the intramolecular reaction, also an intermolecular carbonylation (generation of the branched methylester) followed by trans-esterification to generate **2a** is conceivable. Unfortunately, no positive influence was observed by the addition of MeOH. By increasing the amount of MeOH more of the undesired branched methylester was observed. LiCl was tested as Lewis acid additives since it might accelerate the final rate-determining alcoholysis by coordination to the carbonyl group (entry 10; see SI for the commonly accepted mechanism of alkoxycarbonylations).[16] However, a white precipitate and no lactone were observed. The corresponding intermolecular transformation of styrene with phenol under this reaction conditions was not successful, which might be reasoned with steric effects.

Furthermore, a solvent screening was performed considering Kamlet-Taft parameters (Figure 1).[17] The choice of the solvent depends on its properties and other factors, such as waste management. On one side the solvent has to be polar in order to dissolve the acid and other reaction components, on the other side the solvent should not be too basic, because otherwise it can coordinate to the catalyst. Other important factors influencing the search of a suitable solvent, for example the viscosity plays an important role if one reaction partner is a gas, such as CO in carbonylations.[18]

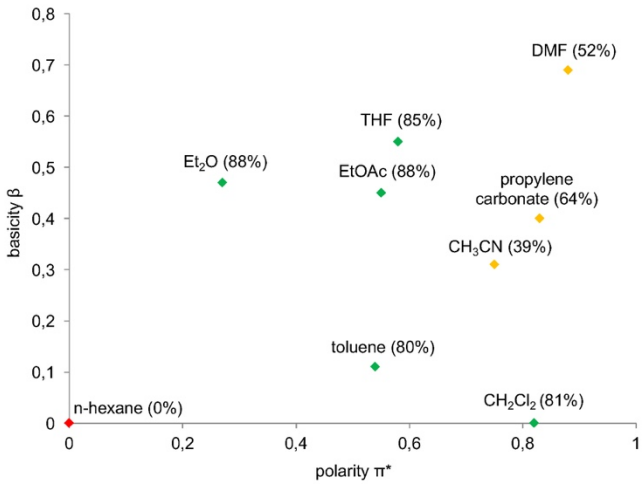


Figure 1. Solvent screening considering Kamlet-Taft parameters.[17]

Various solvents were tested and the yield could be increased to 88% by using Et_2O or EtOAc, instead of CH_2Cl_2 (81%). As expected no yield was observed by using hexane, because of its poor ability to solubilize reaction components. The lower yield in propylene carbonate can be traced back to the high viscosity and acetonitrile can coordinate to the catalyst and therefore deactivate

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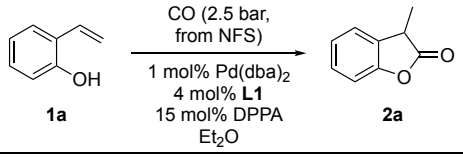
it (acetonitrile is a better ligand because of π-backbonding). We decided to use Et_2O for further studies, since it can be easily removed after the reaction also in case of more volatile products. For the final optimizations, the temperature was increased to 30 °C, which led to higher yield of 95% (Table 2).

Table 2. Final optimizations for the lactonization of 2-vinylphenol.[a]



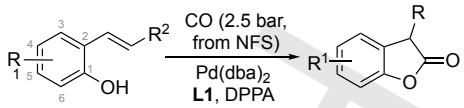
1a **2a**

Entry	Time [h]	Temp [°C]	Yield[b] [%]
1	24	RT	88
2	24	30	95
3	48	RT	94

[a] reaction conditions: The reaction was carried out in a 2-chamber system. Chamber A: CO generation (2.5 bar): NFS (2.13 mmol, 450 mg), Na_2CO_3 (3.20 mmol, 339 mg) in DMF (1 mL); Chamber B: 2-vinylphenol (115 µL, 1.0 mmol), $Pd(dba)_2$ (5.8 mg, 10 µmol, 1 mol%), **L1** (21 mg, 40 µmol, 4 mol%), DPPA (38 mg, 150 µmol, 15 mol%), Et_2O (1 mL). [b] determined by quantitative NMR using $OHCNPh_2$ as an internal standard. .No 6-membered lactone was detected.

Almost the same result was observed by performing the reaction for 48 h at room temperature. Since most of the envisaged substrates show a high polymerization tendency, which is significantly influenced by the temperature, 48 h and RT were chosen as the optimized reaction conditions. Subsequently, the substrate scope for the lactonization of 2-vinylphenol derivatives was evaluated (Table 3). Therefore, 1 mol% of $Pd(dba)_2$, 4 mol% of **L1**, 15 mol% of DPPA in Et_2O for 48 h at RT were applied in order to carbonylate aryl-, α- or β- substituted substrates by using 2.5 bar of *ex situ* generated CO. Methyl substituents in 3´ and 5´ positions are well tolerated, whereas there is breakdown in activity for double 3´,6´-substitution (entries 2-4). The steric influence of the methyl groups next to both reaction sites seems to be too strong. Another challenge is the carbonylation of vinyl phenols containing electron donating methoxy groups, due to polymerization issues. Under the mild reaction conditions, we were able to convert 4´-and 6´-MeO-substituted substrates in excellent yields (88%, 90%, entries 5, 7). However, a polymerization was observed for 5-methoxy-2-vinylphenol (**1f**) under the reaction conditions (entry 6), and also already during its synthesis. To our delight, ^{t}Bu- and COOMe-groups were tolerated in 4´ position, providing good yields of 85% and 77% respectively (entries 8, 9). Then, we examined the influence of substituents on the double bond. For α-substituted substrates such as **1j**, the formation of five membered lactone was not observed. This was the only case were the six-membered lactone **2j** was generated albeit in low yield of 22% (entry 10). By applying the β-substituted alkene **1k**, **2k** was observed in excellent yield of 88%, whereas **1l** led to the same product in 78% yield *via* initial isomerization. As expected, carbonylation of sterically demanding **1m** generated **2m** in low yield of 11%. Double substitution in β-position seems to be a limitation of the catalytic system.

Table 3. Carbonylation of different aryl-, α- or β- substituted 2-vinylphenols.[a]



1a-m **2a-m**

Entry	Substrate	Product	Yield[b][%]
1	**1a**	**2a**	95
2	**1b**	**2b**	87
3	**1c**	**2c**	83
4	**1d**	**2d**	11[c]
5	**1e**	**2e**	88
6	**1f**	**2f**	0[d]
7	**1g**	**2g**	90
8	**1h**	**2h**	85
9	**1i**	**2i**	78
10	**1j**	**2j**	22
11[e]	**1k**	**2k**	88
12	**1l**	**2k**	77
13	**1m**	**2m**	11

[a] reaction conditions: The reaction was carried out in a 2-chamber system. Chamber A: CO generation (2.5 bar): NFS (2.13 mmol, 450 mg), Na_2CO_3 (3.20 mmol, 339 mg) in DMF (1 mL); Chamber B: **1a - 1m** (1.0 mmol), $Pd(dba)_2$ (5.8 mg, 10 µmol, 1 mol%), **L1** (21 mg, 40 µmol, 4 mol%), DPPA (38 mg, 150 µmol, 15 mol%), Et_2O (1 mL), RT, 48 h. [b] Isolated yields. [c] 31% conversion. [d] Complete polymerization. [e] E/Z (77/33) mixture.

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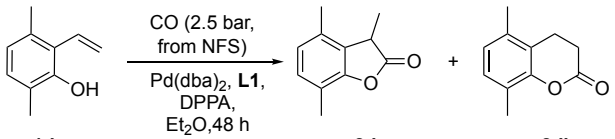
Subsequently, we turned our attention back to the challenging substrate **1d** and an additional optimization was performed (Table 4). It became apparent that simple optimizations, such as increasing pressure, temperature and catalyst amount enable carbonylation also for sterically demanding substrates. The amount of acid was always maintained in order to prevent polymerization. Almost full conversion was observed by carrying out the reaction at 35 °C with doubled amount of palladium and ligand, generating 62% of the desired five-membered lactone **2d** and 36% of **2d´**.

Table 4. Optimization of the carbonylation of 3,6-dimethyl-2-vinylphenol (**1d**).[a]



1d **2d** **2d'**

Entry	p(CO) [bar]	Temp [°C]	Ratio [Pd]/lig/H$^+$	Conv.[b] [%]	Yield **2d**[b] [%]	Yield **2d'**[b] [%]
1	2.5	RT	2/8/15	65	44	23
2	5	RT	1/4/15	58	30	23
3	2.5	35	1/4/15	88	51	34
4	2.5	35	2/8/15	97	62	36

[a] reaction conditions: The reaction was carried out in a 2-chamber system. Chamber A: CO generation: 2.5 bar → NFS (2.13 mmol, 450 mg), Na_2CO_3 (3.20 mmol, 339 mg) in DMF (1 mL); 5 bar → NFS (4.26 mmol, 900 mg), Na_2CO_3 (6.40 mmol, 678 mg) in DMF (2 mL); Chamber B: **1d** (165 µL, 1.0 mmol), $Pd(dba)_2$ (5.8 mg, 10 µmol, 1 mol%; 11.6 mg, 20 µmol, 2 mol%), **L1** (21 mg, 40 µmol, 4 mol%; 42 mg, 80 µmol, 8 mol%), DPPA (38 mg, 150 µmol, 15 mol%), Et_2O (1 mL), RT/35 °C, 48 h. [b] determined by quantitative NMR using $OHCNPh_2$ as an internal standard.

In conclusion, we investigated a highly active catalytic system for the lactonization of alkenylphenols, which proceeds at room temperature and therefore allows to employ various substrates with the polymerization tendency. This enabled a new substrate scope of vinyl phenols with substituents on the aryl ring. In addition, single substitution at both positions of the double bond was tolerated. The avoidance of gaseous carbon monoxide and heating render this transformation an environmentally friendly way of generating lactones, with a good functional group tolerance also for sterically demanding and electron donating substituents.

Acknowledgements

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Keywords: carbonylation • palladium • cyclization • CO surrogate • lactones

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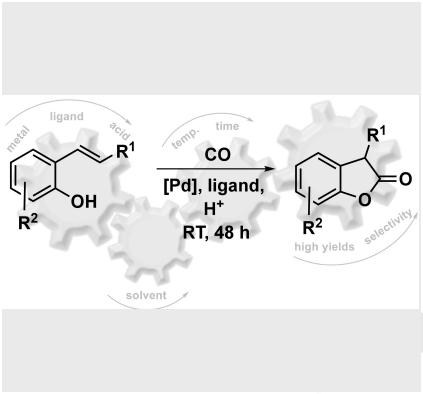
Carbonylative lactonization at ambient reaction conditions provides benzofuranones. Various vinyl phenols with substituents on the aryl ring were converted in good yields.



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