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# Microwave-Assisted Palladium Acetate-Catalyzed C−P Cross-Coupling of Arylboronic Acids and >P(O)H Reagents in the Absence of the Usual Mono- and Bidentate P-Ligands: Mechanistic Insights

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**ABSTRACT:** A less-studied halogen-free variation of the Hirao reaction involving the coupling of arylboronic acids with >P(O)H reagents, such as diarylphosphine oxides, diethyl phosphite, and ethyl phenyl-*H*-phosphinate, was investigated in detail using Pd(OAc)$_2$ as the catalyst precursor and applying some excess of the P-reagent to supply the ligand via its trivalent tautomeric (>P−OH) form. The optimum conditions (1.2 equiv of the P-reagent, 135−150 °C, and air) were explored for the synthesis of diaryl-phenylphosphine oxides, aryl-diphenylphosphine oxides, diethyl arylphosphonates, ethyl diphenylphosphinate, and two bisphosphi-noyl derivatives. In the reaction of 4-chlorophenyl- or 3-chlorophenylboronic acid with Ph$_2$P(O)H, triphenylphosphine oxide was also formed as a byproduct. Theoretical calculations suggested that the catalytic cycle of the P−C coupling of PhB(OH)$_2$ with Ph$_2$P(O)H is different from that of the usual cross-coupling reactions. It comprises the addition of a phenyl anion and then the tautomeric form >P−OH of the >P(O)H reagent to the Pd$^{2+}$ catalyst complex. This is then followed by reductive elimination affording Ph$_3$PO that is accompanied with the conversion of Pd$^{2+}$ to Pd$^0$. There is a need for a subsequent stoichiometric oxidation of Pd(0) by molecular oxygen. The spontaneous formation of the self-assembling ligands around the Pd$^{2+}$ center from the >P(O)H reactant plays a crucial role in the mechanism and promotes the efficiency of the catalyst.
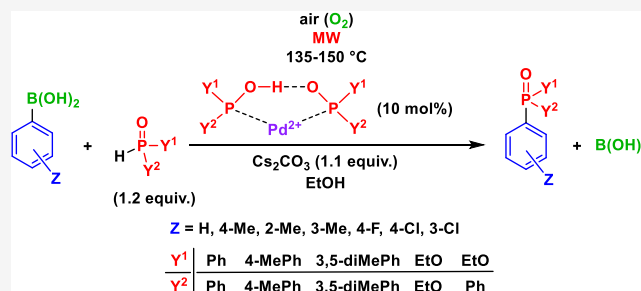
## INTRODUCTION

A heteroatomic variation of the cross-coupling reactions is the C−P coupling discovered by Hirao in 1980.[1,2] Since then, this new reaction between bromoarenes and dialkyl phosphites or secondary phosphine oxides providing dialkyl arylphospho-nates or tertiary phosphine oxides has become an important method.[3−5] The original Pd(PPh$_3$)$_4$ catalyst was replaced by Pd(II) salts used together with mono- and bidentate P-ligands, and the scope of the reaction components was extended.[6,7] The mechanism was evaluated.[6,8] Efforts were made to perform the P−C coupling under green chemical condi-tions.[9,10] Later on, Ni- and Cu-catalyzed versions were also elaborated.[3,4,11,12]

The Hirao reaction of arylboronic acids with different >P(O)H reagents is a less-studied field. The coupling of arylboronic acids with diphenylphosphine oxide, ethyl phenyl-*H*-phosphinate, and diethyl phosphite was best performed at 90 °C for 24 h applying Pd(OAc)$_2$/bis(diphenylphosphino)-butane (dppb) as the catalyst system, K$_2$CO$_3$ as the base in 1,4-dioxane as the solvent with the use of air as an oxidant. The corresponding tertiary phosphine oxides, phosphinates, and phosphonates were obtained in 48−94% yields after a reaction time of 24 h.[13] The second example for the Pd(II) salt-catalyzed case is the microwave (MW)-assisted reaction of

arylboronic acids with diethyl phosphite in the presence of Pd(OAc)$_2$/2,9-dimethyl-1,10-phenanthroline (dmphen) in di-methylformamide. After an irradiation at 100 °C for 20−30 min, the dialkyl arylphosphonates were obtained in yields of 51−90%. The couplings were promoted by the addition of *p*-benzoquinone as an oxidating agent.[14] A series of pyridylbor-onic acids also underwent the coupling reaction with dialkyl phosphites at 100 °C, in this case, using PdCl$_2$/PPh$_3$ as the catalyst precursor in *N*-,*N*-dimethylacetamide, in the presence of Ag$_2$O as an additive. After a 2 h reaction time, the yields fell in the range of 51−95%.[15] A NiBr$_2$/pyridine-catalyzed coupling of arylboronic acids and mainly diarylphosphine oxides carried out at 100 °C for 24 h in dichloroethane in the presence of K$_2$CO$_3$ furnished the corresponding triarylphos-phine oxides in variable 5−99% yields.[16] Last but not least, Cu$_2$O/1,10-phenantrolin (phen) and a special Cu(II) complex were also applied as catalysts at 26 °C for 24−72 h in the

**Table 1. Optimization of the Coupling Reaction between Phenylboronic Acid and Diphenylphosphine Oxide**

$$\text{PhB(OH)}_2 \; + \; \text{Ph}_2\text{P(O)H} \xrightarrow[\text{Solvent}]{\substack{\text{air} \\ \text{MW} \\ 135\ ^\circ\text{C, t} \\ \text{Pd(OAc)}_2\ (10\ \text{mol\%}) \\ \text{Base (1.1 equiv.)}}} \text{Ph}_3\text{PO}$$

(1.2 equiv.)                                                                    **1a**

| entry | base | solvent | $t$ (h) | conversion (%)[a] | product composition (%)[a,b] | | yield (%) of 1a |
|---|---|---|---|---|---|---|---|
| | | | | | **1a** | (EtO)Ph$_2$PO | |
| 1 | Cs$_2$CO$_3$ | MeCN | 2.5[c] | 80 | 80 | | |
| 2[c] | Cs$_2$CO$_3$ | EtOH | 1.5 | 100 | 95 | 5 | 83 |
| 3 | Cs$_2$CO$_3$ | dioxane | 1.5 | 100 | 100 | | 79 |
| 4 | K$_2$CO$_3$ | MeCN | 2.5[d] | 96 | 96 | | 78 |
| 5 | K$_2$CO$_3$ | EtOH | 1.5 | 100 | 97 | 3 | 80 |
| 6 | Et$_3$N | MeCN | 1.5 | 11 | 11 | | |
| 7 | Et$_3$N | EtOH | 1.5 | 22 | 22 | | |

[a]On the basis of relative $^{31}$P NMR intensities. [b]The average of two or three parallel experiments. [c]The coupling was also performed on a larger scale applying 1.0 mmol of PhB(OH)$_2$ and 1.2 mmol of Ph$_2$P(O)H. In this case, the yield of **1a** was 87%. [d]The extrapolated reaction time is 3 h.

**Table 2. Coupling Reaction between Phenylboronic Acid and Different >P(O)H Reagents**

| Y$^1$ | Ph | 4-MeC$_6$H$_4$ | 3,5-diMeC$_6$H$_3$ | EtO | EtO |
|---|---|---|---|---|---|
| Y$^2$ | Ph | 4-MeC$_6$H$_4$ | 3,5-diMeC$_6$H$_3$ | EtO | Ph |
| | **1a** | **1b** | **1c** | **1d** | **1e** |

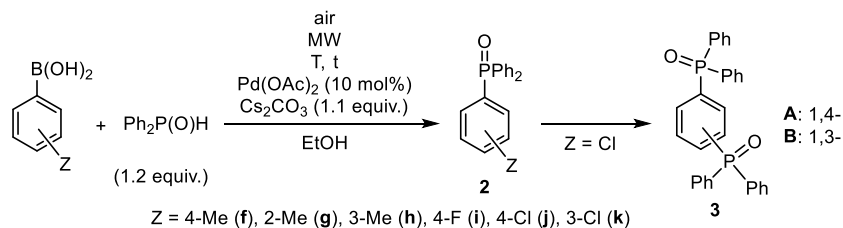| entry | Y$^1$, Y$^2$ | base | solvent | $t$ (h) | conversion (%)[a] | product composition (%)[a,b] | | yield (%) |
|---|---|---|---|---|---|---|---|---|
| | | | | | | **1** | Ar$_3$PO | |
| 1 | Ph | Cs$_2$CO$_3$ | EtOH | 1.5 | 100[b] | 95[c] | | 83 (**1a**) |
| 2 | Ph | K$_2$CO$_3$ | MeCN | 2.5 | 96 | 96 | | 78 (**1a**) |
| 3 | 4-MeC$_6$H$_4$ | Cs$_2$CO$_3$ | EtOH | 2 | 100 | 85 | 15 | 78 (**1b**) |
| 4 | 4-MeC$_6$H$_4$ | K$_2$CO$_3$ | MeCN | 3 | 100 | 81 | 19 | 72 (**1b**) |
| 5 | 3,5-diMeC$_6$H$_3$ | Cs$_2$CO$_3$ | EtOH | 2.5 | 100 | 88 | 12 | 74 (**1c**) |
| 6 | 3,5-diMeC$_6$H$_3$ | K$_2$CO$_3$ | MeCN | 4 | 100 | 79 | 21 | 56 (**1c**) |
| 7 | EtO | Cs$_2$CO$_3$ | EtOH | 4 | 100 | 100 | | 84 (**1d**) |
| 8 | EtO | Cs$_2$CO$_3$ | EtOH | 0.5[d] | 100 | 100 | | 82 (**1d**) |
| 9 | EtO | K$_2$CO$_3$ | MeCN | 4 | 63 | 63 | | |
| 10 | EtO | K$_2$CO$_3$ | MeCN | 2[d] | 100 | 100 | | 73 (**1d**) |
| 11 | EtO, Ph | Cs$_2$CO$_3$ | EtOH | 4 | 100 | 100 | | 82 (**1e**) |
| 12 | EtO, Ph | Cs$_2$CO$_3$ | EtOH | 0.5[d] | 100 | 91[e] | | 86 (**1e**) |

[a]On the basis of relative $^{31}$P NMR intensities. [b]The average of two or three parallel experiments. [c]5% of (EtO)Ph$_2$PO as the byproduct. [d]The temperature was 150 °C. [e]9% of (EtO)$_2$PhPO as the byproduct.

reaction under discussion to provide dialkyl arylphosphonates in variable yields (47−96%) using diisopropylethylamine in acetonitrile and KOAc in tetrahydrofuran, respectively.[17,18] The disadvantages of the coupling reactions with arylboronic acids include the need, in most cases, for bidentate P-ligands or N-ligands, variable yields, and often long reaction times. In the Pd(II)/(bidentate) phosphine-catalyzed cases, the involvement of an oxidizing agent (even air) may seem somewhat unusual, as in the P−C coupling of bromoarenes, there was no need for this actor.

In the past few years, we developed a P−C coupling, where it was not necessary to add the usual mono- or bidentate P-

ligands. Under MW conditions, the reaction between bromoarenes and >P(O)H reagents (dialkyl phosphites and secondary phosphine oxides) took place if the catalyst precursor, Pd(OAc)$_2$ was combined with some excess of the P-reagent.[19] The point was that the trivalent tautomeric form (>P−OH) of the >P(O)H species may act as a ligand to Pd(0). Upon applying 10% of the Pd(II) salt, there was a need for 30% extra quantity of the P-reagent. One equivalent of the >P(O)H species to the precursor ensured the Pd(II) → Pd(0) reduction, while the remaining two equivalent quantities served as the P-ligands to Pd(0).[20] The detailed mechanism for the "P-ligand-free" Hirao reaction was explored by high-

**Table 3. P−C Coupling of Substituted Arylboronic Acids with Diphenylphosphine Oxide**



Z = 4-Me (**f**), 2-Me (**g**), 3-Me (**h**), 4-F (**i**), 4-Cl (**j**), 3-Cl (**k**)

| entry | Z | T | t (h) | conversion (%)[a] | product composition (%)[a,b] | | | | yield (%) |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | 2 | 3 | (EtO)Ph$_2$PO | Ph$_3$PO (**1a**) | |
| 1 | H | 135 | 1.5 | 100[b] | 95 (**1a**) | | 5 | | 83 (**1a**) |
| 2 | 4-Me (**f**) | 135 | 1.5 | 100 | 81 | | 5 | 14 | 73 (**2f**) |
| 3 | 2-Me (**g**) | 135 | 1.5 | 100 | 71 | | 13 | 16 | 67 (**2g**) |
| 4 | 3-Me (**h**) | 135 | 1.5 | 100 | 87 | | 8 | 5 | 80 (**2h**) |
| 5 | 4-F (**i**) | 135 | 1.5 | 100 | 75 | | 10 | 15 | 70 (**2i**) |
| 6 | 4-Cl (**j**) | 135 | 1.5 | 100 | | 49 (**3A**) | | 51 | 23 (**3A**) |
| 7 | 4-Cl (**j**) | 90 | 4 | 100 | 46 | 5 | 11 | 38 | (**2j**)[c] |
| 8 | 4-Cl (**j**) | 90[d] | 4 | 77 | 12 | 41 (**3A**) | 6 | 18 | |
| 9 | 4-Cl (**j**) | 135[e] | 1 | 100 | | 23 (**3A**) | 5 | 72 | |
| 10 | 3-Cl (**k**) | 135 | 1.5 | 100 | | 53 (**3B**) | 6 | 41 | 25 (**3B**) |
| 11 | 3-Cl (**k**) | 90 | 4 | 96 | 35 | 22 (**3B**) | 11 | 28 | (**2k**)[f] |
| 12 | 3-Cl (**k**) | 90[c] | 22 | 100 | 33 | 44 (**3B**) | 4 | 19 | |

[a]On the basis of relative $^{31}$P NMR intensities of the P-components. [b]The average of two or three parallel experiments. [c]$^{31}$P NMR (CDCl$_3$) δ 28.5, $δ_P$ lit.[23] (CDCl$_3$) 28.2; HRMS (m/z): calcd for C$_{18}$H$_{15}$OPCl [M + H]$^+$, 313.0549; found, 313.0542. [d]On conventional heating. [e]2.4 equiv of Ph$_2$P(O)H was used. [f]$^{31}$P NMR (CDCl$_3$) δ 28.1, $δ_P$ lit.[24] (CDCl$_3$) 28.1; HRMS (m/z): calcd for C$_{18}$H$_{15}$OPCl [M + H]$^+$, 313.0549; found, 313.0538.

level quantum chemical calculations.[20,21] It was found that the rate-determining step is the reagent insertion into the Pd complex or the Pd−C bond formation that may be promoted by MW assistance. Our procedure meant a green approach, as there was no need to add the usual expensive P-ligands; hence, cost and environmental burden can be saved. Regarding atomic efficiency, starting from arylboronic acids means an advantage over the variation applying bromoarenes, not speaking about the fact that the former protocol is halogen-free. It was a challenge for us to develop a new protocol combining the halogen-free option with our MW-assisted method lacking the use of the usual P-ligands. It was another challenge to justify the need for an oxidizing agent and to evaluate the mechanism.

## RESULTS AND DISCUSSION

**Preparative Results.** The coupling of phenylboronic acid with diphenylphosphine oxide was chosen as the basic model of the MW-assisted Pd-catalyzed process. 10 mol % Pd(OAc)$_2$ was applied as the catalyst precursor at 135 °C using different bases in a quantity of 1.1 equiv and acetonitrile or ethanol as the solvent. The P-reagent was measured in a 1.2 equiv quantity in order to provide the two Ph$_2$POH ligands. We worked at aerobic conditions (Table 1). The crude reaction mixtures were analyzed by $^{31}$P NMR and liquid chromatography−mass spectrometry (LC−MS). Performing the reaction in the presence of Cs$_2$CO$_3$ in acetonitrile, after a 2.5 h irradiation the conversion was 80% (Table 1, entry 1). The next run carried out in ethanol was complete after 1.5 h (Table 1, entry 2). In this case, 5% of ethyl diphenylphosphinate could be detected as a byproduct. 1,4-Dioxane was also a suitable solvent under similar conditions (Table 1, entry 3). Changing for K$_2$CO$_3$, a treatment at 135 °C for 2.5 h in acetonitrile also led to almost quantitative (96%) conversion (Table 1, entry 4). However, the accomplishment in ethanol was more efficient, as

required a shorter irradiation time of 1.5 h (Table 1, entry 5). Only 3% of (EtO)Ph$_2$PO contaminated the product (**1a**). The use of triethylamine as the base led, after a treatment of 1.5 h, in both solvents to low (11/22%) conversions (Table 1, entries 6 and 7). From the best experiments (marked by entries 2−4), triphenylphosphine oxide (**1a**) was obtained in 78−81% yields after flash column chromatography. Under an inert atmosphere, the P−C coupling did not take place.

In general, the couplings were performed using 0.41 mmol of the phenylboronic acid. Carrying out the reaction on a 1.0 mmol scale, the yield of Ph$_3$PO was 87% (footnote "c" of Table 1/entry 2). As a comparison, 10% Pd(PPh$_3$)$_4$ was also tested in the coupling reaction of phenylboronic acid with Ph$_2$P(O)H at 135 °C for 1.5 h using 1.1 equiv of Cs$_2$CO$_3$ in ethanol. In this case, the reaction was not entirely clear-cut, and the yield of Ph$_3$PO was 65%.

In the next series of experiments, the reaction of phenylboronic acid with different >P(O)H reagents was investigated at 135 °C applying 10 mol % Pd(OAc)$_2$ as the catalyst precursor. The base/solvent combinations included Cs$_2$CO$_3$/EtOH and K$_2$CO$_3$/MeCN (Table 2). The coupling with bis(4-methylphenyl)phosphine oxide was somewhat slower than that with Ph$_2$P(O)H, no matter if it was carried out using Cs$_2$CO$_3$ in EtOH or K$_2$CO$_3$ in MeCN (Table 2, entries 3 and 4 vs entries 1 and 2). After an irradiation of 2 and 3 h, respectively, the conversion was complete. Beyond the 85/81% proportion of the expected bis(4-methylphenyl)-phenylphosphine oxide (**1b**), there was 15/19% of tris(4-methylphenyl)phosphine oxide as the byproduct (Table 2, entries 3 and 4). A similar situation was observed, when bis(3,5-dimetylphenyl)-phosphine oxide was the reagent; however, in this instance, the coupling became even slower, as the complete conversion required a reaction time of 2.5 and 4 h, respectively (Table 2, entries 5 and 6). Diaryl-phenylphosphine oxide **1c** was formed

in 88 and 79%, respectively. The corresponding tris(3,5-dimethylphenyl)phosphine oxide was present in the mixture as a minor (12/21%) byproduct. From the best experiments, the diaryl-phenylphosphine oxides **1a−c** were isolated in yields of 74−83% after chromatography. Changing for diethyl phosphite, the coupling with phenylboronic acid was slower at 135 °C, as the completion took 4 h (Table 2, entry 7). However, at 150 °C, an irradiation of 0.5 h was enough (Table 2, entry 8). In both cases, the reaction was clear-cut, and diethyl phenylphosphonate (**1d**) was obtained in 84/82% yield after purification. The combination of $K_2CO_3$/MeCN was, in this case, less efficient: after an irradiation at 135 °C for 4 h, the conversion was only 63% (Table 2, entry 9). However, at 150 °C/2 h, phosphonate **1d** was the only product prepared in 73% yield (Table 2, entry 10). The next >P(O)H reagent, ethyl phenyl-*H*-phosphinate behaved similarly as $(EtO)_2P(O)H$, and complete conversion could be attained after 4 h at 135 °C or 0.5 h at 150 °C (Table 2, entries 11 and 12). In the latter instance, 9% of $(EtO)_2PhPO$ also appeared in the crude mixture. Ethyl diphenylphosphinate (**1e**) was isolated in 82/86% yields.

In the next round, $Ph_2P(O)H$ was reacted with a series of arylboronic acids, in the first approach, under the conditions applied above using $Cs_2CO_3$ in EtOH (Table 3). The coupling of 4-Me, 2-Me, 3-Me, and even the 4-F-substituted phenylboronic acids took place similarly as that with the unsubstituted $PhB(OH)_2$. Complete conversions were attained after an irradiation of 1.5 h at 135 °C. The proportion of the expected products (**2f−i**) was 71−87%, while that of the $(EtO)Ph_2PO$ was 5−13%. Compounds **2f−i** were prepared in 67−80% yield (Table 3, entries 2−5). It was surprising that the similar reaction of 4-chlorophenylboronic acid with 1.2 equiv of $Ph_2P(O)H$ at 135 °C/1.5 h afforded 1,4-bis-(diphenylphosphinoyl)benzene **3A**. The crude mixture contained 49% of bisphosphinoyl compound **3A** and 51% of $Ph_3PO$ (Table 3, entry 6). There was no expected 4-chlorophenyl-diphenylphosphine oxide **2j** in the mixture. Product **3A** was isolated by chromatography in a yield of 23%. To promote the formation of the phosphinoyl-chlorobenzene **2j**, the coupling was performed at a lower temperature of 90 °C for 4 h. Sure enough, the mixture comprised 46% of the monophosphinoyl product **2j**, 5% of bisphosphinoyl **3A**, 11% of $(EtO)Ph_2PO$, and 38% of $Ph_3PO$ formed probably by dechlorination of 4-chlorophenyl-diphenylphosphine oxide (**2j**) (Table 3, entry 7). The small quantity of bisphosphinoyl compound **3A** among the components referred to the crucial role of temperature on the selectivity toward the mono- and bisphosphinoylated products (**2j** and **3A**). Repeating the previous P−C coupling on conventional heating at 90 °C/4 h, the conversion remained incomplete (77%), and the proportion of species **2j**, **3A**, and $Ph_3PO$ was 12, 41, and 18%, respectively, suggesting that the competitive dechlorination of 4-chlorophenyl-diphenylphosphine oxide (**2j**) was suppressed, and hence, more bis($Ph_2P(O)$) product (**3A**) could be formed (Table 3, entry 8). Returning to the result of the experiment marked by Table 3, entry 6, the low yield of 23% of the selective phosphinoylation may be explained by the fact that the 1.2 equiv quantity of $Ph_2P(O)H$ was not enough. Considering that a quantitative bisphosphinoylation would require 2.4 equiv of $Ph_2P(O)H$, an experiment was carried out using this higher amount of the P-reactant. However, under such conditions, the proportion of bis-product **3A** was not

increased, and the excess of $Ph_2P(O)H$ was involved in side reactions. In respect of the 3-chlorophenylboronic acid, the outcome of the P−C coupling with $Ph_2P(O)H$ was similar to the reaction of the 4-chlorophenyl reagent. After an irradiation at 135 °C for 1.5 h, only 53% of bisphosphinoyl derivative **3B**, 6% of $(EtO)Ph_2PO$, and 41% of $Ph_3PO$ were present (Table 3, entry 10). The major component (**3B**) was isolated in a yield of 25%. Repeating the Hirao reaction at 90 °C for 4 h, the monophosphinoyl compound **2k** was also present in 35%, beyond the 22% proportion of bis derivative **3B** (Table 3, entry 11), and hence, the significant effect of the temperature was confirmed. In the thermal variation carried out, this occasion at 90 °C for 22 h, the proportion of 1,3-bis(diphenylphosphinoyl)benzene (**3B**) was increased to 44% (Table 3, entry 12). It can be noted that on MW irradiation, the statistically occurring local overheatings[22] may cause the more intensive dechlorination of the primarily formed chlorophenyl-diphenylphosphine oxides (**2j** and **2k**).

Finally, the substituted arylboronic acids were reacted with diethyl phosphite measured in a 1.2 equiv quantity using $Cs_2CO_3$ as the base and EtOH as the solvent (Table 4). The

**Table 4. Hirao Reaction between Substituted Arylboronic Acids and Diethyl Phosphite**



Z = H (**1d**), 4-Me (**f**), 2-Me (**g**), 3-Me (**h**), 4-F (**i**), 4-Cl (**j**), 3-Cl (**k**)

| entry | Z | conversion (%)[a] | proportion of 4 (%)[a,b] | yield (%) |
|---|---|---|---|---|
| 1 | H | 100 | 95 | 83 (**1d**) |
| 2 | 4-Me | 100 | 100 | 77 (**4f**) |
| 3 | 2-Me | 100 | 100 | 78 (**4g**) |
| 4 | 3-Me | 100 | 100 | 80 (**4h**) |
| 5 | 4-F | 100 | 100 | 77 (**4i**) |
| 6 | 4-Cl | 100[c] | 81 | 66 (**4j**) |
| 7 | 3-Cl | 100[d] | 84 | 71 (**4k**) |

[a]On the basis of relative $^{31}P$ NMR intensities. [b]The average of two or three parallel experiments. [c]19% of $(EtO)_2PhPO$ as the byproduct. [d]16% of $(EtO)_2PhPO$ as the byproduct.

couplings with 4-MePh-, 2-MePh-, 3-MePh-, and 4-FPh-boronic acids were efficient on irradiation at 150 °C for 30 min. The diethyl arylphosphonates (**1d** and **4f−i**) were isolated in yields of 77−83% (Table 4, entries 1−7). The similar reactions of the 4-ClPh- and 3-ClPh-boronic acids carried out under similar conditions were accompanied by the formation of 19% and 16% of $(EtO)_2PhPO$ (**1d**), respectively, and the expected products **4j** and **4k** could be obtained in 66/71% yields. The reductive dechlorination was a side reaction also in this case.

The diaryl-phenylphosphine oxides (**1a−c**), aryl-diphenylphosphine oxides (**2f−i**), diethyl arylphosphonates (**1d**, **4f−k**), ethyl diphenylphosphinate (**1e**), and bisphosphinoyl derivatives **3A** and **3B**, all together 17 compounds, were prepared by the method developed, and they were fully characterized by $^{31}P$, $^{13}C$ and $^{1}H$ NMR, as well as HRMS. The resulting phosphine oxides and related compounds may be utilized as P-ligands after deoxygenation.

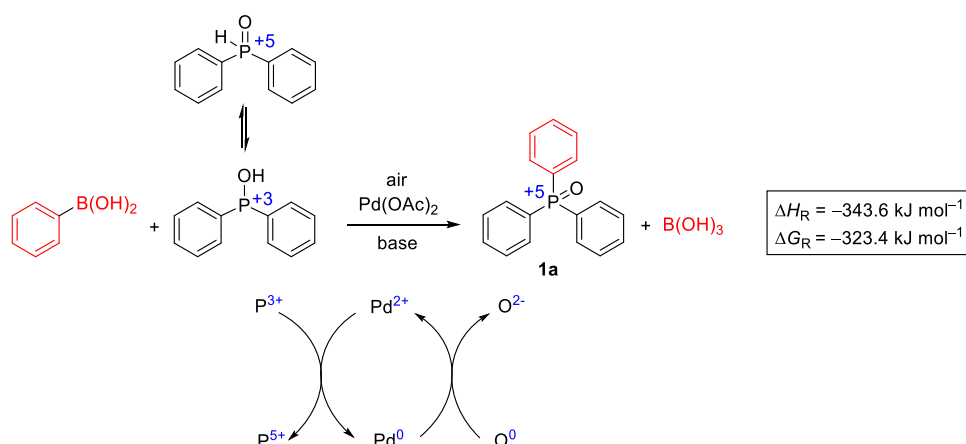**Figure 1.** Overall transformation and reaction enthalpy ($\Delta H_R$), as well as Gibbs free energy ($\Delta G_R$) for the Hirao reaction of $Ph_2P(O)H$ with phenylboronic acid.



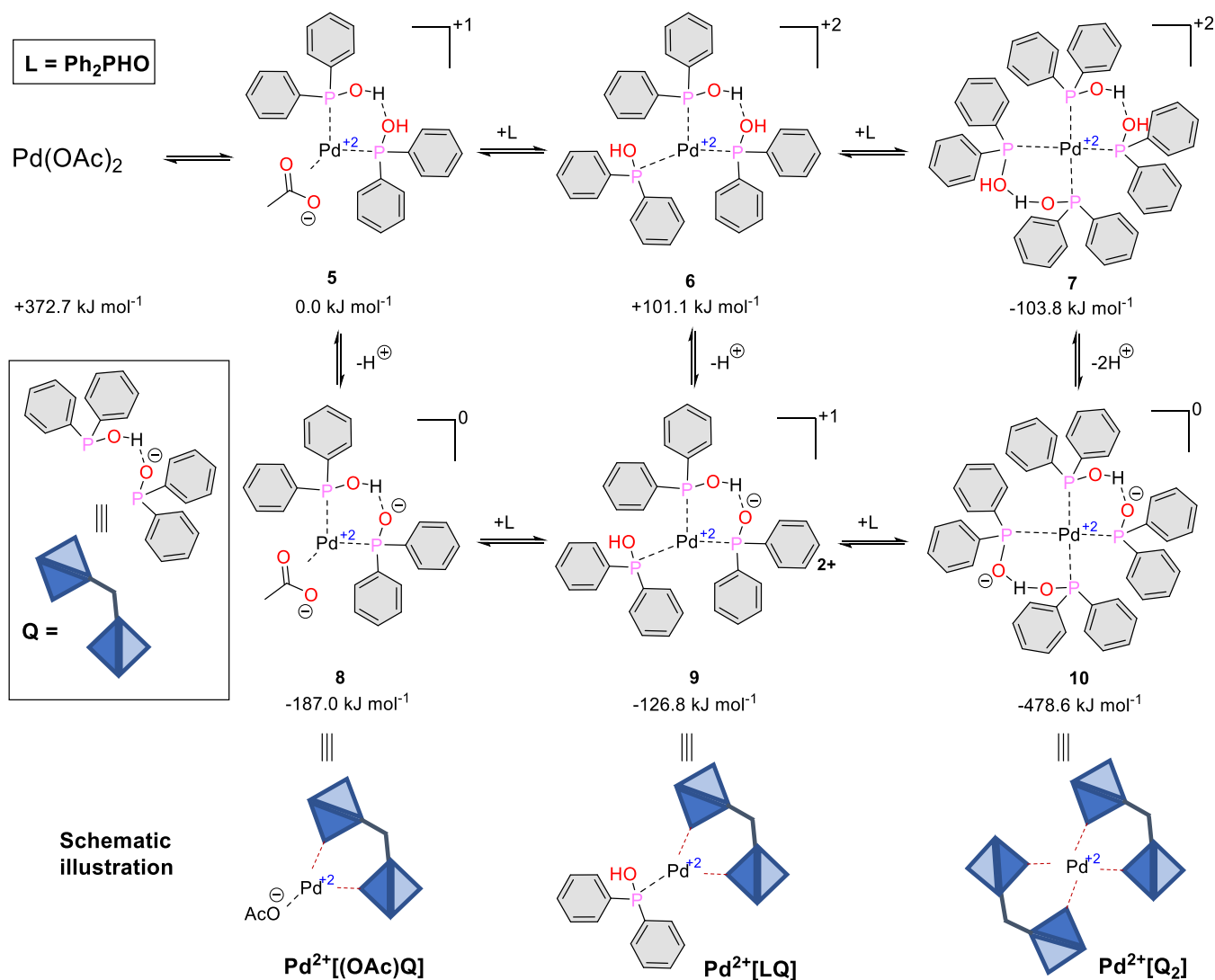**Figure 2.** Equilibrium system of complexes formed from $Pd^{2+}$ and $Ph_2P(O)H$.

**Theoretical Calculations.** There are only a few examples in the literature for Hirao reactions starting from arylboronic acids. There is no detailed mechanistic study for this version of the P–C coupling, and only a putative cycle was described.[13] However, it occurred that an oxidant is needed to promote the

reaction.[13–15] Looking at the overall reaction, the +3 oxidation number of the P atom in the tautomeric form of diphenylphosphine oxide is increased to +5 in the product triphenylphosphine oxide (1a). At the same time, the oxidation numbers of the boron and carbon atoms of the boronic acid
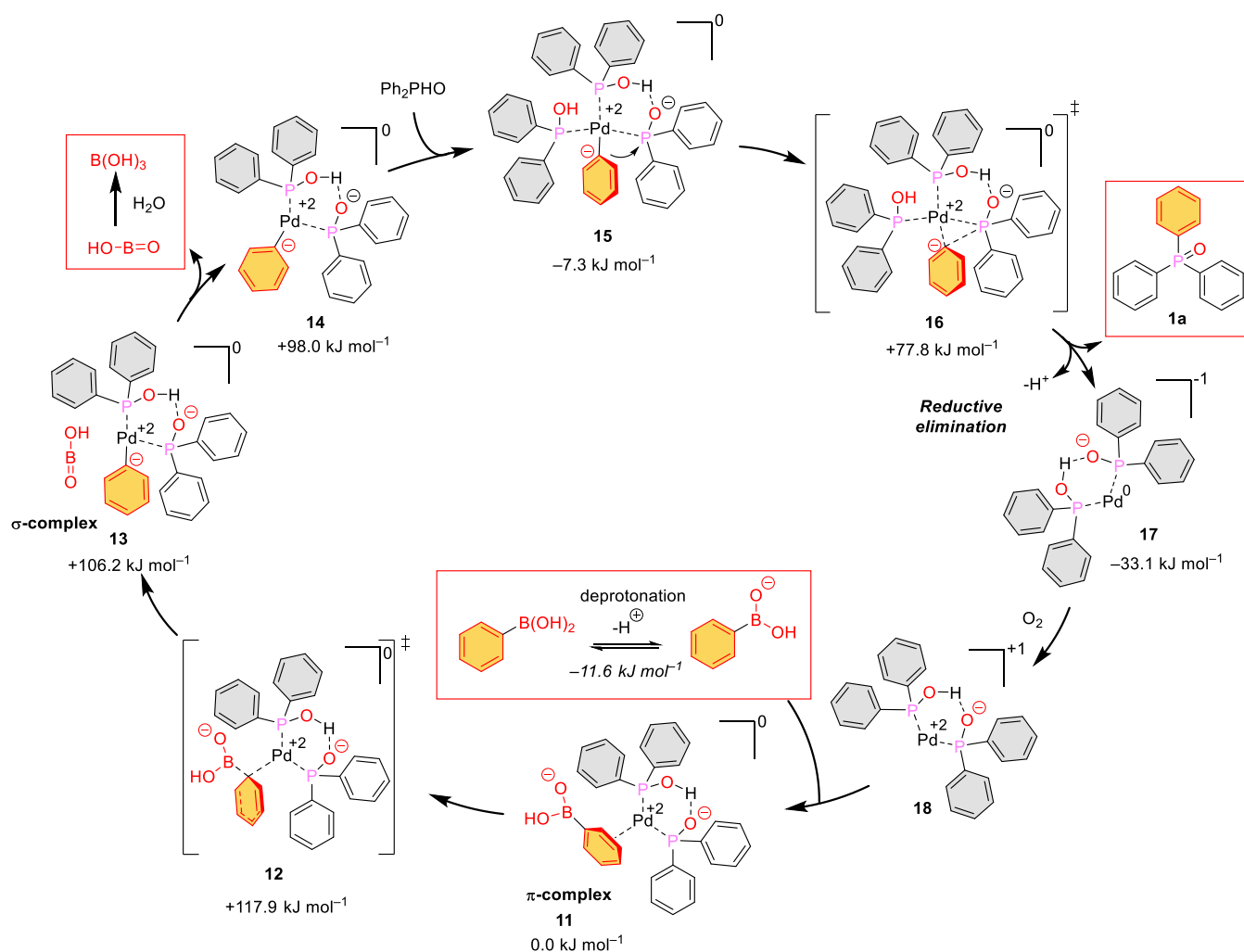
**Figure 3.** Formation of the desired triphenylphosphine oxide (**1a**) via a Pd-catalyzed reaction cycle.
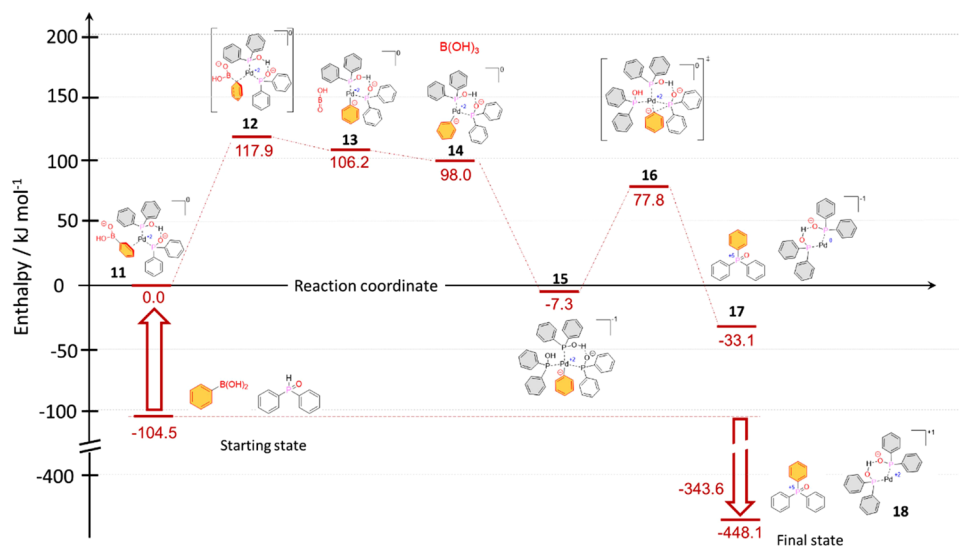


**Figure 4.** Enthalpy diagram for the Pd(OAc)$_2$-catalyzed P−C coupling reaction of phenylboronic acid and diphenylphosphine oxide.

remains unchanged. The main process is exothermic (Figure 1). We confirm that during the course of the reaction, Pd$^{2+}$ is reduced to Pd$^0$ that is then oxidized back by the oxygen present. The O$_2$ is reduced from the state 0 to −2 during the transformation.

First, we explored a complex equilibrium of Pd(OAc)$_2$ in the presence of excess of Ph$_2$P(O)H as the ligand (L), including two-, three-, and tetraligations to afford species **5**, **6**, and **7**, respectively. The tautomeric form Ph$_2$POH of Ph$_2$P(O)H is able to organize a strong hydrogen bond net around the Pd$^{2+}$.
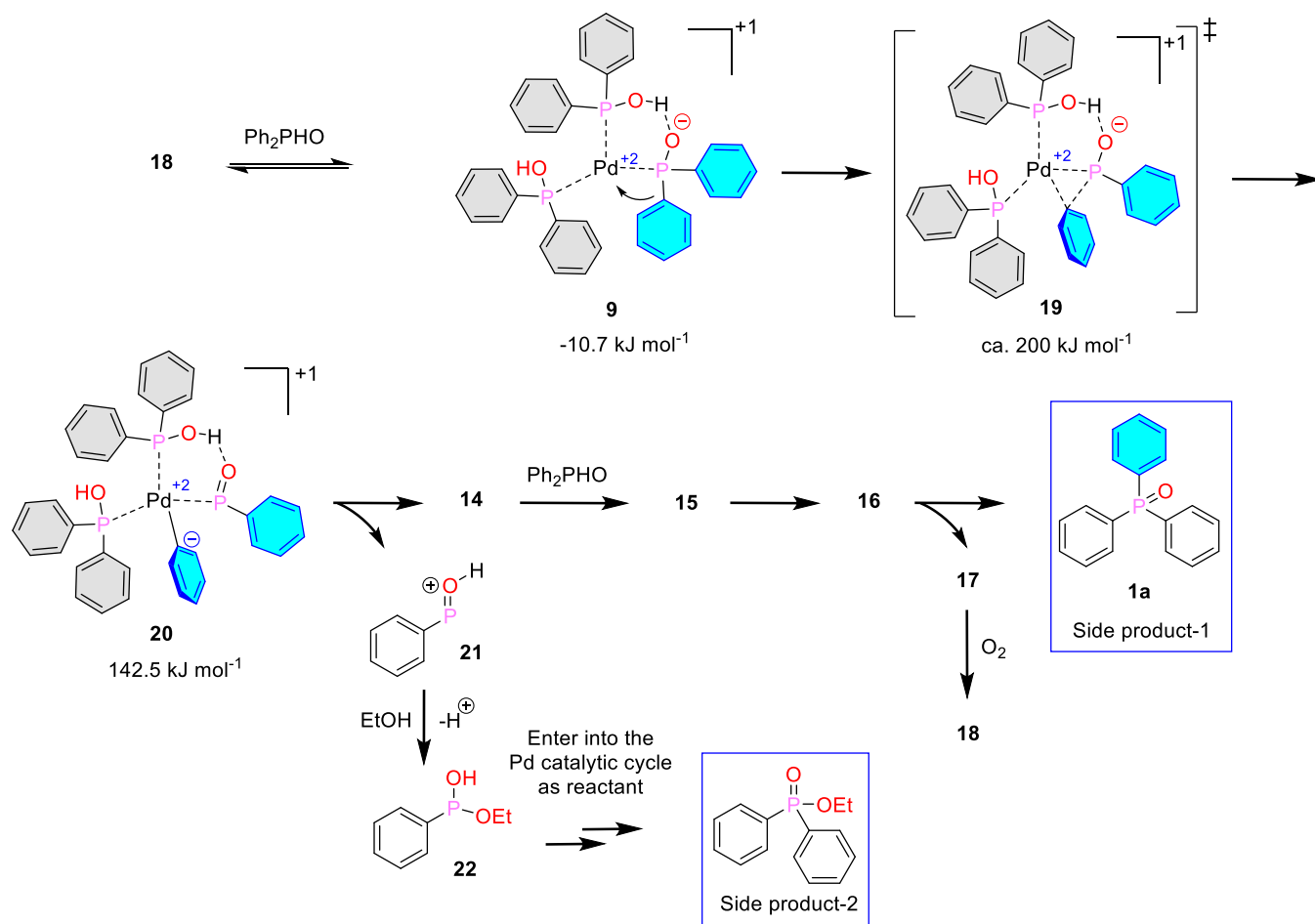
**Figure 5.** Proposed route for the formation of the triphenylphosphine oxide (**1a**) and ethyl diphenylphosphine oxide side products.

An inorganic base (e.g., $K_2CO_3$) may deprotonate one or two $Ph_2POH$ units to provide complexes **8**, **9**, and **10**, and as a consequence, the bonded $Ph_2POH$ pairs are stabilized, forming one (as in **8** or **9**) or two (as in **10**) quasi bidentate ligands (Figure 2). This spontaneous arrangement around the $Pd^{2+}$ ion may be considered, as if a self-assembling bidentate P-ligand or two bidentate P-ligands were (indicated as Q; blue diamonds) around the central $Pd^{2+}$ ion. Formation of the tetraligated $Pd^{2+}$ complex (**10**) is the most favorable in the series. This quasi bidentate anionic ligands activate the $Pd^{2+}$ center for the coupling reaction.

Then, we studied the catalytic cycle (Figure 3). In the first step, the boronic acid is deprotonated by the base present. Then, a weak $\pi$-complex (**6**) is formed between the $Pd^{2+}$ center of the catalyst complex and the aryl ring of the boronic acid anion ($\Delta H = -11.6$ kJ mol$^{-1}$). The $\pi$-complex (**11**) is transformed to the $\sigma$-complex (**13**) via a well-determined TS (**12**) with a $+117.9$ kJ mol$^{-1}$ enthalpy gap, which can be considered as a moderate barrier at elevated reaction temperature. The resulting $\sigma$-complex with an aryl anion (**13**) is of a high enthalpy content (106.2 kJ mol$^{-1}$). The elimination of metaboric acid (HOBO) is favorable, but the entry of an additional $Ph_2POH$ ligand leading to complex **15** with an enthalpy of $-7.3$ kJ mol$^{-1}$ is the real driving force. In the next step, the aryl anion is transferred from the central $Pd^{2+}$ to the P atom of the adjacent ligand via TS **16** with a lower enthalpy content of 77.8 kJ mol$^{-1}$ yielding the final tiphenylphosphine oxide (**1a**). During the reductive elimi-

nation step, the $Pd^{2+}$ is converted to $Pd^0$. Finally, the $Pd^0$ is regenerated to $Pd^{2+}$ by reaction with the $O_2$ of air. Then, the catalytic cycle may start again. The enthalpy diagram for the P−C coupling under discussion can be seen in Figure 4. The suggested mechanism comprises two steps (involving transition states **12** and **16**), which have impact on the overall reaction rate. As the first step leading to transition state **12** exhibits the higher enthalpy barrier, the route via species **12** is the rate-determining step. The overall reaction enthalpy follows a slightly exothermic run until the formation of the triphenylphosphine oxide (**1a**) that is connected with the elimination of $Pd^0$ complex **17**. However, the subsequent reoxidation of $Pd^0$ complex **17** to $Pd^{2+}$ catalyst **18** with the oxygen of air is rather exothermic, making the "quasi" catalytic process irreversible.

During the P−C coupling of $Ph_2P(O)H$ and arylboronic acids, a significant amount of triphenylphosphine oxide (**1a**) was also formed beside the expected aryl-diphenylphosphine oxide (**2f−k**) as discussed above (Table 3). In the case of 4-chlorophenyl- and 3-chlorophenylboronic acid, the dehalogenation by the Pd catalyst may also be a reasonable side reaction; however, for the 4-, 2- and 3-methylphenyl- and 4-fluorophenylboronic acid derivatives, the question arises how the triphenylphosphine oxide (**1a**) byproduct may be formed. Well, catalyst complex **18** may take up a $Ph_2POH$ ligand to give complex **9** (Figure 5). Migration of the phenyl ring from the $Pd^{2+}$ to the adjacent P atom via transition state **19** leads to key intermediate **20**, which then enters into the previously

discussed catalytic process, yielding triphenylphosphine oxide (**1a**) without the involvement of the arylboronic acid. The activation enthalpy for the **9 → 20** transformation is *ca* 200 kJ mol$^{-1}$ that is significantly higher than the activation barrier of the rate-determining step of the main reaction (117.9 kJ mol$^{-1}$). For this, the side reaction remains a minor component. The other byproduct, Ph$_2$P(O)OEt may be formed by the P–C coupling of Ph(OEt)(OH) (**22**) with Ph$_2$P(O)H. Species **22** is the result of the interaction of intermediate **21** and ethanol.

## CONCLUSIONS

In summary, the less applied, halogene-free Hirao reaction of arylboronic acids and a series of >P(O)H reagents, such as diarylphosphine oxides, diethyl phosphite, and ethyl phenyl-*H*-phosphinate, was studied in detail. Another green aspect was that not traditional (cost-meaning and environment-burdening) mono- or bidante P-ligands were used to serve the P-ligand to the Pd(OAc)$_2$ precursor (10%) but the excess (20%) of the >P(O)H reagent via its >P–OH trivalent tautomer form. MW assistance enhanced the P–C couplings that were optimized for the different substituted cases. Theoretical calculations supported that there is no oxidative addition step, as the primary Pd$^{2+}$/>P–OH···$^-$O–P< complex remains unchanged during the addition of the aryl anion and the addition of the tautomer form of the P-reagent. In the last reductive elimination step, the central Pd$^{2+}$ ion of the catalyst is reduced to Pd$^0$. For this, it is necessary to apply a stoichiometric oxidant, that is, in our case, air. The ligation of Pd$^{2+}$ with two >P(O)H units that form a dimer-like associate enhances the reactivity of the central Pd$^{2+}$ in complexation with the aryl anion. Formation of the typical byproducts, e.g., (EtO)Ph$_2$PO and Ph$_3$PO, the latter formed also by dechlorination, was also explained.

## EXPERIMENTAL SECTION

**General Information.** The reactions were carried out in a CEM Discover Model SP (300 W) focused microwave reactor (CEM Microwave Technology Ltd., Buckingham, U.K.) equipped with a stirrer and a pressure controller using 80–100 W irradiation under isothermal conditions. The reaction mixtures were irradiated in sealed glass vessels (with a volume of 10 mL) available from the supplier of CEM. The reaction temperature was monitored by an external IR sensor.

The $^{31}$P, $^{13}$C, and $^{1}$H NMR spectra were taken on a Bruker Avance 300/Avance 500 spectrometer (Rheinstetten, Germany) operating at 121.5/202.4, 75.5/125.7, and 300/500 MHz, respectively, in CDCl$_3$ solution. The $^{31}$P chemical shifts are downfield relative to H$_3$PO$_4$, while the $^{13}$C and $^{1}$H chemical shifts are downfield relative to TMS. The couplings are given in Hz. The exact mass measurements were performed using an Agilent 6545 Q-TOF mass spectrometer (Santa Clara, CA) in high-resolution, positive electrospray mode. The melting points of products **1a**, **1b**, **1c**, **2f**, **2g**, **2h**, **2i**, and **3A** were determined using a Setaram differential scanning calorimetry 92 device.

**General Procedure for the P–C Coupling of Phenylboronic Acid and >P(O)H Reagents (Table 2, Entries 1, 3, 5, 8, and 12).** To a MW glass vessel were added 1 mL of ethanol, 0.038 mmol (0.0085 g) of Pd(OAc)$_2$, 0.41 mmol (0.050 g) of phenylboronic acid, 0.49 mmol of diarylphosphine oxide [diphenylphosphine oxide: 0.10 g, bis(4-methylphenyl)phosphine oxide: 0.11 g, bis(3,5-dimethylphenyl)phosphine oxide: 0.13 g], 0.49 mmol (0.063 mL) of diethyl phosphite, or 0.49 mmol (0.074 mL) of ethyl phenyl phosphinate, and 0.45 mmol (0.15 g) of cesium carbonate. Then, the vial was closed and irradiated in the MW reactor isothermally at 135–150 °C for 0.5–2.5 h (Table 2, entries 1, 3, 5, 8, and 12). The

reaction mixture was diluted with 3 mL of EtOH, filtrated, and the residue obtained after evaporation of the filtrate was filtered through a thin (2–3 cm) layer of silica gel using ethyl acetate as the eluant. The crude mixture was analyzed by $^{31}$P NMR spectroscopy. Then, if the sample was relevant, it was purified further by column chromatography (silica gel, ethyl acetate–hexane 1:1 as the eluant) to afford products **1a–e**.

This procedure was repeated on a larger scale starting from 1.0 mmol (0.12 g) of phenylboronic acid, 1.2 mmol (0.24 g) of diphenylphosphine oxide, 1.1 mmol (0.36 g) of Cs$_2$CO$_3$, 0.10 mmol (0.022 g) of Pd(OAc)$_2$ and 3.5 ml of ethanol. After an irradiation at 135 °C for 1.5 h, the work-up was similar as above to furnish 0.24 g (87%) of Ph$_3$PO.

**Following Compounds Were Thus Prepared.** *Triphenylphosphine Oxide (1a) (Table 2, Entry 1).* Eluant: ethyl acetate–hexane 1:1; Yield: 0.087 g (83%) obtained as white crystals; mp. 156–157 °C, mp lit.[25] 156.6–157.4 °C; $^{31}$P{$^1$H} NMR (121.5 MHz, CDCl$_3$) δ 29.1, δ$_P$ lit.[25] (162 MHz, CDCl$_3$) 29.5; $^{13}$C{$^1$H} NMR (75.5 MHz, CDCl$_3$) δ 132.7 (d, *J* = 103.8 Hz), 132.2 (d, *J* = 9.9 Hz), 132.0 (d, *J* = 2.8 Hz), 128.6 (d, *J* = 12.1 Hz), δ$_C$ lit.[25] (100 MHz, CDCl$_3$) 132.8 (d, *J* = 104.6 Hz), 132.5 (d, *J* = 9.9 Hz), 131.9 (d, *J* = 2.2 Hz), 128.4 (d, *J* = 12.1 Hz); $^1$H NMR (300 MHz, CDCl$_3$) δ 7.72–7.59 (m, 6H), 7.56–7.48 (m, 3H), 7.48–7.38 (m, 6H), δ$_H$ lit.[25] (400 MHz, CDCl$_3$) 7.70–7.64 (m, 6H), 7.56–7.52 (m, 3H), 7.48–7.43 (m, 6H); HRMS (m/z): calcd for C$_{18}$H$_{16}$OP [M + H]$^+$, 279.0939; found, 279.0941.

*Bis(4-methylphenyl)phenylphosphine Oxide (1b) (Table 2, Entry 3).* Eluant: ethyl acetate–hexane 1:1; Yield: 0.090 g (78%) obtained as white crystals; mp. 76 °C, mp lit.[11] 78–79 °C; $^{31}$P{$^1$H} NMR (121.5 MHz, CDCl$_3$) δ 27.8, δ$_P$ lit.[26] (162 MHz, CDCl$_3$) 30.5; $^{13}$C{$^1$H} NMR (75.5 MHz, CDCl$_3$) δ 142.4 (d, *J* = 2.8 Hz), 133.1 (d, *J* = 104.1 Hz), 132.1 (d, *J* = 10.3 Hz), 132.1 (d, *J* = 9.8 Hz), 131.8 (d, *J* = 2.7 Hz), 129.4 (d, *J* = 106.6 Hz), 129.3 (d, *J* = 12.5 Hz), 128.5 (d, *J* = 12.1 Hz), 21.6 (s), δ$_C$ lit.[26] (100 MHz, CDCl$_3$) 142.6 (d, *J* = 2.9 Hz), 133.0 (d, *J* = 102.5 Hz), 132.2 (d, *J* = 10.2 Hz), 132.0 (d, *J* = 8.7 Hz), 131.9 (d, *J* = 3.2 Hz), 129.4 (d, *J* = 106.9 Hz), 129.4 (d, *J* = 12.6 Hz), 128.6 (d, *J* = 11.8 Hz), 21.7; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.73–7.61 (m, 2H), 7.61–7.47 (m, 5H), 7.47–7.37 (m, 2H), 7.32–7.18 (m, 4H), 2.39 (s, 6H), δ$_H$ lit.[26] (400 MHz, CDCl$_3$) 7.68–7.62 (m, 2H), 7.53 (dd, *J*$_1$ = 11.8 Hz, *J*$_2$ = 8.0 Hz, 4H), 7.48 (m, 1H), 7.24 (dd, *J*$_1$ = 8.4 Hz, *J*$_2$ = 2.4 Hz, 4H), 2.38 (s, 6H); HRMS (m/z): calcd for C$_{20}$H$_{20}$OP [M + H]$^+$, 307.1252; found, 307.1252.

*Bis(3,5-dimethylphenyl)phenylphosphine Oxide (1c) (Table 2, Entry 5).* Eluant: ethyl acetate–hexane 1:1; Yield: 0.094 g (74%) obtained as white crystals; mp. 159 °C, mp. lit.[26] 158.6–159.2 °C; $^{31}$P{$^1$H} NMR (121.5 MHz, CDCl$_3$): δ 29.6, δ$_P$ lit.[26] (162 MHz, CDCl$_3$) 30.9; $^{13}$C{$^1$H} NMR (75.5 MHz, CDCl$_3$) δ 138.1 (d, *J* = 12.7 Hz), 133.7 (d, *J* = 2.8 Hz), 133.1 (d, *J* = 103.1 Hz), 132.4 (d, *J* = 105.3 Hz), 132.1 (d, *J* = 9.9 Hz), 131.7, 129.7 (d, *J* = 9.8 Hz), 128.4 (d, *J* = 12.0 Hz), 21.4 (s), δ$_C$ lit.[26] (100 MHz, CDCl$_3$) 138.3 (d, *J* = 12.2 Hz), 133.9 (d, *J* = 2.3 Hz), 133.1 (d, *J* = 102.7 Hz), 132.4 (d, *J* = 102.6 Hz), 132.3 (d, *J* = 9.7 Hz), 131.9 (d, *J* = 2.2 Hz), 129.8 (d, *J* = 10.0 Hz), 128.6 (d, *J* = 11.7 Hz), 21.56; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.73–7.62 (m, 2H), 7.55–7.39 (m, 3H), 7.28 (d, *J* = 12.2 Hz, 4H), 7.15 (s, 2H), 2.31 (s, 12H), δ$_H$ lit.[26] (400 MHz, CDCl$_3$) 7.68–7.63 (m, 2H), 7.55–7.51 (m, 1H), 7.47–7.42 (m, 2H), 7.26 (d, *J* = 12.4 Hz, 4H), 7.15 (s, 2H), 2.31 (s, 12H); HRMS (m/z): calcd for C$_{22}$H$_{24}$OP [M + H]$^+$, 335.1565; found, 335.1566.

*Diethyl Phenylphosphonate (1d) (Table 2, Entry 8).* Eluant: ethyl acetate–hexane 1:1; Yield: 0.068 g (84%) obtained as colorless oil; $^{31}$P{$^1$H} NMR (121.5 MHz, CDCl$_3$) δ 18.9, δ$_P$ lit.[9] (162 MHz, CDCl$_3$) 18.8; $^{13}$C{$^1$H} NMR (75.5 MHz, CDCl$_3$) δ 132.5 (d, *J* = 3.0 Hz), 131.9 (d, *J* = 9.8 Hz), 128.6 (d, *J* = 15.0 Hz), 128.5 (d, *J* = 188.0 Hz), 62.2 (d, *J* = 5.4 Hz), 16.4 (d, *J* = 6.5 Hz), δ$_C$ lit.[9] (100 MHz, CDCl$_3$) 132.3 (d, *J* = 2.7 Hz), 131.7 (d, *J* = 9.2 Hz), 128.44 (d, *J* = 15.2 Hz), 128.41 (d, *J* = 187.6 Hz), 62.0 (d, *J* = 5.9 Hz), 16.3 (d, *J* = 6.5 Hz); $^1$H NMR (300 MHz, CDCl$_3$) δ 7.84–7.71 (m, 2H), 7.56–7.37 (m, 3H), 4.21–3.97 (m, 4H), 1.29 (t, *J* = 7.1 Hz, 6H), δ$_H$ lit.[9] (400 MHz, CDCl$_3$) 7.82 (m, 2H), 7.55 (~tq, *J*$_1$ = 7.5 Hz, *J*$_2$ = 1.4 Hz, 1H), 7.47 (m, 2H), 4.12 (m, 4H), 1.32 (td, *J*$_1$ = 7.0 Hz, *J*$_2$ = 0.5 Hz,

6H); HRMS ($m/z$): calcd for $C_{10}H_{16}O_3P$ [M + H]$^+$, 215.0837; found, 215.0835.

*Diphenyl Ethylphosphinate (1e) (Table 2, Entry 12).* Eluant: ethyl acetate–hexane 1:1; Yield: 0.080 g (86%) obtained as colorless oil; $^{31}P\{^1H\}$ NMR (121.5 MHz, CDCl$_3$) $\delta$ 32.2, $\delta_P$ lit.[27] (120 MHz, CDCl$_3$) 30.8; $^{13}C\{^1H\}$ NMR (75.5 MHz, CDCl$_3$) $\delta$ 132.0 (d, $J$ = 2.8 Hz), 131.7 (d, $J$ = 137.0 Hz), 131.6 (d, $J$ = 10.1 Hz), 128.4 (d, $J$ = 13.1 Hz), 61.1 (d, $J$ = 5.9 Hz), 16.5 (d, $J$ = 6.6 Hz), $\delta_C$ lit.[27] (75 MHz, CDCl$_3$) 139.9 (d, $J$ = 11.1 Hz), 133.7 (d, $J$ = 143.4 Hz), 130.9 (d, $J$ = 12.9 Hz), 127.0, 59.0, 16.7; $^1H$ NMR (300 MHz, CDCl$_3$) $\delta$ 7.88–7.75 (m, 4H), 7.58–7.39 (m, 6H), 4.16–4.01 (m, 2H), 1.36 (t, $J$ = 7.1 Hz, 3H), $\delta_H$ lit.[27] (300 MHz, CDCl$_3$) 7.70–7.63 (m, 4H), 7.43–7.31 (m, 6H), 4.16–4.09 (m, 2H), 1.30 (t, $J$ = 7.3 Hz, 3H); HRMS ($m/z$): calcd for $C_{14}H_{16}O_2P$ [M + H]$^+$, 247.0888; found, 247.0889.

**General Procedure for the P–C Coupling of Arylboronic Acids and Diphenylphosphine Oxide or Diethyl Phosphite (Table 3, Entries 2–6 and 10 and Table 4, Entries 2–7).** To 0.038 mmol (0.0085 g) of Pd(OAc)$_2$ in 1 mL of ethanol were added 0.41 mmol of the arylboronic acid [4-, 2-, or 3-methylphenylboronic acid: 0.056 g, 4-fluorophenylboronic acid: 0.057 g, 4- or 3-chlorophenylboronic acid: 0.064 g], 0.49 mmol (0.10 g) of diphenylphosphine oxide or 0.49 mmol (0.063 mL) of diethyl phosphite, and 0.45 mmol (0.15 g) of cesium carbonate. Then, the resulting mixture was irradiated in a closed vial in the MW reactor isothermally at 135 or 150 °C for 1.5 or 0.5 h (Table 3, entries 2–6 and 10 and Table 4). The reaction mixture was diluted with 3 mL of EtOH, filtrated, and the residue obtained after evaporation of the filtrate was filtered through a thin (2–3 cm) layer of silica gel using ethyl acetate as the eluant. The crude mixture obtained was analyzed by $^{31}P$ NMR spectroscopy. Then, if the sample was relevant, it was purified further by column chromatography (silica gel, ethyl acetate–hexane 1:1 as the eluant) to afford products **2f–4k**.

**Following Compounds Were Thus Prepared.** *(4-Methylphenyl)diphenylphosphine Oxide (2f) (Table 3, Entry 2).* Eluant: ethyl acetate–hexane 1:1; Yield: 0.081 g (73%) obtained as a white solid; mp 118–119 °C, mp. lit.[13] 129.5–130.2 °C; $^{31}P\{^1H\}$ NMR (121.5 MHz, CDCl$_3$) $\delta$ 29.3, $\delta_P$ lit.[13] (162 MHz, CDCl$_3$) 29.1; $^{13}C\{^1H\}$ NMR (125.7 MHz, CDCl$_3$) $\delta$ 142.4 (d, $J$ = 2.8 Hz), 132.8 (d, $J$ = 105.9 Hz), 132.1 (d, $J$ = 10.2 Hz), 132.0 (d, $J$ = 9.9 Hz), 131.8 (d, $J$ = 2.7 Hz), 129.2 (d, $J$ = 12.6 Hz), 129.1 (d, $J$ = 106.4 Hz), 128.4 (d, $J$ = 12.1 Hz), 21.6 (s), $\delta_C$ lit.[13] (100 MHz, CDCl$_3$) 142.5 (d, $J$ = 2.6 Hz), 132.9 (d, $J$ = 104.1 Hz), 132.2 (d, $J$ = 10.2 Hz), 132.1 (d, $J$ = 10.0 Hz), 131.9 (d, $J$ = 2.8 Hz), 129.3 (d, $J$ = 12.5 Hz), 129.2 (d, $J$ = 106.4 Hz), 128.5 (d, $J$ = 11.9 Hz), 21.6; $^1H$ NMR (500 MHz, CDCl$_3$) $\delta$ 7.80–7.40 (m, 12H), 7.29–7.11 (m, 2H), 2.40 (s, 3H), $\delta_H$ lit.[13] (400 MHz, CDCl$_3$) 7.67–7.62 (m, 4H), 7.56–7.48 (m, 4H), 7.44–7.40 (m, 4H), 7.26–7.23 (m, 2H), 2.37 (s, 3H); HRMS ($m/z$): calcd for $C_{19}H_{18}OP$ [M + H]$^+$, 293.1095; found, 293.1101.

*(2-Methylphenyl)diphenylphosphine Oxide (2g) (Table 3, Entry 3).* Eluant: ethyl acetate–hexane 1:1; Yield: 0.074 g (67%) obtained as white crystals; mp 120–121 °C, mp. lit.[28] 121.5–122.9 °C; $^{31}P\{^1H\}$ NMR (202.4 MHz, CDCl$_3$) $\delta$ 31.8, $\delta_P$ lit.[28] (202 MHz, CDCl$_3$) 31.8; $^{13}C\{^1H\}$ NMR (125.7 MHz, CDCl$_3$) $\delta$ 143.4 (d, $J$ = 8.0 Hz), 133.5 (d, $J$ = 12.9 Hz), 132.8 (d, $J$ = 103.6 Hz), 132.1 (d, $J$ = 2.6 Hz), 132.0 (d), 131.8 (d, $J$ = 2.7 Hz), 130.8 (d, $J$ = 103.2 Hz), 128.6 (d, $J$ = 12.0 Hz), 125.2 (d, $J$ = 12.8 Hz), 21.7 (d, $J$ = 4.7 Hz), $\delta_C$ lit.[28] (125 MHz, CDCl$_3$) 143.2 (d, $J$ = 8.2 Hz), 133.4 (d, $J$ = 12.4 Hz), 132.6 (d, $J$ = 102.6 Hz), 132.0 (d, $J$ = 2.7 Hz), 131.8 (d, $J$ = 10.0 Hz), 131.7 (d, $J$ = 2.7 Hz), 130.7 (d, $J$ = 103.5 Hz), 128.5 (d, $J$ = 12.7 Hz), 125.1 (d, $J$ = 12.7 Hz), 21.6 (d, $J$ = 5.4 Hz); $^1H$ NMR (500 MHz, CDCl$_3$) $\delta$ 7.66 (m, 4H), 7.55 (tq, $J_1$ = 7.3 Hz, $J_2$ = 1.6 Hz, 2H), 7.47 (td, $J_1$ = 7.7 Hz, $J_2$ = 2.8 Hz, 4H), 7.42 (tt, $J_1$ = 7.6 Hz, $J_2$ = 1.6 Hz, 1H), 7.28 (dd, $J_1$ = 7.6 Hz, $J_2$ = 4.1 Hz, 1H), 7.13 (td, $J_1$ = 7.6 Hz, $J_2$ = 2.9 Hz, 1H), 7.03 (ddd, $J_1$ = 14.1 Hz, $J_2$ = 7.8 Hz, $J_3$ = 1.1 Hz, 1H), 2.45 (s, 3H), $\delta_H$ lit.[28] (500 MHz, CDCl$_3$) 7.68–7.62 (m, 4H), 7.57–7.52 (m, 2H), 7.49–7.45 (m, 4H), 7.44–7.39 (m, 1H), 7.30–7.26 (m, 1H), 7.15–7.10 (m, 1H), 7.05–7.00 (m, 1H), 2.45 (s, 3H); HRMS ($m/z$): calcd for $C_{19}H_{18}OP$ [M + H]$^+$, 293.1095; found, 293.1094.

*(3-Methylphenyl)diphenylphosphine Oxide (2h) (Table 3, Entry 4).* Eluant: ethyl acetate–hexane 1:1; Yield: 0.089 g (80%) obtained as a white solid; mp 122–123 °C, mp. lit.[26] 123.7–124.2 °C; $^{31}P\{^1H\}$ NMR (202.4 MHz, CDCl$_3$) $\delta$ 29.3, $\delta_P$ lit.[29] (162 MHz, CDCl$_3$) 29.5; $^{13}C\{^1H\}$ NMR (125.7 MHz, CDCl$_3$) $\delta$ 138.5 (d, $J$ = 12.1 Hz), 132.8 (d, $J$ = 3.0 Hz), 132.7 (d, $J$ = 104.0 Hz), 132.5 (d, $J$ = 9.5 Hz), 132.3 (d, $J$ = 96.7 Hz), 132.1 (d, $J$ = 9.9 Hz), 131.9 (d, $J$ = 2.6 Hz), 129.2 (d, $J$ = 10.2 Hz), 128.5 (d, $J$ = 12.0 Hz), 128.3 (d, $J$ = 12.9 Hz), 21.4 (s), $\delta_C$ lit.[29] (100 MHz, CDCl$_3$) 138.4 (d, $J$ = 15.9 Hz), 133.1, 132.8 (d, $J$ = 2.4 Hz), 132.5 (d, $J$ = 9.5 Hz), 132.2 (d, $J$ = 103.4 Hz), 132.0 (d, $J$ = 9.8 Hz), 131.8 (d, $J$ = 2.5 Hz), 129.2 (d, $J$ = 10.2 Hz), 128.5 (d, $J$ = 12.1 Hz), 128.2, 21.5; $^1H$ NMR (500 MHz, CDCl$_3$) $\delta$ 7.72–7.67 (m, 4H), 7.61–7.55 (m, 3H), 7.50–7.47 (m, 4H), 7.42–7.34 (m, 3H), 2.39 (s, 3H), $\delta_H$ lit.[29] (400 MHz, CDCl$_3$) 7.64 (dd, $J_1$ = 11.6 Hz, $J_2$ = 7.6 Hz, 4H), 7.56–7.49 (m, 3H), 7.44–7.43 (m, 4H), 7.32 (m, 3H), 2.33 (s, 3H); HRMS ($m/z$): calcd for $C_{19}H_{18}OP$ [M + H]$^+$, 293.1095; found, 293.1097.

*(4-Fluorophenyl)diphenylphosphine Oxide (2i) (Table 3, Entry 5).* Eluant: ethyl acetate–hexane 1:1; Yield: 0.079 g (70%) obtained as pale yellow crystals; mp 134–135 °C, mp. lit.[30] 134–135 °C; $^{31}P\{^1H\}$ NMR (121.5 MHz, CDCl$_3$) $\delta$ 28.5, $\delta_P$ lit.[23] (162 MHz, CDCl$_3$) 28.3; $^{13}C\{^1H\}$ NMR (125.7 MHz, CDCl$_3$) $\delta$ 165.0 (dd, $J_1$ = 3.2 Hz, $J_2$ = 253.6 Hz), 134.5 (dd, $J_1$ = 11.3 Hz, $J_2$ = 8.8 Hz), 132.3 (d, $J$ = 105.0 Hz), ~132.1 (d, $J$ ~ 3.0 Hz), 132.0 (d, $J$ = 12.2 Hz), 128.53 (d, $J$ = 12.2 Hz), 128.52 (dd, $J_1$ = 106.5 Hz, $J_2$ = 3.4 Hz), 115.8 (dd, $J_1$ = 13.2 Hz, $J_2$ = 21.4 Hz), $\delta_C$ lit.[23] (100 MHz, CDCl$_3$) 165.0 (dd, $J_1$ = 254.2 Hz, $J_2$ = 3.2 Hz), 134.6 (dd, $J_1$ = 11.3 Hz, $J_2$ = 8.9 Hz), 132.5 (d, $J$ = 105.2 Hz), 132.1 (d, $J$ = 4.1 Hz), 132.0, 128.7 (dd, $J_1$ = 106.6 Hz, $J_2$ = 3.1 Hz), 128.6 (d, $J$ = 12.5 Hz), 115.9 (dd, $J_1$ = 22.6 Hz, $J_2$ = 13.3 Hz); $^1H$ NMR (500 MHz, CDCl$_3$) $\delta$ 7.75–7.37 (m, 12H), 7.20–7.06 (m, 2H), $\delta_H$ lit.[23] (400 MHz, CDCl$_3$) 7.67–7.60 (m, 6H), 7.53–7.49 (m, 2H), 7.44–7.41 (m, 4H), 7.11 (t, $J$ = 8.5 Hz, 2H); HRMS ($m/z$): calcd for $C_{18}H_{15}FOP$ [M + H]$^+$, 297.0845; found, 297.0850.

*1,4-Phenylenebis(diphenylphosphine oxide) (3A) (Table 3, Entry 6).* In this case, dichloromethane–methanol 97:3 was used as the eluant. Yield: 0.021 g (23%) obtained as white crystals; mp 300–301 °C, mp. lit.[25] >300 °C; $^{31}P\{^1H\}$ NMR (202.4 MHz, CDCl$_3$) $\delta$ 28.6, $\delta_P$ lit.[25] (162 MHz, CDCl$_3$) 30.5; $^{13}C\{^1H\}$ NMR (125.7 MHz, CDCl$_3$) $\delta$ 137.0 (dd, $J_1$ = 100.6 Hz, $J_2$ = 2.7 Hz), 132.3, 132.06 (d, $J$ = 10.1 Hz), 132.06, 131.7 (d, $J$ = 105.2 Hz), 128.7 (d, $J_1$ = 12.8 Hz), $\delta_C$ lit.[25] (100 MHz, CDCl$_3$) 136.9 (d, $J$ = 100.2 Hz), 132.3, 132.0 (d, $J$ = 13.9 Hz), 131.9, 131.0, 128.7 (d, $J$ = 12.2 Hz); $^1H$ NMR (500 MHz, CDCl$_3$) $\delta$ 7.76 (m, 4H), 7.66 (ddd, $J_1$ = 12.1 Hz, $J_2$ = 8.4 Hz, $J_3$ = 1.3 Hz, 8H), 7.57 (tq, $J_1$ = 7.4 Hz, $J_2$ = 1.5 Hz, 4H), 7.48 (td, $J_1$ = 7.8 Hz, $J_2$ = 2.8 Hz, 8H), $\delta_H$ lit.[25] (400 MHz, CDCl$_3$) 7.77–7.74 (m, 4H), 7.69–7.64 (m, 8H), 7.58–7.55 (m, 4H), 7.50–7.46 (m, 8H); HRMS ($m/z$): calcd for $C_{30}H_{25}O_2P_2$ [M + H]$^+$, 479.1330; found, 479.1320.

*1,3-Phenylenebis(diphenylphosphine oxide) (3B) (Table 3, Entry 10).* In this instance, dichloromethane–methanol 97:3 was used as the eluant. Yield: 0.023 g (25%) obtained as colorless oil; $^{31}P\{^1H\}$ NMR (202.4 MHz, CDCl$_3$) $\delta$ 28.5, $\delta_P$ lit.[25] (162 MHz, CDCl$_3$) 30.5; $^{13}C\{^1H\}$ NMR (125.7 MHz, CDCl$_3$) $\delta$ 135.5 (dd, $J_1$ = 10.1 Hz, $J_2$ = 3.1 Hz), 135.4 (t, $J$ = 11.2 Hz), 133.6 (dd, $J_1$ = 101.8 Hz, $J_2$ = 10.7 Hz), 132.2 (d, $J$ = 2.3 Hz), 132.0 (d, $J$ = 10.2 Hz), 131.7 (d, $J$ = 105.1 Hz), 129.0 (t, $J$ = 11.3 Hz), 128.6 (d, $J$ = 12.5 Hz), $\delta_C$ lit.[25] (100 MHz, CDCl$_3$) 135.4–135.2 (m, 2C), 135.1, 133.5 (dd, $J_1$ = 101.7 Hz, $J_2$ = 10.7 Hz), 132.0, 131.8 (d, $J$ = 10.3 Hz), 131.5 (d, $J$ = 104.9 Hz), 128.8 (t, $J$ = 11.2 Hz), 128.4 (d, $J$ = 12.6 Hz), 127.1; $^1H$ NMR (500 MHz, CDCl$_3$) $\delta$ 7.96 (ddm, $J_1$ = 12.5 Hz, $J_2$ = 7.7 Hz, 2H), 7.69 (tt, $J_1$ = 11.7 Hz, $J_2$ = 1.5 Hz, 1H), 7.62 (tt, $J_1$ = 7.7 Hz, $J_2$ = 2.5 Hz, 1H), 7.58 (dd, $J_1$ = 12.1 Hz, $J_2$ = 7.9 Hz, 8H), 7.53 (t, $J$ = 7.4 Hz, 4H), 7.41 (td, $J_1$ = 7.7 Hz, $J_2$ = 2.8 Hz, 8H), $\delta_H$ lit.[25] (400 MHz, CDCl$_3$) 7.98–7.93 (m, 2H), 7.71 (t, $J$ = 11.7 Hz, 1H), 7.63–7.50 (m, 13H), 7.43–7.38 (m, 8H); HRMS ($m/z$): calcd for $C_{30}H_{25}O_2P_2$ [M + H]$^+$, 479.1330; found, 479.1323.

*Diethyl (4-Methylphenyl)phosphonate (4f) (Table 4, Entry 2).* Eluant: ethyl acetate–hexane 1:1; Yield: 0.067 g (77%) obtained as colorless oil; $^{31}P\{^1H\}$ NMR (121.5 MHz, CDCl$_3$) $\delta$ 20.5, $\delta_P$ lit.[17] (162 MHz, CDCl$_3$) 19.5; $^{13}C\{^1H\}$ NMR (75.5 MHz, CDCl$_3$) $\delta$ 142.8 (d, $J$ = 3.1 Hz), 131.7 (d, $J$ = 10.3 Hz), 129.1 (d, $J$ = 15.4 Hz), 125.0

(d, $J$ = 190.1 Hz), 61.9 (d, $J$ = 5.3 Hz), 21.6 (d, $J$ = 1.15 Hz), 16.2 (d, $J$ = 6.5 Hz), $\delta_C$ lit.[17] (100 MHz, CDCl$_3$) 142.9 (d, $J$ = 3.3 Hz), 131.8 (d, $J$ = 10.4 Hz), 129.3 (d, $J$ = 15.4 Hz), 125.0 (d, $J$ = 190.2 Hz), 61.9 (d, $J$ = 5.3 Hz), 21.6, 16.3 (d, $J$ = 6.3 Hz); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.75−7.63 (m, 2H), 7.25−7.20 (m, 2H), 4.19−3.94 (m, 4H), 2.37 (s, 3H), 1.28 (t, $J$ = 7.1 Hz, 6H), $\delta_H$ lit.[17] (400 MHz, CDCl$_3$) 7.63 (dd, $J_1$ = 12.9 Hz, $J_2$ = 7.8 Hz 2H), 7.24−7.16 (m, 2H), 4.12−3.93 (m, 4H), 2.33 (s, 3H), 1.24 (t, $J$ = 6.9 Hz, 6H); HRMS ($m/z$): calcd for C$_{11}$H$_{18}$O$_3$P [M + H]$^+$, 229.0994 found 229.0996.

*Diethyl (2-Methylphenyl)phosphonate (4g) (Table 4, Entry 3).* Eluant: ethyl acetate−hexane 1:1; Yield: 0.067 g (78%) obtained as colorless oil; $^{31}$P{$^1$H} NMR (202.4 MHz, CDCl$_3$) $\delta$ 19.5, $\delta_P$ lit.[17] (162 MHz, CDCl$_3$) 19.4; $^{13}$C{$^1$H} NMR (125.7 MHz, CDCl$_3$) $\delta$ 141.8 (d, $J$ = 10.1 Hz), 133.9 (d, $J$ = 10.4 Hz), 132.4 (d, $J$ = 2.8 Hz), 131.2 (d, $J$ = 15.0 Hz), 126.8 (d, $J$ = 184.0 Hz), 125.4 (d, $J$ = 14.8 Hz), 61.9 (d, $J$ = 5.5 Hz), 21.2 (d, $J$ = 3.7 Hz), 16.3 (d, $J$ = 6.6 Hz), $\delta_C$ lit.[17] (100 MHz, CDCl$_3$) 141.8 (d, $J$ = 10.4 Hz), 133.9 (d, $J$ = 10.3 Hz), 132.4 (d, $J$ = 2.9 Hz), 131.1 (d, $J$ = 15.5 Hz), 127.0 (d, $J$ = 184.4 Hz), 125.3 (d, $J$ = 14.9 Hz), 61.8 (d, $J$ = 5.6 Hz), 21.2 (d, $J$ = 3.7 Hz), 16.3 (d, $J$ = 6.6 Hz); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.96−7.90 (m, 1H), 7.47−7.43 (m, 1H), 7.32−7.25 (m, 2H), 4.24−4.05 (m, 4H), 2.60 (s, 3H), 1.35 (t, $J$ = 7.1 Hz, 6H), $\delta_H$ lit.[17] (400 MHz, CDCl$_3$) 7.95−7.88 (m, 1H), 7.45−7.40 (m, 1H), 7.29−7.23 (m, 2H), 4.20−4.03 (m, 4H), 2.58 (s, 3H), 1.33 (t, $J$ = 7.0 Hz, 6H); HRMS ($m/z$): calcd for C$_{11}$H$_{18}$O$_3$P [M + H]$^+$, 229.0994; found, 229.0993.

*Diethyl (3-Methylphenyl)phosphonate (4h) (Table 4, Entry 4).* Eluant: ethyl acetate−hexane 1:1; Yield: 0.069 g (80%) obtained as colorless oil; $^{31}$P{$^1$H} NMR (202.4 MHz, CDCl$_3$) $\delta$ 19.5, $\delta_P$ lit.[17] (162 MHz, CDCl$_3$) 19.2; $^{13}$C{$^1$H} NMR (125.7 MHz, CDCl$_3$) $\delta$ 138.3 (d, $J$ = 14.9 Hz), 133.2 (d, $J$ = 3.1 Hz), 132.3 (d, $J$ = 10.0 Hz), 128.8 (d, $J$ = 9.6 Hz), 128.4 (d, $J$ = 15.8 Hz), 128.1 (d, $J$ = 187.6 Hz), 62.1 (d, $J$ = 5.4 Hz), 21.3 (s), 16.3 (d, $J$ = 6.5 Hz), $\delta_C$ lit.[17] (100 MHz, CDCl$_3$) 138.2 (d, $J$ = 14.8 Hz), 133.1 (d, $J$ = 3.0 Hz), 132.2 (d, $J$ = 9.7 Hz), 128.7 (d, $J$ = 9.7 Hz), 128.3 (d, $J$ = 15.4 Hz), 128.0 (d, $J$ = 187.0 Hz), 61.9 (d, $J$ = 5.2 Hz), 21.2, 16.3 (d, $J$ = 6.2 Hz); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.67−7.57 (m, 2H), 7.38−7.34 (m, 2H), 4.19−4.03 (m, 4H), 2.40 (s, 3H), 1.33 (t, $J$ = 7.1 Hz, 6H), $\delta_H$ lit.[17] (400 MHz, CDCl$_3$) 7.63−7.52 (m, 2H), 7.33−7.27 (m, 2H), 4.16−3.97 (m, 4H), 2.34 (s, 3H), 1.27 (t, $J$ = 7.1 Hz, 6H); HRMS ($m/z$): calcd for C$_{11}$H$_{18}$O$_3$P [M + H]$^+$, 229.0994; found, 229.0992.

*Diethyl (4-Fluorophenyl)phosphonate (4i) (Table 4, Entry 5).* Eluant: ethyl acetate−hexane 1:1; Yield: 0.068 g (77%) obtained as colorless oil; $^{31}$P{$^1$H} NMR (121.5 MHz, CDCl$_3$) $\delta$ 18.7, $\delta_P$ lit.[17] (162 MHz, CDCl$_3$) 17.7; $^{13}$C{$^1$H} NMR (75.5 MHz, CDCl$_3$) $\delta$ 165.2 (dd, $J_1$ = 3.9 Hz, $J_2$ = 253.4 Hz), 134.2 (dd, $J_1$ = 11.2 Hz, $J_2$ = 8.9 Hz), 124.4 (dd, $J_1$ = 192.7 Hz, $J_2$ = 3.4 Hz), 115.6 (dd, $J_1$ = 16.3 Hz, $J_2$ = 21.4 Hz), 62.0 (d, $J$ = 5.4 Hz), 16.2 (d, $J$ = 6.4 Hz), $\delta_C$ lit.[17] (100 MHz, CDCl$_3$) 165.3 (dd, $J_1$ = 253.1 Hz, $J_2$ = 4.1 Hz), 134.5 (dd, $J_1$ = 11.2 Hz, $J_2$ = 8.8 Hz), 124.4 (d, $J$ = 192.7 Hz), 115.8 (dd, $J_1$ = 22.1 Hz, $J_2$ = 16.2 Hz), 62.1 (d, $J$ = 5.4 Hz), 16.3 (d, $J$ = 6.2 Hz); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.81−7.70 (m, 2H), 7.11−7.00 (m, 2H), 4.15−3.93 (m, 4H), 1.32−1.15 (m, 6H), $\delta_H$ lit.[17] (400 MHz, CDCl$_3$) 7.80 (ddd, $J_1$ = 14.0 Hz, $J_2$ = 7.4 Hz, $J_3$ = 6.9 Hz, 2H), 7.17−7.09 (m, 2H), 4.19−4.00 (m, 4H), 1.30 (t, $J$ = 7.2 Hz, 6H); HRMS ($m/z$): calcd for C$_{10}$H$_{15}$FO$_3$P [M + H]$^+$, 233.0743; found, 233.0742.

*Diethyl (4-Chlorophenyl)phosphonate (4j) (Table 4, Entry 6).* Eluant: ethyl acetate−hexane 1:1; Yield: 0.062 g (66%) obtained as colorless oil; $^{31}$P{$^1$H} NMR (121.5 MHz, CDCl$_3$) $\delta$ 18.5, $\delta_P$ lit.[31] (162 MHz, CDCl$_3$) 18.1; $^{13}$C{$^1$H} NMR (75.5 MHz, CDCl$_3$) $\delta$ 139.0 (d, $J$ = 4.1 Hz), 133.2 (d, $J$ = 10.7 Hz), 128.9 (d, $J$ = 15.6 Hz), 127.1 (d, $J$ = 190.9 Hz), 62.3 (d, $J$ = 5.5 Hz), 16.4 (d, $J$ = 6.4 Hz), $\delta_C$ lit.[31] (62.5 MHz, CDCl$_3$) 138.5, 134.5, 129.2, 123.3, 58.0, 16.8; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.81−7.65 (m, 2H), 7.51−7.40 (m, 2H), 4.21−4.00 (m, 4H), 1.32 (t, $J$ = 7.0 Hz, 6H), $\delta_H$ lit.[31] (250 MHz, CDCl$_3$) 7.69−7.61 (m, 2H), 7.38−7.33 (m, 2H), 4.04−3.95 (m, 4H), 1.22 (t, 6H); HRMS ($m/z$): calcd for C$_{10}$H$_{15}$ClO$_3$P [M + H]$^+$, 249.0447; found, 249.0446.

*Diethyl (3-Chlorophenyl)phosphonate (4k) (Table 4, Entry 7).* Eluant: ethyl acetate−hexane 1:1; Yield: 0.067 g (71%) obtained as colorless oil; $^{31}$P{$^1$H} NMR (121.5 MHz, CDCl$_3$) $\delta$ 17.4, $\delta_P$ lit.[32] (202.4 MHz, CDCl$_3$) 16.7; $^{13}$C{$^1$H} NMR (125.7 MHz, CDCl$_3$) $\delta$ 134.7 (d, $J$ = 20.3 Hz), 132.4 (d, $J$ = 3.0 Hz), 131.6 (d, $J$ = 10.7 Hz), 130.7 (d, $J$ = 187.9 Hz), 129.74 (d, $J$ = 16.3 Hz), 129.69 (d, $J$ = 9.2 Hz), 62.3 (d, $J$ = 5.5 Hz), 16.2 (d, $J$ = 6.4 Hz), $\delta_C$ lit.[32] (125.7 MHz, CDCl$_3$) 134.8 (d, $J$ = 20.3 Hz), 132.5 (d, $J$ = 3.0 Hz), 131.6 (d, $J$ = 10.7 Hz), 130.7 (d, $J$ = 188.2 Hz), 130.0 (d, $J$ = 16.2 Hz), 129.8 (d, $J$ = 9.1 Hz), 62.5 (d, $J$ = 5.5 Hz), 16.3 (d, $J$ = 6.4 Hz); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.81−7.59 (m, 2H), 7.51−7.43 (m, 1H), 7.40−7.31 (m, 1H), 4.20−3.96 (m, 4H), 1.30 (t, $J$ = 7.1 Hz, 6H), $\delta_H$ lit.[32] (500 MHz, CDCl$_3$) 7.78−7.37 (m, 4H), 4.18−4.02 (m, 4H), 1.31 (t, $J$ = 7.0 Hz, 6H); HRMS ($m/z$): calcd for C$_{10}$H$_{15}$ClO$_3$P [M + H]$^+$, 249.0447; found, 249.0448.

**Computational Methods.** All computations were carried out with the Gaussian16 program package (G16),[33] using standard convergence criteria for the gradients of the root-mean-square (RMS) force, maximum force, and RMS displacement and maximum displacement vectors ($3.0 \times 10^{-4}$, $4.5 \times 10^{-4}$, $1.2 \times 10^{-3}$, and $1.8 \times 10^{-3}$). Computations were carried out at the M06-2X level of theory.[34] The basis set of 6-31G(d,p) was applied for C, H, O, P, N, and B and SDD/MWB28 for Pd.[35] The vibrational frequencies were computed at the same levels of theory, in order to confirm properly all structures as residing at minima on their potential energy hypersurfaces (PESs). Thermodynamic functions U, H, G, and S were computed at 398.15 K. Besides the vacuum calculations, the IEFPCM method was also applied to model the solvent effect, by using the default settings of G16, setting the $\varepsilon$ = 24.852 (for ethanol).[36] See the Supporting Information for details.

## ■ ASSOCIATED CONTENT

### Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

### Ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.3c01269.

$^{31}$P, $^{13}$C, and $^1$H NMR spectra and data of the theoretical calculations (PDF)

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### Notes

The authors declare no competing financial interest.

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