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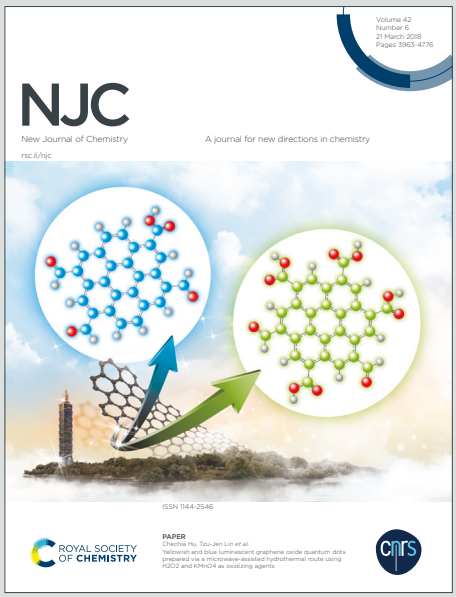

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ARTICLE

Preparation of aromatic γ-hydroxyketones by means of Heck coupling of aryl halides and 2,3-dihydrofuran, catalyzed by palladium(II) glycine complex under microwave irradiation

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A series of aromatic γ-hydroxyketones were prepared by means of Heck coupling reaction of aryl halides and 2,3-dihydrofuran, catalyzed by $PdCl_2$·Gly_2 and under microwave irradiation. This synthetic transformation involves the formation of an aryl-dihydrofuranoic intermediate, followed by an unusual opening of the heterocycle promoted by a water molecule and the formation of the ketone carbonyl function through keto-enol tautomerism.

Introduction

Palladium is a transition metal that is widely employed in organic synthesis for C–C bond formation via cross-coupling reactions.[1] In this regard, a particularly useful methodology where palladium involvement is essential corresponds to the coupling reaction developed by Heck in 1968.[2] The so-called Heck reaction consists in the formation of a C–C bond between an alkene and an aryl halide catalyzed by palladium, in the presence of a base, and has been employed for example, in the preparation of highly relevant synthetic intermediates.[3]

On the other hand, in the last years the use of microwave irradiation as a convenient source of energy has gained significant importance for improvement of the Heck coupling reaction.[4] In this context, Larhed *et al.*[5] employed aryl bromides and aryl iodides for the efficient preparation of aryl-substituted olefins in the presence of $Pd(OAc)_2$, while Xie *et al.*[6] achieved arylation of various olefins in less than 2 minutes reaction time with Pd/C catalyst under microwave irradiation. Furthermore, Andersson *et al.*[7] employed microwave activation in the asymmetric cross coupling of aryl tosylates and 2,3-dihydrofuran, employing phosphine-thiazol complexes of $Pd_2(dba)_3$.[8] A most interesting finding consisted in the enantioselective arylation of 2,3-dihydrofuran accomplished by Morel *et al.*[9] when using $Pd(OAc)_2$ as catalyst and proline salts dissolved in ionic liquid, whereas Xu *et al.*[10] performed the arylation of 2-substituted-2,3-dihydrofuran using $Pd(dba)_2$ and (*R*)-BINAP as catalyst.

Another interesting development in Pd-catalyzed methodology consists in the study of the involved reaction mechanisms. One of the methods employed for the study of reaction mechanisms in solution is electrospray ionization mass spectrometry (ESI-MS) as well as tandem ESI-MS/MS. This is a technique that gently transfers ionic species or ionized forms of neutral species (reaction intermediaries) directly from solution to the gas phase, allowing the identification of transient species that cannot be identified by other spectroscopic techniques.[11] In this regard, a few years ago Eberlin *et al.*[12] proposed a mechanism for the Heck reaction between alkenes and 4-methoxybenzene diazonium tetrafluoroborate catalyzed by dibenzylideneacetone-palladium. In particular, Eberlin *et al.* detected ionic species arising from oxidative addition. Moreover, the proposed intermediaries were identified as responsible for C–C bond formation via migratory insertion. In this sense, a significant number of mechanistic studies have been supported by theoretical modeling.[13] For example, Gooßen *et al.*[14] described the mechanism of the oxidative addition of aryl halides to Pd catalysts with base on DFT calculations. Recently, Rueping *et al.*[15] using hybrid functional GGA-DFT and PBE0, described the addition of inactivated alkyl bromides to α,β-insaturated acids via Heck coupling. Also very recently, Grimaud *et al.*[16] reported the reaction mechanism in the opening of a benzofuran ring promoted by palladium.

Results and Discussion

Owing to the importance of the Heck reaction, one central field of interest has been the development of novel Pd catalysts. In this sense, the use of amino acids such as *N,N*-dimethylglycine, *N,N*-dimethyl-β-alanine and *N,N*-dimethyl-γ-aminobutyric acid that are used as ligands in Pd catalysts have afforded excellent results in the Heck reaction of aryl halides.[17] We decided to

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Electronic Supplementary Information (ESI) available: Characterization data for all compounds, figures and coordinates of structures of minima along the catalytic cycle. See DOI: 10.1039/x0xx00000x

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prepare the $PdCl_2{\cdot}Gly_2$ complex **1** and examined it as a catalyst in the Heck coupling of aryl halides and 2,3-dihydrofuran.

Catalyst $PdCl_2{\cdot}Gly_2$ (**1**) was prepared via reaction between 0.84 mmol of glycine and 0.42 mmol of palladium chloride (II) ($PdCl_2$) under reflux in acetonitrile (CH_3CN) for 24 hours. Suitable crystals of **1** were obtained by crystallization from CH_2Cl_2/MeOH (1:1) and a single crystal was subjected to X-ray diffraction analysis[18] (Figure 1). The structure showed that the complex presents square geometry where the chlorine atoms are oriented *trans* and two glycine molecules are also attached to the Pd. Additionally, it was confirmed that the carboxylic groups were esterified during the crystallization process.

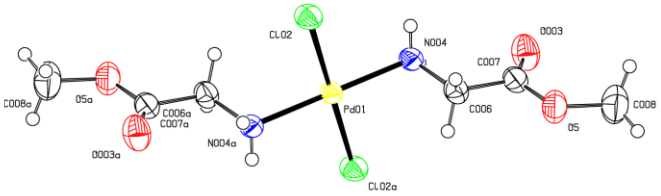
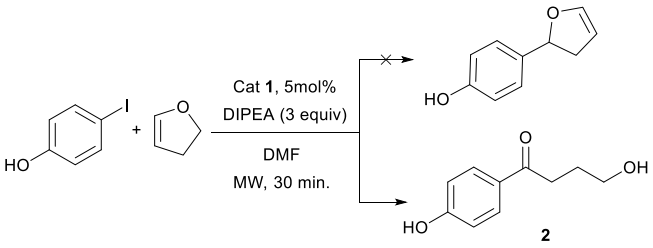


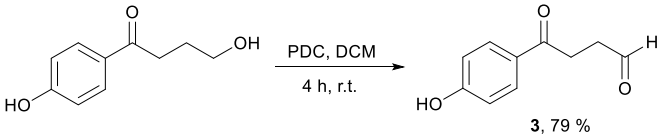
Figure 1. X-ray diffraction crystallographic structure and conformation of **1**.

With complex **1** in hand, its ability to catalyze the Heck coupling reaction between 4-iodophenol (one equivalent) and 2,3-dihydrofuran (2,3-DHF, five equivalents) was evaluated, employing three equivalents of diisopropyl ethyl amine (DIPEA) as base, dimethylformamide (DMF) as solvent, and under microwave activation (60 W, for 30 minutes). Unexpectedly, this reaction afforded γ-hydroxy-ketone **2** (61 % yield) instead of the anticipated 4-(2,3-dihydrofuranyl)-phenol.[19] Product **2** is the result of phenol insertion at position 2 of the heterocyclic ring, followed by ring opening (Scheme 1).



Scheme 1. Heck reaction between 4-iodophenol and 2,3-dihydrofuran.

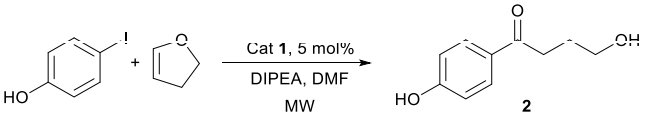
The structure of product **2** was determined from analysis of the corresponding ^1H and ^{13}C spectra; furthermore, mass spectrometry exhibits the molecular ion M^+ with *m/z* 180.08, instead of the ion at 162.07 that would be expected for the normal Heck product. Finally, the γ-hydroxyl group was characterized by oxidation of primary alcohol **2** with pyridinium dichromate (PDC) in methylene dichloride at ambient temperature that afforded aldehyde **3** in 79 % yield (Scheme 2).



Scheme 2. Selective oxidation of γ-hydroxy-ketone **2** to aldehyde **3**.

In a further attempt to obtain Heck product 2-aryl-2,3-dihydrofuran, the reaction depicted in Scheme 2 was repeated, using anhydrous DMF solvent in order to prevent opening of the furan ring by water attack. However, hydroxy-ketone **2** was obtained again in 22 % yield. Table 1 summarizes the results when ethanol, THF, DMSO, and water itself were used as solvent. The highest yield of **2** was observed with DMF and 60 watts of MW power (entry 2, Table 1).

Table 1. Solvent effect on the Pd catalyzed reaction between 4-iodophenol and 2,3-DHF under MW activation.

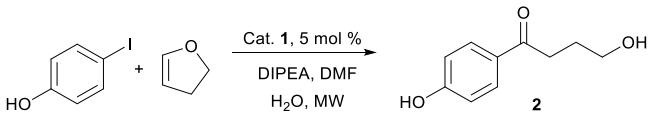


Entry	Solvent	MW, power (W)	Time (min)	Yield (%)
1[a]	DMF	---	1440	26
2	DMF	60	30 (60)	61(79)
3	DMF	100	30	60
4	DMF	150	30	53
5[a]	THF	60(150)	30(60)	0
6[a]	DMSO	60(150)	30	0
7	MeCN	60	30	0
8	Acetone	60	30	0
9	1,4-dioxane	60	30	0
10[a]	ethylene glycol	60	30	0
11	MeOH	60	30	0
12	EtOH	60	30	0
13	H_2O	60	30	0
14	H_2O/EtOH	60	30	0

[a] Oil bath at 80° C and 24 h of reaction time.

In order to corroborate the influence of water in the ring opening and formation of hydroxy-ketone **2**, the reaction was carried out in a closed vessel microwave synthesizer, anhydrous DMF and with addition of water (2 and 4 equiv.) at 3 bar pressure (Table 2). The reaction does not proceed in anhydrous solvents, whereas highest yield of **2** was observed with the addition of 4 equivalents of water.

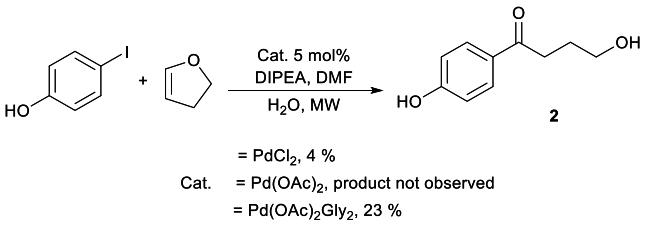
Table 2. Water effect on the reaction between 4-iodophenol and 2,3-DHF.



Entry	H_2O	MW power (W)	Time (min)	Yield (%)
1	---	60	30	0
2	---	140	15	0
3	2 equiv.	60	30	79
4[a]	2 equiv.	140	15	95
5[b]	4 equiv.	140	15	96

[a] 3 bar pressure, [b] 5 bar pressure. The reaction did not proceed when water was replaced by nucleophiles such as ethylenediamine, MeOH and EtOH.

On the other hand, the reaction did not take place when $Pd(OAc)_2$ alone was used. By contrast, hydroxy-ketone **2** was obtained in 23% yield under $Pd(OAc)_2{\cdot}Gly_2$ and 4% yield under $PdCl_2$ catalysis (Scheme 3) confirming the importance of glycine as a ligand in catalyst **1**.



Scheme 3. Glycine ligand effect on the Heck reaction.

Aromatic γ-hydroxyketones are molecules of high synthetic value, since they constitute important analogs of well-known non-steroidal anti-inflammatory agents,[20] and are useful precursors in the preparation of GABA as well as other compounds with inhibitory activity over endonucleases of the virus influenza,[21] inhibitors of tumoral growth,[22] and natural chalcones with antifungal activity.[23] Considering the importance of aromatic γ-hydroxy-ketones of type **2**, it was decided to prepare a series of analogs **4**-**10** by reaction of 2,3-DHF with several substituted 4-iodophenols as well as 1-bromonaphthalene (Table 3). It is appreciated that the desired γ-hydroxy-ketones **4**-**10** are obtained in good 80 to 98 % yield (entries 2-7 in Table 3). Best results are achieved by carrying out the high pressure reaction in a closed vessel, obtaining the 4-hydroxy-1-(4-benzyloxyphenyl)butan-1-one (**9**) in 98% yield (entry 5 in Table 3). On the other hand, reaction between 2,3-DHF and 4-iodophenyl acetate (entry 7) proceeded with hydrolysis of the acetyl group providing compound **2**. The reaction with 4-iodoanisol afforded two products, 4-hydroxy-1-(4-methoxyphenyl)-butan-1-one (**4**) in 89 % yield (entry 2) and 4-hydroxy-1,4-bis(methoxyphenyl)-butan-1-one (**5**) in 22 % yield. By the same token, when microwave power and the reaction time were increased ethoxy-4-iodobenzene afforded 4-hydroxy-1-(4-ethoxyphenyl)-butan-1-one (**6**) in 92% yield and 4-hydroxy-1,4-bis(ethoxyphenyl)-butan-1-one (**7**) in a 41% yield (entry 3, Table 3). Derivatives **5** and **7** are produced by double Heck coupling (entry 2 and 3), while reaction with iodopyrazine provided the compound **11**, through homocoupling of the iodopyrazine (entry 8). Finally, to explore the scope of the reaction, it was decided to use dihydro-2*H*-pyran as substrate instead of 2,3-DHF (entry 9-11, Table 3), obtaining the double addition products **12**, **13** and **14**, while simultaneously recovering the starting aryl halide.

Table 3. Scope of the reaction, preparation of hydroxy ketones **4**-**14**.

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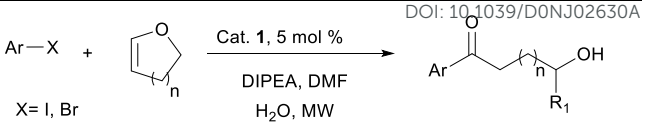
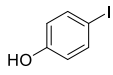
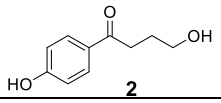
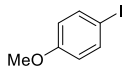
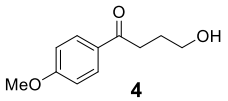
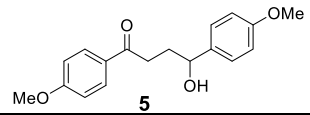
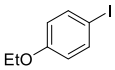
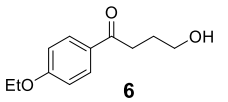
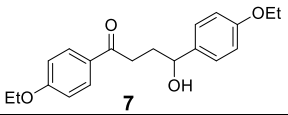
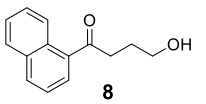
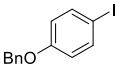
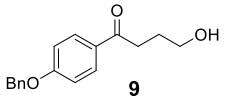
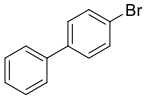
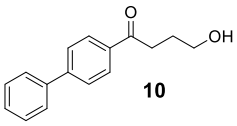
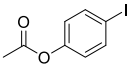
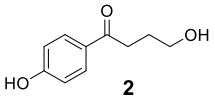
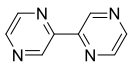
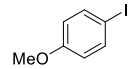
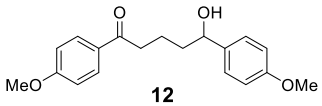
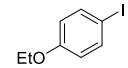
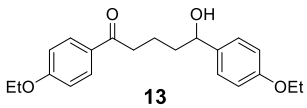
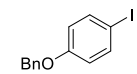
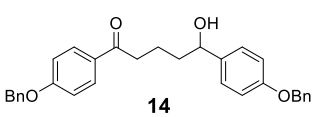


Entry	Ar-X	Product	Yield (%)
1		 **2**	79[a] 95[b]
2		 **4**  **5**	51[a] 89[b] 22[a] <2[b]
3		 **6**  **7**	71[a] 92[b] 37[c] 41[c]
4		 **8**	76[a] 85[b]
5		 **9**	80[a] 98[b]
6		 **10**	52[a] 90[b]
7		 **2**	21[a]
8		 **11**	98[a,b]
9		 **12**	63[a]
10		 **13**	20[c]
11		 **14**	58[c]

[a] CEM reactor 60 W, 30 minutes, open vessel. [b] Microwave synthesizer Biotage 100 W, 15 minutes, closed vessel. [c] CEM reactor 120 W, 90 minutes.

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A suitable crystal[24] of product **5** was obtained by crystallization from hexane/acetone (8:2) and was subjected to X-ray diffraction analysis (Figure 2).[25] The structure that was determined confirms the presence of the carbonyl and hydroxyl groups, and it can be appreciated that adopts a stretched conformation where these groups adopt an *anti*-orientation.

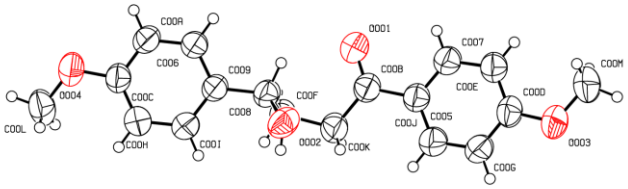
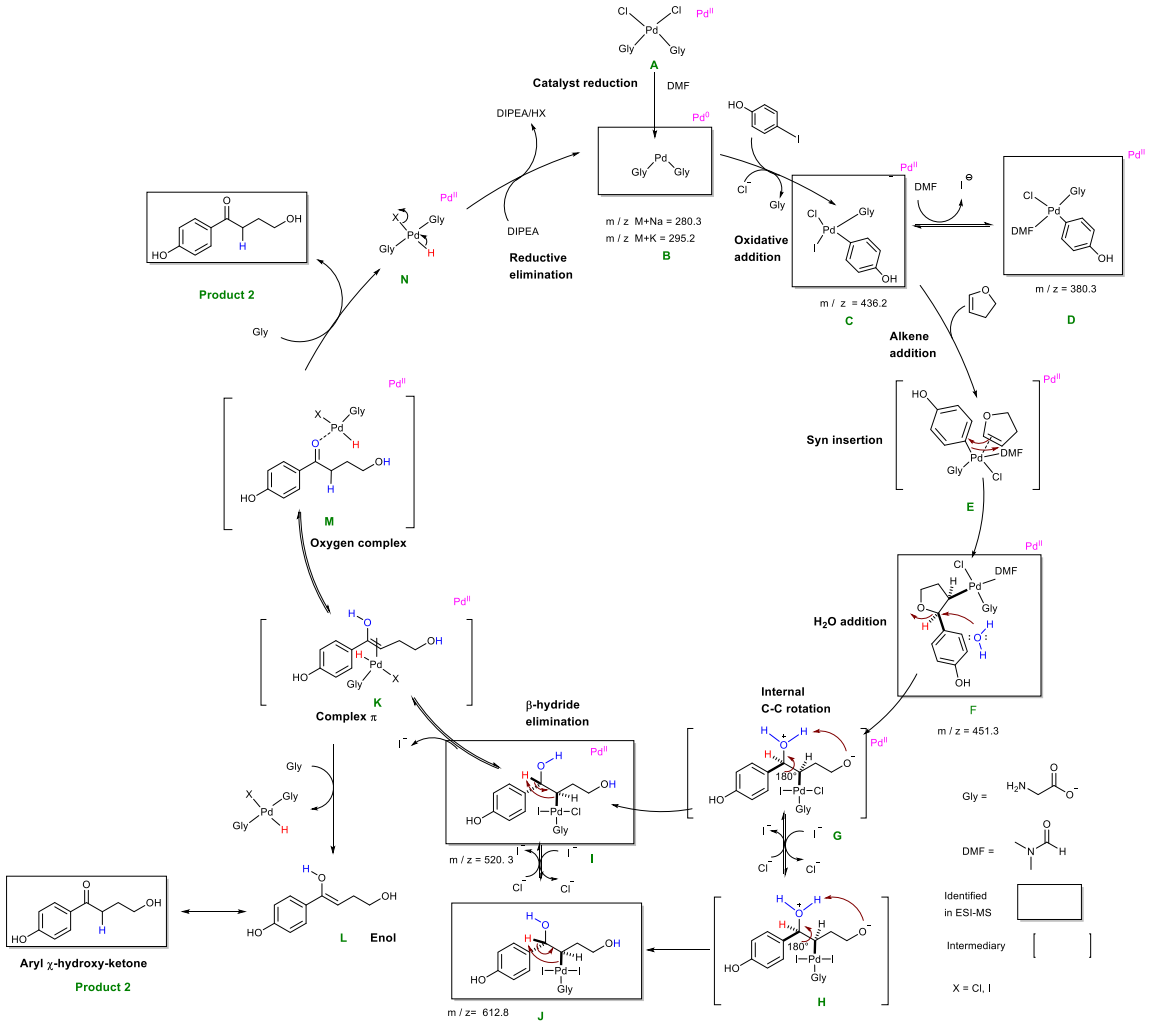


Figure 2. X-ray diffraction crystallographic structure of γ-hyroxyketone **5** showing its solid-state conformation.

A plausible mechanism for the catalytic cycle leading to the formation of aromatic γ-hydroxy-ketones **2-10** is presented in Scheme 4. According to this proposal, the first step involves the reduction of the catalyst palladium Pd(II) to Pd(0), favoured in DMF, to give complex **B**. This is followed by the oxidative addition of aryl halide to catalyst **1**, which involves Pd(0) to Pd(II) oxidation to provide intermediate **C.**[26] Subsequent addition of 2,3-dihydrofuran provides π complex **E**, which enables C–C bond formation between the olefin and the aromatic ring in *syn* fashion to afford intermediate **F**. The regiochemistry of the migration step is understood in terms of the negative charge that is highly localized at the *ipso* C atom, that is transferred to the positive α-carbon atom of the vinyl ether generating the σ-complex on the beta-carbon.[27] Addition of water at the activated benzylic position gives rise to species **G** with subsequent opening of the furan ring.



Scheme 4. Plausible mechanism for the palladium-catalyzed formation of aryl γ-hydroxy-ketones **2-10.**

As expected from a typical Heck mechanism,[28] the catalytic cycle is completed by rotation of the new C–C bond in order to orient the benzylic hydrogen *syn*-periplanar to the palladium metal (**I**), inducing β-hydride elimination to produce π complex **K**,[29] with concomitant regeneration of the catalyst, as well as separation of enol **L**, that gives rise to aryl γ-hydroxy-ketone **2** via tautomerization. The π complex **K** could also lead to intermediate **M**,[30] subsequently giving rise to **2**. Seeking to

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support the proposed mechanism, in particular in order to identify the most important catalytic species with *m/z* ratio 280.3 [M⁺Na], the Heck coupling reaction with 4-iodophenol and 2,3-DHF in oil bath was monitored by ESI-MS (Figure 3 top). The loss of atomic palladium isotope ion [^{106}Pd⁺Na]⁺ of *m/z* 130.2 (60%) characteristic Pd(0) together with four ionic species, was detected after one hour of reaction. The most abundant of the recorded ions being that of *m/z* 450 (100%) that was identified as intermediate [**F**]⁺, product of *syn* insertion. Besides, product [**C**]⁺ resulting from the oxidative addition of aryl halide, of *m/z* 436 (7%) was also detected. Finally, the opening of the ring was clearly detected as [**G**]⁺ and [**H**]⁺, with *m/z* 520 and 612, respectively, formed by the addition of one water molecule to active catalytic species **F**. Interestingly, the composition of the mixture of cationic intermediates does not change significantly after 6 hours (Figure 3 bottom) and highlights the presence of ion [**D**]⁺, a species with *m/z* 380.3 arising from oxidative addition of aryl halide with a DMF molecule attached to the metal center (see Scheme 4).

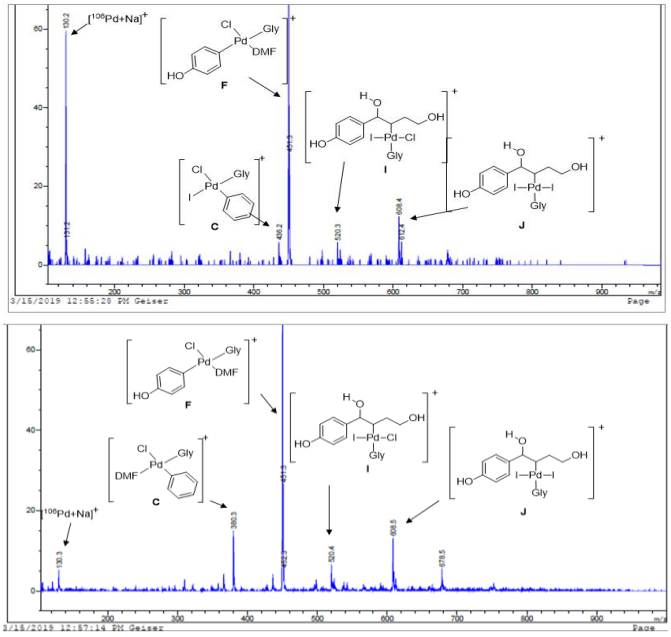
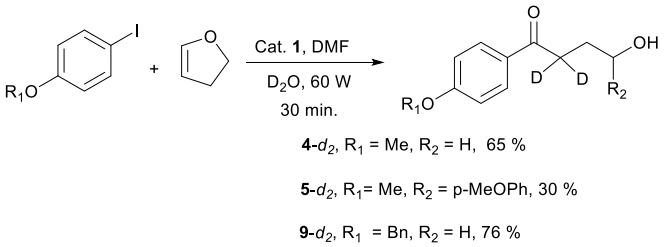


Figure 3. Top, ESI-MS spectrum following the adition of 2,3-DHF. Bottom, ESI-MS spectrum after 6 hours of reaction.

Support for the mechanism advanced in Scheme 4 was also provided by the fact that condensation of 1-benzyloxy-4-iodobenzene and 2,3-DHF, in the presence of 2 equiv. of deuterium oxide (Scheme 5) afforded 1-(4-(benzyloxy)phenyl)-4-hydroxybutan-1-one-2,2-d_2 (**9**-d_2, 86% deuterium incorporation) which is in line with water being incorporated in the final aryl-γ-hydroxy-ketones. In this context, when the reaction was carried out with iodoanisole (Scheme 5), products **4** and **5** containing two deuteriums at the carbonyl's alpha position, suggest that formation of **5** takes place via a tautomeric process subsequent to β-hydride elimination. To corroborate that the deuterium incorporation to Cα occurs as part of the catalytic cycle and not as an exchange by deuterium of the alpha carbonyl protons of γ-hydroxy-ketone formed, **9** was submitted to 5 mol % of **1**, 3 equiv. of *N,N*-diisopropyl ethyl amine, in DMF and 8 equiv. of deuterium oxide, in the microwave reactor at 60 W. The reaction does not proceed, recovering substrate **9.**



Scheme 5. Heck reaction in the presence of D_2O.

DFT calculations, at the PBE0/TZDP(COSMO-DMF)//PBE0/DZ level of theory, have confirmed the plausibility of the catalytic cycle mechanism showed in Scheme 4. Energetic profiles showing minima along the potential energy surface are displayed in Figure 4. The largest energetic drop observed corresponds to the catalyst reduction, going from **A** to **B** and represents an exergonic process of 42.4 kcal/mol. By contrast, the oxidative addition of furan and iodine is an endoergic process of 5.9 kcal/mol to reach **C**. Substitution of iodine by DMF represents a drop of 10.6 kcal/mol in energy, giving structure **D**. Addition of 2,3-dihydrofuran to obtain **E** increases the energy by about 16.6 kcal/mol. Observe that the π-complex formation of this structure enables C–C bond formation between the olefin and the aromatic ring to get **F** with an exergonicity of 24.8 kcal/mol. Regarding the possibility that **F** triggers the elimination of the catalyst, we have calculated the energetic cost of such elimination and the results suggest that this process is not possible because the end product of this elimination would be 114.37 kcal/mol higher in energy. In addition, it is evident that in intermediate **F** glycine is taking part in a hydrogen bond with the phenyl moiety, stabilizing the energy of the molecule (Details in the Supporting Information) and increasing the binding strength of the catalyst with the molecule in process of being transformed. In addition, breaking a palladium-carbon bond will result in a large activation energy, making this reaction path rather unlikely. Addition of water to **F** gives rise to **G** with a small energetic cost of 4.8 kcal/mol. The rotation of the new C–C bond to orient the benzylic hydrogen *syn*-periplanar to the palladium metal to get **I** increases energy in only 2.4 kcal/mol. On the other hand, three different pathways seem feasible to obtain product **2** and recover the active catalyst through **K** and **M**. Formation of complex **K** from **I** increases energy content by 5.6, 6.8 and 11.4 kcal/mol for DMF, iodine and chlorine, respectively. Formation of oxygen complex **M** increases energy by 1.1 kcal/mol in the case of X = Cl, but results in a reduction of 2.8 and 12.9 kcal/mol for X = iodine and X = DMF, respectively. Regarding the formation of γ-hydroxy-ketone **2**, it is observed that the product with X = DMF is the most stable, followed by X = iodine with 5.9 kcal/mol and by the compound with X = chlorine with an energy of 9.3 kcal/mol. Finally, the recovery of the catalyst is an endergonic process of 20.9, 24.3 and 30.2 kcal/mol for X = Cl, X = I and X = DMF,

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respectively. Sub-cycle **G**-**I**-**J**-**H** is showed in the orange inset, being **J** the most stable structure, with a relative energy of 7.9 kcal/mol.

Regarding the estimation of the energy associated to the reduced palladium species (**B**), we proceeded in the following manner. The overall reduction reaction from **A** to **B** was modelled in the following way:

$$\boldsymbol{A} + 2\,\boldsymbol{e}^{-} \;\rightarrow\; \boldsymbol{B}$$

Reduced palladium is only present in species **B**, for this reason in order to include **B** in the overall mechanism it is needed to compute the energy of two electrons located in the highest occupied molecular orbital (HOMO) of **B**. Such procedure ensures the adequate energetic comparison. The relationship between reduction-oxidation potentials has been discussed previously by Dance.[31]

The calculation of energetic barriers is fundamental for the description of the kinetic characteristics of a chemical reaction. The kinetic description of the present catalytic cycle is in progress.

Details of structures, coordinates and other computation details are placed in the Supplementary Material.

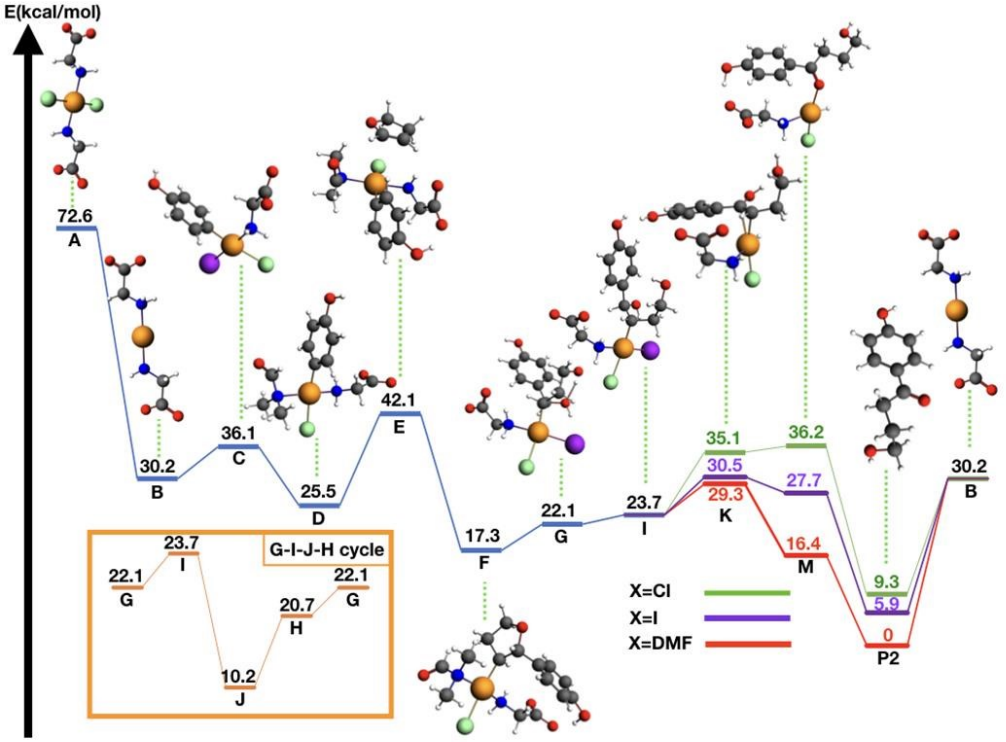
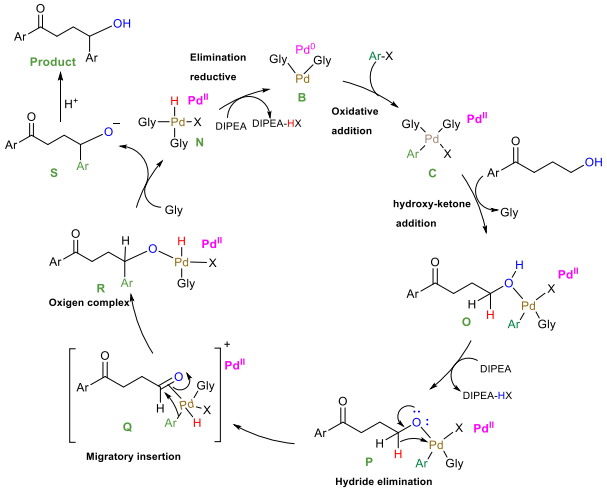


Figure 4. Energetic profile for the modeled mechanism for the palladium-catalyzed formation of aryl γ-hydroxy-ketones based on Scheme 4. Color code: carbon atoms as grey spheres, nitrogen atoms as blue spheres, oxygen atoms as red spheres, hydrogen atoms as white spheres, palladium atoms as orange spheres, chlorine atoms as green spheres, iodine atoms as purple spheres. The final part of profile shows three ramifications depending on the substituent, green profile holds for X = chlorine, purple profile holds for X = iodine, red profile holds for X = DMF. The inset in orange represents the energetic profile of the **G-I-J-H** sub-cycle.

Furthermore, the formation of double Heck intermediates may be explained through the plausible mechanistic pathway advanced in Scheme 6. Oxidative addition of aryl halide to reduced catalyst **B** provides intermediate **C** and subsequent addition of aryl-hydroxyketone provides intermediary **O** that suffers β-hydride elimination to form π complex **Q.**[32] The aryl migratory insertion in the carbonyl group gives rise to oxygen complex **R**,[33] which gives rise to the final hydroxy-ketone, with concomitant regeneration of the catalyst trough reductive elimination of **N**.[34]



Scheme 6. Plausible mechanism of double Heck reaction.

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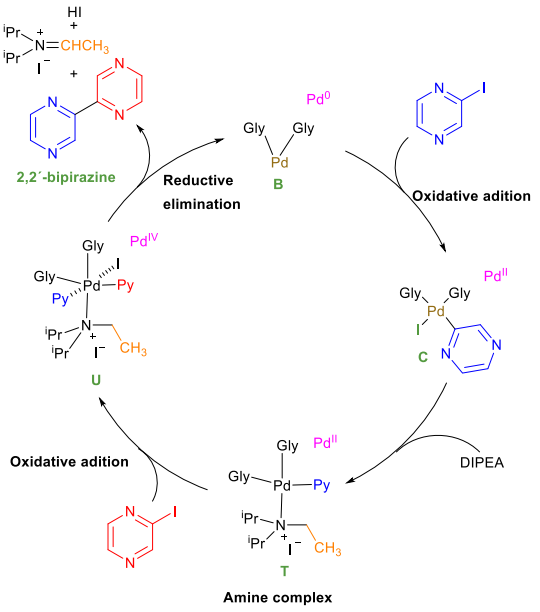
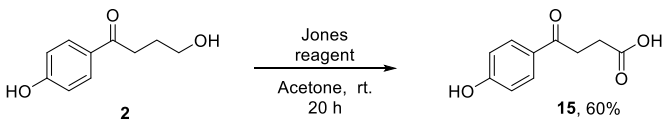
On the other hand, the homo-coupling product **11** is particularly interesting since the synthesis of bis-heteroaryls usually requires of Ullmann reductive homo-coupling reaction catalyzed by Pd/C. The Ullman reaction is carried out under elevated temperatures in the presence of reducing agents such as H_2(g), Zn, In, and inorganic salts to regenerate the Pd(0) active species from Pd(II).[35,36] A plausible reaction mechanism is shown in Scheme 7. The oxidative addition of 2-iodopyrazine to the reduced catalyst forms complex **C**. The replacement of iodo with DIPEA followed by another oxidative addition of 2-iodopyrazine affords the complex Pd(IV) **U** and its reductive elimination produces the 2,2'-bis-pyrazine **11**.[37]



Scheme 7. Plausible mechanism of homocoupling reaction of 2-iodopirazine.

Finally, oxidation of γ-hydroxy-ketone **2** with Jones reagent provided 4-(4-hydroxyphenyl)-4-oxobutanoic acid (**15**)[38] (CAS No. 56872-39-0),[39] a keto-acid with choleretic[40] and antiaggregation[41] activity (Scheme 8). Moreover, this is an important synthon in the synthesis of bioactive compounds that are used as binding and inhibiting agents of the endonuclease influenza virus.[21] Finally, γ-hydroxy-ketone **2** is an intermediate for the synthesis of aryl gpr120 receptor agonist.[42]



Scheme 8. Selective oxidation of γ-hydroxy-ketone **2** to carboxylic acid **15**.

Experimental

Materials and methods

Column chromatography was carried out with Merck Silica Gel (70-230 Mesh). TLC was performed with Merck 60-F25 plates employing UV light and iodine vapor for visualization. Melting points were measured with a Fischer model 1237 apparatus and are uncorrected. IR spectra were recorded on a Thermo Scientific Nicolet iS10 apparatus. NMR spectra were obtained with Varian Mercury plus (100 and 400 MHz) spectrometer. Mass spectra were obtained with Thermo Scientific ISQ CT spectrometer using electronic impact ionization. High resolution mass spectrometry data were obtained with a Thermo Scientific Q Exactive Plus spectrometer. The EDX spectrum was obtained with Bruker AXS Microanalysis GmbH electronic microscope. Crystallographic data were collected with Bruker D8 Venture X-ray diffractometer with a PHOTON 2 detector. The γ-hydroxyketones were synthesized in CEM Discover microwave 201A15, 20 MHz and in Biotage® Initiator organic microwave synthesizer.

Computational details: Geometries along the catalytic cycle where calculated. Single points at the PBE0/TZDP(COSMO-DMF) over full optimizations at the PBE0/DZ level of theory where performed using the Amsterdam Density Functional software.[43] An exploration of the possible conformations of all geometries where addressed, the resulting geometries with the lowest energies where used to study the catalytic mechanism. The final minimum geometries along the catalytic cycle where confirmed by calculation of frequencies.

Glycine palladium (II) chloride (1). Palladium chloride ($PdCl_2$) (200 mg, 1.22 mmol) dissolved in CH_3CN was heated to reflux for 2h under N_2 atmosphere and to the resulting mixture was added glycine (177 mg, 2.36 mmol). The reaction was heated to reflux for 20 h. The reaction was quenched carefully with ice-cold H_2O. The solid obtained was filtered and washed with cold ethanol and CH_3CN. Yellow solid (0.239 g, 85 %); mp. 184-187 °C (CH_3OH/CH_2Cl_2). ^{1}H NMR (400 MHz; DMSO-d_6; TMS) δ ppm: 3.75 (2H, s, NH_2), 3.70 (2H, s, CH_2). ^{13}C NMR (100 MHz; DMSO-d_6; TMS) δ ppm: 168.0, 52.5. *m/z*: 269 (M+, 4%), 235(29), 219(20), 45(100); IR ν_{max}/cm^{-1}: 3299, 3241, 2970, 2579, 1698, 1436, 1249, 1063, 926, 708.

General procedure for the preparation of γ-hydroxy-phenylketones, and their analytical data.

Procedure A. A mixture of aryl halide (1 equiv.), diisopropylethylamine (3 equiv.) and 2,3-dihydrofuran (5.1 equiv.) in 3 ml of DMF and 0.2 ml of H_2O was treated with catalyst **1** (5 mol%). The resulting mixture was placed in a microwave reactor provided with a condenser and irradiated at 60 watts of power for a period of 30 min.

Procedure B. A mixture of aryl halide (1 equiv.), diisopropylethylamine (3 equiv.) and 2,3-dihydrofuran (5.1 equiv.) in 1 ml of DMF and 0.2 ml of H_2O was treated with catalyst **1** (5 mol%) in a closed vessel. The resulting mixture was placed in a Microwave Synthesizer Biotage and irradiated at 100 watts of power for 15 min with the pressure indicated in each case.

Procedure C. A mixture of aryl halide (1 equiv.), diisopropylethylamine (3 equiv.) and 3,4-dihydro-2*H*-pyran or 2,3-dihydrofuran (5.1 equiv.) in 3 ml of DMF and 0.2 ml of H_2O was treated with catalyst **1** (5 mol%). The resulting mixture was placed in a microwave reactor provided with a condenser and irradiated at 120 watts of power for a period of 30 min.

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In the procedures **A**, **B** and **C** the reaction mixture was washed with H_2O and the product was extracted with EtOAc (3x20 ml). The combined organic phase was dried with Na_2SO_4 and concentrated under vacuum.

4-Hydroxy-1-(4-hydroxyphenyl)-butan-1-one (2). It was obtained by the procedures A and B. The crude product was purified by chromatography using a mixture hexane/EtOAc (1:1) to provide the product, whose experimental properties were in agreement with those reported in the literature.[44a] White solid (32 mg, 79% procedure A and 23 mg, 95% procedure B), mp 112-114 °C (Hex/Acetone). ^{1}H NMR (400 MHz; CD_3OD; TMS) δ ppm: 7.89 (2H, d, J = 8.8 Hz, Ar-H), 6.83 (2H, d, J = 8.8 Hz, Ar-H), 3.62 (2H, t, J = 6.4 Hz, CH_2), 3.02 (2H, t, J = 7.3 Hz, CH_2), 1.89 (2H, qt, J = 6.5, 7.4 Hz, CH_2). ^{13}C NMR (100 MHz; CD_3OD; TMS) δ ppm: 201.1, 163.7, 131.7, 130.0, 116.2, 62.3, 35.3, 28.5. *m/z*: 162 (M-18, 83%), 133(17), 121(100), 93(15); IR v_{max}/cm^{-1}: 3431, 3145, 2970, 1654, 1582, 1206, 1046, 1015, 827.

4-(4-Hydroxyphenyl)-4-oxobutanal (3). 25 mg (0.13 mmol) of **2** it was treated with 3 equiv. (15 mg, 0.41 mmol) of pyridinium dichromate (PDC) in methylene dichloride at ambient temperature for 3 h, the reaction mixture was washed with water and the product was extracted with AcOEt (3X15 ml), dried with Na_2SO_4 and concentrated under vacuum. The crude product was purified by chromatography using a mixture hexane/EtOAc (8:2), to provide the product, whose experimental properties were in agreement with those reported in the literature.[44b] Oil white (19 mg, 79 %). ^{1}H NMR (400 MHz; $CDCl_3$; TMS) δ ppm: 9.91 (1H, s, CHO), 7.93 (2H, d, J = 8.8 Hz, Ar-H), 6.88 (2H, d, J = 8.8 Hz, Ar-H), 5.53 (1H, s, OH), 3.28 (2H, t, J = 6.4 Hz, CH_2), 2.92 (2H, t, J = 6.4 Hz, CH_2). ^{13}C NMR (100 MHz; $CDCl_3$; TMS) δ ppm: 201.0, 196.3, 160.1, 130.6, 115.3, 37.6, 30.6.

4-Hydroxy-1-(4-methoxyphenyl)-butan-1-one, (4) and 4-hydroxy-1,4-bis(4-methoxyphenyl)butan-1-one (5). The crude product was purified by chromatography using a mixture hexane/EtOAc (7:3), obtaining two products **4** (procedures A and B) and **5** (procedure A), whose experimental properties were in agreement with those reported in the literature.[44c,d] Compound **4** was isolated as a white solid, (28 mg, 51% procedure A and 22 mg, 89 % procedure B) mp 104-106 °C (Hex/AcOEt). ^{1}H NMR (400 MHz; $CDCl_3$; TMS) δ ppm: 7.97 (2H, d, J = 9.0 Hz, Ar-H), 6.94 (2H, d, J = 8.9 Hz, Ar-H), 3.87 (3H, s, CH_3), 3.74 (,2H, t, J = 6.0 Hz, CH_2), 3.09 (2H, t, J = 6.9 Hz, CH_2), 2.15 (1H, s, OH), 2.01 (2H,m, CH_2). ^{13}C NMR (100 MHz; $CDCl_3$; TMS) δ ppm: 199.2, 163.5, 130.4, 129.8, 113.7, 62.4, 55.4, 35.0, 27.0. *m/z*: 194 (M+, 4%), 176 (83), 150(79), 135(100), 107(26), 92(22). IR v_{max}/cm^{-1}: 3357, 2932, 1676, 1596, 1361, 1018, 827, 764. Compound **5** is a crystalline solid (14 mg, 22%); mp 67-69 °C (Hex/CH_2Cl_2). ^{1}H NMR (400 MHz; $CDCl_3$; TMS) δ ppm: 7.93 (2H, d, J = 9.0 Hz, Ar-H), 7.30 (2H, d, J = 8.8 Hz, Ar-H), 6.92 (2H, d, J = 9.0 Hz, Ar-H), 6.89 (2H, d, J = 8.7 Hz, Ar- H), 4.77 (1H, t, J = 6.3 Hz, CH), 3.87 (3H, s, CH_3), 3.81 (3H,s, CH_3), 3.05 (2H, dd, J = 7.6, 6.9 Hz, CH_2), 2.46 (1H, s, OH), 2.17 (2H, m, CH_2). ^{13}C NMR (100 MHz; $CDCl_3$; TMS) δ ppm: 199.2, 163.5, 159.0, 136.5, 130.4, 129.9, 127.0, 113.8, 113.8, 73.3, 55.4, 55.3, 34.5, 33.2. *m/z*: 299(M-18, 2 %), 280(79), 265(87), 164(44), 151(50), 135(100), 92(12). IR v_{max}/cm^{-1}: 3315, 2953, 2848, 1663, 1597,1242, 1169, 1021, 833, 808.

4-Hydroxy-1-(4-methoxyphenyl)-butan-1-one-2,2-*d*$_2$, (4-*d*$_2$) and 4-hydroxy-1,4-bis(4-methoxyphenyl)butan-1-one-2,2-*d*$_2$ (5-*d*$_2$). **4**-*d*$_2$ ^{1}H NMR (400 MHz; $CDCl_3$; TMS) δ ppm: 7.97 (2H, d, J = 8.9 Hz, Ar-H), 6.94 (2H, d, J = 8.9 Hz, Ar-H), 3.88 (3H, s, CH_3), 3.74 (2H, t, J = 6.0 Hz, CH_2), 3.08 (1H, m, CH_2, 50% deuterium incorporation), 2.01 (3H, m, CH_2, OH). ^{13}C NMR (100 MHz; $CDCl_3$; TMS) δ ppm: 199.2, 163.5, 130.3, 129.85, 113.7, 62.4, 55.4, 35.0, 26.9, 26.9. **5**-*d*$_2$ ^{1}H NMR (400 MHz; $CDCl_3$; TMS) δ ppm: 7.93 (2H, d, J = 9.0 Hz, Ar-H), 7.30 (2H, d, J = 8.5 Hz, Ar-H), 6.92 (2H, d, J = 9.0 Hz, Ar-H), 6.89 (2H, d, J = 8.7 Hz, Ar-H), 4.77 (1H, t, J = 6.3 Hz, CH), 3.87 (3H, s, CH_3), 3.81 (3H, s, CH_3), 3.05 (0.5H, m, CH_2, 78% deuterium incorporation), 2.46 (1H, s, OH), 2.17 (2H, m, J = 6.8 Hz, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 199.1, 163.4, 159.0, 136.5, 130.3, 129.8, 126.9, 113.8, 113.6, 73.3, 55.4, 55.2, 34.5, 33.1.

1-(4-Ethoxyphenyl)-4-hydroxybutan-1-one (6). The crude product was purified by chromatography using a mixture hexane/EtOAc (7:3) to afford the expected product, whose experimental properties were in agreement with those reported in the literature.[44e,f] Yellow oil (32 mg, 71% procedure A; 26 mg; 92% procedure B and 9 mg, 37% procedure C). ^{1}H NMR (400 MHz; $CDCl_3$; TMS) δ ppm: 7.95 (2H, d, J = 8.9 Hz, Ar-H), 6.92 (2H, d, J = 8.9 Hz, Ar-H), 4.10 (2H, q, J = 7.0 Hz, CH_2), 3.74 (2H, t, J = 6.0 Hz, CH_2), 3.09 (2H, t, J = 6.9 Hz, CH_2), 2.17 (1H, s, OH), 2.05–1.96 (2H, m, CH_2), 1.44 (3H, t, J = 7.0 Hz, CH_3). ^{13}C NMR (100 MHz; $CDCl_3$; TMS) δ ppm: 199.2, 162.9, 130.3, 129.6, 114.1, 63.7, 62.3, 34.9, 27.0, 14.6. *m/z*: 207 (M-18, 100%), 161(27),149(84), 133(23), 121(93). IR v_{max}/cm^{-1}: 3201, 2971, 2930, 1671, 1598, 1239, 1168, 1041, 840.

1,4-bis(4-Ethoxyphenyl)-4-hydroxybutan-1-one (7). The General procedure C was followed and the crude product was purified by chromatography using a mixture hexane/EtOAc (8:2). Clear oil (16 mg, 41%). ^{1}H NMR (400 MHz; $CDCl_3$; TMS) δ ppm: 7.92 (2H, d, J = 8.9 Hz, Ar-H), 7.29 (2H, d, J = 8.7 Hz, Ar-H), 6.90 (2H, d, J = 8.9 Hz, Ar-H), 6.87 (2H, d, J = 8.7 Hz, Ar-H), 4.77 (1H, t, J = 5.6 Hz, CH), 4.09 (2H, q, J = 7.0 Hz, CH_2), 4.03 (2H, q, J = 7.0 Hz, CH_2), 3.04 (2H, m, CH_2), 2.42 (1H, s, OH), 2.17 (2H, m, CH_2), 1.44 (3H, t, J = 7.0 Hz, CH_3), 1.41 (3H, t, J = 7.0 Hz, CH_3). ^{13}C NMR (100 MHz; $CDCl_3$; TMS) δ ppm: 199.1, 162.9, 158.3, 136.3, 130.3, 129.7, 126.9, 114.4, 114.0, 73.3, 63.7, 63.4, 34.4, 33.1, 14.8, 14.6. *m/z*: 310 (M-18, 4%), 149(100), 121(69), 93(19). HRMS (ESI-MS, m/z): calcd. for [$C_{20}H_{24}O_4^+$] 328.1669; found 328.1625.

4-Hydroxy-1-(naphthalen-1-yl)butan-1-one (8). The crude product was purified by chromatography using a mixture was purified by chromatography using hexane. Experimental properties were in agreement with those reported in the literature.[44e] Yellow oil (53 mg, 76% procedure A and 23 mg, 85% procedure B). ^{1}H NMR (400 MHz; $CDCl_3$; TMS) δ ppm: 8.58 (1H, d, J = 8.4 Hz, Ar-H), 7.99 (1H, d, J = 8.2 Hz, Ar-H), 7.90 (2H, dd, J = 9.3, 8.3 Hz, Ar-H), 7.63–7.48 (3H, m, Ar-H), 3.79 (2H, t, J = 5.9 Hz, CH_2), 3.22 (2H, t, J = 6.9 Hz, CH_2), 2.13–2.05 (2H, m, CH_2), 1.73 (1H, s, OH). ^{13}C NMR (100 MHz; $CDCl_3$; TMS) δ ppm; 204.8, 135.9, 133.9, 132.6, 130.0, 128.4, 127.8, 127.4, 126.4,

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125.7, 124.3, 62.3, 38.8, 27.3. *m/z*: 196 (M-18, 100%), 165(46), 155(100), 127(75). IR v_{max}/cm^{-1}: 3470, 2928, 1678, 1508, 1239, 1065, 802, 775.

4-Hydroxy-1-(4-(benzyloxy)phenyl)butan-1-one (9). The crude product was purified by chromatography using a mixture hexane/EtOAc (8:2) to afford the expected product, whose experimental properties were in agreement with those reported in the literature.[44g,f] White solid (49 mg, 80% procedure A and 34 mg, 80% procedure B); mp 94-96 °C (Hex/Acetone). ^{1}H NMR (400 MHz; $CDCl_3$; TMS) δ ppm: 7.97 (2H, d, J = 8.8 Hz, Ar-H), 7.44-7.34 (5H, m, Ar-H), 7.01 (2H, d, J = 8.7 Hz, Ar-H), 5.14 (2H, s, CH_2), 3.74 (2H, t, J = 5.6 Hz, CH_2), 3.09 (2H, t, J = 6.9 Hz, CH_2), 2.04-1.97 (2H, m, CH_2), 1.87 (1H, s, OH). ^{13}C NMR (100 MHz; $CDCl_3$; TMS) δ ppm: 199.1, 162.6, 136.1, 130.3, 128.6, 128.2, 127.4, 114.5, 70.1, 62.4, 35.0, 27.0. *m/z*: 252(M-18, 18%), 91(100). IR v_{max}/cm^{-1}: 3335, 2979, 1675, 1601, 1249, 1171, 1014, 621, 741.

4-Hydroxy-1-(4-(benzyloxy)phenyl)butan-1-one-2,2-d_2 (9-d_2). ^{1}H NMR (400 MHz; $CDCl_3$; TMS) δ ppm: 7.96 (2H, d, J = 8.8 Hz, Ar-H), 7.47–7.31 (5H, m, Ar-H), 7.01 (1H, d, J = 8.8 Hz, Ar-H), 5.13 (1H, s, CH_2), 3.73 (2H, t, J = 6.0 Hz, CH_2), 3.09 (0.5H, t, J = 6.9 Hz, CH_2, 86% deuterium incorporation), 2.06 (1H, s, OH), 1.99 (2H, t, J = 6.1 Hz, CH_2).^{13}C NMR (100 MHz; $CDCl_3$; TMS) δ ppm: 199.2, 162.6, 136.1, 130.3, 130.0, 128.6, 128.2, 127.4, 114.5, 70.0, 62.3, 26.9, 26.9. *m/z*: 254.12 (M-18, 5.0%), 252(93), 91(100).

1-([1,1'-Biphenyl]-4-yl)-4-hydroxybutan-1-one (10). The crude product was purified by chromatography using a mixture hexane/EtOAc (7:3) to afford the expected product, whose experimental properties were in agreement with those reported in the literature.[44i] Oil colorless (17 mg, 52% procedure A and 30 mg, 90% procedure B). ^{1}H NMR (400 MHz; $CDCl_3$; TMS) δ ppm: 8.06 (2H, *d*, J = 8.5 Hz, Ar-H), 7.69 (2H, d, J = 8.5 Hz, Ar-H), 7.63 (2H, d, J = 7.1 Hz, Ar-H), 7.53 – 7.44 (2H, m, Ar-H), 7.44 – 7.37 (1H, m, Ar-H), 3.77 (2H, t, J = 6.0 Hz, CH_2), 3.18 (2H, t, J = 6.9 Hz, CH_2), 2.05 (2H, qt, J = 6.8 Hz, CH_2), 1.83 (1H, s, OH). ^{13}C NMR (100 MHz; $CDCl_3$; TMS) δ ppm: 200.1, 145.7, 139.8, 135.5, 128.9, 128.6, 128.2, 127.2, 62.3, 35.3, 26.9. *m/z*: 240(M^+, 1%), 222(100), 181(84), 152(91). IR v_{max}/cm^{-1}: 3436, 2932, 2864, 1681, 1639, 1263, 1024, 562.

2,2'-Bipyridine (11). For homocoupling the general procedure B was followed and the crude product was purified by chromatography using a mixture hexane/Acetone (7:3) to afford **11**, whose experimental properties were in agreement with those reported in the literature.[44j] Crystalline solid (20 mg, 98%); mp 72-74 °C (CH_2Cl_2/Acetone). ^{1}H NMR (400 MHz; DMSO-d_6; TMS) δ ppm: 9.48 (2H, d, J = 1.4 Hz, Ar-H), 8.82–8.79 (2H, m, Ar-H), 8.78 (2H, d, J = 2.5 Hz, Ar-H). ^{13}C NMR (100 MHz; DMSO-d_6; TMS) δ ppm: 148.6, 145.7, 144.2, 142.6. *m/z*: 156(M-1, 100%), 106(21), 105(15). IR v_{max}/cm^{-1}: 3315, 2953, 2848, 1663, 1597 1242, 1169, 1021, 833, 808.

5-Hydroxy-1,5-bis(4-methoxyphenyl)pentan-1-one (12). The general procedure C was followed and the residue was purified by chromatography using hexane. Clear oil (25 mg, 63%); ^{1}H NMR (400 MHz; $CDCl_3$; TMS) δ ppm: 7.92 (2H, d, J = 8.9 Hz, Ar-H), 7.28 (2H, d, J = 8.6 Hz, Ar-H), 6.92 (2H, d, J = 8.9 Hz, Ar-H), 6.88 (2H, d, J = 8.7 Hz, Ar-H), 4.66 (1H, t, J = 6.2 Hz, CH), 3.87 (3H, s, CH_3), 3.80 (3H, s, CH_3), 2.95 (2H, dd, J = 10.9, 6.9 Hz, CH_2), 2.04 (1H, s, OH), 1.93 – 1.80 (2H, m, CH_2), 1.81–1.68 (2H, m, CH_2). ^{13}C NMR (100 MHz; $CDCl_3$; TMS) δ ppm: 198.8, 137.1, 136.7, 134.4, 130.2, 127.1, 113.8, 113.6, 73.8, 55.4, 55.2, 38.5, 37.8, 20.64. *m/z*: 296(M-18, 17%), 147(26), 135(100), 121 (27), 91(20). HRMS (ESI-MS, m/z): calcd. for [$C_{19}H_{22}O_4^+$] 314.1522; found 314.1469.

1,5-bis(4-Ethoxyphenyl)-5-hydroxypentan-1-one (13). The crude product was purified by chromatography using hexane/AcOEt (8:2). Clear oil (8 mg, 20% procedure C). ^{1}H NMR (400 MHz; $CDCl_3$; TMS) δ ppm: 7.91 (2H, d, J = 8.9 Hz, Ar-H), 7.27 (2H, d, J = 8.5 Hz, Ar-H), 6.90 (2H, d, J = 8.9 Hz, Ar-H), 6.86 (2H, d, J = 8.7 Hz, Ar-H), 4.65, (1H, t, J = 6.0 Hz, CH), 4.09 (2H, q, J = 7.0 Hz, CH_2), 4.02 (2H, q, J = 7.0 Hz, CH_2), 2.95 (2H, dd, J = 11.0, 7.0 Hz, CH_2), 2.01 (1H, s, OH), 1.92 – 1.82 (2H, m, CH_2), 1.82 – 1.67 (2H, m, CH_2), 1.42 (6H, dt, J = 13.8, 7.0 Hz, CH_3). ^{13}C NMR (100 MHz; $CDCl_3$; TMS) δ ppm: 198.8, 162.7, 157.2, 136.5, 131.7, 130.2, 129.8, 129.7, 127.0, 125.8, 114.3, 114.0, 73.9, 63.7, 63.4, 38.5, 37.8, 20.6, 14.8, 14.6. *m/z*: 324(M-18, 8%), 161(14), 149(100), 133(17), 121(45). HRMS (ESI-MS, m/z): calcd. for [$C_{21}H_{26}O_4^+$] 342.1825; found 342.1782.

1,5-bis(4-(Benzyloxy)phenyl)-5-hydroxypentan-1-one (14). The crude product was purified by chromatography using hexane/AcOEt (8:2). White solid (34 mg, 58% procedure C); mp 108-109 °C (Hex/CH_2Cl_2). ^{1}H NMR (400 MHz; $CDCl_3$; TMS) δ ppm: 7.92 (2H, d, J = 8.9 Hz, Ar-H), 7.46 – 7.24 (12H, m, Ar-H), 6.99 (2H, d, J = 8.9 Hz, Ar-H), 6.95 (2H, d, J = 8.7 Hz, Ar-H), 5.12 (2H, s, CH_2), 5.05 (2H, s, CH_2), 4.66 (1H, t, J = 6.0 Hz, CH_2), 2.95 (2H, dd, J = 10.7, 7.0 Hz, CH_2), 2.04 (1H, s, OH), 1.93 – 1.81 (2H, m, CH_2), 1.81 – 1.68 (2H, m, CH_2). ^{13}C NMR (100 MHz; $CDCl_3$; TMS) δ ppm: 198.7, 162.5, 158.2, 136.9, 136.1, 130.2, 130.1, 128.6, 128.5, 128.2, 127.9, 127.4, 127.1, 114.7, 114.5, 73.8, 70.0, 70.0, 38.51, 37.8, 20.6. *m/z*: 467 (M^+, 1%), 147(27), 107(60), 91(69), 55(100). HRMS (ESI-MS, m/z): calcd. for [$C_{31}H_{30}O_4^+$] 466.2139; found 466.2101.

4-(4-Hydroxyphenyl)-4-oxobutanoic acid (15). A mixture of 15 mg (0.083 mmol) of arylhydroxyketone, in 5 ml of acetone was treated with 20 mg (9.2 mmol) of CrO_3 in H_2SO_4 (Jones reagent). The resulting mixture was allowed to react at room temperature for 20 h; the reaction mixture was washed with H_2O and the product was extracted with CH_2Cl_2 (3x5 ml). The combined organic phase was dried with Na_2SO_4 and concentrated under vacuum. The crude product was purified by chromatography using a mixture of hexane/EtOAc (7:3) to provide pure acid **15**, whose experimental properties were in agreement with those reported in the literature.[38,39] White solid (09 mg, 60%), mp 151-152 °C. ^{1}H NMR (400 MHz, CD_3OD, TMS) δ ppm: 7.90 (2H, d, *J* = 8.8 Hz, Ar-H), 6.83 2H, (d, J = 8.8 Hz, 1Ar-H), 3.24 (2H, t, J = 6.4 Hz, CH_2), 2.66 (2H, t, J = 6.4 Hz, CH_2). ^{13}C NMR (100 MHz; CD_3OD; TMS) δ ppm: 199.1, 176.8, 163.7, 131.6, 129.8, 116.2, 33.9, 29.0.

Conclusions

Palladium(II) glycine complex **1** is an efficient catalyst for the preparation of aryl-γ-hydroxy-ketones, which were obtained via Heck coupling reaction, followed by the addition of one molecule of water and simultaneous ring opening. Palladium promoted β-hydride elimination at the benzylic position is

accompanied by recovery of the catalyst and formation of the hydroxy-ketone product via keto-enol tautomerism. The present synthetic methodology benefits from microwave activation and simplifies significantly the preparation of aryl-γ-hydroxy-ketones in short, less than 30 minutes reaction time. Theoretical calculations at the PBE0/TZDP(COSMO-DMF) level provide convincing evidence to support the proposed mechanism of the catalytic cycle.

Conflicts of interest

There are no conflicts to declare.

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The synthesis of phenyl-γ-hydroxyketones through Heck coupling and subsequent opening of the tetrahydrofuran ring by the nucleophilic attack of a water molecule catalyzed by $PdCl_2{\cdot}Gly_2$ under microwave irradiation.