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Pd-catalysed *ortho*-alkoxylation of benzamides *N*-protected with an iminophosphorane functionality

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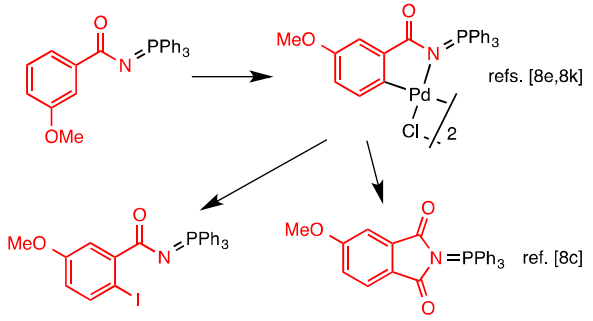
The oxidative coupling of keto-stabilised iminophosphoranes (IPs) $Ph_3P{=}NC(O)C_6H_xR_y$ with alcohols R'OH affords the alkoxylated species $Ph_3P{=}NC(O)C_6H_{x-1}R_y$-2-OR'. The process is catalysed by 10% $PdCl_2(NCMe)_2$, uses oxone® as oxidant and the alcohol R'OH as source of OR' groups and reaction solvent. The reaction takes place at room temperature regioselectively at the *ortho*-position of the benzamide ring, gives only the mono-alkoxylated derivatives, and shows tolerance to a variety of functional groups and different primary and secondary alcohols. Better yields were obtained when the aryl ring contains electron-releasing substituents (OMe, Me). The iminophosphorane moiety plays a dual role as protecting/directing group, and can be hydrolysed to give the corresponding free benzamide.

Introduction

One of the most interesting issues in today's chemistry is the functionalisation of simple organic molecules to yield more complex, high valuable molecules. In this context, the transformation of inert and ubiquitous C–H bonds into more reactive and elaborated C–C or C–X bonds (X = O, N, S, halogen) mediated by transition metals is of paramount importance.[1] While the introduction of the metal (mostly Pd, Ru, Rh or Pt) overcomes the problem of the low reactivity of the C–H bond, the goal of a highly selective orientation has been achieved using several approximations. Among them, the directed C–H activation is probably the most versatile strategy to reach C–C and C–X couplings with good yields and selectivities, specially for C(sp^2)–H bonds.[2] In this way a high number of tranformations have been successfully developed, although not all of them are equally represented. Therefore, while C_{aryl}–C couplings are now easily produced by directed oxidative coupling of two C–H bonds, examples of C_{aryl}–O bond formations are less frequent,[2n,2o,3] this fact being probably related with the different metal-ligand bond strengths, as well as with the different electronegativities of the atoms involved.[4] As a consequence, further development of C_{aryl}–O bond forming reactions is still desirable, because products containing the C–O unit (aryl ethers, among others) are of high practical importance due to their pharmacological activity or as building blocks in fine chemistry.[5] The oxidative coupling of aryl rings and alcohols, promoted by palladium in high oxidation states, affords alkoxylated aryl-derivatives as showed in pionnering works of Sanford and Yu.[6] Despite notable recent progress in this area[7] not only the C–O bond formation by catalysed alkoxylation is still challenging, but certain substrates show particular reluctance to be functionalised, and this reaction is worth to be studied in more depth.

Benzamides are one of the special class of molecules difficult to functionalise through C–H bond activation, due to the strong electronwithdrawing effect of the amide group. However, during our current research on metal-mediated C–H bond activation processes on iminophosphoranes (IPs),[8] we have found a regioselective incorporation of the Pd center to the benzamide ring in the case of keto-stabilised IPs $R_3P{=}NC(O)Ar$ (R = alkyl, aryl; Ar = substituted aryl). This reaction affords orthopalladated benzamide-derivatives under very mild reaction conditions, circumventing the typical low reactivity of benzamides.[8e,8k] Furthermore we have shown that is possible to functionalise the orthopalladated benzamide ring selectively in mild conditions, using IPs as directing/protecting groups in Pd-mediated CO insertions and in oxidative additions of iodine, as it is shown in Scheme 1.[8c]



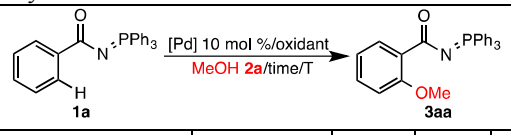
Scheme 1. Iminophosphoranes as protecting/directing groups

In this way, the protection of the benzamide nitrogen as an IP group -N=PR_3 plays several roles besides its character as N-directing group, being the most important the tuning of the reactivity of the aryl ring by change of the electron density, shifting the positive charge towards the P atom, and activating this ring towards the incorporation of the Pd center.[8e]
Because both the C–H bond activation and the subsequent reactivity of the orthopalladated intermediate take place smoothly, we hypothesize that the use of IPs as protecting-directing groups could allow room-temperature catalytic functionalisation of benzamides. We report here our results in the Pd-catalysed *ortho*-alkoxylation of benzamides protected as keto-stabilised iminophosphoranes. This process shows some remarkable improvements with respect to previous works, such as performance at room temperature (avoiding usual harsh conditions),[7c-7i] tolerance to a variety of substituents in the benzamide moiety and to different primary and secondary alcohols, and easy removal of the IP moiety.

Results and discussion

We started our studies on alkoxylation of Ph_3P=NC(O)Ph **1a** with methanol **2a** using $Pd(OAc)_2$ as catalyst (10%), based on the easy orthopalladation of **1a** by $Pd(OAc)_2$ observed in our previous works.[8e,8k] The oxidant was the first parameter to be changed and optimised. The use of $PhI(OAc)_2$ as oxidant results in a complete lack of reactivity (entry 1), even at 100 ºC (entry 2) while the use of oxone® allows to obtain the methoxylated derivative **3aa** in 30% isolated yield (entry 3). This yield was not improved by a further increase of the temperature (entry 4), neither by an increase of the amount of oxidant (entry 5).

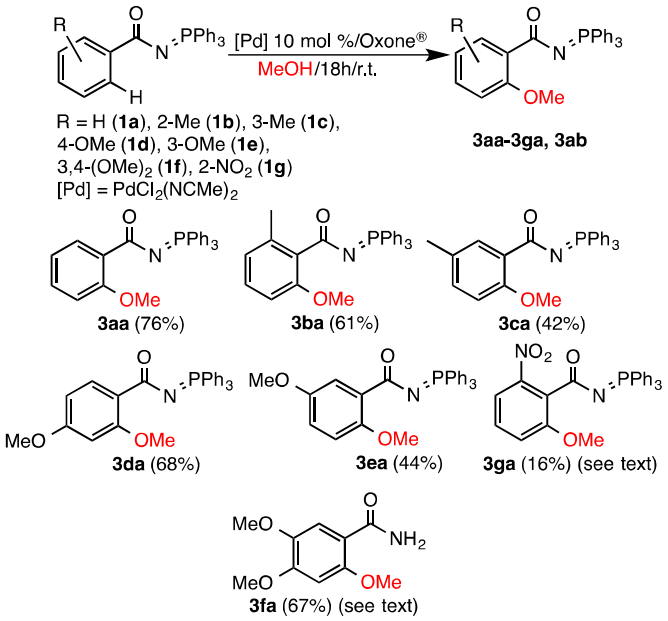
Table 1. Optimization of the reaction conditions for the catalytic synthesis of **3aa**[a]



Entry	Catalyst	Oxidant	T (ºC)	t (h)	**3aa** (%)[b]
1	$Pd(OAc)_2$	$PhI(OAc)_2$	23	18	0
2	$Pd(OAc)_2$	$PhI(OAc)_2$	100	2	0
3	$Pd(OAc)_2$	oxone®[c]	23	18	30
4	$Pd(OAc)_2$	oxone®[c]	40	18	8
5	$Pd(OAc)_2$	oxone®[d]	23	68	18
6	$Pd(OAc)_2$	$Cu(OAc)_2$	23	18	0
7	$Pd(OAc)_2$	AgOAc[e]	23	18	0
8	$Pd(OAc)_2$	benzoq.	23	18	0
9	$Li_2[PdCl_4]$	oxone®[c]	23	18	24
10	$PdCl_2(NCMe)_2$	oxone®[c]	23	18	76
11	$PdCl_2(NCMe)_2$[f]	oxone®[c]	23	18	61

a) Standard reaction conditions: **1a** (0.5 mmol), $PdCl_2(NCMe)_2$ [Pd] (0.05 mmol), and the oxidant (1 mmol) in MeOH were stirred at the indicated temperature during the specified time; b) isolated yield (%); c) 1 mmol; d) 2 mmol; e) the same result was obtained at 100 ºC; f) 5 mol % $PdCl_2(NCMe)_2$.

Other oxidants used in Pd-catalysed oxidative couplings, such as $Cu(OAc)_2$, AgOAc or benzoquinone (entries 6-8), were not efficient in the alkoxylation of **1a** and only products derived from the decomposition of the starting IP (mainly O=PPh_3) were detected. We then decided to screen new catalysts, using oxone® as oxidant, and we selected different Pd salts among typical complexes used as C–H activation promoters. The use of $Li_2[PdCl_4]$ gave only a low 24% yield of **3aa** (entry 9) but, fortunately, the use of $PdCl_2(NCMe)_2$ allowed the obtention of functionalised **3aa** in a good 76% isolated yield (entry 10). Further attempts to optimise the reaction conditions using $PdCl_2(NCMe)_2$ as catalyst did not resulted in additional improvements of the reaction yield. A control experiment using $C_6H_5C(O)NH_2$ under conditions described in entry 10 showed a 10 % conversion of benzamide to give 2-methoxybenzamide.
Once the reaction conditions were optimised we have studied the scope of the reaction. In a first step we have checked the reactivity of IPs **1a-1g** towards methanol **2a**, which acts as methoxide source and as reaction solvent. IPs **1a-1g** contain substituents of different nature (electron-releasing and electron-withdrawing groups) at different positions of the benzamide ring (*o*-, *m*-, *p*-). The obtained results are shown in Scheme 2.



Scheme 2. Scope of the alkoxylation of iminophosphoranes: change of substrate. Standard reaction conditions: IPs **1a-g**, catalyst $PdCl_2(NCMe)_2$ [Pd], and oxone® (amounts specified in experimental) in MeOH were stirred at 23 ºC (r.t.) for 18h

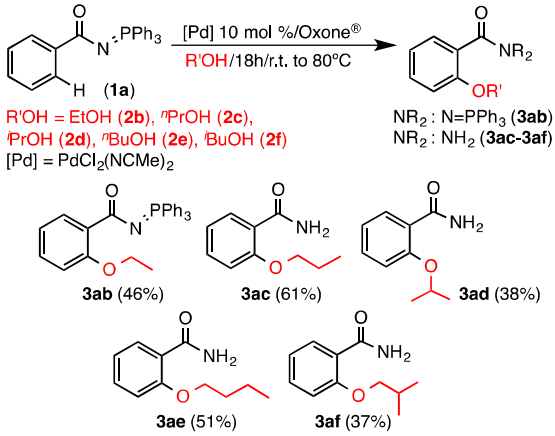
In all studied cases the alkoxylation is Pd-catalysed and takes place with complete conversion at room temperature in 18 h. The mild reaction conditions and the short reaction times at this temperature are clear advantages with respect to previous published reports, which use prolongued heating.[7c-7i] It is remarkable that the reaction occurs with preservation of the N=P functional group (at least in examples **3aa-3ga** and **3ab**, see below); no alcoholysis of the N=P bond was observed in

spite of the protic nature of the solvent. In addition, the reaction occurs with regioselective incorporation of one methoxide group at the ortho position of the benzamide ring. Even when two positions are available, only one OMe group is added to the starting IP. The regioselectivity in the methoxide incorporation is notable in the cases of compounds **3ca**, **3ea** and **3fa** whose precursors **1c**, **1e** and **1f** contain a substituent in 3-position or two substituents in 3,4-positions and, therefore, can generate two isomers. In the studied cases only the products resulting of the C–H activation at the less sterically hindered position were obtained, instead of the typical mixtures of isomers. The isolated yields are from moderate to good when electron-donating substituents are present (**3aa-3fa**), with major differences in the cases of **3ca** and **3ea** due to difficulties in purification of the crude products. However, this yield drops notably when the IP contains an electron-attracting group, for instance **1g**. In this case partial conversion has been observed, most of the starting material remains unreacted and **3ga** represents only 16% of the final mixture (see Experimental). We assign this effect to the strong deactivating nature of the 2-nitro substituent. Attempts carried out with other electron-withdrawing groups as aryl substituents (2-Cl, 4-Cl and 2-Br) did not resulted in the expected alkoxylated products, and this type of groups were not further investigated.

The case of compound **3fa** merits a more detailed explanation. After usual work-up of the crude only $Ph_3P{=}O$ was obtained from column chromatography (see Experimental). The amount of phosphine oxide obtained was higher than in the preceding cases, suggesting that extensive hydrolysis occurred in this case. An increase of the solvent polarity for chromatographic elution allowed to obtain free benzamide **3fa** in 67% yield. The analysis of the crude by ^{31}P NMR before chromatography showed the presence of $O{=}PPh_3$ as the unique P-containing species, suggesting that the hydrolysis has occurred during the reaction, and not during the purification of the product.

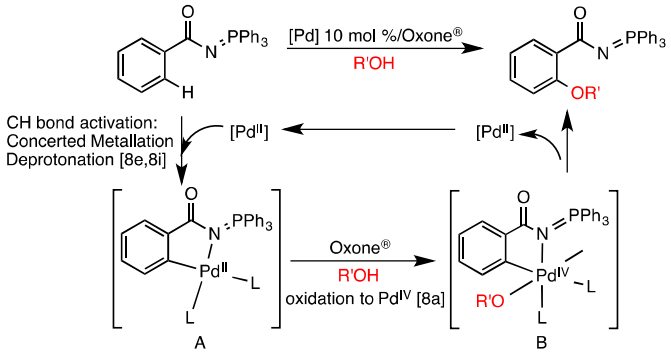
Once the range of IPs has been examined, we tested the scope of alcohols amenable to give oxidative coupling. Usually the range of alcohols used is quite limited, being methanol the only alcohol used in many cases. The obtained results are shown in Scheme 3. The oxidative coupling of **1a** with ethanol **2b** occurs in smooth conditions to give iminophosphorane **3ab** in 46% yield, which is similar to yields of other ethoxylation processes found in the literature.[7] Compound **3ab** shows the incorporation of a single OEt unit, as described above for the incorporation of the OMe group.However, no reaction was observed when the alkoxylation of **1a** was attempted with ^{n}PrOH **2c**, ^{i}PrOH **2d**, ^{n}BuOH **2e** or ^{i}BuOH **2f** at room temperature. In these cases an increase of the reaction temperature was necessary to trigger the oxidative coupling, although this increase of temperature promoted an unavoidable hydrolysis of the expected alkoxylated IP intermediate. In this way, *ortho*-functionalised free benzamides **3ac-3af** were obtained in moderated yields, as shown in Scheme 3.

Compounds **3ac-3af** were already known, and they show interest due to their antifungal, analgesic and antipyretic properties.[9,10] Although the free benzamide is obtained at the end of the reaction, the presence of the IP moiety is mandatory for the successful functionalisation of the benzamide ring. This is clearly shown when benzamide $C_6H_5C(O)NH_2$ was subjected to identical alkoxylation conditions than IP $C_6H_5C(O)N{=}PPh_3$ **1a** [$PdCl_2(NCMe)_2$ 10%, ^{i}PrOH, oxone®, 80 ºC, 18 h), because no reaction at all was observed in the case of the free benzamide. Therefore, species **1a** undergoes the Pd-catalysed incorporation of the alkoxy moiety, giving the corresponding 2-$ROC_6H_4C(O)N{=}PPh_3$ compounds, which then hydrolyse under the reaction conditions affording benzamides **3ac-3af**.



Scheme 3. Scope of the alkoxylation of iminophosphoranes: change of alcohol. Standard reaction conditions: **1a**, catalyst $PdCl_2(NCMe)_2$ [Pd], and oxone® (amounts in experimental) in alcohol ROH were stirred at 23 (r.t.), 60 or 80 ºC (depending of the alcohol) for 18h.

Concerning the mechanism of this process, our proposal is presented in Scheme 4, and it is based on the following steps. The first step is the formation of the corresponding ortho-palladated species A through C–H bod activation. This step has been studied in depth in our group recently, and takes place through a concerted metallation-deprotonation mechanism (CMD).[8e,8i]



Scheme 4. Proposed mechanism for the alkoxylation of keto-stabilised iminophosphoranes

The next step is the oxidation of the Pd^{II} center to a more electrophilic Pd^{IV} center B, achieved by the use of oxone® as

oxidant. This highly electrophilic Pd^{IV} center should able to coordinate at least one alkoxide from the alcohol. We have recently isolated and characterize Pd^{IV} derivatives containing simultaneously orthometallated iminophosphoranes and anionic O-donor ligands,[8a] therefore this step is really likely to occur. Final C-O coupling and reductive elimination affords the alkoxylated iminophosphorane and regenerates the active Pd^{II} species.

Conclusions

In summary, we have shown that the N-protection of benzamides under the form of iminophosphoranes (IPs) is very useful for the obtention of *ortho*-functionalised benzamides otherwise not achievable or obtained less efficiently. In the present contribution we have applied this concept to the always difficult C–O oxidative coupling between keto-stabilised IPs and alcohols catalysed by palladium. The reaction gives the corresponding *ortho*-alkoxylated IPs where the benzamide ring has undergone the regioselective incorporation of the alkoxy moiety, and takes place under very mild conditions (room temperature). From the *ortho*-alkoxylated IPs it is possible to obtain the corresponding *ortho*-alkoxylated free benzamides. Further applications of IPs as protecting/directing groups in other metal-catalysed reactions are currently in progress.

Experimental

General methods

Solvents were dried and distilled using standard procedures before use. All reactions were carried out under Ar atmosphere using standard Schlenck techniques. Flash column liquid chromatographies were performed on basic Al_2O_3 of 90 neutral (50-200 μm) grade. Elemental analyses were performed on a PerkinElmer 2400 Series II microanalyser. Infrared spectra (4000-380 cm^{-1}) were recorded on a Perkin-Elmer Spectrum One IR spectrophotometer. ^1H, $^{13}C\{^1H\}$ and $^{31}P\{^1H\}$ NMR spectra were recorded in $CDCl_3$ solutions at 25 ºC on a Bruker AV400 spectrometer (δ in ppm, *J* in Hz) at ^1H operating frequency of 400.13 MHz. ^1H and $^{13}C\{^1H\}$ NMR spectra were referenced using the solvent signal as internal standard, while $^{31}P\{^1H\}$ NMR spectra were referenced to H_3PO_4 (85%). ESI (ESI^+) mass spectra were recorded using an Esquire 3000 ion-trap mass spectrometer (Bruker Daltonic GmbH) equipped with a standard ESI/APCI source. Samples were introduced by direct infusion with a syringe pump. Nitrogen served both as the nebulizer gas and the dry gas. Compound $PdCl_2(NCMe)_2$ was prepared as previously reported.[11] Iminophosphoranes **1a-1g** were prepared following methods previously reported.[8b,8e,8k,12]

Synthesis of *ortho*-alkoxylated iminophosphoranes

Synthesis of 3aa. To a suspension of $Ph_3P{=}NC(O)Ph$ **1a** (0.250 g, 0.655 mmol) in MeOH **2a** (15 mL), $PdCl_2(NCMe)_2$ (16.8 mg, 0.065 mmol) and oxone® (0.806 g, 1.31 mmol) were added, and the resulting mixture was stirred for 18 h at room temperature. The yellow suspension thus formed was dissolved with EtOAc (150 mL) and washed with aqueous Na_2SO_3 (10%, 3×30 mL) and then with a saturated NaCl solution (2×30 mL). The organic phase was separated, dried with anhydrous $MgSO_4$, filtered and evaporated to dryness, affording a residue containing impure **3aa**. Compound **3aa** was purified by column chromatography on basic alumina using ethyl acetate/ether (8:5) as eluent. The first colourless band was collected and evaporated to dryness affording pure **3aa** as a white solid. Obtained: 0.205 g, 0.498 mmol (76% yield). Further elution afforded a second colorless band which was $Ph_3P{=}O$. ^1H NMR ($CDCl_3$): δ 3.86 (3H, s, OMe), 6.91-6.96 (2H, m, H_3+H_5, C_6H_4), 7.22 (H_4, td, 1H, C_6H_4, $^3J_{HH}$ = 7.5, $^4J_{HH}$ = 1.9), 7.36 (6H, m, H_m, PPh_3), 7.44 (3H, m, H_p, PPh_3), 7.76 (6H, m, H_o, PPh_3), 8.02 (1H, dd, H_6, C_6H_4, $^3J_{HH}$ = 7.5, $^4J_{HH}$ = 1.8). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 56.03 (s, OMe), 112.00 (s, C_3, C_6H_4), 119.93 (s, C_5, C_6H_4), 128.36 (d, C_i, PPh_3, $^1J_{PC}$ = 99.1) 128.50 (d, C_m, PPh_3, $^3J_{PC}$ = 12.3), 129.77 (d, C_1, C_6H_4, $^3J_{PC}$ = 20.4), 130.60 (s, C_4, C_6H_4), 131.67 (s, C_6, C_6H_4), 132.11 (d, C_p, PPh_3, $^4J_{PC}$ = 2.9), 133.32 (d, C_o, PPh_3, $^2J_{PC}$ = 10.0), 158.24 (s, C_2, C_6H_4), 177.38 (d, C=O, $^2J_{PC}$ = 8.0). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ 19.96 (s). IR (ν, cm^{-1}): 1598 (C=O), 1339 (P=N). MS (ESI^+): 412.1 (98 %) $[M+H]^+$. Found: C, 75.80; H, 5.44; N, 3.28. Calc. for $C_{26}H_{22}NO_2P$: C, 75.90; H, 5.39; N, 3.40%.

Synthesis of 3ba. Compound **3ba** was prepared using the same method than **3aa**, but starting from $Ph_3P{=}NC(O)C_6H_4$-2-Me **1b** (0.260 g, 0.657 mmol), $PdCl_2(NCMe)_2$ (17.1 mg, 0.066 mmol) and oxone® (0.806 g, 1.31 mmol) in MeOH **2a** (15 mL). **3ba** was purified by column chromatography on basic Al_2O_3 using ethyl acetate/hexane (8:5) as eluent, and obtained as a white solid. Obtained: 0.171 g, 0.400 mmol (61% yield). ^1H NMR ($CDCl_3$): δ 2.30 (3H, s, Me-6) 3.83 (3H, s, OMe-2), 6.71-6.74 (2H, m, H_3+H_5, C_6H_3), 7.08 (1H, t, H_4, C_6H_3, $^3J_{HH}$ = 7.9), 7.47 (6H, m, H_m, PPh_3), 7.56 (3H, m, H_p, PPh_3), 7.86 (6H, m, H_o, PPh_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 19.29 (s, Me-6), 56.01 (s, OMe-2), 108.68 (s, C_3, C_6H_3), 122.43 (s, C_5, C_6H_3), 127.43 (s, C_4, C_6H_3), 128.28 (d, C_i, PPh_3, $^1J_{PC}$ = 98.5), 128.50 (d, C_m, PPh_3, $^3J_{PC}$ = 12.3), 132.13 (d, C_p, PPh_3, $^4J_{PC}$ = 2.9), 132.62 (d, C_1, C_6H_3, $^3J_{PC}$ = 8.8) 133.38 (d, C_o, PPh_3, $^2J_{PC}$ = 10.0), 135.0 (s, C_6, C_6H_3), 155.78 (s, C_2, C_6H_3), 179.08 (d, C=O, $^2J_{PC}$ = 8.8). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ 19.48 (s). IR (ν, cm^{-1}): 1577 (C=O), 1332 (P=N). MS (ESI^+): 426.1 (97 %) $[M+H]^+$. Found: C, 76.37; H, 5.39; N, 3.11. Calc. for $C_{27}H_{24}NO_2P$: C, 76.22; H, 5.69; N, 3.29%.

Synthesis of 3ca. Compound **3ca** was prepared using the same method than **3aa**, but starting from $Ph_3P{=}NC(O)C_6H_4$-3-Me **1c** (0.202 g, 0.511 mmol), $PdCl_2(NCMe)_2$ (13.2 mg, 0.051 mmol) and oxone® (0.620 g, 1.01 mmol) in MeOH **2a** (15 mL). **3ca** was purified by column chromatography on basic Al_2O_3 using ethyl acetate/hexane (8:5) as eluent, and obtained as a white solid. Obtained: 0.091 g, 0.213 mmol (42% yield). ^1H NMR ($CDCl_3$): δ 2.29 (3H, s, Me-5) 3.84 (3H, s, OMe-2), 6.82 (1H, d, H_3, C_6H_3, $^3J_{HH}$ = 8.3), 7.11 (1H, dd, H_4, C_6H_3, $^3J_{HH}$ = 8.3, $^4J_{HH}$ = 2.4), 7.46 (6H, m, H_m, PPh_3), 7.54 (3H, m, H_p, PPh_3), 7.79 (1H, d, H_6, C_6H_3, $^4J_{HH}$ = 2.4), 7.86 (6H, m, H_o, PPh_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 20.50 (s, Me-5), 56.34 (s, OMe-4), 112.26 (s, C_3, C_6H_3), 128.37 (d, C_i, PPh_3, $^1J_{PC}$ = 99.0), 128.60 (d, C_m, PPh_3, $^3J_{PC}$ = 12.3), 129.10 (s, C_5, C_6H_3),

129.48 (d, C_1, C_6H_3, $^3J_{PC}$ = 20.2), 130.95 (s, C_4, C_6H_3), 131.66 (s, C_6, C_6H_3), 132.10 (d, C_p, PPh_3, $^4J_{PC}$ = 2.8), 133.34 (d, C_o, PPh_3, $^2J_{PC}$ = 9.9), 156.20 (s, C_2, C_6H_3), 177.61 (d, CO, $^2J_{PC}$ = 5.1). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ 20.21 (s). IR (ν, cm^{-1}): 1614 (C=O), 1339 (P=N). MS (ESI^+): 426.1 (100 %) $[M+H]^+$. Found: C, 76.08; H, 5.51; N, 3.34. Calc. for $C_{27}H_{24}NO_2P$: C, 76.22; H, 5.69; N, 3.29%.

Synthesis of 3da. Compound **3da** was prepared using the same method than **3aa**, but starting from Ph_3P=NC(O)C_6H_4-4-OMe **1d** (0.250 g, 0.608 mmol), $PdCl_2(NCMe)_2$ (15.5 mg, 0.060 mmol) and oxone® (0.75 g, 1.22 mmol) in MeOH **2a** (15 mL). **3da** was purified by column chromatography on basic Al_2O_3 using ethyl acetate/hexane (8:5) as eluent, and obtained as a white solid. Obtained: 0.183 g, 0.414 mmol (68% yield). ^1H NMR ($CDCl_3$): δ 3.82 (3H, s, OMe), 3.86 (3H, s, OMe), 6.46-6.50 (2H, m, H_3 + H_5, C_6H_3), 7.45 (6H, m, H_m, PPh_3), 7.53 (3H, m, H_p, PPh_3), 7.84 (6H, m, H_o, PPh_3), 8.20 (1H, d, H_6, C_6H_3, $^3J_{HH}$ = 8.3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 55.35 (s, OMe), 56.04 (s, OMe), 99.25 (s, C_3, C_6H_3), 103.93 (s, C_5, C_6H_3), 121.97 (d, C_1, C_6H_3, $^3J_{PC}$ = 20.7), 128.52 (d, C_m, PPh_3, $^3J_{PC}$ = 12.3), 128.76 (d, C_i, PPh_3, $^1J_{PC}$ = 99.2), 131.95 (d, C_p, PPh_3, $^4J_{PC}$ = 2.9), 133.31 (d, C_o, PPh_3, $^2J_{PC}$ = 9.9), 133.88 (d, C_6, C_6H_3, $^4J_{PC}$ = 1.9), 160.48, 162.24 (C_2, C_4, C_6H_3), 176.34 (d, CO, $^2J_{PC}$ = 4.5). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ 19.58 (s). IR (ν, cm^{-1}): 1599 (C=O), 1333 (P=N). MS (ESI^+): 442.1 (100%) $[M+H]^+$. Found: C, 73.71; H, 5.56; N, 3.18. Calc. for $C_{27}H_{24}NO_3P$: C, 73.46; H, 5.48; N, 3.17%.

Synthesis of 3ea. Compound **3ea** was prepared using the same method than **3aa**, but starting from Ph_3P=NC(O)C_6H_4-3-OMe **1e** (0.252 g, 0.612 mmol), $PdCl_2(NCMe)_2$ (15.9 mg, 0.061 mmol) and oxone® (0.75 g, 1.22 mmol) in MeOH **2a** (15 mL). **3ea** was purified by column chromatography on basic Al_2O_3 using ethyl acetate/hexane (8:5) as eluent, and obtained as a white solid. Obtained: 0.120 g, 0.272 mmol (44.5% yield). ^1H NMR ($CDCl_3$): δ 3.78 (3H, s, OMe), 3.83 (3H, s, OMe), 6.86-6.87 (2H, m, H_3 + H_4, C_6H_3), 7.46 (6H, m, H_m, PPh_3), 7.52-7.56 (4H, m, H_6 (C_6H_3) + H_p (PPh_3)), 7.85 (6H, m, H_o, PPh_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 55.89 (s, OMe), 57.17 (s, OMe), 114.14, 116.11 (C_3, C_4, C_6H_3), 116.27 (d, C_6, C_6H_3, $^4J_{PC}$ = 1.4), 128.26 (d, C_i, PPh_3, $^1J_{PC}$ = 99.2), 128.60 (d, C_m, PPh_3, $^3J_{PC}$ = 12.3), 130.78 (d, C_1, C_6H_3, $^3J_{PC}$ = 20.4), 132.16 (d, C_p, PPh_3, $^4J_{PC}$ = 2.9), 133.32 (d, C_o, PPh_3, $^2J_{PC}$ = 10.0), 152.64, 153.13 (C_2, C_5, C_6H_3), 176.93 (d, CO, $^2J_{PC}$ = 8.1). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ 20.08 (s). IR (ν, cm^{-1}): 1599 (C=O), 1333 (P=N) cm^{-1}. MS (ESI^+): 442.1 (100 %) $[M+H]^+$. Found: C, 72.98; H, 5.33; N, 3.27. Calc for $C_{27}H_{24}NO_3P$: C, 73.46; H, 5.48; N, 3.17%.

Synthesis of 3ga. The reaction between Ph_3P=NC(O)C_6H_4-2-NO_2 **1g** (0.157 g, 0.368 mmol), $PdCl_2(NCMe)_2$ (9.5 mg, 0.037 mmol) and oxone® (0.453 g, 0.736 mmol) in MeOH **2a** (15 mL) was carried following the same procedure than that described for **3aa**. After 18 h stirring at room temperature, the analysis of the crude showed a mixture of **3ga** (16%), **1a** and O=PPh_3 (84% together). Despite repeated attempts, **3ga** could not be obtained as an analytically pure product due to contamination with **1a**. It could be characterized by ^{31}P NMR spectroscopy (δ ($CDCl_3$) = 19.85 ppm (s)).

Synthesis of 3ab. Compound **3ab** was prepared using the same method than **3aa**, but starting from Ph_3P=NC(O)C_6H_5 **1a** (0.138 g, 0.362 mmol), $PdCl_2(NCMe)_2$ (9.4 mg, 0.036 mmol) and oxone® (0.445 g, 0.724 mmol) in EtOH **2b** (15 mL). **3ab** was purified by column chromatography on basic Al_2O_3 using ethyl acetate/hexane (8:5) as eluent, and obtained as a white solid. Obtained: 0.070 g, 0.165 mmol (46% yield). ^1H NMR ($CDCl_3$): δ 1.32 (3H, t, CH_3, OEt, $^3J_{HH}$ = 7.0), 4.02 (2H, q, CH_2, OEt), 6.82-6.86 (2H, m, H_3 + H_5, C_6H_4), 7.18 (1H, td, H_4, C_6H_4, $^3J_{HH}$ = 7.8, $^4J_{HH}$ = 1.8), 7.39 (6H, m, H_m, PPh_3), 7.48 (3H, m, H_p, PPh_3), 7.69 (1H, dd, H_6, C_6H_4, $^3J_{HH}$ = 7.8, $^4J_{HH}$ = 1.9), 7.79 (6H, m, H_o, PPh_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 15.15 (s, $OCH_2\mathit{CH_3}$), 64.46 (s, $O\mathit{CH_2}CH_3$), 113.38 (s, C_3, C_6H_4), 120.10 (s, C_5, C_6H_4), 128.34 (d, C_i, PPh_3, $^1J_{PC}$ = 98.9), 128.56 (d, C_m, PPh_3, $^3J_{PC}$ = 13.0), 129.96 (s, C_4, C_6H_4), 130.25 (s, C_6, C_6H_4), 132.09 (d, C_p, PPh_3, $^4J_{PC}$ = 2.9), 133.33 (d, C_o, PPh_3, $^2J_{PC}$ = 10.0), 157.00 (s, C_2, C_6H_4). The signals attributed to C_1 (C_6H_4) and C=O were not observed, in spite of the use of long accumulation trials. $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ 19.87 (s). IR (ν, cm^{-1}): 1600 (C=O), 1330 (P=N). MS (ESI^+): 426.1 (100 %) $[M+H]^+$. Found: C, 76.09; H, 5.31; N, 3.06. Calc. for $C_{27}H_{24}NO_2P$: C, 76.22; H, 5.69; N, 3.29%.

Synthesis of *ortho*-alkoxylated benzamides

Synthesis of 3fa. Compound **3fa** was prepared using the same method than **3aa**, but starting from Ph_3P=NC(O)C_6H_3-3,4-$(OMe)_2$ **1f** (0.150 g, 0.340 mmol), $PdCl_2(NCMe)_2$ (8.8 mg, 0.034 mmol) and oxone® (0.418 g, 0.68 mmol) in MeOH **2a** (15 mL). However, the workup of the reaction was different, because purification of **3fa** proved to be more difficult than in previous cases. Thus, after extensive elution of the chromatographic column (Al_2O_3) with ethyl acetate/hexane (8:5) as eluent, only O=PPh_3 was obtained. The change of the solvents ratio to ethyl acetate/hexane (4:1) developed a new colourless band from which, after evaporation, **3fa** was obtained as a white solid. Obtained: 0.048 g, 0.228 mmol (67.0% yield). Characterization of **3fa** has been performed by comparison of its spectral data with those recently published.[13]

Synthesis of 3ac. Compound **3ac** was prepared using the same method than **3aa**, but starting from Ph_3P=NC(O)C_6H_5 **1a** (0.250 g, 0.655 mmol), $PdCl_2(NCMe)_2$ (16.8 mg, 0.065 mmol) and oxone® (0.806 g, 1.31 mmol) in ^{n}PrOH **2c** (15 mL) at 60 ºC. After the reaction time (18 h) the solvent was evaporated to dryness and the residue purified by column chromatography using silica as support and ethyl acetate as eluent. Compound **3ac** was obtained as a white solid. Obtained: 0.072 g, 0.4 mmol (61.2% yield). Characterization of **3ac** has been performed by comparison of its spectral data with those previously published.[14]

Synthesis of 3ad. Compound **3ad** was prepared using the same method than **3ac**, but starting from Ph_3P=NC(O)C_6H_5 **1a** (0.250 g, 0.655 mmol), $PdCl_2(NCMe)_2$ (16.8 mg, 0.065 mmol) and oxone® (0.806 g, 1.31 mmol) in ^{i}PrOH **2d** (15 mL) at 80 ºC. Compound **3ad** was purified by column chromatography using silica as support and a mixture ethyl acetate/diethyl ether (4/1) as eluent, and obtained as a pale yellow solid. Obtained: 0.045 g, 0.25 mmol (38.1% yield). **3ad** has been previously published, but its spectroscopic data were

not reported.[15] Due to this reason they are here included. ^{1}H NMR ($CDCl_3$): δ 1.41 (6H, d, CH_3, $^3J_{HH}$ = 6.1), 4.65 (1H, heptuplet, OCH, $^3J_{HH}$ = 6.1), 5.90 (2H, br s, NH_2), 6.98 (2H, m, H_4+H_5, C_6H_4), 7.50 (1H, dd, C_6H_4, $^3J_{HH}$ = 8.4, $^4J_{HH}$ = 2.4), 7.56 (1H, dd, C_6H_4, $^3J_{HH}$ = 7.9, $^4J_{HH}$ = 2.0). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 21.84 (s, CH_3), 71.84 (s, OCH), 113.71, 116.83, 120.47, 133.92, 134.13, 159.96 (C_6H_4). The signal due to C=O was not observed, in spite of long accumulation times. IR (ν, cm^{-1}) = 1595 (C=O), 3062 (N-H).

Synthesis of 3ae. Compound **3ae** was prepared using the same method than **3ac**, but starting from Ph_3P=NC(O)C_6H_5 **1a** (0.250 g, 0.655 mmol), $PdCl_2(NCMe)_2$ (16.8 mg, 0.065 mmol) and oxone® (0.806 g, 1.31 mmol) in ^{n}BuOH **2e** (15 mL) at 60 ºC. Compound **3ae** was purified by column chromatography using silica as support and a mixture ethyl acetate/diethyl ether (4/1) as eluent, and obtained as a pale yellow solid. Obtained: 0.065 g, 0.34 mmol (51.9% yield). **3ae** has been previously published, but its spectral data were not reported.[9] Due to this reason they are here included. ^{1}H NMR ($CDCl_3$): δ 0.91 (3H, t, CH_3, $^3J_{HH}$ = 6.4), 1.46 (2H, m, CH_2), 1.75 (2H, m, CH_2), 3.99 (2H, t, OCH_2, $^3J_{HH}$ = 6.2), 5.92 (2H, br s, NH_2), 6.89 (2H, m, H_4+H_5, C_6H_4), 7.45 (2H, m, H_3+H_6, C_6H_4). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 13.80 (s, CH_3), 19.15 (s, CH_2), 30.95 (s, CH_2), 68.75 (s, OCH_2), 112.22, 116.57, 120.53, 133.74, 134.31, 160.87 (C_6H_4), 172.65 (CO). IR (ν, cm^{-1}) = 1597 (C=O), 3070 (N-H).

Synthesis of 3af. Compound **3af** was prepared using the same method than **3ac**, but starting from Ph_3P=NC(O)C_6H_5 **1a** (0.250 g, 0.655 mmol), $PdCl_2(NCMe)_2$ (16.8 mg, 0.065 mmol) and oxone® (0.806 g, 1.31 mmol) in ^{i}BuOH **2f** (15 mL) at 60 ºC. Compound **3af** was purified by column chromatography using silica as support and a mixture ethyl acetate/diethyl ether (4/1) as eluent, and obtained as a pale yellow solid. Obtained: 0.048 g, 0.245 mmol (37.4% yield). **3af** has been previously published, but its spectral data were not reported.[10] Due to this reason they are here included. ^{1}H NMR ($CDCl_3$): δ 0.99 (6H, d, CH_3, $^3J_{HH}$ = 6.8), 2.09 (1H, m, CH), 3.75 (2H, d, OCH_2, $^3J_{HH}$ = 6.4), 6.85-6.90 (2H, m, C_6H_4), 7.42-7.47 (2H, m, C_6H_4). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 19.13 (s, CH_3), 28.19 (s, CH), 75.20 (s, OCH_2), 112.25, 116.15, 120.54, 133.73, 134.29, 160.93 (C_6H_4). The signal due to C=O was not observed, in spite of long accumulation times. IR (ν, cm^{-1}) = 1597 (C=O), 3080 (N-H).

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Notes and references

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ARTICLE

Text (for Table of Contents)

The mild Pd-catalysed *ortho*-alkoxylation of benzamides, protected as keto-stabilised iminophosphoranes, with alcohols, is regioselective and tolerates different substituents and alcohols

Graphical Abstract (for Table of Contents)