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Catalyst-free P–C coupling reactions of halobenzoic acids and secondary phosphine oxides under microwave irradiation in water

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ABSTRACT

4-Bromo and 3-bromobenzoic acids along with 4-iodobenzoic acid underwent P–C coupling reactions with diarylphosphine oxides in the absence of any catalyst in water as the solvent under microwave irradiation. The phosphinoylbenzoic acids obtained were converted into the corresponding ethyl esters in yields of 59–82%.

A widely used method for the synthesis of arylphosphonates is the Hirao reaction involving the P–C coupling of bromoarenes and dialkyl phosphites in the presence of $Pd(PPh_3)_4$ as the catalyst and triethylamine as the base.[1,2] Subsequently, the reaction was extended to other aryl derivatives and different >P(O)H reagents including *H*-phosphinates and secondary phosphine oxides using Pd(0)-, Pd(II)- and Ni(II)-catalysts with mono- and bidentate P-ligands.[3,4]

It is a significant challenge to carry out the Hirao reaction under 'green' chemical conditions. The first step was taken when a catalytic amount of water was added to a somewhat related coupling reaction of dialkyl phosphites and substituted benzyl halides using $Pd(OAc)_2$/Xantphos and *N*,*N*-diisopropylethylamine in THF. The corresponding benzylphosphonates were obtained in 71–98% yields.[5] It was a valuable observation that the coupling of 4-iodotoluene and diethyl phosphite was quantitative in MeCN–H_2O (1:1) at 25 °C applying $Pd(PPh_2(m\text{-}C_6H_4SO_3M))_3$ (M = Na^+ or K^+) as the catalyst, and triethylamine as the base.[6] Next, the coupling of substituted aryl halides and diisopropyl phosphite was performed successfully in water (containing three molar equivalents of ^{i}PrOH) using a ferrocene-based palladacycle with a P- and an N-ligand, and applying KF at reflux temperature. One equivalent of tetrabutylammonium bromide was also present in the mixture as an additive and the yields of the arylphosphonates fell in the range of 53–94%.[7] The coupling of reactive diphenylphosphine oxide with aryl bromides was also described in water at 70 °C in the presence of $NiCl_2{\cdot}6H_2O$ as the catalyst and Zn along with 2,2′-bipyridine as the additives to afford aryl(diphenyl)phosphine oxides in yields of 78–97%.[8] A recent exciting development was that halobenzoic acids and diphenylphosphine oxide undergo P–C coupling in water at 180 °C under microwave (MW) irradiation in the presence of Pd/C as the catalyst, and K_2CO_3 as the base.[9] Interestingly, the authors of this communication found that the Hirao reaction of aryl bromides and different >P(O)H species, such as dialkyl phosphites and secondary phosphine oxides took place in the presence of P-ligand-free $Pd(OAc)_2$ under solvent-free and MW-assisted conditions.[10,11] Recently, we have aimed at the simplification of different catalytic systems under MW irradiation.[12,13] Thus, it was a challenge for us to try to elaborate a catalyst-free MW-assisted variation of the Hirao reaction in water as the solvent.

The first model reaction was the coupling of 4-bromobenzoic acid (**1A**) and diphenylphosphine oxide (**2a**) or di(4-methylphenyl)phosphine oxide (**2b**)[14–16] in water in the presence of three equivalents of K_2CO_3 at 180 °C under MW irradiation. It was necessary to carry out the P–C coupling reactions under a nitrogen atmosphere to avoid the oxidation of the secondary phosphine oxide reagents (**2a** and **2b**). For the two cases (1. **1A**+**2a**, and 2. **1A**+**2b**), the reaction times were 1 h and 3 h, respectively, and the products, which were prepared and identified as the ethyl esters **4a** and **4b**, were obtained in 78% and 73% yields, respectively, (Scheme 1, entries 1 and 2).[17,18] The esterification of the 4-phosphinoylbenzoic acids **3a** and **3b**, which had been isolated by precipitation,

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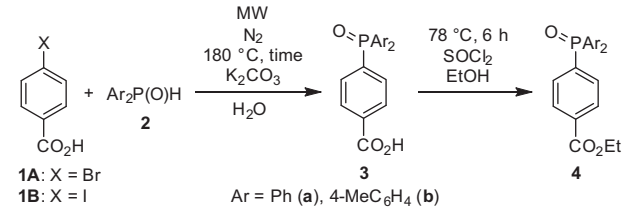
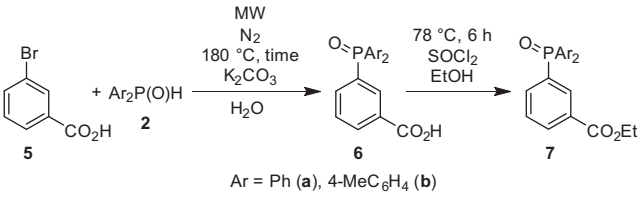


Entry	Aryl halide	P reagent	Time (h)	Yield of ester[a] (%)
1	**1A**	**2a**	1	78 (**4a**)
2	**1A**	**2b**	3	73 (**4b**)
3	**1B**	**2a**	1	82 (**4a**)
4	**1B**	**2b**	3	80 (**4b**)

[a] Regarding the transformation **1** → **4**.

Scheme 1. Reactions of 4-halobenzoic acids with diarylphosphine oxides.



Entry	P reagent	Time (h)	Yield of ester[a] (%)
1	**2a**	3	70 (**7a**)[b]
2	**2b**	6	59 (**7b**)[b]

[a] Regarding the transformation **5** → **7**.
[b] Benzoic acid was obtained as a by-product.

Scheme 2. Reaction of 3-bromobenzoic acid with diarylphosphine oxides.

was carried out using thionyl chloride in boiling ethanol. Starting from 4-iodobenzoic acid (**1B**), the outcomes were similar but the overall yields of the two-step procedure were somewhat higher. 4-Phosphinoylbenzoic acid esters **4a** and **4b** were prepared in yields of 82% and 80%, respectively (Scheme 1, entries 3 and 4).[17,18]

The reaction of 4-bromobenzoic acid (**1A**) and diphenyl-phosphine oxide (**2a**) was also attempted under conventional heating and similar conditions, but the desired P–C coupling reaction was reluctant and incomplete. After heating for three hours at 180 °C, the conversion was only 43%.

In the next stage, the analogous coupling reaction of 3-bromobenzoic acid (**5**) with diarylphosphine oxides **2a** and **2b** was investigated. Under similar conditions, longer reaction times (3 h and 6 h, respectively) were required,[17] and after the esterification of intermediates **6a** and **6b**, the corresponding 3-phosphinoylbenzoic acid esters **7a** and **7b** were obtained in 70% and 59% yields, respectively[18] (Scheme 2, entries 1 and 2). It is noted that the P–C couplings discussed took place in a homogeneous (water) medium. In the latter cases, a minor debromination side reaction also occurred under the conditions applied.

Finally, a mixed diarylphosphine oxide, phenyl-(4-methylphenyl)phosphine oxide (**8**), prepared by us for the first time,[14] was reacted with 4-iodobenzoic acid (**1B**) under similar conditions to those applied above. After the usual esterification of the intermediate **9**, the corresponding 4-phosphinoylbenzoic acid ester **10** was obtained in a yield of 62% (Scheme 3). The product **10** is a triarylphosphine oxide with three different aryl groups.

The intermediates, diarylphosphinoylbenzoic acids **3a**, **3b**, **6a**, **6b** and **9** were identified by ^{31}P NMR and IR spectroscopy and by HRMS, as shown in Table 1. The $\nu_{P=O}$ and $\nu_{C=O}$ stretching vibrations appeared at around 1180 cm^{-1} and 1684 cm^{-1}, respectively.

The phosphinoylbenzoic acid esters **4a**, **4b**, **7a**, **7b** and **10** were characterized by ^{31}P, ^{13}C and ^{1}H NMR spectroscopy, as well as by HRMS. With one exception (**4a**[19]), the triarylphosphine oxides **4**, **7** and **10** are new compounds.

In conclusion, an environmentally friendly catalyst-free and MW-assisted variation of the Hirao reaction is described, which allows the synthesis of new phosphinoylbenzoic acid derivatives in water.

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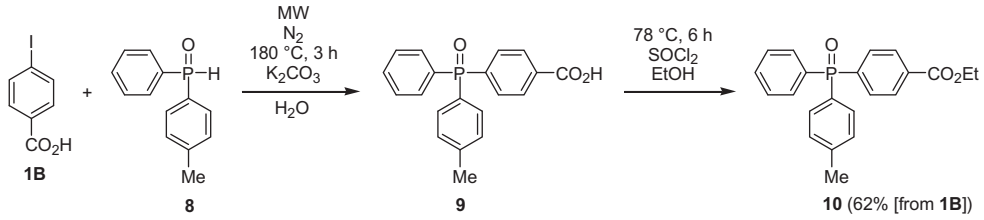

Scheme 3. The synthesis of triarylphosphine oxides with three different aryl groups.

Table 1
Selected spectral data for the diarylphosphinoylbenzoic acid intermediates **3a**, **3b**, **6a**, **6b** and **9**

Intermediate	^{31}P NMR (D_2O)[a]	δ_P (DMSO-d_6)	$[M+H]^+_{found}$	$[M+H]^+_{required}$	IR (cm^{-1})
3a	23.6	26.4[9]	323.0837	323.0832	760, 696, 1181, 1682
3b	23.6	26.5[9]	323.0844	323.0832	751, 694, 1180, 1687
6a	24.1	–	351.1154	351.1145	750, 704, ~1180, 1687
6b	24.0	–	351.1157	351.1145	751, 695, 1180, 1687
9	23.9	–	337.0997	337.0988	758, 695, 1179, 1680

[a] Obtained using a Bruker AV-300 spectrometer at 121.5 MHz.

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14. *General procedure for the synthesis of diarylphosphine oxides* ***2b*** *and* ***8****:* The Grignard reagent (20.0 mmol) formed from Mg (0.48 g, 20.0 mmol) and 4-bromotoluene (3.4 g, 20.0 mmol) in Et_2O (15 mL) was added dropwise to the >P(O)H reagent (diethyl phosphite: 0.9 mL, 6.7 mmol or ethyl phenyl-*H*-phosphinate: 2 mL, 13.3 mmol) in Et_2O (10 mL) at 0 °C. The resulting mixture was stirred at 26 °C for 1.5 h. The mixture was hydrolyzed with 10% HCl solution (20 mL) and the aqueous phase was extracted with Et_2O (2 × 50 mL). The combined organic phases were dried (Na_2SO_4). Evaporation of the solvent provided a residue that was purified by column chromatography using silica gel and 1% MeOH in CH_2Cl_2 as the eluent to give secondary phosphine oxides **2b** and **8**.
    *Di(4-methylphenyl)phosphine oxide (****2b****):* Yield: 61%; white crystals; mp.: 98–99 °C, mp[15]: 95–96 °C; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 20.7, δ_P ($CDCl_3$)[16] 21.2; HRMS: *m/z* $[M+H]^+$ = 231.0920, $C_{14}H_{16}OP$ requires 231.0933.
    *Phenyl-(4-methylphenyl)phosphine Oxide (****8****):* Yield: 42%; dense oil; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 21.9; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.5 (CH_3), 127.7 (d, *J* = 104.1 Hz, C1′)[a], 128.7 (d, *J* = 12.8 Hz, C2′)[b], 129.5 (d, *J* = 13.3 Hz, C2)[b], 130.3 (d, *J* = 103.9 Hz, C1)[a], 130.5 (d, *J* = 11.5 Hz, C3′)[b], 130.6 (d, *J* = 11.9 Hz, C3)[b], 132.3 (d, *J* = 2.8 Hz, C4′), 143.1 (d, *J* = 2.9 Hz, C4′),[a,b] tentative assignments; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.42 (s, 3H, CH_3), 7.28–7.77 (m, 9H, ArH), 8.06 (d, *J* = 480.6 Hz, 1H, PH); HRMS: *m/z* $[M+H]^+$ = 217.0776, $C_{13}H_{14}OP$ requires 217.0777.
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17. *General procedure for the reaction of halobenzoic acids* ***1A***, ***1B*** *and* ***5*** *and secondary phosphine oxides* ***2a***, ***2b*** *and* ***8****:* A mixture of a halobenzoic acid (0.50 mmol) [4-bromobenzoic acid or 3-bromobenzoic acid (0.10 g) or iodobenzoic acid (0.12 g)], the secondary phosphine oxide (0.50 mmol) [diphenylphosphine oxide (0.10 g), di(4-methylphenyl)phosphine oxide (0.12 g), phenyl-(4-methylphenyl)phosphine oxide (0.11 g)] and K_2CO_3 (0.21 g, 1.5 mmol) in degassed H_2O (2.5 mL) was irradiated under an N_2 atmosphere in a closed vial using a 300 W CEM Discover reactor (operating at 20–30 W) at 180 °C for the appropriate time (see Schemes 1–3). After cooling to 25 °C, H_2O (20 mL) was added to the mixture. A dilute (18%) HCl solution (ca. 1.9 mL) was added dropwise until pH 3–4. The tertiary phosphine oxides **3a**, **3b**, **6a**, **6b** and **9** were obtained as white precipitates and were filtered and dried under vacuum. Selected spectral data of the products **3a, 3b**, **6a**, **6b** and **9** are shown in Table 1. The diarylphosphinoylbenzoic acids **3a, 3b**, **6a**, **6b** and **9** were characterized as the corresponding ethyl esters. See next procedure.
18. *General procedure for the esterification of the diarylphosphinoylbenzoic acids* ***3a***, ***3b***, ***6a***, ***6b*** *and* ***9****:* 0.11 mL (1.5 mmol) of $SOCl_2$ was added slowly to a suspension of ca. 0.40–0.45 mmol of the phosphinoylbenzoic acid **3a, 3b**, **6a**, **6b** and **9** obtained above in 10 mL of EtOH. The solution was stirred under reflux until HCl formation was complete (~6 h). Evaporation of the solvent provided a residue that was purified by column chromatography (silica gel, 3% MeOH in CH_2Cl_2) to give products **4a, 4b**, **7a**, **7b** and **10** as dense oils.
    *Ethyl 4-(diphenylphosphinoyl)benzoate (****4a****):* ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 28.6, δ_P ($CDCl_3$)[19] 28.2; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.3 (CH_2CH_3), 61.5 (OCH_2), 128.7 (d, *J* = 12.2 Hz, C2′)[a], 129.4 (d, *J* = 12.2 Hz, C2)[b], 131.9 (d, *J* = 104.8 Hz, C1′), 132.1 (d, *J* = 10.0 Hz, C3′)[b], 132.2 (d, *J* = 10.1 Hz, C3)[b], 132.3 (d, *J* = 2.8 Hz, C4′), 133.6 (d, *J* = 2.8 Hz, C4), 137.5 (d, *J* = 100.9 Hz, C1), 165.8 (C=O),[a,b] tentative assignments; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.38 (t, 3H, *J* = 7.1 Hz, CH_2CH_3), 4.39 (q, 2H, *J* = 14.2 Hz, OCH_2), 7.80–7.31 (m, 12H, ArH), 7.95–8.18 (m, 2H, ArH); IR (neat) 694, 750, 1193, 1270, 1440, 1715 cm^{-1}; HRMS: *m/z* $[M+H]^+$ = 351.1145, $C_{21}H_{20}O_3P$ requires 351.1145.
    *Ethyl 4-[di(4-methylphenyl)phosphinoyl]benzoate (****4b****):* ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 28.7; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1 (CH_2CH_3), 21.5 (C4′-Me), 61.3 (OCH_2), 128.7 (d, *J* = 107.2 Hz, C1′), 129.1 (d, *J* = 12.0 Hz, C2)[a], 129.2 (d, *J* = 12.6 Hz, C2′)[b], 131.9 (d, *J* = 10.3 Hz, C3 and C3′)[a,b], 133.2 (d, *J* = 2.7 Hz, C4), 138.0 (d, *J* = 100.8 Hz, C1), 142.5 (d, *J* = 2.8 Hz, C4′), 165.7 (C=O),[a,b] tentative assignments; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.39 (t, 3H, *J* = 7.1 Hz, CH_2CH_3), 2.40 (s, 6H, C4′-CH_3), 4.39 (q, 2H, *J* = 14.1 Hz, OCH_2), 7.21–7.31 (m, 4H, ArH), 7.49–7.60 (m, 4H, ArH), 7.70–7.82 (m, 2H, ArH), 8.06–8.16 (m, 2H, ArH); IR (neat) 700, 757, 1197, 1270, 1438, 1720 cm^{-1}; HRMS: *m/z* $[M+H]^+$ = 379.1455, $C_{23}H_{24}O_3P$ requires 379.1458.
    *Ethyl 3-(diphenylphosphinoyl)benzoate (****7a****):* ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 28.7; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.2 (CH_2CH_3), 61.4 (OCH_2), 128.6 (d, *J* = 12.3 Hz, C2′)*, 130.9 (d, *J* = 12.0 Hz, C2), 131.97 (d, *J* = 104.7 Hz, C1′), 132.03 (d, *J* = 10.0 Hz, C3′)*, 132.2 (d, *J* = 2.8 Hz, C4′), 132.8 (d, *J* = 14.2 Hz, C6), 132.9 (d, *J* = 2.7 Hz, C4), 133.0 (d, *J* = 12.5 Hz, C5), 133.3 (d, *J* = 102.6 Hz, C1), 136.1 (d, *J* = 9.9 Hz, C3), 165.6 (C=O), *tentative assignments; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (t, 3H, *J* = 7.1 Hz, CH_2CH_3), 4.34 (q, 2H, *J* = 14.2 Hz, OCH_2), 7.41–7.73 (m, 11H, ArH), 7.80–7.94 (m, 1H, ArH), 8.21 (d, 1H, *J* = 7.6 Hz, ArH), 8.36 (d, 1H, *J* = 12.2 Hz, ArH); IR (neat) 690, 751, 1183, 1264, 1446, 1716 cm^{-1}; HRMS: *m/z* $[M+H]^+$ = 351.1156, $C_{21}H_{20}O_3P$ requires 351.1145.
    *Ethyl 3-[di(4-methylphenyl)phosphinoyl]benzoate (****7b****):* ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 28.7; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.2 (CH_2CH_3), 21.6 (C4′-Me), 61.3 (OCH_2), 128.5 (d, *J* = 11.6 Hz, C2), 128.9 (d, *J* = 107.4 Hz, C1′), 129.3 (d, *J* = 12.6 Hz, C2′)*, 130.8 (d, *J* = 11.9 Hz, C5), 132.0 (d, *J* = 10.3 Hz, C3′)*, 132.7 (d, *J* = 2.4 Hz, C4), 132.9 (d, *J* = 10.7 Hz, C6), 133.9 (d, *J* = 103.2 Hz, C1), 136.1 (d, *J* = 9.8 Hz, C3), 142.6 (d, *J* = 2.8 Hz, C4′), 165.7 (C=O), *tentative assignments; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (t, 3H, *J* = 7.1 Hz, CH_2CH_3), 2.40 (s, 6H, C4′-CH_3), 4.35 (q, 2H, *J* = 14.2 Hz, OCH_2), 7.20–7.31 (m, 5H, ArH), 7.48–7.60 (m, 5H, ArH), 8.20 (d, 1H, *J* = 7.7 Hz, ArH), 8.36 (d, 1H, *J* = 12.1 Hz, ArH); IR (neat) 697, 763, 1182, 1270, 1446, 1715 cm^{-1}; HRMS: *m/z* $[M+H]^+$ = 379.1470, $C_{23}H_{24}O_3P$ requires 379.1458.
    *Ethyl 4-[phenyl(4-methylphenyl)phosphinoyl]benzoate (****10****):* ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 28.8; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.2 (CH_2CH_3), 21.6 (C4′-Me), 61.4 (OCH_2), 128.4 (d, *J* = 103.9 Hz, C1″), 128.5 (d, *J* = 2.9 Hz, C4″), 128.6 (d, *J* = 12.2 Hz, C2″)[a], 129.3 (d, *J* = 12.1 Hz, C2′)[b], 129.4 (d, *J* = 12.7 Hz, C2)[c], 131.97 (d, *J* = 10.0 Hz, C3)[c], 132.03 (d, *J* = 10.1 Hz, C3′ and C3″)[a,b], 132.1 (d, *J* = 104.7 Hz, C1′), 133.4 (d, *J* = 2.8 Hz, C4), 137.7 (d, *J* = 100.9 Hz, C1), 142.8 (d, *J* = 2.8 Hz, C4′), 165.7 (C=O),[a–c] tentative assignments; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40 (t, 3H, *J* = 7.1 Hz, CH_2CH_3), 2.41 (s, 3H, C4′-CH_3), 4.40 (q, 2H, *J* = 14.0 Hz, OCH_2), 7.21–7.32 (m, 3H, ArH), 7.43–7.85 (m, 9H, ArH), 8.11 (d, 1H, *J* = 7.9 Hz, ArH); IR (neat) 695, 764, 1184, 1270, 1437, 1716 cm^{-1}; HRMS: *m/z* $[M+H]^+$ = 365.1310, $C_{22}H_{22}O_3P$ requires 365.1301.
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