Palladium-catalyzed aryloxy- and alkoxycarbonylation of aromatic iodides in  $\gamma$ -valerolactone as bio-based solvent

József M. Tukacs, Bálint Marton, Eszter Albert, Imre Tóth, László T. Mika

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1	Palladium-catalyzed aryloxy- and alkoxycarbonylation of
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5	József M. Tukacs, <sup>a</sup> Bálint Marton, <sup>a</sup> Eszter Albert, <sup>a</sup> Imre Tóth <sup>b</sup> and László T. Mika <sup>a*</sup>
6 7	<sup>a</sup> Department of Chamical and Environmental Process Environming Dudanast
/ 8	University of Technology and Economics, Műegyetem rkp. 3., H–1111, Budapest
9	Hungary.
10	<sup>b</sup> Institute of Chemistry, University of Pannonia, Egyetem u. 10, H-8200 Veszprém,
11	Hungary.
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13	De directed to Desfrance I for 16 Kellferer the second second in 61 is 65 <sup>th</sup> birthday
14 15	Dedicated to Professor Laszlo Kollar on the occasion of his 65° birthday.
16	
17	Keywords
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19	Green solvents, aryl halides, homogeneous carbonylation, aromatic substituent
20	effects, palladium
21	
22	Abstract
23 24	Fossil-based solvents and triethylamine as a toxic and volatile base were successfully
25	replaced with $\gamma$ -valerolactone as a non-volatile solvent and $K_2CO_3$ as inorganic base
26	in the alkoxy- and aryloxycarbonylation of aryl iodides using phosphine-free Pd
27	catalyst systems. By this, the traditional systems were not simply replaced but also
28	significantly improved. In the study, the effects of different reaction parameters, i.e.
29	the use of several other solvents, the temperature, the carbon monoxide pressure, the
30	base and the catalyst concentrations, were evaluated in details on the efficiency of the
31	carbonylations. To gather some information on the mechanism of these reactions, the
32	effects of electronic parameters ( $\sigma$ ) of various aromatic substituents of the aryl iodides
33	as well as the influence of para-substitution of phenol were investigated on the
34	activity. For a comparison, the aryl-substituted aryl iodides were also reacted with
35	methanol and aryl iodide was also alkoxycarbonylated using several different lower
36	alcohols. From the observed correlations between the electronic parameters of the
37	aromatic substituents and the rates, it appears that the rate determining step is the
38	oxidative addition of Ar–I to Pd <sup>0</sup> , provided that sufficient amounts of nucleophiles are

39 present for the ester formation. If this is not the case, the rate of nucleophile attack40 might determine the overall rate.

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# 43 **1. Introduction**

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45 Since the discovery of the Roelen reaction (hydroformylation) [1] and the 46 Reppe carbonylation, the transition metal-catalyzed carbonylation reactions, 47 providing facile and versatile methods for the introduction of C=O functionality to various skeletons, have gained tremendous importance in numerous fields of synthetic 48 49 chemistry from laboratories to industrial applications [2]. While several functional 50 groups, *i.e.* C=C, C=C, C=OH etc. can be subjected to carbonylation [3,4,5,6], the 51 conversion of alkyl- and aryl-X compounds (X = I, Cl, Br) and carbon monoxide in 52 the presence of a nucleophile represent a fundamental catalytic method for manufacturing various amides, carboxamides, carboxylic acids, esters, heterocycles, 53 54 azides, etc. [7,8,9,10]. The transformation of aryl halides with alcohols and phenols as 55 O-nucleophiles provides a direct route towards the synthesis of aromatic esters. These 56 structures have been widely used as building blocks of biologically active compounds 57 [11] including anti-inflammatory and antiseptic pharmaceuticals [12,13] like those 58 found in liquid crystals [14,15], photosensitizers [16]. Thus, both alkoxycarbonylation 59 and aryloxycarbonylation reactions continue to receive significant interest.

60 From the series of transition metals, Pd-based catalysts exhibit the highest 61 efficiencies for alkoxy- and aryloxycarbonylation reactions [7,10] operating under 62 either homogeneous [17,18,19] or heterogeneous conditions [20, 21, 22]. From the view of green chemistry, most of the alkoxycarbonylation reactions could be 63 64 completed in the corresponding alcohols, *i.e.* in methanol or ethanol, which serve both 65 as the reagent and as the solvent. However, aryloxy- and aminocarbonylations either in homogeneous or heterogeneous systems have been generally performed in fossil-66 67 based common organic solvents such as toluene, tetrahydrofuran, 1,4-dioxane, N,N-68 dimethylformamide or even in dichloromethane or 1,2-dichloroethane [6, 7]. 69 Solvents, which have high toxicity and/or high vapor pressure, could have negative 70 impact on the environment. According to the FDA guidance for industry [23], these 71 solvents were classified into Class 1 and Class 2, which utilizations should be avoided 72 or strictly limited, particularly in the pharmaceutical industry [23]. Thus from this

respect, the use of most of the above-mentioned solvents including methanol should be restricted. It is well-known that conjugate bases including alkoxides, aryloxides or amides are always better nucleophiles than their corresponding acid forms, *i.e.* alcohols, phenols or amines, respectively. Thus, the problems associated with the use of environmentally risky protic reagents and harmful solvents can be circumvented in the carbonylation aryl or alkyl halides by using the appropriate conjugated base as reagents in an appropriate aprotic solvent.

80 To exclude hazardous solvents from such alkoxy- and aryloxycarbonylation reaction, supercritical carbon dioxide [24,25] and ionic liquids [26, 27] were already 81 successfully utilized as surrogates of conventional ones. However, if a "solvent from 82 83 nature" [28] can exhibit appropriate properties such as stability and polarity, which have been described by Kamlet-Taft parameters [29], those applications should be 84 85 preferred. Horváth and co-workers identified  $\gamma$ -valerolactone (GVL) as a renewable platform molecule [30]. Due to its outstanding physical and chemical properties e.g. 86 87 low-vapor pressure [31], low toxicity (LD<sub>50(rat. oral)</sub> = 8800 mg/kg) [30], low 88 flammability [32], no peroxide formation [33], GVL can be used as a surrogate of 89 conventional organic solvents for synthesis and catalysis. Beyond its first application 90 as a solvent for the dehydration of carbohydrates [34, 35], several important transition 91 metal catalyzed reactions such as cross-coupling [36, 37, 38], Pt- and Rh-catalyzed 92 hydroformylation [39, 40], and Pd-catalyzed aminocarbonylation [41] reactions were 93 successfully performed in GVL without significant changes in the efficiency of the 94 catalytic systems. Thus, its application for aryloxy- and alkoxycarbonylation reactions 95 of organic halides could also open an environmentally benign alternative for these 96 important catalytic transformations.

97 Herein we report on the phosphine-free Pd-catalyzed aryloxy- and 98 alkoxycarbonylation reactions of iodoaromatic compounds using  $\gamma$ -valerolactone as a 99 renewable, environmentally benign reaction medium. The effects of different reaction 100 parameters, *i.e.* the use of several other solvents, the temperature, the carbon 101 monoxide pressure, the base and the catalyst concentrations, were investigated in 102 details on the efficiency of the carbonylation. The functional group tolerances of 103 iodoaromatic compounds and O-nucleophiles were also studied.

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# 107 **2. Experimental**

### 108

# 109 *2.1 General*

Toluene,  $\gamma$ -valerolactone, iodobenzene and its derivatives, phenol and its 110 111 derivatives, palladium(II)-acetate, triethylamine, inorganic salts (Na<sub>2</sub>CO<sub>3</sub>, K<sub>2</sub>CO<sub>3</sub>, 112 KH<sub>2</sub>PO<sub>4</sub>) were obtained from Sigma-Aldrich Kft. Budapest, Hungary. Conversions 113 and yields were determined by GC-FID analysis performed on HP 5890 instrument 114 (column RESTEC 30 m  $\times$  0.25 m  $\times$  0.25  $\mu$ m, injection temperature: 250 °C; starting 115 oven temperature: 50 °C; rate-1: 2 °C/min; final temperature: 150 °C; rate-2: 25 116 °C/min; final temperature: 230 °C/min; carrier gas: H<sub>2</sub> 1.30 mL/min). For the 117 analysis, 10 µL of the reaction mixture was added to 1 mL of methylene chloride 118 followed by the addition of 10 µL p-xylene as an internal standard. The products were 119 identified by GC-MS using Shimadzu QP2010 SE instrument.

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# 121 2.2 Carbonylation reactions

In a typical experiment, catalyst precursor (Pd(OAc)<sub>2</sub>, if otherwise not stated: 122 0.280 mg, 0.00125mmol), 0.5 mmol of iodoaromatic compounds, 0.625 mmol (1.5 123 124 equiv.) of O-nucleophile were dissolved in 2.5 mL solvent followed by addition of 125 1.25 mmol (2.5 equiv.) of base. The reaction mixture was placed in a glass inlet tube 126 into a 25 mL Parr Hastelloy-C high-pressure reactor equipped with manometer, safety 127 relief, thermometer and a magnetic stirrer. The reactor was flushed with 10 bar of CO 128 three times and placed into a pre-heated oil bath to the given temperature. The final 129 pressure was adjusted at the elevated temperature. The reaction mixture was then 130 stirred for 4 h. The pressure was monitored and maintained throughout the reaction. 131 After cooling and venting of the autoclave after a given reaction time, the solution 132 was removed and immediately analyzed by GC-FID and/or GC-MS.

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# 134 **3. Results and Discussion**

3.1 Phenoxycarbonylation reactions

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138 In order to verify the utilization of  $\gamma$ -valerolactone as a biomass-based alternative 139 solvent for aryloxycarbonylation reactions, the carbonylative transformation of 0.5 140 mmol of iodobenzene (**1a**) and 1.5 equiv. of phenol (**2a**) to phenyl benzoate (**3a**) was 141 selected as a model reaction in 2.5 mL of solvent (Scheme 1). First, the yields were

142 compared in the presence of 2.5 equiv. of Et<sub>3</sub>N as a base using the selected conventional organic solvents and GVL under literature conditions [18]. Expectedly, 143 144 the model substrates showed negligible reactivity in the apolar n-octane (Table 1, 145 entry 1), however, by the use of common aprotic dipolar media, moderate yields of 3a 146 were detected at 100 °C after 3 h. GVL gave the highest yield of 3a (70%, TON=280), which was 1.3 times higher compared to DMSO under identical condition 147 148 (Table 1, entries 2-6). Because there are no significant differences between the polarity/polarizability of DMF, DMSO, and GVL, on the other hand their dielectric 149 constant is quite similar; its effect on the reaction could be rather limited. The 150 differences may be explained by the different rates of the oxidative addition of PhI to 151 zero-valent Pd-carbonyl (Pd(CO)<sub>n</sub>, n = 1-3) species in different solvents (see step II 152 153 in Scheme 2 vide infra), where n probably also depends on the nature of the reaction 154 medium. Kégl and co-workers have recently calculated that the addition of PhI (1a) was the most favorable to a 14 electronic Pd-species in DMF, which is the dicarbonyl, 155  $Pd(CO)_2$  in the absence of a strong donor  $PPh_3$  ligand. [42]. The same might be the 156 case with GVL, which has quite similar solvatochromic parameters to DMF (Table 1). 157

$$\begin{array}{c|c} & & & \\ \hline \\ 1a & & 2a \end{array} \xrightarrow{Pd} \begin{array}{c} & & & \\ \hline \\ base, CO \end{array} \xrightarrow{Q} \begin{array}{c} & & \\$$

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159 Scheme 1. Phenoxycarbonylation of iodobenzene (1a) in the presence of palladium-catalyst

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162 **Table 1.** Phenoxycarbonyaltion reaction of iodobenzene (1a) in different solvents<sup>a</sup>

#	Solvent <sup>b</sup>	$LD_{50}$ oral rat	Kamle	t–Taft paraı	Yield <b>3a</b>	TON <sup>f</sup>	
		$(mg kg^{-1})^{c}$	α	β	π	(%) <sup>d</sup>	
1	n-octane	5000	0.00	0.00	0.01	< 5	< 20
2	toluene	5000 <sup>[41]</sup>	0.00	0.11	0.54	37	148
3	1,4-dioxane	5200 <sup>[41]</sup>	0.00	0.37	0.55	30	120
4	DMF	2800 <sup>[41]</sup>	0.00	0.69	0.88	51	204
5	DMSO	14500 <sup>[43]</sup>	0.00	0.76	1.00	52	208
6	GVL	8800 <sup>[32]</sup>	0.00	0.60	0.83	70	280

<sup>a</sup> Reaction conditions: 0.5 mmol of iodobenzene (**1a**), 0.625 mmol of phenol (**2a**), 0.00125 mmol 164 (0.25 mol%) of Pd(OAc)<sub>2</sub>, 2.5 equiv. of Et<sub>3</sub>N,  $p_{CO} = 7$  bar, 2.5 mL of GVL, T = 100 °C, t = 3 h; RPM 165 = 400 min<sup>-1</sup>; <sup>b</sup>  $\alpha$ : DMF: *N*,*N*-dimethylformamide, DMSO: dimethyl sulfoxide; <sup>c</sup> LD<sub>50</sub> from references; 166 <sup>d</sup>  $\alpha$ : acidity,  $\beta$ : basicity,  $\pi$ : polarity/polarizability obtained from ref. [29]; <sup>e</sup> GC yield; <sup>f</sup> TON: Turnover 167 Number = mmol product/mmol Pd catalyst.

Next, we have focused on the replacement of  $Et_3N$  as volatile and toxic ( $LD_{50,rat(oral)} =$ 169 170 560–590 mg/kg [44]) base in the carbonylation protocol. Thus, the model reaction 171 was also carried out by using several different of non-volatile, inorganic bases by 172 varying parallel also the catalyst concentration. By comparing the results (Table 2, 173 entries 1–6), it was observed that at the catalyst loading above (0.25 mol%), the use of 174  $K_2CO_3$  gave slightly lower yield of **3a** than an equivalent amount of Et<sub>3</sub>N. Similar 175 difference was reported by Bhanage et al. [18]. By increasing the catalyst 176 concentration, the difference between the inorganic and organic base become negligible, except in the case of  $K_2$ HPO<sub>4</sub>, proving the Et<sub>3</sub>N can be replaced either by 177 potassium or sodium carbonate in this system. Thus, K<sub>2</sub>CO<sub>3</sub> was selected for the 178 179 subsequent experiments. The investigation of the effect of catalyst concentration on the conversion reveals that the Pd-loading could be lowered to 0.5 mol% without a 180 181 significant drop in product yields (Table 2, entries 6–10). However, when the activity or the catalyst costs are considered, 0.1 mol % of Pd-loading or lower seems to be the 182 183 best. The carbon monoxide pressure could also be a crucial factor. It was shown that too low pressure has a deteriorating effect on the yields below 7 bar (Table 2, entries 184 7, 14, 15), but the yields were not increased by increasing the pressure from 7 to 14 185 bar. Apparently in this range, CO-insertion either into a Pd-Ph bond (or eventually 186 into a Pd–OPh bond, Scheme 2) is already fast enough not to be rate determining. By 187 188 monitoring the influence of the temperature on the activity it appears that temperatures below 100 °C are not advantageous for the production of 3a in GVL 189 190 (Table 2, entries 8, 11–13).

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Table 2. Phenoxycarbonylation reaction of iodobenzene (1a) and phenol (2a) in  $GVL^a$ 

#	Catalyst loading (mol%)	p <sub>CO</sub> (bar)	Base	T (°C)	Time (h)	Yield (%) <sup>b</sup>	TON <sup>c</sup>
1	0.25	7	Et <sub>3</sub> N	100	3	70	280
2	0.25	7	K <sub>2</sub> CO <sub>3</sub>	100	3	60	240
3	2	14	Et <sub>3</sub> N	100	4	97	48
4	2	14	K <sub>2</sub> HPO <sub>4</sub>	100	4	31	15
5	2	14	Na <sub>2</sub> CO <sub>3</sub>	100	4	97	48
6	2	14	K <sub>2</sub> CO <sub>3</sub>	100	4	98	49
7	1	14	$K_2CO_3$	100	4	97	97
8	0.5	14	$K_2CO_3$	100	4	92	184
9	0.25	14	$K_2CO_3$	100	4	69	276
10	0.1	14	$K_2CO_3$	100	4	59	590

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11	0.5	7	K <sub>2</sub> CO <sub>3</sub>	100	4	91	182			
12	0.5	3.5	K <sub>2</sub> CO <sub>3</sub>	100	4	65	130			
13	0.5	1	$K_2CO_3$	100	4	39	78			
14	1	14	$K_2CO_3$	90	4	78	78			
15	1	14	K <sub>2</sub> CO <sub>3</sub>	80	4	34	34			

194	<sup>a</sup> Reaction conditions: Catalyst precursor: Pd(OAc) <sub>2</sub> , 0.5 mmol iodobenzene (1a), 0.625
195	mmol phenol (2a), 2.5 equiv. of base, 2.5 mL of GVL, <sup>b</sup> GC yield, <sup>c</sup> TON: Turnover Number
196	= mmol product/mmol Pd catalyst.
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**Scheme 2.** Plausible mechanisms for the alkoxy- and aryloxycarbonylation of aryl halogenides using homogeneous ligand-free Pd-systems based on proposals for Pd-PPh<sub>3</sub> analogues.

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Regarding the extensive literature on metal-catalyzed carbonylation [2] relatively little is known about the exact mechanism of aryloxycarbonylation of aryl halides using phosphine-free Pd-catalyst systems in the presence of added bases [42]. Generally, two major paths, an alkoxycarbonyl (or aryloxycarbonyl) route (**A**) and acyl route (**B**) have been proposed for phosphine modified Pd-catalysts (Scheme 2) [45]. Generally, the acyl-route (**B**) was found to be the operative path with the

210 alcoholysis, phenolysis of the formed acyl complexes as rate determing steps (V in 211 Scheme 2), especially in the absence of added bases [45,46,47]. It has also been 212 revealed that route A is strongly retarded under CO-pressure in methanol as 213 coordinated CO blocks the coordination of <sup>-</sup>OMe (from added NaOMe) to form a Pd-214 C(O)OMe (Pd-carbalkoxy) group using Pd-phosphine systems (Scheme 3) [48,49]. It 215 is not yet known whether this would be also the case using phosphine-free Pd 216 catalysts. Hartwig and co-workers have found that in the presence of an added base, 217 the oxidative addition of aryl iodide (step II in Scheme 2) can be considered as the 218 rate determining step and it is zero order in kinetics in most of the Pd-catalyzed 219 carbonylation reaction due to the presence of a reactive nucleophile. [50]. It is also 220 known that CO insertion into a phosphine-ligated Pd-alkyl (step IV) or into a 221 phosphine-ligated Pd-OMe (step III) bond is frequently undetectably fast similar to 222 the reaction of an acyl group with an alkoxide nucleophile [49, 51]. Similar findings 223 were made for the insertion of CO into ligated Pd-aryl bonds and somewhat indirectly 224 into a ligated Pd-OEt bond [47]. In another study, the reaction of a specific 225 arylcarbonyl complex, p-CH<sub>3</sub>-C<sub>6</sub>H<sub>4</sub>(CO)Pd(PPh<sub>3</sub>)<sub>2</sub>I with aryl-substituted phenols was 226 found to be a pseudo first order in rate and the ester formation from the approriate 227 Pd-benzoyl complex was proposed as rate determining [17]. However, in this case, a 228 tertiary amine (Bu<sub>3</sub>N) was used instead of a stronger base, possibly limiting the formation aryloxy nucleophiles. Thus, perhaps the rate of aryloxy nucleophile 229 230 formation was determined in the study instead of the phenolysis of a benzoyl-Pd, (p-231  $CH_3-C_6H_4(CO)Pd$ ) compound. The importance of the nucleophile formation, thereby 232 also its crucial effect on the overall rate was emphasized by comparing the much 233 better rates achieved with NaOEt than with Et<sub>3</sub>N and EtOH as bases in the 234 alkoxycarbonylation of substituted aryl iodides using a Pd–PPh<sub>3</sub> catalyst system [52]. 235 However, as mentioned above, the mechanisms of analogous carbonylations using 236 phosphine-free Pd-systems have scarcely been studied compared to those of the 237 traditional Pd-triphenylphosphine systems, probably due to instability of the Pd-238 species involved and the difficulties in the adequate analyses. What well-established 239 is that Pd(OAc)<sub>2</sub>, which can be present in different coordination modes [53, 54], 240 undergoes reduction to zevovalent Pd-carbonyls (step I, Scheme 2) at higher 241 temperatures under CO-pressure in the presence of water [53], alcohols [52] or 242 phenols [55].

$$\begin{bmatrix} CO \\ OC \end{bmatrix} P d^{II} \begin{pmatrix} R^2 \\ CO \end{bmatrix} X^{\Theta} + \Theta_{OR^1} \xrightarrow{?} \begin{bmatrix} CO \\ CO \end{bmatrix} P d^{II} \begin{pmatrix} R^2 \\ CO \end{bmatrix} X^{\Theta} X^{\Theta}$$

Scheme 3. CO-pressure and the coordination of CO to Pd retards the coordination of alkoxide or an attack of the alkoxy nucleophile on the carbonyl resulting in the formation of a phosphine-ligated Pd-alkyl-alkoxycarbonyl complex, thus turning reaction path from A to the acyl route B [49]. The question is whether is this also the case with phosphine-free Pd-complexes.

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In order to extend the knowledge about aryloxy- and alkoxycarbonation of aryl iodide using such phosphine-free systems, particularly the effect of substituents on the reagents, which could limit or influence the yields of products, were further investigated in this study. For the sake of comparison all of these reactions were done under similar reaction conditions and ratios using 0.25 mol% of Pd-loading at 100 °C for 3 hours of reaction time.

256 First, the effect of aryl substituents of aryl iodide was studied on the yield and 257 rate, by using numerous aryl iodides bearing various electron donating or withdrawing 258 functional groups (Table 3). If the reaction is indeed zero order for the aryl iodide 259 concentration, turnover frequencies (TOF) can be used for the direct comparison of 260 reaction rates. However, the TOF values are meaningless when calculated from full or 261 very close to full conversions as it is not known when they were reached. Also, in the 262 absence of strong stabilizing ligands, homogenous zerovalent Pd-complexes tend to 263 coagulate to various extents under the applied carbonylation conditions [53]. For this 264 reason, only the turnover numbers (TON), (which can otherwise readily be calculated 265 to TOF values) are given below in the Tables for the comparison of catalyst 266 effectivity. Evaluating the results shown in Table 3, it appears that aryl iodides 267 bearing aryl-substituents with strongly positive electronic parameters ( $\sigma$ +) [56] (**1g**-268 **1m**) on the phenyl ring (typically electron withdrawing groups in para position) 269 facilitate the rate of the reaction. Thus, possibly the rate of the crucial oxidative 270 addition step of R-I (step II in Scheme 2) is increased by the increased polarization of 271 the C-I bond. To obtain more exact kinetic data, the reactions should be repeated by 272 using significantly lower Pd-loading in multiple parallel experiments. It should be 273 noted for these experiments that the reaction of p- and m-bromo iodobenzene (and 274 also that of *p*-chloro) leads exclusively to the conversion of iodo functionality, which 275 allows the use of bromo-substituted esters in subsequent reaction schemes, for 276 example, involving cross coupling reactions.

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279	Table 3. Phenoxycarbonylation reaction of iodoaromatic
280	compounds (1a–1o) and phenol (2a) in GVL <sup>a</sup>
	$R^{1}-I + \sqrt{-}OH \xrightarrow{Pd} R^{1}O - \sqrt{-}$
281	1a-o 2a 3a-o
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#	Aroma	atic s	Product	Yield (%) <sup>b</sup>	σ <sup>c</sup>	TON <sup>d</sup>
1	1a		3a	60	0	240
2	1b	H <sub>3</sub> C	3b	77	-0.17	308
3	1c	H <sub>3</sub> C	3c	83	-0.07	332
4	1d		3d	79	n.a.	316
5	1e	H <sub>3</sub> CO	3e	84	-0.27	336
6	1f	tBu —	3f	39	-0.20	156
7	1g	CI	3g	> 99	+0.23	> 396
8	1h	Br-	3h	> 99	+0.23	> 396
9	1i	Br	3i	> 99	+0.39	> 396
10	1j	F <sub>3</sub> CO-	3j	> 99	+0.35	> 396
11	1k	н₃соос-√_>	3k	> 99	+0.45	> 396
12	11	H₃COC-√_	<b>3</b> 1	> 99	+0.50	> 396
13	1m		3m	> 99	+0.66	> 396
14	1n	O_N-{}-I	3n	79	n.a.	316
15	10	⟨⊢ı	30	> 99	n.a.	> 396

<sup>a</sup> Reaction conditions: Catalyst precursor: Pd(OAc)<sub>2</sub> (0.25 mol%), 0.5 mmol of aryl iodide (**1a-1o**), 0.625 mmol of phenol (**2a**), 2.5 equiv. of K<sub>2</sub>CO<sub>3</sub>,  $p_{CO} = 7$  bar, 2.5 mL of GVL, T = 100 °C, t = 3 h. <sup>b</sup> GC yield.<sup>c</sup> Hammett electronic parameter [56], <sup>d</sup> TON: Turnover Number = mmol product/mmol Pd catalyst, n.a.: not applicable or not available.

It was also shown in an already quoted study that the presence of different substituents of phenols at para position, affected the reaction efficiency in the presence of tributylamine [17]. Particularly, both  $+\sigma_p$  and  $-\sigma_p$  substituents on the

292	aromatic ring of phenol significantly enhanced the reaction rate compared to
293	unsubstituted phenol. For this reason, the carbonylation of iodobenzene (1a) was
294	investigated with various <i>p</i> -substituted phenols (2a–m) but in the presence of $K_2CO_3$
295	as base instead of tributylamine Table 4. As it can be seen, there is no unambiguous
296	tendency in this case neither way between the electronic parameters (0, negative or
297	positive $\sigma$ ) of the substituent and the activity. In fact, all the observed activities
298	(TOF's between 70–20 h <sup>-1</sup> ) can fall in the range of acceptable experimental errors of
299	non-stabilized phosphine-free homogeneous Pd-systems. In this sense many parallel
300	experiments would be required to get statistically reliable data for these systems.
301	Ultimately, the formation of phenoxy nucleophile is expected to be significantly more
302	facile using the stronger base $K_2CO_3$ than with NBu <sub>3</sub> or NEt <sub>3</sub> for a plausible
303	explanation, in addition to that the two catalytic systems are different. As mentioned
304	above, NaOEt as base also provided much higher rates than Et <sub>3</sub> N + EtOH in the
305	alkoxycarbonylation of aryl-substituted aryl iodides using Pd–PPh <sub>3</sub> systems [52].
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321 270	Table 4 Dhanovy and any dation reaction of indetermine (1) and
32ð 320	<b>Table 4.</b> Phenoxycardonylation reaction of follopenzene (1a) and $nara$ substituted phenols (2b, a) in CVI <sup>a</sup>
329	para-substituted phenois (20–0) in GVL
	/─\ Pd    Ŭ



#	С	-nucleophile	Product	Yield (%) <sup>b</sup>	σ <sup>c</sup>	TON
1	2a	Он	<b>3</b> a	60	0	240
2	<b>2</b> b	н₃с−√_рон	<b>4</b> b	76	-0.17	304
3	2c	н₃со-√_−он	<b>4</b> c	88	-0.27	352
4	2d	iPrOH	4d	50	-0.12	200
5	2e	онс-	<b>4e</b>	87	+0.42	348
6	2f	PhO-	4f	91	-0.03	364
7	2g	FОН	4g	67	+0.06	268
8	2h	BrОН	4h	70	+0.23	280
9	2i	F₃C-√_ОН	<b>4</b> i	86	+0.54	344
10	2ј	EtOOC-OH	<b>4</b> j	88	+0.45	352
11	2k	ОНС-ОН СН <sub>3</sub>	4k	84	n.a.	336
12	21	ноос-	41	0	+0.45	0

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331 332 333 <sup>a</sup> Reaction conditions: Catalyst precursor: Pd(OAc)<sub>2</sub> (0.25 mol%), 0.5 mmol iodobenzene (**1a**), 0.625 mmol of substituted phenol (**2a-2o**), 2.5 equiv. of K<sub>2</sub>CO<sub>3</sub>,  $p_{CO} = 7$  bar, 2.5 mL GVL, T = 100 °C, t = 3 h. <sup>c</sup> Hammett electronic parameter, <sup>d</sup> TON: Turnover Number = mmol product/mmol Pd catalyst, n.a.: not applicable or not available.

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In general, an increased concentration and nucleophile attack of the corresponding phenoxide anion on the benzoylpalladium complexes [Ph(C=O)Pd<sup>(II)</sup>I (CO)n], (n=1,2) is very important for a fast ester formation [52]. The effect of increased concentration of anionic nucleophile on the esterification reaction was also demonstrated for Cocatalyzed system, which was optimized for production of methyl-3-pentenoate in methanol [57].

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348 3.2 Alkoxycarbonylation reactions

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350 The GVL-based carbonylation protocol was further explored for the 351 alkoxycarbonylation of aryl iodides with aliphatic alcohols to form the corresponding

esters. The conversion of iodobenzene (1a) with CO in the presence of MeOH (5a) to
methyl-benzoate (6a) was selected as model reaction (Scheme 4).

**Scheme 4.** Methoxycarbonylation of iodobenzene (**1a**) in the presence of palladium catalyst

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The solvent screening (Table 5) gave similar effectivities compared to those obtained for phenoxycarbonylation of **1a** in polar, aprotic solvents using Et<sub>3</sub>N as base. The formation of the methyl ester, **6a** was only slightly faster than that of the phenyl ester, **3a** in GVL (Table 1 entry 6). Similarly, lowering the CO pressure from 14 to 7 bar did not affected the yield of **6a**, however, by applying 3.5 bar, the product yield dropped by ca. 10% (91%).

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365 366	<b>Table</b> iodob	e 5. Methoxycarbonyl benzene (1a) in different sol	ation reactio vents <sup>a</sup>	n of
	#	Solvent	Yield <b>6a</b> (%) <sup>b</sup>	TON <sup>c</sup>
	1	n-octane	< 5	20
	3	N,N-dimethylformamide	52	208
	4	dimethyl sufloxide	61	244
	5	GVL	79	316
367	<sup>a</sup> Re	action conditions: 0.5 mmo	l of iodobenzer	ne ( <b>1a</b> ), 0.625
368	mm	ol of methanol (5a), 0.25 m	ol% of Pd(OAc	c) <sub>2</sub> , 2.5 equiv.
369	of I	$Et_3N$ , $p_{CO} = 14$ bar, 2.5 mL o	of GVL, $T = 10$	$0^{\circ}C, t = 3 h;$

of Et<sub>3</sub>N,  $p_{CO} = 14$  bar, 2.5 mL of GVL, T = 100 °C, t = 3 h; RPM = 400 min<sup>-1</sup>; <sup>b</sup> GC yield. <sup>c</sup> TON: Turnover Number = mmol product/mmol Pd catalyst.

As above with phenol (**2a**), the effect of aryl substituents of aryl iodide was also studied on the yield and rate, by using numerous aryl iodides bearing various electron donating or withdrawing functional groups with MeOH under the standard reaction conditions (Table 6).

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379 Table 6. Alkoxycarbonylation reaction of iodoaromatic compounds
380 (1a-o) and methanol (5a) in GVL<sup>a</sup>

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			DH Pd base, 0		о-сн3		
		1a-r 5a		R <sup>1</sup>	6a-r		
#	Iodoard	omatic compounds	Base	Product	Yield (%) <sup>b</sup>	$\sigma^{c}$	TON <sup>d</sup>
1	<b>1</b> a		Et <sub>3</sub> N	6a	79	0	316
2	1a		K <sub>2</sub> CO <sub>3</sub>	6a	> 99	0	> 396
3	1b	H <sub>3</sub> C	Et <sub>3</sub> N	6b	71	-0.17	284
4	1b	H <sub>3</sub> C	K <sub>2</sub> CO <sub>3</sub>	6b	82	-0.17	328
5	1d	CH <sub>3</sub>	Et <sub>3</sub> N	6d	83	n.a.	332
6	1e	H <sub>3</sub> CO	Et <sub>3</sub> N	6e	84	-0.27	336
7	1e	H <sub>3</sub> CO-	$K_2CO_3$	6e	86	-0.27	344
8	1f	tBu —	Et <sub>3</sub> N	6f	13	-0.20	52
9	1f	tBu —	K <sub>2</sub> CO <sub>3</sub>	6f	36	-0.20	144
10	1g	CI-	Et <sub>3</sub> N	6g	74	+0.23	296
11	1g	CI	K <sub>2</sub> CO <sub>3</sub>	6g	> 99	+0.23	> 396
12	1p		K <sub>2</sub> CO <sub>3</sub>	6р	> 99	+0.37	> 396
13	1q	F-	K <sub>2</sub> CO <sub>3</sub>	6q	> 99	+0.23	> 396
14	1r		Et <sub>3</sub> N	6r	58	+0.78	232

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<sup>a</sup> Reaction conditions: Catalyst precursor:  $Pd(OAc)_2$  (0.25 mol%), 0.5 mmol of aryliodides (**1a-1j**), 0.625 mmol methanol (**5a**), 2.5 equiv of base,  $p_{CO} = 7$  bar, 2.5 mL of GVL, T = 100 °C, t = 3 h. <sup>b</sup> GC yield, <sup>c</sup> Hammett electronic parameter, <sup>d</sup> mmol product/mmol Pd catalyst, . n.a.: not applicable or not available.

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387 When the yields or TON's of the carbonylation of iodobenzene are compared in the 388 presence of phenol (Table 3, entry 1) and of methanol (Table 6, entry 2), it occurs that 389 phenol gives significantly lower yield than methanol. This is not unexpected as 390 phenoxide is much worse nucleophile than methoxide, regardless that its formation is 391 about 5 magnitudes more favorable from  $K_2CO_3$  than that of the methoxide in the 392 equilibria based on known pKa values. It is also worthwhile to compare the results of 393 the methoxycarbonylation of iodobenzene using trimethylamine (Table 6, entry 1) and 394  $K_2CO_3$  (Table 6, entry 2) as bases in the reactions. The inorganic base gives 395 significantly higher rate than  $Et_3N$ , parallel with its higher basicity (pKa ~ 12 vs.

396 10.8), *i.e.* parallel with its higher effectivity in the formation of methoxide 397 nucleophile. This is again in agreement with the already quoted study by Hu et al. 398 [52]. Regarding the influence of the electronic parameters of the aromatic substituents 399 using  $K_2CO_3$  as base in Table 6, similar conclusions can be drawn as above in the 400 analogous phenoxycarbonylation experiments (Table 3). Thus, possibly the rate of the 401 crucial oxidative addition step of R-I (step II) is increased by the increased 402 polarization of the ipso-C-I bond, as the rate of CO insertion and the nucleophilic 403 attack on the arylcarbonyl-Pd (steps IV in Scheme 2) should be very fast under these 404 conditions. In agreement with this reasoning electron donating,  $-\sigma$  substituents retard 405 the rates compared to the unsubstituted derivative. However, when a similar trend is sought by the use of Et<sub>3</sub>N as base in Table 6, there is no unambiguous correlations is 406 407 found between  $\sigma$  and the rate. Apparently, the presence of MeOH and Et<sub>3</sub>N as base 408 levels off the differences in the oxidative addition aryl iodides indicating that in these 409 particular systems not the oxidative addition but probably the nucleophilic attack of 410 the methoxide (step IV) should be the rate determining step (see also the results 411 below). Interestingly, the presence of p-t-butyl groups as any substituent is also 412 disadvantageous in the methoxycarbonylation of aryl iodide in the presence of neither 413 base, seemingly not for an electronic reason (see also Table 3).

414 Finally, the effects of the alkyl groups of several lower alcohols were 415 investigated in the alkoxycarbonylation of iodobenzene under the standard conditions (Table 7). Among the used alcohols, methanol was found to be the most effective, 416 417 which points again to the importance of the strength and concentration of 418 nucleophiles. Methoxide is the strongest nucleophile among the other alkoxides or 419 aryloxides, which can be formed from alcohols or phenols. Other than the strength of the nucleophile, its concentration is certainly also important as discussed above. 420 421 Phenoxide is weaker nucleophile than methoxide but its formation is magnitudes 422 faster and very favorable from K<sub>2</sub>CO<sub>3</sub> as compared to that of methoxide. Thus, 423 possibly the high concentration of the phenoxide facilitates high yields and also 424 prevents the nucleophile attack (step IV) to be the rate limiting step in the 425 phenoxycarbonylations above (Table 3). Although the methoxide formation is not favorable using  $K_2CO_3$ , and even less by using  $Et_3N$  as base in the equilibria based on 426 427 pKa's, the formation of higher or branched alkoxides is even more suppressed. Beside 428 the weaker strength of nucleophiles from higher alkoxides, their lower concentration 429 can also contribute to their observed lower effectivity in the alkoxycarbonylations as

compared to that of MeOH (Table 7). The lower effectivity of the branched
propoxide as sterically hindered nucleophile is also in line with this representation.
Thus, in these systems, with the exception of methanol, the nucleophile attack on the
benzoyl-Pd complex (step IV) is plausibly also involved in rate-limitation.

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**Table 7** Alkoxycarbonylation reaction of iodobenzene (1a)with lower alcohols (5b–50) in GVL<sup>a</sup>

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		$\langle \rangle$	—I + R <sup>2-</sup> OH	Pd Et <sub>3</sub> N, CO	Ŭ O-R <sup>2</sup>	
437		1a	5a-e	~	7b-e	
-	#		Alcohol	Product	Yield (%) <sup>b</sup>	TON <sup>c</sup>
-	1	5a	H <sub>3</sub> C—OH	6a	>99	>396
	2	5b	C <sub>2</sub> H <sub>5</sub> —OH	7b	50	200
	3	5c	C <sub>3</sub> H <sub>7</sub> —OH	7c	48	192
	4	5d	C <sub>4</sub> H <sub>9</sub> —OH	7d	46	184
	5	5e	iC <sub>3</sub> H <sub>7</sub> —OH	7e	51	204

<sup>a</sup> Reaction conditions: Catalyst precursor:  $Pd(OAc)_2$  (0.25 mol%), 0.5 mmol of iodobenzene (**1a**), 0.625 mmol of alcohol (**5a-5e**), 2.5 equiv. of K<sub>2</sub>CO<sub>3</sub>, p<sub>CO</sub> = 7 bar, 2.5 mL of GVL, *T* = 100 °C, *t* = 3 h. <sup>c</sup> mmol product/mmol Pd catalyst.

# 443 **3.** Conclusion

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Fossil-based solvents and triethylamine as toxic and volatile base were successfully 445 446 replaced with  $\gamma$ -valerolactone as non-volatile solvent and K<sub>2</sub>CO<sub>3</sub> as also non-volatile 447 base in the alkoxy- and aryloxycarbonylation of aryl iodides using phosphine-free Pd 448 catalysts system. By this, the traditional systems were not simply replaced but also significantly improved. In fact, the applied Pd-loading could be substantially 449 450 decreased as the typically applied relatively low, 0.25 mol% loading proved to be 451 unnecessary too high in many cases. In the study, the effects of different reaction 452 parameters, *i.e.* the use of several other solvents, the temperature, the carbon 453 monoxide pressure, the base and the catalyst concentrations, were evaluated in details 454 striving for the highest efficiency in the carbonylations. In order to collect some 455 information on the mechanism of these reactions, the effects of electronic parameters  $(\sigma)$  of various aromatic substituents of the aryl iodides as well as the influence of 456 457 para-substitution of phenol were investigated on the activity. For a comparison, the 458 aryl-substituted aryl iodides were also reacted with methanol and aryl iodide was also

459 alkoxycarbonylated using several different lower alcohols. From the observed 460 correlations between the electronic parameters of the aromatic substituents and the 461 rates, furthermore excluding the expectedly very fast CO-insertion from the 462 competition, it appears that the rate determining step is the oxidative addition of Ar–I 463 to  $Pd^0$ , provided that sufficient amounts of nucleophiles are present for the ester 464 formation. If this is not the case, the rate of nucleophile attack might determine the 465 overall rate.

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# Palladium-catalyzed aryloxy- and alkoxycarbonylation of aromatic iodides in $\gamma$ -valerolactone as bio-based solvent

József M. Tukacs,<sup>a</sup> Bálint Marton,<sup>a</sup> Eszter Albert,<sup>a</sup> Imre Tóth<sup>b</sup> and László T. Mika<sup>a\*</sup>

<sup>a</sup> Department of Chemical and Environmental Process Engineering, Budapest University of Technology and Economics, Műegyetem rkp. 3., H–1111, Budapest, Hungary. <sup>b</sup> Institute of Chemistry, University of Pannonia, Egyetem u. 10, H–8200 Veszprém, Hungary.

# Highlights

- A green protocol for Pd-catalyzed aryloxycarbonylation aryl iodides were developed.
- A green protocol for Pd-catalyzed alkoxycarbonylation aryl iodides were developed.
- Fossil-based solvent was replaced by a biomass-originated alternative one.



BUDAPEST UNIVERSITY OF TECHNOLOGY AND ECONOMICS DEPARTMENT OF CHEMICAL AND ENVIRONMENTAL PROCESS ENGINEERING

Dr. László T. Mika Assoc. Professor and Head laszlo.t.mika@mail.bme.hu

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### **Declaration of interests**

 $\boxtimes$  The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

□The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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László T. Mika Corresponding author