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Aqueous α-arylation of mono- and diarylethanone enolates at low catalyst loading

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Abstract.
Acetophenone and deoxybenzoin derivatives are selectively α-arylated using a combination of very small amounts of palladium acetate and diphenylphosphine oxide as catalyst system and water as the only solvent. Target di- and triarylethanones are isolated virtually free of metal residues, and the reaction is amenable to gram-scale. A mechanistic proposal based on TEM images, poisoning experiments, kinetic plot and ESI-MS spectrometry is also provided.

Keywords: water; palladium; aryl halides; ketones

Among the compounds bearing the α-aryl carbonyl motif, 1,2-diaryl- and 1,2,2-triarylethanones are present in a number of natural products and biologically active compounds (*Gramidenoxybenzoin* A-H, *Belamphenone*, *O-Desmethylangolensin*, Sitaxentan (TBC-11251), *inter alia*).[1] In addition, these privileged carbonyl compounds have been used as the main ingredients of flame retardants and other advanced materials,[2] and as intermediates for the synthesis of natural products and phase III- and marketed drugs such as Tamoxifen, Droloxifene, Daidzein, Oxcarbazepine, (+)-AM-8553 and AMG 232,[1f,1j,3a-g] and several heterocyclic systems (e.g. dibenzophenanthridines, phenantrofurans, isoindoloisoquinolines, triazoles and indazoles).[3h-l]

A straightforward approach to 1,2-diaryl- and 1,2,2-triarylethanones relies on the α-arylation of ketone enolates, a reaction that has evolved remarkably over the past two decades.[3b,4] However, most of the commonly used palladium and nickel catalysts require relatively high catalyst loadings (10-0.5 mol% of the metal catalyst). With regard to palladium-catalyzed arylation of acetophenones and other aryl ketones, the efficient systems described by the groups of Nolan[5a-b] and Colacot[5c] using catalyst amounts as low as 0.2-0.02- mol % should be noted. Interestingly, there is only one report of palladium-catalyzed α-arylation of ketone in aqueous media,[6] although 2.5 mol% of $Pd_2(dba)_3$ and 10 mol% of $(^tBu)_3PHBF_4$ were required respectively.

Water is a non-toxic, non-flammable solvent with a high heat capacity at a cheap price. Very high selectivities and reaction rates have been found for a number of "on water" processes,[7] and the combination of metal catalysis and water is becoming increasingly common in reactions such as cross couplings and direct arylations,[8,9] conjugated additions,[10] hydroformylations,[11] oxidation processes,[12] hydrogenations,[13] isomerizations and polymerizations,[14] and olefin metathesis reactions,[15] among others.[16] With regard to the efficiency in metal-catalyzed reactions, it is not only essential for a more sustainable use of limited resources but also a pivotal requirement for the reduction of metal contents in biologically active synthetic compounds, thus avoiding cumbersome purification steps (several crystallizations, scavenger resins, etc.).[17]

It is therefore highly desirable to develop an efficient method for the palladium-catalyzed α-arylation of ketones enolates in water. Following our research on 1,2-diaryl and 1,1,2-triarylethanones,[18] we envisaged that the use of a phosphine oxide ligand and water could be the key to a significantly more efficient arylative approach. After the pioneering work by Li,[19] several palladium-phosphinous acid complexes have been used for Suzuki, Heck, Sonogashira, Kumada-Corriu, Hiyama, Stille, Negishi, *N*- and *S*-arylation, oxidative esterification of aldehydes, nucleophilic and conjugated arylation with arylsiloxanes, and related reactions,[20] some of them carried out in water.[16b-c,20g-l] However, to the best of our knowledge, there has been only one report on an intramolecular palladium-catalyzed α-arylation of amides in the presence of a 5 mol% of $Pd(OAc)_2$ and a 10 mol% of $(1\text{-Ad})_2P(O)H$ in 1,4-dioxane.[20r]

Herein, we report a very efficient catalytic procedure for the intermolecular α-arylation of ketone enolates using water as the only solvent. In addition to the low catalyst loadings achieved, the catalytic system is based on commercially available and relatively inexpensive palladium(II) acetate and diphenylphosphine oxide.

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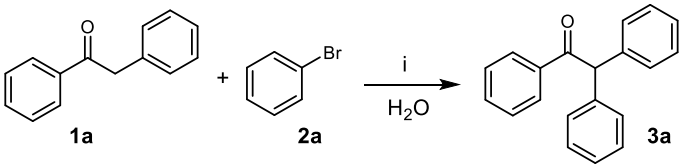
Table 1. Palladium-catalyzed phenylation of deoxybenzoin **1a** with bromobenzene **2a**. Optimization assays[a]



Entry	[Pd]	ligand	base	additive	H_2O (M)	T (ºC)[b]	t (h)	**3a** (%)[c]
1	$Pd(OAc)_2$		K_3PO_4 (3 equiv.)		1	160	24	<5
2	$PdCl_2$	$Ph_2P(O)H$	Cs_2CO_3 (3 equiv.)		1	140	24	<5
3	$Pd(OAc)_2$	$Ph_2P(O)H$	K_3PO_4 (3 equiv.)		1	150	24	<5
4	$Pd(OAc)_2$		K_3PO_4 (3 equiv.)	TBAB (50 mol%)	0.5	160	12	19
5	$Pd(OAc)_2$	$Ph_2P(O)H$	K_3PO_4 (3 equiv.)	TBAB (10 mol%)	0.5	160	12	22
6	$Pd(OAc)_2$	$Ph_2P(O)H$	Cs_2CO_3 (3 equiv.)	TBAB (10 mol%)	1	150	24	34
7	$Pd(OAc)_2$	$Ph_2P(O)H$	Cs_2CO_3 (1.5 equiv.)	TBAB (5 mol%)	0.1	160	24	26
8	$Pd(OAc)_2$	$Ph_2P(O)H$	Cs_2CO_3 (1.3 equiv.)	TBAB (5 mol%)	0.5	160	24	40
9	$Pd(OAc)_2$	$Ph_2P(O)H$	K_3PO_4 (1 equiv.)	TBAB (5 mol%)	0.5	160	24	67
10	$Pd(COD)Cl_2$	$Ph_2P(O)H$	K_3PO_4 (1 equiv.)	TBAB (5 mol%)	0.5	160	24	< 5
11	$Pd(COD)Cl_2$	$Ph_2P(O)H$	K_3PO_4 (1 equiv.)	TBAB (5 mol%)	0.1	160	24	< 5
12	Pd/C	$Ph_2P(O)H$	K_3PO_4 (1 equiv.)	TBAB (5 mol%)	0.5	160	24	< 5
13	Pd_2dba_3	$Ph_2P(O)H$	K_3PO_4 (1 equiv.)	TBAB (5 mol%)	0.5	160	24	< 5
14	$Pd(OAc)_2$	$Ph_2P(O)H$	K_3PO_4 (1.3 equiv.)	TBAB (5 mol%)	0.5	160	24	99 (*97*)
15	$PdCl_2$	$Ph_2P(O)H$	K_3PO_4 (1.3 equiv.)	TBAB (5 mol%)	0.5	160	24	6
16	$Pd(OAc)_2$	$Ph_2P(O)H$	K_3PO_4 (1.3 equiv.)	TBAB (5 mol%)	0.25	160	24	17
17	$Pd(OAc)_2$	$Ph_2P(O)H$	K_3PO_4 (1.3 equiv.)	TBAB (5 mol%)	2	160	24	51
18	$Pd(OAc)_2$	$Ph_2P(O)H$	K_3PO_4 (1.3 equiv.)	TBAB (5 mol%)	0.5	150	24	65
19	$Pd(OAc)_2$	$Ph_2P(O)H$	K_3PO_4 (1.3 equiv.)	TBAB (5 mol%)	0.5	140	24	21
20	$Pd(OAc)_2$	$^tBu_2P(O)H$	K_3PO_4 (1.3 equiv.)	TBAB (5 mol%)	0.5	160	24	84
21	$Pd(OAc)_2$	Ph_3PO	K_3PO_4 (1.3 equiv.)	TBAB (5 mol%)	0.5	160	24	59
22	$Pd(OAc)_2$	Ph_3P	K_3PO_4 (1.3 equiv.)	TBAB (5 mol%)	0.5	160	24	67
23	$Pd(OAc)_2$	Ph_2PCl	K_3PO_4 (1.3 equiv.)	TBAB (5 mol%)	0.5	160	24	12-78[d]
24		$Ph_2P(O)H$	K_3PO_4 (1.3 equiv.)	TBAB (5 mol%)	0.5	160	24	<5
25	$Pd(OAc)_2$		K_3PO_4 (1.3 equiv.)	TBAB (5 mol%)	0.5	160	24	14
26	$Pd(OAc)_2$	$Ph_2P(O)H$		TBAB (5 mol%)	0.5	160	24	<5
27	$Pd(OAc)_2$	$Ph_2P(O)H$	K_3PO_4 (1.3 equiv.)		0.5	160	24	<5
28	$NiBr_2$	$Ph_2P(O)H$	K_3PO_4 (1.3 equiv.)	TBAB (5 mol%)	0.5	160	24	<5
29	CuI	$Ph_2P(O)H$	K_3PO_4 (1.3 equiv.)	TBAB (5 mol%)	0.5	160	24	<5

[a] Reaction conditions: Deoxybenzoin **1a** (0.4 mmol), bromobenzene **2a** (1.2 mmol), metal source (10^{-2} mol%), ligand (10^{-2} mol%), base, additive.
[b] Temperature of the heating bath. A thermocouple probe was used to adjust and to monitor the temperature of the heating bath.
[c] NMR yields determined using 3,4,5-trichloropyridine as an internal standard. Isolated yields are shown in parentheses.
[c] Range of NMR yields (set of 5 assays) determined using 3,4,5-trichloropyridine as an internal standard.

A number of palladium sources, ligands, bases, additives and temperatures were screened for the coupling of model substrates deoxybenzoin **1a** with bromobenzene **2a**. A limit of 0.01 mol% was established for the amount of both palladium sources and ligand in these initial assays. From this survey it became apparent that only by heating above 120ºC was target triarylethanone **3a** isolated in appreciable yields. In addition, bases such as Et_3N, K_2CO_3, Na_2CO_3, NaOAc, or NaOH or non-phosphorus ligands (pyrazole, IMesCl, pyridine or TMEDA) provided negligible results. As shown in Table 1, a further optimization of the parameters was then performed, showing that $Pd(OAc)_2$ was much more effective than other Pd(II) and Pd(0) sources and that better yields were obtained using phosphorus ligands combined with potassium phosphate as a base. Another distinctive feature was the need of catalytic amounts of $^nBu_4NBr$ as an additive. Higher amounts of the latter trialkylammonium salt or the use of bases other that K_3PO_4 led to the formation of diphenylmethane in variable amounts, a phenomenon already described by Leadbeater and col.[21] In order to avoid this side-reaction and to increase the yield of **3a** further adjustments on the dilution, catalytic amount of $^nBu_4NBr$, temperature and the nature of the phosphorus ligand were made.

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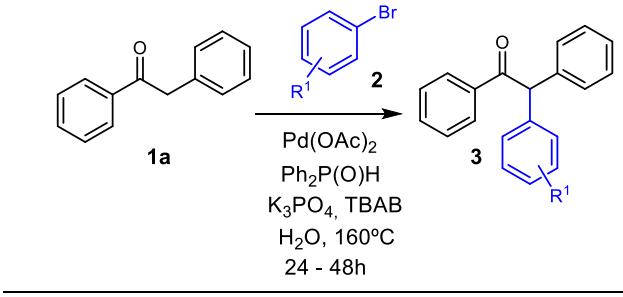
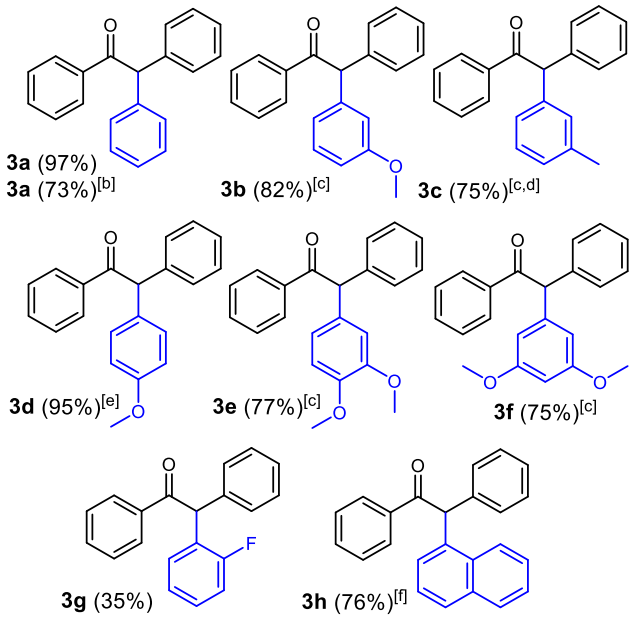
Table 2. Substrate scope for the α-arylation of deoxybenzoin.[a]





[a] Isolated yields. Reaction conditions: **1a** (0.4 mmol), **2** (1.2 mmol), K_3PO_4 (0.52 mmol), Bu_4NBr (5 mol%), $Pd(OAc)_2$ (10^{-2} mol%), $Ph_2P(O)H$ (10^{-2} mol%), H_2O (0.8 mL), 160ºC, 24h.

[b] Iodobenzene was used as the arylating agent.

[c] K_3PO_4 (1.2 mmol), 48h.

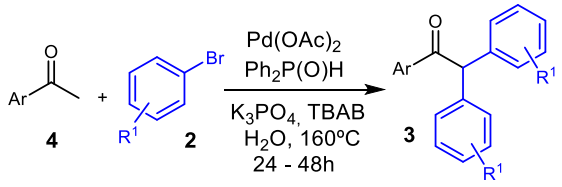
[d] 3-Iodotoluene was used as the arylating agent.

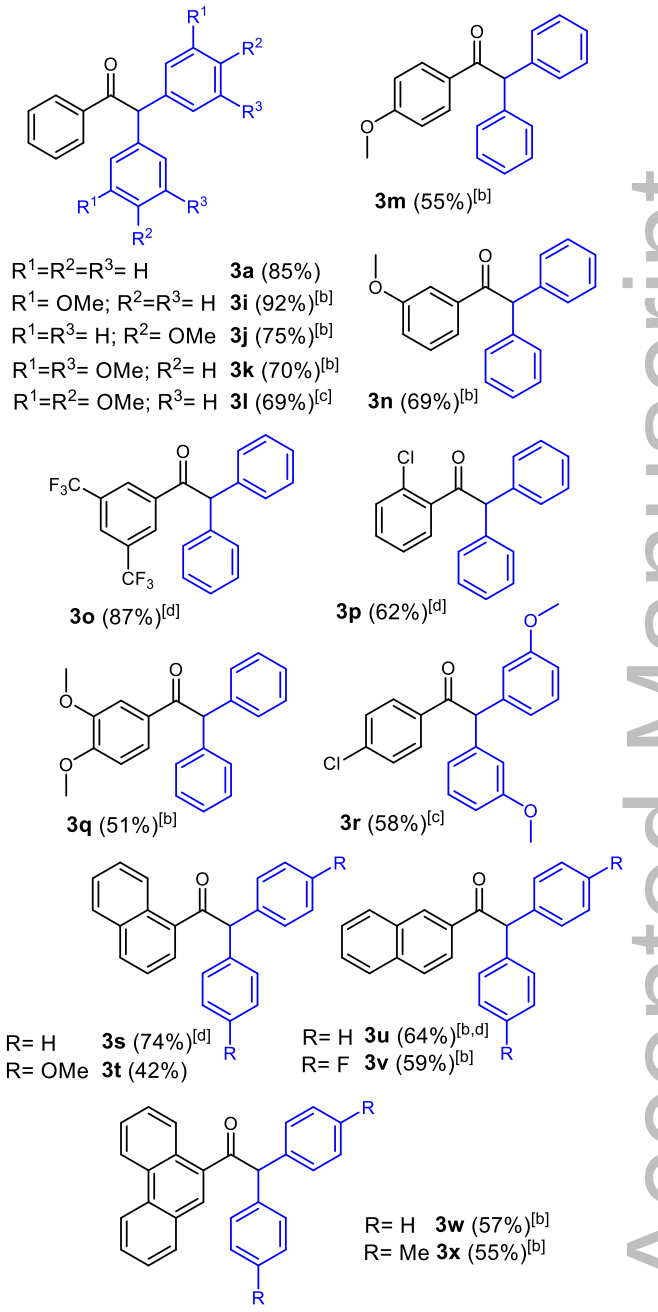
[e] $Pd(OAc)_2$ ($5x10^{-2}$ mol%), $Ph_2P(O)H$ ($5x10^{-2}$ mol%).

[f] K_3PO_4 (1.2 mmol), $Pd(OAc)_2$ ($5x10^{-2}$ mol%), $Ph_2P(O)H$ ($5x10^{-2}$ mol%), 48h.

In this regard, although acceptable results were obtained in some cases from Ph_2PCl, a lack of reproducibility was also observed, probably due to the partial formation of Ph_2POH. However, reproducible results were obtained from several phosphine oxides, and among them, $Ph_2P(O)H$ turned out to be the most effective, providing target **3a** in almost quantitative yields (Table 1, entry 14). Blank experiments in the absence of the palladium source, phosphine oxide, base or additive were also carried out in order to test the need for all the ingredients/components of the optimized procedure. Finally, other metal sources were also tested in replacement of $Pd(OAc)_2$.

Table 3. Substrate scope for the α,α-diarylation of aryl methyl ketones.[a]





[a] Isolated yields. Reaction conditions: **4** (0.4 mmol), **2** (1.2 mmol), K_3PO_4 (1.2 mmol), Bu_4NBr (5 mol%), $Pd(OAc)_2$ (10^{-2} mol%), $Ph_2P(O)H$ (10^{-2} mol%), H_2O (0.8 mL), 160ºC, 48h.

[b] $Pd(OAc)_2$ ($5x10^{-2}$ mol%), $Ph_2P(O)H$ ($5x10^{-2}$ mol%).

[c] K_3PO_4 (0.52 mmol), $Pd(OAc)_2$ ($5x10^{-2}$ mol%), $Ph_2P(O)H$ ($5x10^{-2}$ mol%).

[d] 24h.

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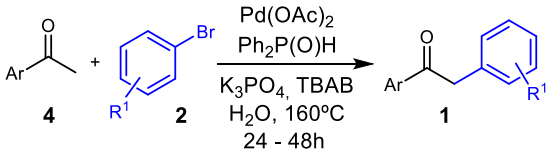
Several aryl bromides **2** were submitted to the optimized reaction conditions to provide 1,2,2-triarylethanones **3a-h** shown in Table 2. Moderate to good yields were obtained in all cases, even from electronically deactivated substrates bearing electron-donating groups. Slight variations in the reaction time, catalyst loading or amount of base were required in some cases to get a higher yield. Interestingly, the use of an excess of the aryl halide reagent neither induced *o*-arylation nor provoked the formation of polyarylation products.

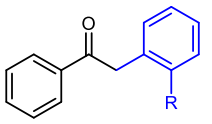
In addition, two iodoarenes, iodobenzene and *m*-iodotoluene, were also coupled with deoxybenzoin to provide the corresponding triarylethanones **3a** and **3c** respectively. The formation of the sterically crowded 2-(naphthalen-1-yl)-1,2-diphenylethan-1-one **3h** should be noted. However, *ortho*-substituted **3g** was obtained with a moderate yield from 1-bromo-2-fluorobenzene, and unreacted starting materials were recovered from the reactions with chlorobenzene and 1,2-dibromobenzene.

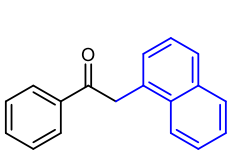
As shown in Table 3, the same procedure was then applied to a number of acetophenones and other aryl methyl ketones **4** and aryl bromides **2**. 1,1-Diarylated products **3a-x** were efficiently prepared in good yields from sterically and electronically divergent methyl ketone derivatives. Besides, regarding the bromoarene coupling partner, good results were obtained from neutral and electron-rich aryl bromides, whereas the use of electron-deficient bromo- and iodoarenes (e.g. 4-bromobenzonitrile, 3-bromobenzaldehyde, 1-bromo-4-(trifluoromethyl)benzene, 1-bromo-3-(trifluoromethyl)benzene, 1-iodo-4-nitrobenzene, methyl 2-iodobenzoate) had a deleterious effect on the reaction outcome (yields <5%).[22] Interestingly, sterically bulky ketones such as 1-(naphthalen-1-yl)ethan-1-one and 1-(phenanthren-9-yl)ethan-1-one provided α,α-diarylation products **3s-t** and **3w-x** with moderate yields. As in the case of the arylation of deoxybenzoin, no reaction was observed with 1,2-dibromobenzene as the arylating agent. Unfortunately, only starting material was recovered from aromatic ketones other than 1,2-diaryl- and 1,2,2-triarylethanones (propiophenone, 1-indanone, or 4-chomanone).

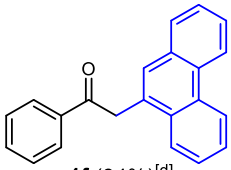
A reduction in the number of equivalents of the arylating agent allowed the selective monoarylation of acetophenone, acetonaphthone, 2-acetylthiophene and 2-acetylpyridine. Table 4 shows a number of 1-(hetero)aryl-2-aryl-ethanones **1b-j** prepared by this procedure. Moderate to good results were obtained from *o*-substituted or sterically hindered bromoarenes (see ketones **1b-f**), and in this case, monoarylation was performed even with a bromoarene bearing an electron-withdrawing substituent (1-bromo-4-(trifluoromethyl)benzene) to provide ethanone **1g**, albeit with a moderate yield (40%).

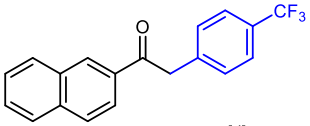
Table 4. Substrate scope for the α-monoarylation of aryl methyl ketones.[a]

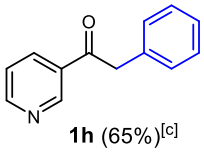


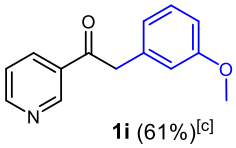


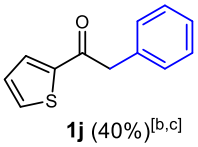

1e (85%)[b]


1f (34%)[d]


1g (40%)[d]


1h (65%)[c]


1i (61%)[c]


1j (40%)[b,c]

[a] Isolated yields. Reaction conditions: **4** (0.4 mmol), **2** (0.8 mmol), K_3PO_4 (0.52 mmol), Bu_4NBr (5 mol%), $Pd(OAc)_2$ ($5x10^{-2}$ mol%), $Ph_2P(O)H$ ($5x\ 10^{-2}$ mol%), H_2O (0.8 mL), 160ºC, 24h.

[b] $Pd(OAc)_2$ (10^{-2} mol%), $Ph_2P(O)H$ (10^{-2} mol%).

[c] 48h.

[d] K_3PO_4 (1.2 mmol).

Hence, considering the potential industrial interest of the reported procedure, a gram-scale diarylation of **1a** was carried out, furnishing triarylethanone **3a** with excellent yield (92%) and selectivity (>99%). Furthermore, ICP-MS measurement of the palladium content in the latter diarylated ketone revealed extremely low contamination level, with a value below the detection limit of 0.1 ppm and therefore safe for oral or parentheral administration in terms of trace palladium content.[23]

Transmission electron microscopy (TEM) images from the reaction crude showed the presence of a few scattered palladium nanoparticles with a diameter of 3-7 nm (Figure 1). In this regard, the interference caused by the presence of potassium ion derived from the base K_3PO_4 was avoided by using a cationic exchange resin (Dowex).

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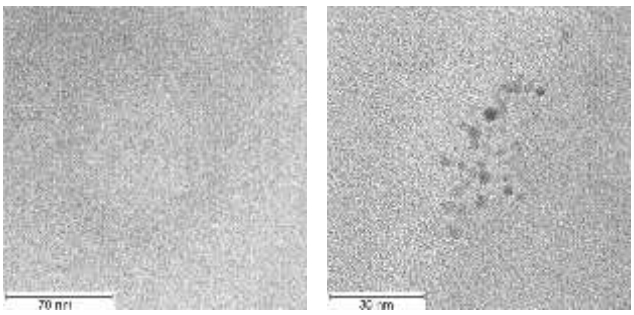


Figure 1. TEM images of the crude.

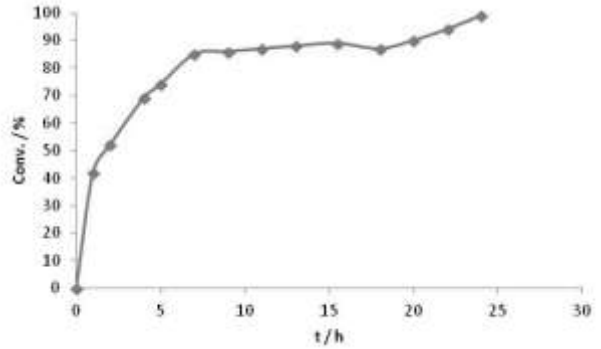


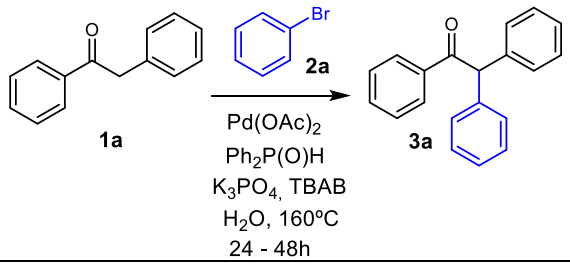
Figure 2. Conversion rate (%) of deoxybenzoin **1a** vs time.

A complete inhibition of the reaction in the presence of a drop of mercury (positive mercury drop test)[24] was observed, and a substantial decrease in the conversion rate was also detected when comparing reactions performed in the presence of overstoichiometric amounts of pyridine and polyvinylpyridine (PVP)[25] (Table 5, entries 1, and 7 *vs* 8).

In contrast with this evidence indicative of the participation of palladium nanoparticles, the kinetic plot conversion rate vs time (Figure 2) showed neither induction time nor sigmoidal shape and therefore the participation of homogeneous catalytic species cannot be discarded. Moreover, the addition of other poisoning agents in sub- and overstoichiometric amounts[25] had no effect on the reaction outcome.

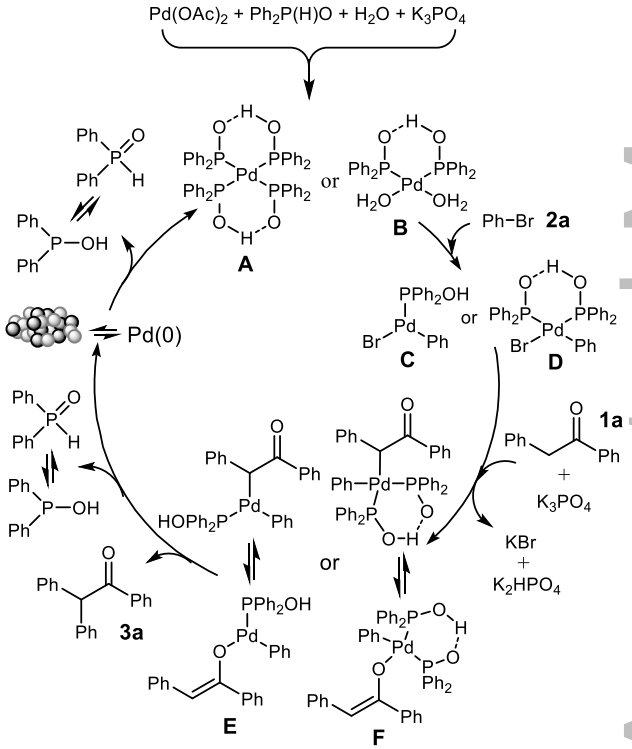
On account of the above experiments, we propose that the catalytic cyclic starts with an initial, fast *in situ* formation of Pd(0) species[26] **A** and **B** which undergo oxidative addition leading to Pd(II) complexes **C** and **D**.[27] Ligand exchange would generate palladium enolates **E** or **F** which upon reductive elimination would provide target triarylethanone **3a** and regenerate Pd(0) complexes **A** and **B** by complexation with diphenylphosphinous acid (Scheme 1). Transient species **A-F** were detected by ESI-MS spectroscopy.[22]

Table 5. Summary of poisoning experiments.



Entry	Additive	Conv. (%)[a]
1	Hg (one drop)	0
2	CS_2 (0.5 eq. per metal atom)	82
3	CS_2 (2.0 eq. per metal atom)	88
4	PPh_3 (0.03 eq. per metal atom)	83
5	PPh_3 (0. 3 eq. per metal atom)	81
6	PPh_3 (4.0 eq. per metal atom)	93
7[b)]	Py (150 eq. per metal atom)	97
8[c)]	PVPy (300 eq. per metal atom)	8

[a] Measured by ^{1}H-NMR. 3,4,5-Trichloropyridine was used as internal standard
[b] Py: Pyridine.
[c] PVPy: Polyvinylpyridine.



Scheme 1. Tentative catalytic cycle for the aqueous α-arylation of deoxybenzoin **1a** in the presence of $Pd(OAc)_2$-$Ph_2P(H)O$.

To sum up, a number of di- and triarylethanones have been prepared by an efficient palladium-catalyzed α-arylation of acetophenone and deoxybenzoin derivatives on water. This advantageous catalyst system is based on very small

amounts of a commercially available, cheap phosphine oxide together with palladium acetate and TBAB. This unprecedented combination of very low catalyst loading and water as a solvent allows for isolation of products with minimal traces of residual palladium. On the basis of the data derived from TEM images, poisoning experiments and kinetic plot, a tentative mechanism based on the participation of palladium phosphinous acid complexes is suggested.

Experimental Section

General Information

Commercially available reagents were used throughout without purification unless otherwise stated. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-300 instrument (300 MHz for ^{1}H and 75.4 MHz for ^{13}C) at 20 ºC. Chemical shifts (δ) are given in ppm downfield from Me_4Si and are referenced as internal standard to the residual solvent (unless indicated) $CDCl_3$ (d=7.26 for ^{1}H and d=77.00 for ^{13}C). Coupling constants, J, are reported in hertz (Hz). Melting points were determined in a capillary tube and are uncorrected. TLC was carried out on SiO_2 (silica gel 60 F254, Merck), and the spots were located with UV light. Flash chromatography was carried out on SiO_2 (silica gel 60, Merck, 230–400 mesh ASTM). IR spectra were recorded on Perkin–Elmer 1600 FT and JASCO FTIR-4100 infrared spectrophotometers as KBr plates or thin films, and only noteworthy absorptions are reported in cm^{-1}. Drying of organic extracts during work-up of reactions was performed over anhydrous Na_2SO_4. Evaporation of solvents was accomplished with a Büchi rotatory evaporator. ICP-MS measurements were carried out on a Thermo Elemental X7 Series ICP-MS equipped with an ASX-520 autosampler. MS spectra were recorded on an Agilent 5975 mass spectrometer under electronic impact (EI) conditions or on an Acquity UPLC-Spectrometer of Mass QTOF from Waters under electrospray ionization (ESI). HRMS were recorded using a Micromass GCT spectrometer by electronic impact (EI) or electrospray ionization (ESI). Reactions carried out under microwave irradiation were performed using a CEM Discover 1-300W system equipped with a built-in pressure measurement sensor and a vertically focused IR temperature measurement sensor.

General Procedure for the α-arylation of deoxybenzoin.

Deoxybenzoin **1a** (0.4 mmol), aryl halide **2** (1.2 mmol), potassium phosphate (0,52 mmol) and tetrabutylammonium bromide (0.02 mmol) were charged in a heavy-wall pressure tube at room temperature with a magnetic stir bar under argon. Then, H_2O (0.8 mL), a solution of palladium(II) acetate (20 µL of a $2{\cdot}10^{-6}$ M solution in 1,4-dioxane, $4{\cdot}10^{-5}$ mmol) and of diphenylphosphine oxide (20 µL of a $2{\cdot}10^{-6}$ M solution in 1,4-dioxane, $4{\cdot}10^{-5}$ mmol) were added under argon, and heated in an oil bath at 160 ºC for 24 h. After cooling, the reaction mixture was diluted with EtOAc (5 ml) and water (5 ml), the layers were decanted and the aqueous phase extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and filtered, and the solvents were removed *in vacuo*. Purification by flash column chromatography (Hexane:EtOAc) provided target 1,2,2-triarylethanones **3a-h**. (see the Supporting Information Section)

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UPDATE

Aqueous α-arylation of mono- and diarylethanone enolates at low catalyst loading

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