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Nickel-catalyzed C–P cross-coupling of diphenylphosphine oxide with aryl chlorides†

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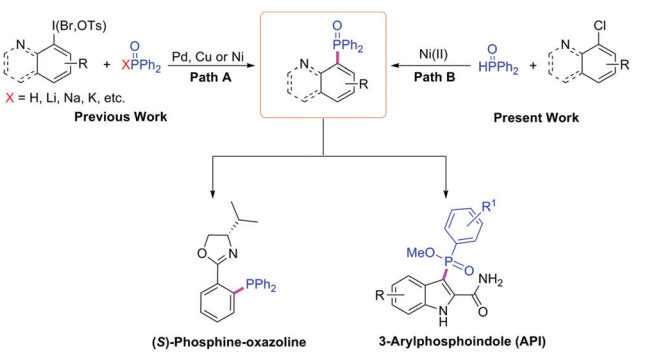
A novel protocol for the preparation of various diarylphosphine oxide compounds *via* a Ni-catalyzed cross-coupling of aryl chlorides with $R_2P(O)H$ has been developed. Notably, this process exhibits the following very attractive features: (i) the process is simpler and operates under mild reaction conditions; (ii) the process is generally cheaper in part because the more accessible aryl chloride is used to form the C–P bond; (iii) the process avoids the need for simultaneous preparation and use of $Ar_2P(O)M$.

Introduction

Transition metal-catalyzed phosphination of aryl halides or triflates has evolved as one of the most powerful methods for the synthesis of aromatic organophosphorus compounds,[1] which play important roles in organic synthesis as well as the pharmaceutical and life sciences.[2] Since the pioneering work of the Hirao group in this area,[3] researchers have developed the palladium-, nickel-, and copper-catalyzed phosphination of aryl halides with phosphorus-based nucleophiles.[4] In general, however, only highly reactive aryl iodides or bromides and triflates can be used as coupling partners (Scheme 1, Path A). To date, very few examples of palladium-catalyzed phosphination of inactive aryl chloride have been reported. In 2001, Montchamp reported the Pd-catalyzed reaction between anilinium hypophosphite and various aromatic electrophiles applied to the synthesis of monosubstituted phosphinic acids. With this catalyst system, the relative activated 4-chlorobenzonitrile also proceeds smoothly and affords the corresponding product in good yield.[5] Recently, there have been significant advances in this field of research, a general palladium-catalyzed cross-coupling to synthesize disubstituted phosphinates between H-phosphinates and aryl chlorides has been performed.[6] Moreover, Buchwald unveiled the only current example of synthesis of dialkylphosphine by palladium-catalyzed cross-coupling with aryl chloride in 2004.[7] Neither nickel nor copper-catalyzed phosphination of aryl chloride, however, has been reported. Therefore, the development of a more concise, efficient method for the C–P cross-coupling of aryl chloride is highly desirable and presents a considerable challenge. Herein, we describe a versatile method of constructing a C–P bond by Ni-catalyzed cross-coupling of aryl chlorides with $R_2P(O)H$ compounds (Scheme 1, Path B). Importantly, this process is simple, operates under mild reaction conditions, and is generally cheaper because the accessible and inexpensive compound aryl chloride is used. Moreover, the process avoids the simultaneous preparation and use of $Ar_2P(O)M$. In addition, use of our method allows for the easy synthesis of different *N*,*P*-ligands such as (*S*)-phosphine oxazoline and 3-arylphosphoindole (API), which are novel non-nucleoside reverse transcriptase inhibitors (NNRTIs) for the treatment of HIV-1 infections.[2i,j] During the preparation of this manuscript, a similar catalytic system was reported by the group of Han *et al.*, they disclosed $NiCl_2$(dppp)-catalyzed C–P bond formation through the cross-coupling of aryl halides with a dialkyl phosphite, diphenylphosphine oxide, and diphenylphosphane.[8] Although their investigation mainly focuses on aryl bromides, part of their work also involves use of aryl chlorides.



Scheme 1 Pathway for the synthesis of diphenylphosphine oxides.

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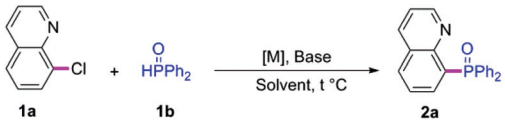
Results and discussion

In the past several years, we have focused our efforts on the development of new and efficient methods for transition metal-catalyzed C–P bond formation. We have made considerable advances in this regard.[9] Recently, we reported a highly efficient protocol for the preparation of various diphenylphosphoryl ligands *via* nickel-catalyzed C–CN bond cleavage.[9b] In light of the above results, we hypothesize that the C–Cl bond might show cleavage under a similar catalytic system because the bond-dissociation energy (BDE) of the C–Cl bond (79 kcal mol^{-1}) is very close to the C–CN bond (83 kcal mol^{-1}).[10] In particular, activating the C–Cl bond is not only cheaper, but also more easily accessible. Furthermore, it also presents a fundamental challenge of considerable scientific interest. In an initial study, we chose 8-chloroquinoline **1a** and $Ph_2P(O)H$ as the model substrates with which to begin our test with 5 mol% $Ni(PPh_3)_2Cl_2$ and 1.5 equiv. *t*-BuOK in dioxane at 120 °C, the expected product of **2a** was obtained in 36% yield (Table 1, entry 1). Encouraged by this result, we further optimized the reaction conditions. Screening of different bases in this transformation was carried out and results indicated that the base plays a crucial role in this reaction system; *t*-BuOLi, NaH, Cs_2CO_3, and K_2CO_3 were also promising. K_2CO_3 gave the best yield with 64% (Table 1, entries 2–5). Investigation of different solvents showed that DMF was the best suitable solvent for this procedure and that **2a** was afforded in a 69% yield (Table 1, entries 6–8). Over time we found that depression of the reaction temperature is beneficial for the reaction, as the yield of **2a** improved to 89% at 50 °C (Table 1, entries 9–11). Finally, the loading of $Ni(PPh_3)_2Cl_2$ was also evaluated and 2 mol% $Ni(PPh_3)_2Cl_2$ is sufficient to afford a smooth reaction, without a significant decrease in reaction yield (Table 1, entries 12–14). We would like to stress that the control experiment clearly shows that the catalyst of $Ni(PPh_3)_2Cl_2$ is essential for the reactions (Table 1, entry 15).

As our comprehensive experimental results show, we selected 2 mol% $Ni(PPh_3)_2Cl_2$ and 1.5 equiv. K_2CO_3 as the base in DMF at 50 °C as our optimization reaction conditions (Table 1, entry 13). The scope of substrates was first examined by varying the *N*-heteroaromatic chloride compounds for the *N*,*P*-based ligands, which are key to many metal-catalyzed organic transformations, including chiral reactions (Table 2).[11] In this way our method provided mild and efficient ways to construct these ligands. Different quinoline chlorides and 4-methyl-2-chloropyridine are also suitable substrates, affording the corresponding *N*,*P*-products in good to high yields (Table 2, entries **1a–1e**). The 2-oxazoline chlorobenzene (**1f**) and 2-tetrazole chlorobenzene (**1g**) reactions occurred smoothly, yielding products of **2f** and **2g**, with 71% and 63% yields, respectively (Table 2, entries **1f–1g**). The ethyl 4-chloroquinoline-3-carboxylate (**1h**) was investigated as a potential *N*,*O*-ligand; this reaction afforded **2h** in 83% yield.

Under the same conditions, we wished to extend the methodology to chlorobenzene and its derivatives. We selected 4-methyl chlorobenzene (**1g**) as a substrate to react with

Table 1 Cross-coupling of 8-chloroquinoline with $Ph_2P(O)H$ under different conditions[a]



1a 1b 2a

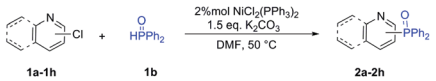
Entry	$NiCl_2(PPh_3)_2$	Base	Solvent	*t* [°C]	Yield[b] [%]
1	5 mol%	*t*-BuOK 1.5 equiv.	Dioxane	120	36
2	5 mol%	*t*-BuOLi 1.5 equiv.	Dioxane	120	31
3	5 mol%	Cs_2CO_3 1.5 equiv.	Dioxane	120	58
4	5 mol%	NaH 1.5 equiv.	Dioxane	120	55
5	5 mol%	K_2CO_3 1.5 equiv.	Dioxane	120	64
6	5 mol%	K_2CO_3 1.5 equiv.	DMF	120	69
7	5 mol%	K_2CO_3 1.5 equiv.	NMP	120	47
8	5 mol%	K_2CO_3 1.5 equiv.	MeOH	120	50
9	5 mol%	K_2CO_3 1.5 equiv.	DMF	90	78
10	5 mol%	K_2CO_3 1.5 equiv.	DMF	70	86
11	5 mol%	K_2CO_3 1.5 equiv.	DMF	50	89
12	3 mol%	K_2CO_3 1.5 equiv.	DMF	50	87
13	**2 mol%**	**K_2CO_3 1.5 equiv.**	**DMF**	**50**	**86**
14	1 mol%	K_2CO_3 1.5 equiv.	DMF	50	65
15	—	K_2CO_3 1.5 equiv.	DMF	50	n.r.

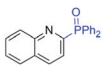
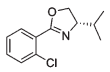
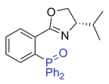
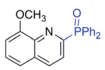
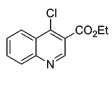
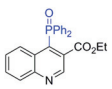
[a] All the reactions were carried out in the presence of 0.5 mmol of **1a** in 3 mL of different solvents. [b] Isolated yield.

$Ph_2P(O)H$ under the former reaction conditions. Disappointingly, however, the results indicated that the reaction failed entirely (Table 3, entry 1). This prompted us to reconsider our screening, which had concentrated on different bases and temperatures because the activity of chlorobenzene was generally lower than heteroaromatic chloride compounds. After extensive experimentation, we found that the use of $NiCl_2(PPh_3)_2$ as a catalyst and *t*-BuONa or *t*-BuOK as a base at 70 °C was critical for obtaining the desired aromatic diphenylphosphine oxides in 40% and 37% yields, respectively (Table 3, entries 2 and 3). Increasing the temperature to 90 °C improved the yield of **2g** to 46% (Table 3, entry 4). However, continuing to raise the temperature accelerated the decomposition of $Ph_2P(O)H$ and led to decreases in yield. A survey showed that all the various nickel catalysts were able to catalyze this reaction, but $NiCl_2(DME)$ gave the highest yield of 51% (Table 3, entries 5–14). A screening of solvents further indicated that DMF was the best choice. Similarly, the control experiment showed that the catalyst of $NiCl_2(DME)$ was essential for the reactions (Table 3, entry 15).

Having established optimized reaction conditions (Table 3, entry 5), we moved on to investigate the cross-coupling of different chlorobenzene derivatives with $Ph_2P(O)H$. The results illustrate that steric and electronic effects play key roles in this reaction. For example, the electron-deficient 4-chlorobenzonitrile reacted very well with $Ph_2P(O)H$ and the product of **2j** was obtained in 85% yield (Table 4, entry **1j**). The reaction of electron-neutral 4-chlorotoluene, electron-rich 4-chloroanisole, and electron-deficient 3-chlorobenzonitrile with $Ph_2P(O)H$ resulted in lower yields (Table 4, entries **1i**, **1n** and **1k**). Nevertheless, 4-trifluoromethyl chlorobenzene also afforded the product of **2m** in 46% yield. Although the electron-deficient or

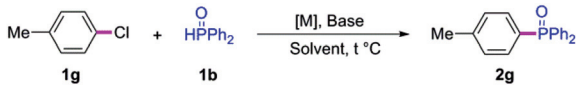
Table 2 Cross-coupling with different *N*-heteroaromatic chlorides[a]



Entry	R–Cl	Products	Yield[b] [%]	Entry	R–Cl	Products	Yield[b] [%]
1a			86	**1e**			70
1b			87	**1f**			71
1c			84	**1g**			63
1d			85	**1h**			83

[a] All the reactions were carried out in the presence of 0.5 mmol of **1a–1f** in 3 mL of DMF at 50 °C. [b] Isolated yields.

Table 3 Cross-coupling of 4-methyl chlorobenzene with $Ph_2P(O)H$ under different conditions[a]



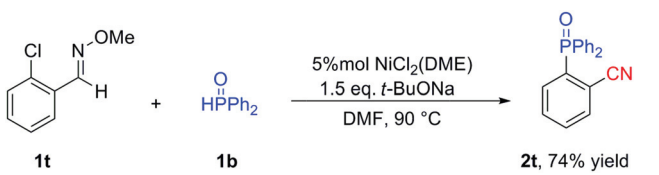
Entry	[M]	Base	*t* [°C]	Yield[b] [%]
1	$NiCl_2(PPh_3)_2$ 5 mol%	K_2CO_3 1.5 equiv.	50	n.r.
2	$NiCl_2(PPh_3)_2$ 5 mol%	*t*-BuONa 1.5 equiv.	70	40
3	$NiCl_2(PPh_3)_2$ 5 mol%	*t*-BuOK 1.5 equiv.	70	37
4	$NiCl_2(PPh_3)_2$ 5 mol%	*t*-BuONa 1.5 equiv.	90	46
5	**$NiCl_2$(DME) 5 mol%**	***t*-BuONa 1.5 equiv.**	**90**	**51**
6	$NiBr_2$(DME) 5 mol%	*t*-BuONa 1.5 equiv.	90	29
7	$NiCl_2$(dppe) 5 mol%	*t*-BuONa 1.5 equiv.	90	26
8	$NiCl_2$(dppp) 5 mol%	*t*-BuONa 1.5 equiv.	90	25
9	$NiCl_2(PCy_3)_2$ 5 mol%	*t*-BuONa 1.5 equiv.	90	38
10	$NiBr_2(PPh_3)_2$ 5 mol%	*t*-BuONa 1.5 equiv.	90	47
11	$Ni(acac)_2$ 5 mol%	*t*-BuONa 1.5 equiv.	90	24
12	$NiCl_2$ 5 mol%	*t*-BuONa 1.5 equiv.	90	41
13	$NiBr_2$ 5 mol%	*t*-BuONa 1.5 equiv.	90	40
14	$Ni(OTf)_2$ 5 mol%	*t*-BuONa 1.5 equiv.	90	38
15	—	*t*-BuONa 1.5 equiv.	90	n.r.

[a] All the reactions were carried out in the presence of 0.5 mmol of **1g** in 3 mL of DMF. [b] Isolated yield.

electron-rich group lies in the *ortho*-position of chlorobenzene, the steric hindrance is nevertheless apparent and the products of **2l** and **2o** were obtained in 56% and 51% yields, respectively (Table 4, entries **1l** and **1o**). It is worth noting that the C–Cl bond cleavage precedes the C–CN bond in this transformation and the cyano group is retained. In addition, the coupling of 1-chloronaphthalene was accomplished and **2q** was obtained in 71% yield (Table 4, entry **1q**). Furthermore, this reaction displays good functional group tolerance and the acetamide was also compatible with this transformation (Table 4, entry **1o**).

To our delight, some heteroaromatic chloride compounds that failed under former reaction conditions such as 2-chloropyrimidine, 3-chloride-*N*-methylindole, 10-chlorobenzoquinoline, 2-chlorobenzothiazole, and 2-chloro-4-methylquinoline could be successfully carried out using our new reaction conditions. Indeed, these compounds afforded the corresponding products in good yield (Table 4, entries **1p** and **1r–1v**).

In the course of exploring the scope of this method, we discovered a new catalytic transformation. As a substrate, (*E*)-2-chlorobenzaldehyde *O*-methyl oxime (**1t**) reacted with $Ph_2P(O)H$ under optimal reaction conditions. To our surprise the 2-diphenylphosphoryl-benzonitrile (**2t**) was obtained in 74% yield (Scheme 2). Simultaneously, the conversion of oxime ether to nitrile also occurred by elimination of methanol. As illustrated, this finding will provide us with a novel and efficient pathway for the synthesis of 2-diphenylphosphoryl-benzonitrile and its derivatives by domino processes.

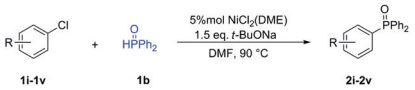


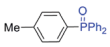
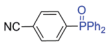
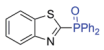
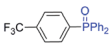
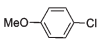
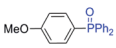
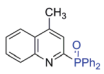
Scheme 2 Phosphination and elimination of 2-chlorobenzaldehyde *O*-methyl oxime.

Conclusions

In summary, we have developed a protocol for the preparation of various diphenylphosphoryl compounds through nickel-catalyzed cross-coupling reactions of $Ph_2P(O)H$ with aromatic

Table 4 Cross-coupling with different aromatic chlorides[a,b]



Entry	R–Cl	Products	Yield[b] [%]	Entry	R–Cl	Products	Yield[b] [%]
1i			51	1q			71
1j			85	1r			53
1k			49	1s			51
1l			56	1t			48
1m			46	1u			76
1n			47	1v			76
1o			51				
1p			79				

[a] All the reactions were carried out in the presence of 0.5 mmol of **1g–1s** in 3 mL of DMF at 90 °C. [b] Isolated yield.

chlorides. Notably, the process is simple and operates under mild reaction conditions. Moreover, the process is generally cheaper in part because the more accessible aryl chloride is used to form the C–P bond. Use of the $Ph_2P(O)H$ also avoids the need to simultaneously prepare $Ar_2P(O)M$. Further application of this approach to the synthesis of chiral ligands is ongoing.

Experimental section

General details

All reactions involving air- or moisture-sensitive reagents were carried out under an argon atmosphere. Toluene, DMF, 1,2-dichloroethane, DMSO, 1,4-dioxide, and CH_3CN were distilled from appropriate drying agents prior to use. All chemicals were purchased from Aldrich and J&K Chemical and used without further purification. Thin-layer chromatography (TLC) was performed using 60 mesh silica gel plates visualized with short-wavelength UV light (254 nm). Silica gel 60 (230–400 mesh) was used for column chromatography. ^1H NMR and ^{13}C NMR spectra were recorded on a 400 instrument (400 MHz for ^1H and 100 MHz for ^{13}C). Chemical shifts (δ) were measured in ppm relative to TMS = 0.0 for ^1H, or to chloroform = 77.0 for ^{13}C as the internal standard. Data were reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants, J, are reported in hertz. Mass data were measured with a Thermo Scientific DSQ II mass spectrometer. IR spectra were recorded on an FT-IR spectrometer and only major peaks are reported in cm^{-1}.

Typical procedure for the preparation of diphenylphosphine oxides of 2a–2h

An oven-dried 10 mL screw-capped vial was charged with aryl chloride (0.5 mmol, 1.0 equiv.), $NiCl_2(PPh_3)_2$ (0.01 mmol, 2 mol%), K_2CO_3 (0.75 mmol, 1.5 equiv.), and $Ph_2P(O)H$ (0.6 mmol, 1.2 equiv.). Then, the vial was purged and filled with Ar three times. After DMF (3.0 mL) was added with a syringe, the reaction mixture was stirred at 50 °C for about 8 to 10 hours. After completion of the reaction, the mixture was cooled to room temperature and $CHCl_3$ (50 mL) and water (50 mL) were added. The organic layer was isolated and the remaining aqueous phase was further extracted with $CHCl_3$ (50.0 mL × 3). The combined organic extracts were washed with saturated brine (50.0 mL × 3) and dried over Na_2SO_4. The desired products of **2a–2f** were obtained in corresponding yields after purification by flash chromatography on silica gel.

2a, White solid, 86% yield, mp 194–196 °C; ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 28.78; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.72–8.73 (d, J = 4.0 Hz, 1 H), 8.34–8.39 (q, J = 7.2 Hz, 1 H), 8.13–8.15 (d, J = 8.4 Hz, 1 H), 8.00–8.02 (d, J = 8.0 Hz, 1 H), 7.82–7.87 (m, 4 H), 7.62–7.66 (t, J = 7.6 Hz, 1 H), 7.44–7.48 (m, 1 H), 7.32–7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 149.78, 148.03, 147.98, 137.35, 137.27, 136.04, 134.23, 133.16, 132.77, 132.74, 132.23, 132.12, 131.82, 131.22, 131.19, 130.81, 128.25, 128.18, 127.95, 127.82, 126.0, 125.89, 121.45; IR (neat, cm^{-1}): 3429.9, 3058.4, 1461.7, 1173.5, 1119.4, 725.1, 563.1; MS (ESI): $[M + H]^+$, 330.2.

2b, White solid, 87% yield, mp 111–113 °C; ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 20.37; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.33–8.36 (m, 1 H), 8.27–8.30 (m, 1 H), 8.15–8.27 (d, J = 7.2 Hz, 1 H), 7.98–8.13 (m, 4 H), 7.82–7.84 (d, J = 8.4 Hz, 1 H), 7.70–7.72 (m, 1 H), 7.57–8.59 (d, J = 7.2 Hz, 1 H), 7.41–7.56 (m, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 157.63, 156.34, 148.09, 147.88, 136.05, 135.96, 132.89, 132.10, 132.01, 131.86, 131.80, 131.77, 131.68, 131.65, 130.15, 129.90, 128.41, 128.29, 128.21, 128.09, 128.02, 127.73, 123.29, 123.07; IR (neat, cm^{-1}): 3430.4, 3055.2, 1585.3, 1436.7, 1191.7, 1118.5, 723.2, 564.9; MS (ESI): $[M + H]^+$, 330.2.

2c, White solid, 84% yield, mp 192–193 °C; ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 28.40; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.42–9.44 (d, J = 8.8 Hz, 1 H), 8.61–8.63 (d, J = 5.6 Hz, 1 H), 7.83–7.88 (m, 5 H), 7.68–7.74 (m, 2 H), 7.61–7.65 (t, J = 7.2 Hz, 1 H), 7.50–7.53 (m, 2 H), 7.42–7.47 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 156.46, 155.17, 141.75, 141.53, 136.15, 136.08, 133.54, 132.50, 132.24, 132.15, 132.03, 131.92, 131.71, 131.68, 131.49, 130.56, 128.53, 128.41, 128.28, 128.16, 127.29, 127.20, 127.19, 122.97, 122.94; IR (neat, cm^{-1}): 3054.4, 1435.5, 1174.5, 1117.0, 752.4, 697.9; MS (ESI): $[M + H]^+$, 330.2.

2d, White solid, 85% yield, mp 98–100 °C; ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 18.71; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.31–8.34 (m, 1 H), 8.21–8.23 (m, 1 H), 8.09–8.13 (m, 4 H), 7.42–7.46 (m, 7 H), 7.34–7.37 (d, J = 8.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 156.08, 155.96, 154.64, 140.44, 140.23, 135.84, 135.75, 133.12, 132.47, 132.15, 132.09, 132.06, 131.88, 131.55, 131.52, 130.61, 130.49, 129.26, 129.23, 128.84, 128.71, 128.48, 128.31, 128.19, 128.07, 123.64, 123.43, 119.44, 108.97, 56.38, 56.34; IR (neat, cm^{-1}): 3426.8, 2927.8, 1725.9, 1554.2, 1460.2, 1437.3, 1197.7, 1104.8, 725.4, 579.0; MS (ESI): $[M + H]^+$, 360.2.

2e, White solid, 70% yield, mp 150–152 °C; ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 20.98; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.61–8.63 (d, J = 4.8 Hz, 1 H), 8.17–8.19 (d, J = 6.4 Hz, 1 H), 7.86–7.91 (m, 4 H), 7.49–7.53 (m, 2 H), 7.41–7.46 (m, 4 H), 7.18–7.19 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 156.41, 155.10, 150.02, 149.82, 147.67, 147.58, 132.80, 132.09, 131.99, 131.78, 131.76, 129.38, 129.18, 128.50, 128.38, 128.31, 128.19, 127.29, 127.20, 127.19, 126.04, 126.02, 122.97, 122.94, 21.02; IR (neat, cm^{-1}): 3440.1, 3056.6, 1589.2, 1433.3, 1193.0, 1154.9, 723.5, 693.5, 563.6; MS (ESI): $[M + H]^+$, 294.2.

2f, The reaction was carried out at 70 °C. White solid, 71% yield; recovery start material: 17%; ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 20.98; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.89–7.91 (m, 1 H), 7.67–7.75 (m, 4 H), 7.56–7.61 (m, 2 H), 7.44–7.52 (m, 7H), 3.77–3.81 (t, J = 4.8 Hz, 1 H), 3.64–3.68 (t, J = 8.4 Hz, 1 H), 3.47–3.54 (q, J = 8.8 Hz, 1 H), 3.77–3.81 (dt, J = 6.8 Hz, 1 H), 3. 0.86–0.87 (d, J = 6.8 Hz, 1 H), 0.75–0.77 (d, J = 6.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 163.19, 134.86, 134.75, 134.05, 133.82, 132.99, 132.76, 132.55, 132.49, 132.21, 131.78, 131.74, 131.64, 131.40, 131.34, 131.30, 131.25, 131.22, 130.81, 130.72, 130.20, 130.08, 128.52, 128.29, 128.16, 77.32, 77.00, 76.68, 72.73, 70.71, 32.61, 19.09, 18.50; IR (neat, cm^{-1}): 3424.4, 3053.1, 1590.8, 1436.7, 1128.9, 726.4, 695.0; MS (ESI): $[M + H]^+$, 390.3.

2g, The reaction was carried out at 70 °C. White solid, 61% yield, mp 181–183 °C; ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 28.94; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.82–7.85 (m, 1 H), 7.63–7.75 (m, 6 H), 7.53–7.56 (t, J = 7.6 Hz, 1 H), 7.45–7.49 (t, J = 7.2 Hz, 2 H), 7.37–7.41 (m, 4 H), 4.06 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 163.88, 134.88, 134.78, 133.56, 132.99, 132.50, 132.00, 131.92, 131.90, 131.76, 131.66, 131.42, 131.39, 131.36, 131.33, 131.30, 131.23, 129.65, 129.53, 128.14, 128.02, 39.06, 39.04; IR (neat, cm^{-1}): 3433.6, 3055.2, 1438.4, 1190.2, 1116.6, 752.8, 704.4, 545.1; MS (ESI): $[M + H]^+$, 361.3.

2h, White solid, 83% yield, mp 162–164 °C; ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 30.57; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 9.01–9.02 (d, J = 4.4 Hz, 1 H), 8.58–8.61 (d, J = 8.8 Hz, 1 H), 3.70–3.76 (q, J = 7.2 Hz, 2 H), 1.10–1.04 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 167.03, 166.97, 148.88, 148.82, 147.93, 147.85, 137.94, 137.06, 132.46, 132.37, 132.34, 132.19, 132.08, 131.96, 131.89, 131.40, 131.35, 130.64, 130.30, 130.29, 128.59, 128.46, 128.37, 128.31, 128.26, 127.94, 127.46, 127.39, 62.10, 13.55; IR (neat, cm^{-1}): 3424.7, 1726.3, 1568.1, 1488.5, 1437.7, 1187.4, 1113.2, 793.8, 696.5; MS (ESI): $[M + H]^+$, 402.3.

Typical procedure for the preparation of diphenylphosphine oxides of 2i–2v

An oven-dried 10 mL screw-capped vial was charged with aryl chloride (0.5 mmol, 1.0 equiv.), $Ni(DME)_2Cl_2$ (0.025 mmol, 5 mol%), NaO^tBu (0.75 mmol, 1.5 equiv.), and $Ph_2P(O)H$ (0.6 mmol, 1.2 equiv.). Then the vial was purged and filled with Ar three times. After DMF (3.0 mL) was added by a syringe, the reaction mixture was stirred at 90 °C for about 8 to 10 hours. After completion of the reaction, the mixture was cooled to room temperature and $CHCl_3$ (50 mL) and water (50 mL) were added. The organic layer was isolated and the remaining aqueous phase was further extracted with $CHCl_3$ (50.0 mL × 3). The combined organic extracts were washed with saturated brine (50.0 mL × 3) and dried over Na_2SO_4. The desired products of **2g–2t** were obtained in the corresponding yields after purification by flash chromatography on silica gel.

2i, White solid, 51% yield, mp 128–130 °C; ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 29.05; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.64–7.69 (m, 4 H), 7.51–7.58 (m, 4 H), 7.43–7.47 (m, 4 H), 7.26–7.27 (d, J = 4.4 Hz 2 H), 2.40 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 142.42, 142.39, 133.38, 132.35, 132.16, 132.10, 132.06, 132.00, 131.88, 131.79, 131.76, 129.73, 129.29, 129.16, 128.67, 128.52, 128.47, 128.40, 128.35, 21.57; IR (neat, cm^{-1}): 3431.8, 3051.5, 1600.4, 1438.2, 1185.7, 1118.7, 752.1, 698.3, 542.0; MS (ESI): $[M + H]^+$, 293.2.

2j, White solid, 85% yield, mp 137–139 °C; ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 27.70; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.74–7.83 (m, 4 H), 7.58–7.68 (m, 6 H), 7.48–7.52 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 138.90, 137.92, 132.60, 132.50, 132.46, 131.98, 131.88, 131.64, 130.59, 128.82, 128.70, 117.80, 115.58, 115.55; IR (neat, cm^{-1}): 3430.3, 3045.1, 2230.2, 1434.3, 1198.6, 1115.5, 751.8, 696.9, 564.1; MS (ESI): $[M + H]^+$, 304.2.

2k, White solid, 49% yield, mp 108–109 °C; ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 27.70; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.74–7.83 (m, 4 H), 7.58–7.68 (m, 6 H), 7.48–7.52 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 135.98, 135.89, 135.75, 135.40, 135.29, 135.05, 135.02, 134.75, 132.52, 132.50, 132.05, 131.96, 131.86, 131.59, 130.54, 129.44, 129.33, 128.85, 128.72, 128.48, 128.35, 117.78, 113.09, 112.96; IR (neat, cm^{-1}): 3433.5, 3054.9, 2228.2, 1436.0, 1196.5, 1115.9, 752.8, 695.3, 542.6; MS (ESI): $[M + H]^+$, 304.2.

2l, White solid, 56% yield, mp 194–196 °C; ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 26.76; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.74–7.78 (m, 1 H), 7.64–7.69 (m, 5 H), 7.48–7.61 (m, 4 H), 7.39–7.44 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 136.85, 135.90, 135.02, 134.94, 134.06, 133.98, 132.48, 132.45, 132.21, 132.09, 131.98, 131.94, 131.81, 130.95, 130.54, 130.43, 129.88, 128.79, 128.65, 128.53; IR (neat, cm^{-1}): 3421.8, 3054.8, 2224.3, 1463.8, 1195.3, 1119.4, 752.7, 699.0, 545.7; MS (ESI): $[M + H]^+$, 304.2.

2m, White solid, 46% yield, mp 89–90 °C; ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 27.98; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.80–7.85 (dd, J = 7.6 Hz, 2H), 7.64–7.74 (m, 6 H), 7.56–7.61 (m, 2 H), 7.74–7.51 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 137.26, 136.27, 133.41, 133.12, 133.09, 132.19, 132.09, 131.97, 131.95, 131.74, 131.67, 131.57, 130.70, 128.38, 128.26, 125.01, 124.98, 124.93, 124.89, 124.86, 124.50; IR (neat, cm^{-1}): 3435.1, 3053.8, 1437.7, 1398.0, 1329.1, 1198.1, 1118.9, 739.7, 535.9; MS (ESI): $[M + H]^+$, 347.2.

2n, White solid, 47% yield, mp 106–108 °C; ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 29.02; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.63–7.69 (m, 4 H), 7.51–7.61 (m, 4 H), 7.43–7.47 (m, 4 H), 6.95–6.98 (m, 2 H), 3.84 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 162.48, 162.45, 133.99, 133.93, 133.87, 133.82, 133.48, 132.44, 132.06, 131.96, 131.76, 131.73, 128.46, 128.40, 128.33, 124.11, 123.01, 55.30; IR (neat, cm^{-1}): 3433.3, 3067.6, 1461.7, 1437.8, 1258.7, 1182.2, 1118.7, 756.0, 697.7, 536.4; MS (ESI): $[M + H]^+$, 309.2.

2o, White solid, 51% yield, mp 133–135 °C; ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 37.01; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.99 (s, 1 H), 8.52–8.55 (m, 1 H), 7.57–7.66 (m, 6 H), 7.47–7.53 (m, 5 H), 6.94–7.04 (m, 2 H), 2.09 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 168.93, 144.22, 144.19, 133.31, 133.29, 132.67, 132.56, 132.44, 132.41, 131.98, 131.94, 131.88, 130.89, 128.74, 128.62, 122.59, 122.46, 121.99, 121.92, 117.55, 116.55, 24.92; IR (neat, cm^{-1}): 3438.4, 3307.7, 3107.4, 1694.5, 1458.7, 1436.0, 752.7, 697.7, 542.2; MS (ESI): $[M + H]^+$, 336.3.

2p, White solid, 79% yield, mp 164–166 °C; ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 19.73; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.88–8.90 (d, J = 4.8 Hz, 2 H), 7.90–7.94 (m, 4 H), 7.52–7.54 (m, 2 H), 7.46–7.47 (m, 4 H), 7.37–7.39 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 168.32, 166.73, 156.80, 156.66, 131.99, 131.89, 131.32, 130.28, 128.16, 128.04, 121.59; IR (neat, cm^{-1}): 3430.6, 3053.0, 1554.6, 1391.3, 1183.2, 724.3, 697.4, 536.3; MS (ESI): $[M + H]^+$, 281.2.

2q, White solid, 71% yield, mp 174–176 °C; ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 32.43; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.58–8.60 (d, J = 8.0 Hz, 1 H), 8.00–8.02 (d, J = 8.0 Hz, 1 H), 7.87–7.89 (d, J = 8.0 Hz, 1 H), 7.66–7.71 (m, 4 H), 7.51–7.56 (m, 2 H), 7.41–7.49 (m, 6 H), 7.35–7.40 (m, 1 H), 7.27–7.32 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 133.84, 133.75, 133.64, 133.57, 133.23, 133.20, 132.16, 132.03, 131.93, 131.85, 131.82, 129.30, 128.70, 128.58, 128.46, 128.29, 127.53, 127.47, 127.29, 126.42, 124.14, 124.00; IR (neat, cm^{-1}): 3429.9, 3055.8, 1433.5, 1188.3, 1145.4, 777.0, 696.0, 54 539; MS (ESI): $[M + H]^+$, 329.2.

2r, White solid, 53% yield, recovery start material: 28%; mp 205–206 °C; ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 21.42; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.75–7.80 (m, 4 H), 7.50–7.52 (m, 2 H), 7.42–7.46 (m, 8 H) 7.35–7.37 (d, J = 8.4 Hz, 2 H), 7.23–7.29 (m, 2 H), 7.05–7.09 (t, J = 4.8 Hz 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 138.32, 138.22, 137.45, 137.26, 134.51, 133.44, 131.81, 131.70, 131.60, 131.57, 128.81, 128.72, 128.43, 128.31, 122.81, 121.40, 121.18, 109.86, 105.34, 104.06, 33.30; IR (neat, cm^{-1}): 3434.6, 3051.7, 1512.4, 1463.5, 1172.1, 1117.8, 761.7, 547.9; MS (ESI): $[M + H]^+$, 332.2.

2s, White solid, 51% yield, recovery start material: 42%; mp 240–246 °C; ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 33.14; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.34–8.36 (d, J = 7.2 Hz, 1 H), 8.20–8.21 (d, J = 4.0 Hz, 1 H), 8.20–8.17 (d, J = 8.0 Hz, 1 H), 8.02–8.05 (m, 1 H), 7.89–7.91 (m, 1 H), 7.70–7.75 (m, 6 H), 7.25–7.39 (m, 7 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 145.20, 143.55, 137.85, 137.61, 137.50, 136.71, 134.81, 134.51, 134.43, 133.39, 133.35, 132.82, 132.80, 130.54, 130.44, 129.90, 129.87, 129.27, 128.25, 128.10, 127.97, 127.85, 127.36, 127.22, 127.04, 126.07, 122.00; IR (neat, cm^{-1}): 3428.9, 3042.1, 1434.1, 1190.9, 719.7, 696.8, 560.7, 538.9; MS (ESI): $[M + H]^+$, 380.3.

2t, White solid, 48% yield, mp 154–156 °C; ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 20.03; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.19–8.21 (d, J = 8.0 Hz, 1 H), 7.94–8.03 (m, 5 H), 7.48–7.60 (m, 8 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 167.41, 166.15, 155.45, 155.23, 136.78, 132.62, 132.60, 131.97, 131.87, 131.49, 130.41, 128.69, 128.56, 126.64, 126.59, 124.74, 122.08; IR (neat, cm^{-1}): 3433.8, 3051.3, 1465.0, 1198.7, 696.1, 536.1; MS (ESI): $[M + H]^+$, 336.2.

2u, Yellow solid, 76% yield; ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 30.14; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.62–8.60 (d, J = 9.2 Hz, 1 H), 8.28–8.30 (d, J = 8.8 Hz, 1 H), 7.69–7.74 (m, 6 H), 7.54–7.58 (dt, J = 1.2 Hz, 7.2 Hz, 2 H), 7.43–7.48 (m, 4 H), 7.31–7.35 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 148.57, 148.49, 134.91, 133.87, 132.21, 132.19, 131.52, 131.42, 130.53, 129.60, 129.02, 128.90, 128.29, 128.22, 127.09, 127.02, 126.66; IR (neat, cm^{-1}): 3436.1, 3056.1, 1458.3, 1169.0, 1115.3, 743.7, 697.0, 528.4; MS (ESI): $[M + H]^+$, 380.2.

2v, White solid, 76% yield, mp 145–147 °C; ^{31}P NMR ($CDCl_3$, 162 MHz): δ = 20.36; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.21–8.22 (d, J = 4.4 Hz, 1 H), 8.13–8.16 (d, J = 8.4 Hz, 1 H), 7.97–8.04 (m, 5 H), 7.71–7.75 (m, 1 H), 7.60–7.64 (m, 1 H),

7.41–7.48 (m, 2 H), 7.41–7.46 (m, 4 H), 2.76 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 157.16, 155.87, 147.99, 147.77, 144.87, 144.78, 133.09, 132.23, 132.14, 132.06, 131.72, 131.69, 130.96, 130.84, 129.56, 128.27, 128.22, 128.15, 127.85, 124.08, 123.87, 18.71; IR (neat, cm^{-1}): 3439.5, 3056.6, 1733.3, 1584.8, 1438.1, 1193.0, 1116.5, 726.4, 696.6; MS (ESI): $[M + H]^+$, 344.3.

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