REVIEW ARTICLE

New Developments on the Hirao Reactions, Especially from "Green" Point of View

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Abstract: *Background*: The Hirao reaction discovered *ca.* 35 years ago is an important P–C coupling protocol between dialkyl phosphites and aryl halides in the presence of $Pd(PPh_3)_4$ as the catalyst and a base to provide aryl phosphonates. Then, the reaction was extended to other *P*-reagents, such as secondary phosphine oxides and *H*-phosphinates and to other aryl and hetaryl derivatives to afford also phosphinic esters and tertiary phosphine oxides. Instead of the $Pd(PPh_3)_4$ catalyst, $Pd(OAc)_2$ and Ni-salts were also applied as catalyst precursors together with a number of mono- and bidentate *P*-ligands.

Objective: In our review, we undertook to summarize the target reaction with a special stress on the developments attained in the last 6 years, hence this paper is an update of our earlier reviews in a similar topic.

Conclusions: "Greener" syntheses aimed at utilizing phase transfer catalytic and microwave-assisted approaches, even under "P-ligand-free. or even solvent-free conditions are the up-to date versions of the classical Hirao reaction. The mechanism of the reaction is also in the focus these days.

Keywords: Hirao reaction, P-C coupling, Pd-catalyst, phosphonates, phosphinates, phosphine oxides, green synthesis.

1. THE TRADITIONAL HIRAO REACTION

The Hirao reaction that is, a P-C coupling to furnish phosphonates or phosphine oxides, was reviewed 7 years ago by us [1, 2]. The purpose of this survey was to give an update on the newer developments. Of course, the most important precedents have also been summarized.

1.1. Palladium(0)-catalyzed Hirao Reactions

Hirao et al. described the first P-C coupling reaction between vinyl- or aryl halides and dialkyl phosphites in the presence of tetrakis(triphenylphosphine)palladium as the catalyst, applying organic bases in toluene as the medium, or without the use of any solvent (Scheme **1**) [3-5].

90-110 °C, 12 min-64 h
$Pd(PPh_3)_4$ (5 mol%)
base
toluene or solvent-free

3-98%
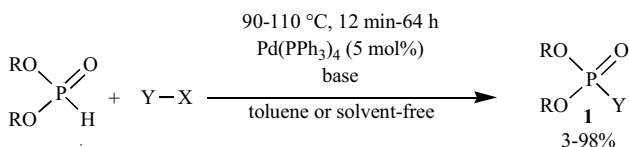
R = Et, ^iPr, Bu

Y = Ph, $4-MeOC_6H_4$, $4-HOC_6H_4$, $4-H_2NC_6H_4$, $4-MeC_6H_4$, $2-MeC_6H_4$, $2-HOCH_2C_6H_4$, $4-ClC_6H_4$, $4-BrC_6H_4$, $2-BrC_6H_4$, $2-MeO(O)CC_6H_4$, $4-MeNH(O)CC_6H_4$, $2-HO(O)CC_6H_4$, $4-Me(O)CC_6H_4$, $4-NCC_6H_4$, $4-O_2NC_6H_4$, 1-naphtyl, 3-piridyl, allyl, 1-cyclohexenyl, styryl, 1-phenylvinyl

X = I, Br

base: Et_3N, Bu_3N, pyridine

Scheme 1.

Then, the $Pd(PPh_3)_4$-catalyzed Hirao reaction was extended to a number of cases. Beside dialkyl phosphites [6-22], *H*-phosphinates

[23-28] and secondary phosphine oxides [29-31] were also reacted with aryl- and vinyl halides, or sulfonates [31-36]. The most commonly used bases were triethylamine and *N*, *N*-diisopropyl-ethylamine, but *N*-methyl morpholine was also used [24, 34]. The solvent may be toluene and THF [35], or dipolar aprotic solvents, *e.g.* acetonitrile [34, 37], DMF [33, 38] or DMSO [38]. The P-C coupling reaction of optically active *H*-phosphinates and alkylarylphosphine oxides proceeded with the complete retention of configuration [39-43].

1.2. P-C Coupling in the Presence of Metal Salts and Ligands
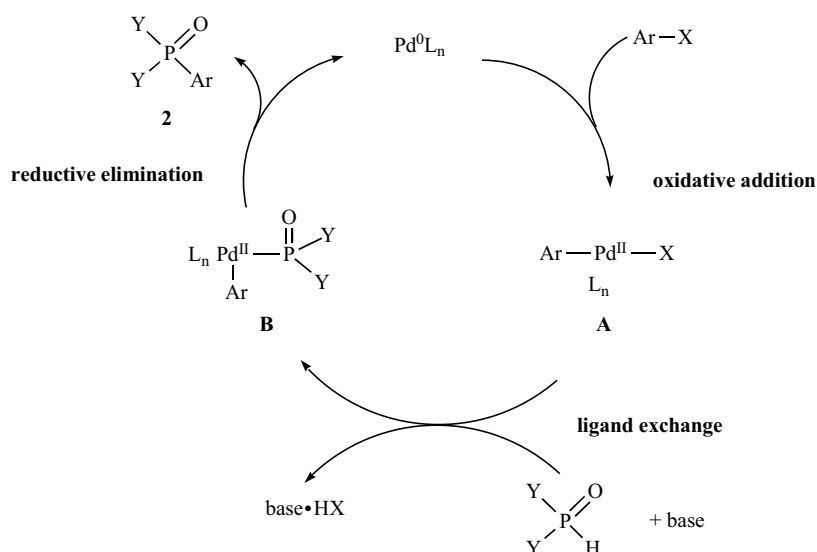
1.2.1. The use of Pd(II) Sources and P-ligands

The use of palladium-precursors (*e.g.* $Pd(OAc)_2$, $PdCl_2$ or even $Pd(dba)_2$) in combination with mono- and bidentate *P*-ligands is more user-friendly than applying the sensitive and rather expensive $Pd(PPh_3)_4$. In this case, the active catalyst is formed *in situ* by reduction of the Pd(II) to Pd(0).

The generally accepted catalytic cycle of the Hirao reaction [44] is similar to the mechanism of the well-known Pd-catalyzed C-C couplings [45], as it follows the classic three steps (Scheme **2**): the oxidative addition of the aryl (or vinyl) halide to the Pd^0L_n to form an "$Ar-Pd^{II}L_n-X$" complex (**A**). The next step is the ligand exchange, when the $Y_2P(O)H$ reagent enters the catalytic cycle and replaces the X^- anion in the Pd(II) complex. Finally, the reductive elimination from species **B** leads to the desired product (**2**), while the active Pd(0) catalyst is regenerated.
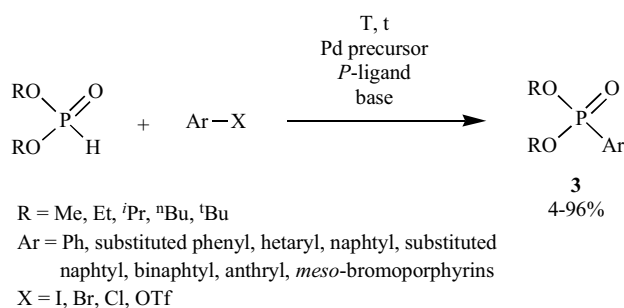
Investigation of the reaction mechanism revealed that, the trivalent tautomeric form (Y_2POH) of the $Y_2P(O)H$ reagent is involved in the change of ligands step [46, 47]. It should also be noted that the presence of PPh_3 and added anions may make the ligand substitution and the whole catalytic cycle more complex [48].

Arylphosphonates (**3**), important building blocks of biologically active compounds [51, 55, 56], flame retardants [54] or catalyst ligands [66, 67] may be easily synthetized by the Hirao reaction of dialkyl phosphites with aryl halides or triflates (Scheme **3**, Table **1**).

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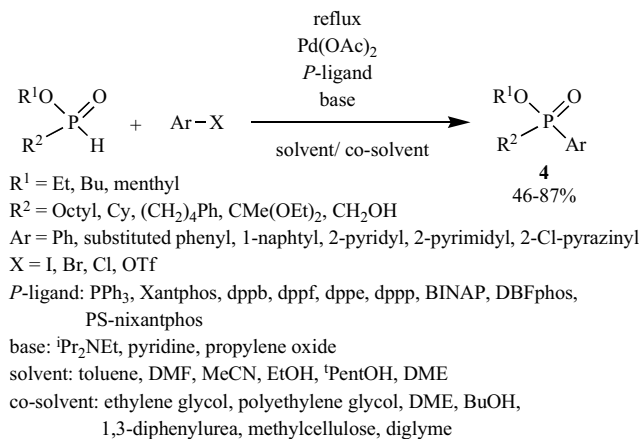
Scheme 2.

R = Me, Et, ^{i}Pr, ^{n}Bu, ^{t}Bu

Ar = Ph, substituted phenyl, hetaryl, naphtyl, substituted
     naphtyl, binaphtyl, anthryl, *meso*-bromoporphyrins

X = I, Br, Cl, OTf

3
4-96%

Scheme 3.

Several arylphosphonates were prepared in the presence of Pd(OAc)$_2$ and the simplest *P*-ligand, PPh$_3$ [49-57]. The addition of tetra-*n*-butylammoniumchloride, -bromide or -acetate as anionic additives could enhance the coupling reactions, when Pd(OAc)$_2$ was used as the catalyst precursor and PPh$_3$ as the ligand [44]. KOAc and NaOAc were also applied as ionic additives in the Hirao reaction [58-62]. In the presence of Pd(OAc)$_2$ or Pd(dba)$_2$ as the Pd precursor, dppf [58-65], dppb [58, 66-70], dppp [58] and BINAP [58] could also be used as ligands. Pd(dppf)$_2$Cl$_2$ was also a suitable catalyst to promote the coupling reaction of dialkyl phosphites [71, 72].

Using *H*-phosphinates as the reactant, both bromoarenes and less reactive chloroarenes were suitable substrates in the cross-coupling (Scheme **4**) [47, 48, 73-75]. The reactions were performed using Pd(OAc)$_2$ as the catalyst precursor and different ligands

(PPh$_3$, Xantphos, dppb, dppf, dppe, dppp, BINAP, DBFphos, PS-nixantphos), along with bases (^{i}Pr$_2$NEt, pyridine, propylene oxide). The best results were obtained applying Xantphos [47, 48, 73], dppb [74] or dppf [75] as the *P*-ligand, and *N,N*-diisopropylethylamine as the base. Employing a solvent/co-solvent system was beneficial, as it may support the tautomerization of the *P*-reagent, and thus the ligand-exchange step of the catalytic cycle. The Hirao reaction of (*R*)-menthyl(hydroxymethyl)-*H*-phosphinate (R^1 = menthyl, R^2 = CH$_2$OH) took place with the retention of the configuration at *P* [73].

R^1 = Et, Bu, menthyl

R^2 = Octyl, Cy, (CH$_2$)$_4$Ph, CMe(OEt)$_2$, CH$_2$OH

Ar = Ph, substituted phenyl, 1-naphtyl, 2-pyridyl, 2-pyrimidyl, 2-Cl-pyrazinyl

X = I, Br, Cl, OTf

P-ligand: PPh$_3$, Xantphos, dppb, dppf, dppe, dppp, BINAP, DBFphos,
         PS-nixantphos

base: ^{i}Pr$_2$NEt, pyridine, propylene oxide

solvent: toluene, DMF, MeCN, EtOH, ^{t}PentOH, DME

co-solvent: ethylene glycol, polyethylene glycol, DME, BuOH,
           1,3-diphenylurea, methylcellulose, diglyme

4
46-87%

Scheme 4.

Table 1.   The synthesis of arylphosphonates using Pd(II) precursors and *P*-ligands.

| Pd-precursor	*P*-Ligand	Base	Solvent	Reaction Conditions	Ref.
Pd(OAc)$_2$	PPh$_3$	Et$_3$N, Cy$_2$MeN, ^{i}Pr$_2$EtN	EtOH	reflux, 16-68 h	[49-56]
		Cs$_2$CO$_3$	toluene	110 °C, 18 h	[57]
Pd(OAc)$_2$	PPh$_3$, dppf, dppb, dppp, BINAP	Et$_3$N, ^{i}Pr$_2$NEt	THF, MeCN, DMF, DMSO, 1,4-dioxane, toluene	60-110 °C, 1.5-72 h	[44, 58-66]
Pd(OAc)$_2$, Pd(dba)$_2$	dppb	^{i}Pr$_2$NEt, Et$_3$N	DMSO, toluene	25-100 °C, 12-72 h	[66-70]
Pd(dppf)Cl$_2$		^{i}Pr$_2$NEt, Et$_3$N	MeCN, toluene	82-90 °C, 15-24 h	[71,72]
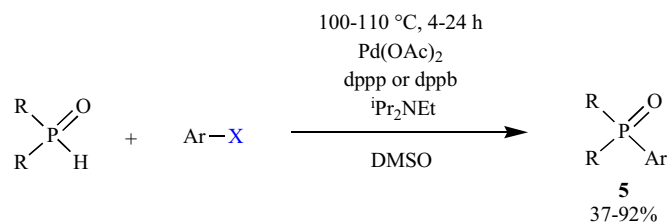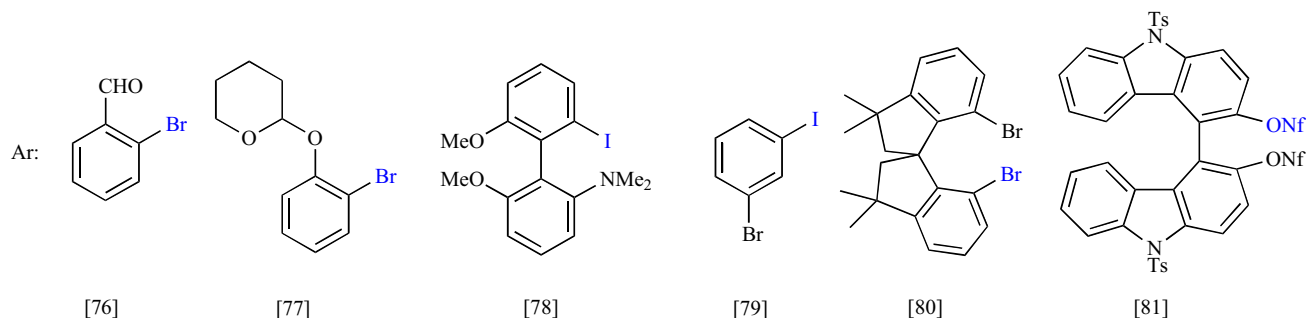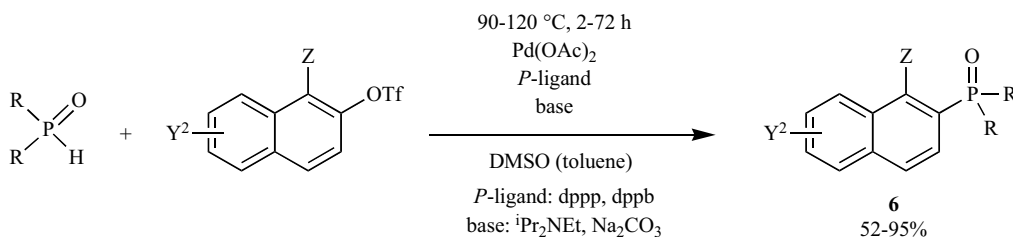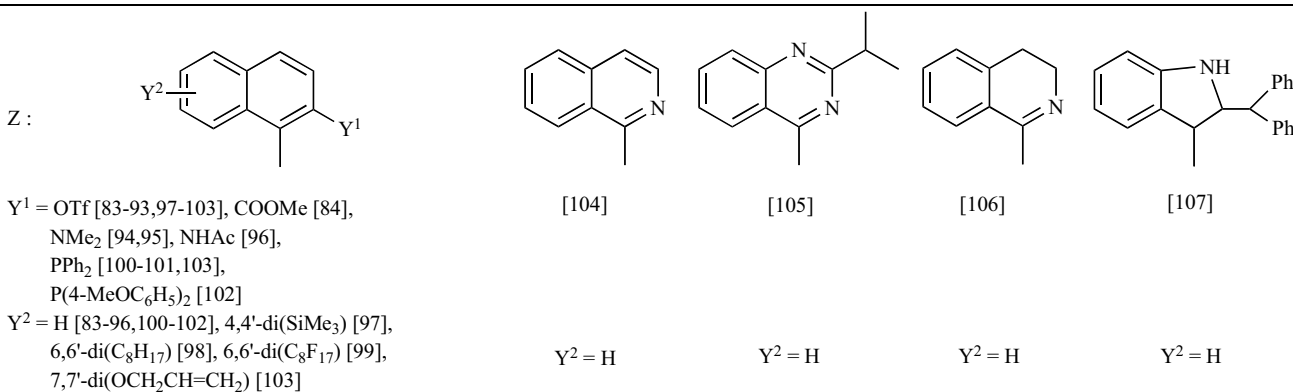
Scheme 5.

Scheme 6.

An important and widely investigated Pd-catalyzed Hirao reaction is the coupling of aromatic species and secondary phosphine oxides, as valuable tertiary phosphines that can be applied as ligands in transition metal complexes can be formed by the reduction of the resulting phosphine oxides. It became clear that the Pd(OAc)₂ - bidentate ligand (dppp or dppb) system has a high tolerance for functional groups (Scheme **5**) [76-81]. During the preparation of various *P*-containing ligands, the phosphorylation of 2-bromobenzaldehyde [76], 2-(2-bromophenoxy)tetrahydro-2*H*-pyran [77] and 2'-iodo-6,6'-dimethoxy-*N*,*N*-dimethyl-[1,1'-biphenyl]-2-amine [78] with diarylphosphine oxides took place in moderate to good yields (37-92%). The selective substitution of the iodide group of 3-bromoiodobenzene could be achieved in rather a good yield (65%) [79]. The cross-coupling of sterically hindered dibromo-3-spirobis(indene) [80] and a dinoflate bis carbazole

derivative [81] with diphenylphosphine oxide took also place with high selectivity.

BINAP (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) can be considered as the most powerful, and one of the most commonly used bidentate chiral ligands in asymmetric catalysis [82]. In the synthesis of BINAP derivatives (**6**), the reaction of axial chiral triflates and diaryl or dialkyl phosphine oxides is most often carried out applying Pd(OAc)₂ as the Pd precursor and ⁱPr₂NEt [83-102, 104-107] or Na₂CO₃ [103] as the base in DMSO (Scheme **6**). Both the (*R*) and (*S*) binaphyl structures could be functionalized in different ways. In the case of binaphthyl bistriflates, the selective phosphorylation of only one triflate unit was possible [83-93]. Hence, the bis-phosphonylation could not be realized, and a "bypass" procedure had to be developed for the preparation of
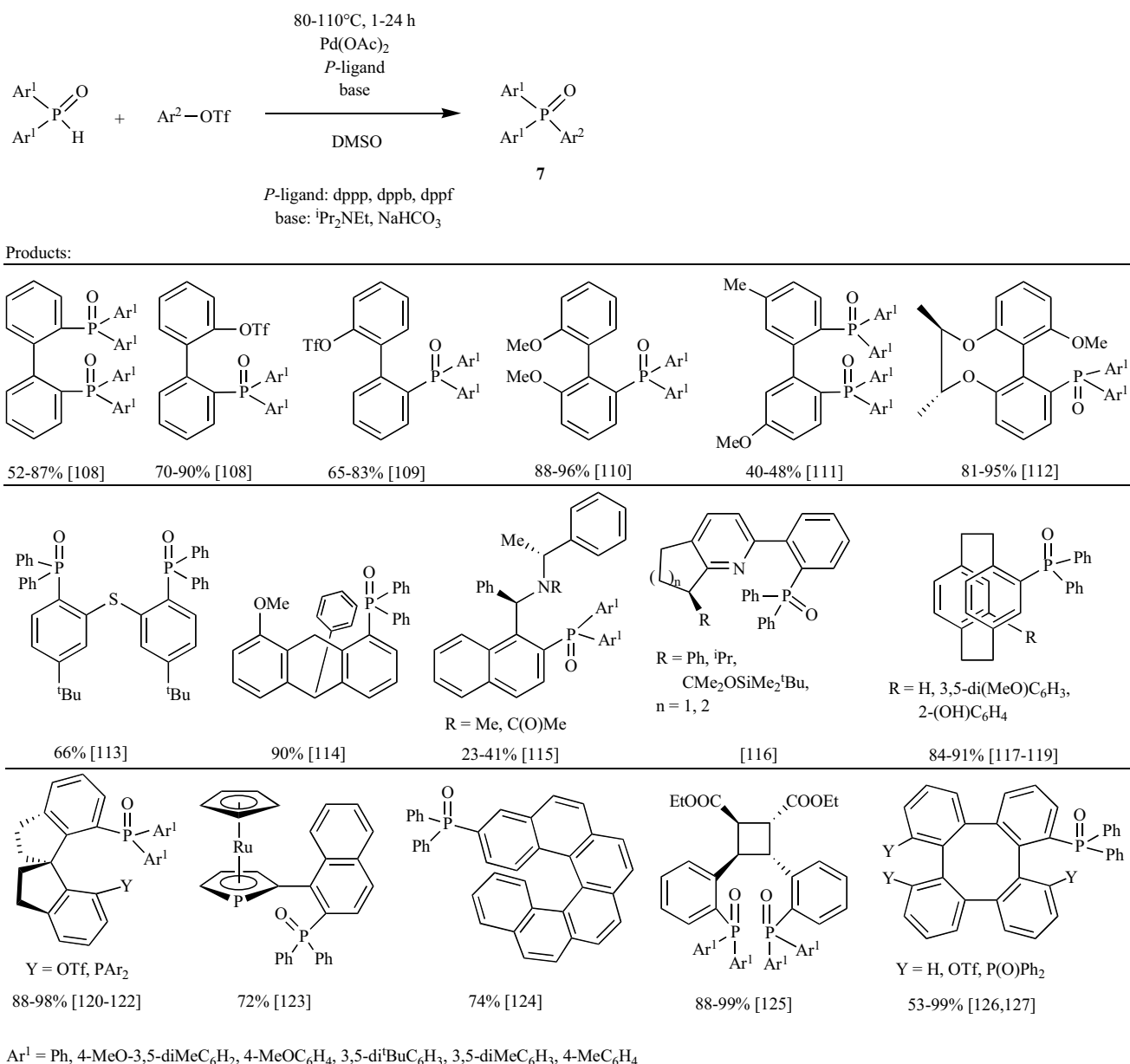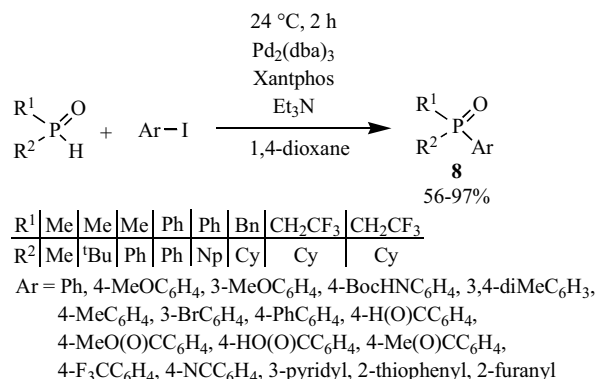
Scheme 7.

bisphosphines: after the mono-phosphonylation, the resulting phosphine oxide was reduced with a silane and then the second cross-coupling took place [100-103]. Heterocyclic analogs of BINAP as potential catalysts of new enantioselective approaches, such as biaryl isoquinolines (called Quinazolinaps) [104, 105], 1-aryl-3,4-dihydroisoquinolines (DHIQs) [106] and a new class of naphthyl-indole heterobiaryl skeletons [107] were also developed.
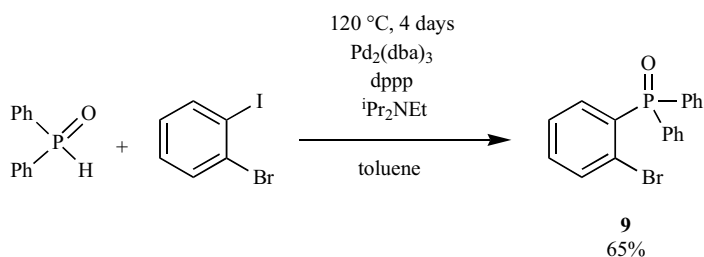
Synthesis of the representatives of other, even more complex aromatic tertiary phosphine oxides (**7**) is shown in Scheme 7 [108-127]. The coupling reaction of sterically hindered substrates means a real challenge and usually requires long reaction times. Despite the difficulties, selective mono- [108, 120-122], double [108, 111, 113, 125-127] and quadruple [125-127] phosphorylations could be achieved.

Beside Pd(OAc)$_2$, tris(dibenzylideneacetone)dipalladium(0) is also a suitable catalyst for P-C coupling reactions to afford tertiary phosphine oxides. A general method was developed for the reaction of aryl iodides and dialkyl-, alkylaryl- or diarylphosphine oxides in

the presence of Pd$_2$(dba)$_3$ and Xantphos using triethylamine as the base (Scheme **8**) [128].

R^1	Me	Me	Me	Ph	Ph	Bn	CH$_2$CF$_3$	CH$_2$CF$_3$
R^2	Me	^{t}Bu	Ph	Ph	Np	Cy	Cy	Cy

Ar = Ph, 4-MeOC$_6$H$_4$, 3-MeOC$_6$H$_4$, 4-BocHNC$_6$H$_4$, 3,4-diMeC$_6$H$_3$, 4-MeC$_6$H$_4$, 3-BrC$_6$H$_4$, 4-PhC$_6$H$_4$, 4-H(O)CC$_6$H$_4$, 4-MeO(O)CC$_6$H$_4$, 4-HO(O)CC$_6$H$_4$, 4-Me(O)CC$_6$H$_4$, 4-F$_3$CC$_6$H$_4$, 4-NCC$_6$H$_4$, 3-pyridyl, 2-thiophenyl, 2-furanyl
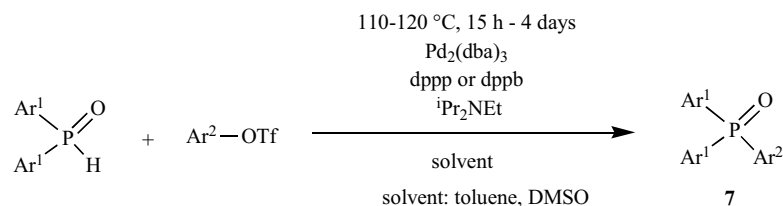
Scheme 8.

Scheme 9.

Ar^1 = Ph, 3,5-di^{t}Bu$_2$-4-MeOC$_6$H$_2$, 4-MeOC$_6$H$_4$, 3,5-diMeC$_6$H$_3$, 4-BuC$_6$H$_4$, 4-MeC$_6$H$_4$,
3-MeC$_6$H$_4$, 3,4-diFC$_6$H$_3$, 4-FC$_6$H$_4$, 4-PhC$_6$H$_4$, 4-F$_3$CC$_6$H$_4$, naphtyl, Cy

Ar^2:

98% [130]   74% [131]   27-71% [132-134]   51-75% [135]   20% [136]
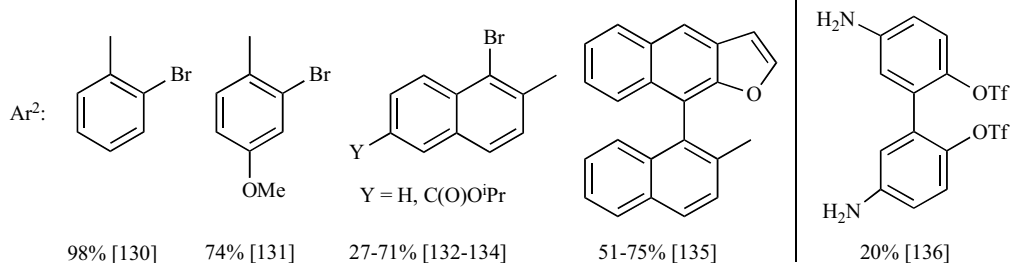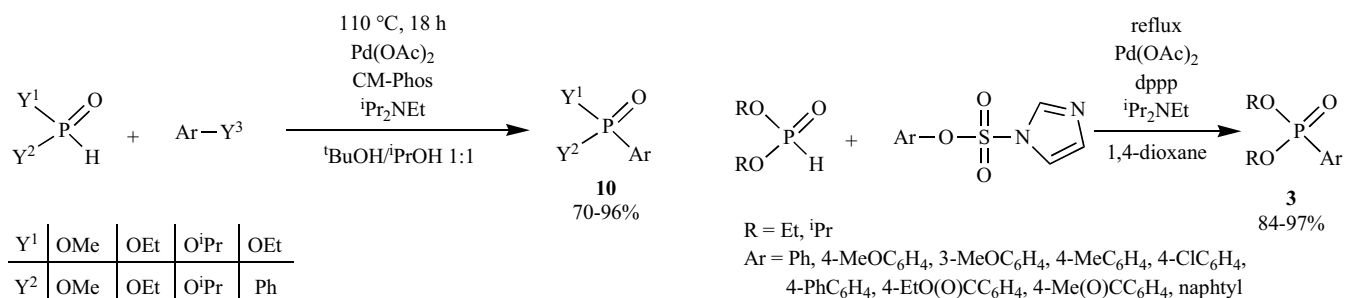
Scheme 10.

Y^1	OMe	OEt	O^{i}Pr	OEt
Y^2	OMe	OEt	O^{i}Pr	Ph

Y^3 = OTs, OMs
Ar = 4-MeOC$_6$H$_4$, 3-H$_2$NC$_6$H$_4$, 3-Me(O)CHNC$_6$H$_4$, 4-^{t}BuC$_6$H$_4$,
     4-EtO(O)CC$_6$H$_4$, 4-Ph(O)CC$_6$H$_4$, 2-MeO-4-Ph(O)CC$_6$H$_3$,
     1,3-benzodioxol-5-yl, 3-(1*H*-pyrrol-1-yl)C$_6$H$_4$,
     3-(thiophen-3-yl)C$_6$H$_4$, 2-methylbenzo[d]thiazol-5-yl,
     naphtyl, pyridyl, isoquinolinyl

Scheme 11.

(2-Bromophenyl)diphenylphosphine oxide (**9**) could be synthetized in a yield of 65% from 2-bromoiodobenzene by applying Pd$_2$(dba)$_3$ as the catalyst, and dppp as the *P*-ligand in toluene (Scheme **9**) [129].

A series of intermediates for *P*-ligands were synthesized by the reaction of aryl triflates and diaryl phosphine oxides using Pd$_2$(dba)$_3$ (Scheme **10**) [130-136]. The selective transformation of the triflate group of 2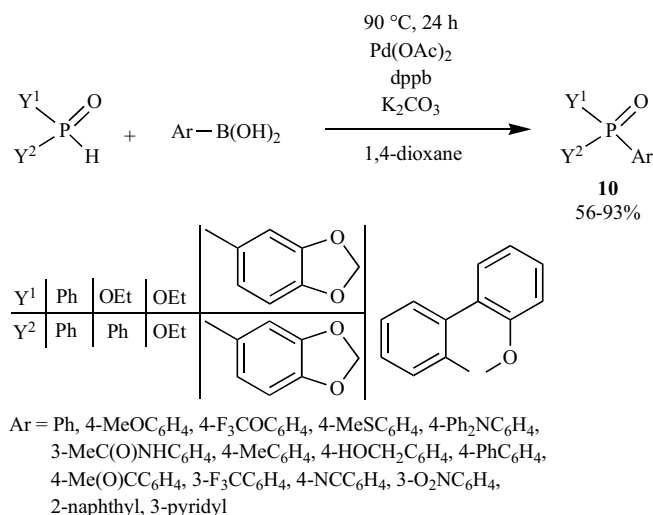-bromophenyl trifluoromethanesulfonate [130], 2-bromo-4-methoxyphenyl trifluoromethanesulphonate [131] and 1-bromonaphthalen-2-yl trifluoromethanesulfonates [132-134] could be achieved in the presence of a dppp ligand and *Hünig*-base

R = Et, ^{i}Pr
Ar = Ph, 4-MeOC$_6$H$_4$, 3-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$,
     4-PhC$_6$H$_4$, 4-EtO(O)CC$_6$H$_4$, 4-Me(O)CC$_6$H$_4$, naphtyl

Scheme 12.

in toluene. (1-(Naphtho[2,3-b]furan-9-yl)naphthalen-2-yl)diaryl-phosphine oxides were obtained by similar cross-coupling reactions employing dppb as the ligand and DMSO as the solvent [135]. A double P-C coupling of 5,5'-diamino-(1,1'-biphenyl)-2,2'-diyl bis(trifluoromethanesulfonate) with diphenylphosphine oxide *via N*-Boc-protection and acidic cleavage resulted in the corresponding product in a 20% overall yield [136].

Finally, methods are summarized that apply other substrates other than aryl halides or triflates. *Fu* et al. reported a convenient method for the coupling reaction of aryl tosylates or mesylates and dialkyl phosphites or ethyl phenyl-*H*-phosphinate. The best results were obtained using Pd(OAc)$_2$ as the catalyst with CM-Phos as the ligand and DIPEA as the base (Scheme **11**) [137].

Chinese researchers described the Pd-catalyzed reactions of dialkyl phosphites and aryl imidazolyl sulfonates (Scheme **12**) [138]. The reaction has a high tolerance of functional groups, although it cannot be regarded as an atom-efficient approach.

90 °C, 24 h
Pd(OAc)$_2$
dppb
K$_2$CO$_3$
1,4-dioxane

10
56-93%

Y^1	Ph	OEt	OEt		
Y^2	Ph	Ph	OEt		

Ar = Ph, 4-MeOC$_6$H$_4$, 4-F$_3$COC$_6$H$_4$, 4-MeSC$_6$H$_4$, 4-Ph$_2$NC$_6$H$_4$,
3-MeC(O)NHC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-HOCH$_2$C$_6$H$_4$, 4-PhC$_6$H$_4$,
4-Me(O)CC$_6$H$_4$, 3-F$_3$CC$_6$H$_4$, 4-NCC$_6$H$_4$, 3-O$_2$NC$_6$H$_4$,
2-naphthyl, 3-pyridyl

Scheme 13.

Arylboronic acids were reacted with diphenylphosphine oxide, ethyl phenyl-*H*-phosphinate or diethyl phosphite. The best results were obtained applying the Pd(OAc)$_2$-dppb system as the catalyst (Scheme **13**) [139].

The desulfitative cross-coupling reaction of sodium benzenesulfinate and dialkyl phosphites was performed in the presence of silver carbonate as the oxidant, and tetrabutyl-ammonium chloride (TBAC) as an additive (Scheme **14**) [140]. The role of Ag$_2$CO$_3$ has not been clarified.

80 °C, 9 h
Pd(PPh$_3$)$_2$Cl$_2$
TBAC
Ag$_2$CO$_3$
DMSO

3
80-95%

R = Me, ^{i}Pr, ^{n}Bu, ^{t}Bu, Bn

Ar = Ph, 4-MeOC$_6$H$_4$, 3-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$,
4-PhC$_6$H$_4$, 4-Et(O)CC$_6$H$_4$, 4-Me(O)CC$_6$H$_4$, naphtyl

Scheme 14.

50-120 °C, 6-24 h
NiCl$_2$L
base
solvent

2
28-97%

Y = OMe, Ph

Ar = 4-MeOC$_6$H$_4$, 4-Me(O)CHNC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-MeO(O)CC$_6$H$_4$,
4-Me(O)CC$_6$H$_4$, 3-Me(O)CC$_6$H$_4$, 4-F$_3$CC$_6$H$_4$, 4-NCC$_6$H$_4$,
3-NCC$_6$H$_4$, 2-NCC$_6$H$_4$, naphthyl, hetaryl

X = Br, Cl

L = (PPh$_3$)$_2$, dppp

base: K$_3$PO$_4$, K$_2$CO$_3$, ^{t}BuONa

solvent: 1,4-dioxane, DMF
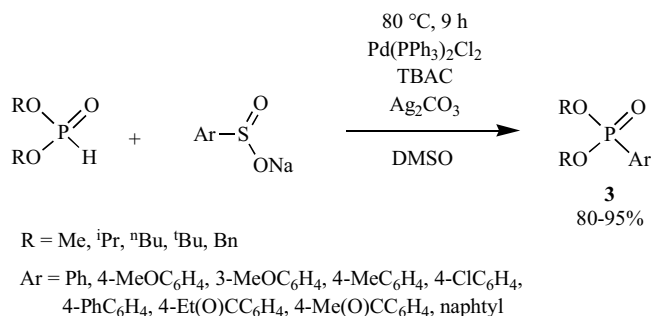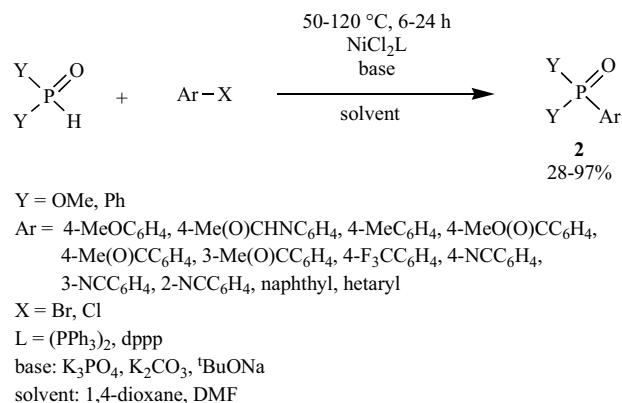
Scheme 15.

1.2.2. Nickel(II)-catalyzed Hirao Reactions

Beside the widely-used Pd catalysts, the cheaper Ni-precursors in combination with *P*- and *N*-ligands may also be used. However, this field is much less investigated. There are a few examples utilizing a Ni(II) precursor - ligand system. During the arylation of

dimethyl phosphite and diphenylphosphine oxide, NiCl$_2$ was combined with *P*-ligands (PPh$_3$ or dppp) (Scheme **15**) [141, 142].

The reaction of aryl boronic acids and >P(O)H reagents was performed in the presence of Ni(II) salts and *N*-ligands (Scheme **16**) [143].

100 °C, 24 h
Ni precursor / L
base
solvent

2
50-97%
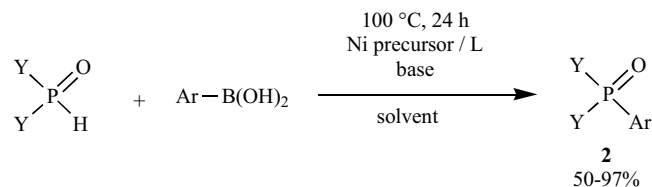
Y = Ph, 4-MeOC$_6$H$_4$, 4-Me$_2$NC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-FC$_6$H$_4$, Pent, OEt
Ar = Ph, 4-MeOC$_6$H$_4$, 4-F$_3$COC$_6$H$_4$, 4-MeC$_6$H$_4$, 2-MeC$_6$H$_4$, 4-FC$_6$H$_4$,
4-ClC$_6$H$_4$, 4-PhC$_6$H$_4$, 4-MeO(O)CC$_6$H$_4$, 4-Me(O)CC$_6$H$_4$,
4-F$_3$CC$_6$H$_4$, 2-naphthyl
Ni precursor: NiBr$_2$, NiCl$_2$, Ni(OAc)$_2$, Ni(acac)$_2$
L: pyridine, byp, tetramethylethylenediamine, 1,10-phenantroline
base: K$_2$CO$_3$, Cs$_2$CO$_3$, pyridine, Et$_3$N
solvent: dichloroethane, 1,4-dioxane, toluene, DMF

Scheme 16.

The coupling of aryl halides, mesylates and tosylates with >P(O)H species using Ni(II)-precursors and dppp or *N*-ligands and zinc dust led to the formation of triarylphosphine oxides, aryl-phosphonates and aryl-phosphinates (Scheme **17**) [144, 145]. According to the authors, the zinc powder was required for the reduction of Ni(II) to Ni(0).

70-150 °C, 15-48 h
Ni salt
L
Zn (1-2 eq.)
solvent

10
29-97%
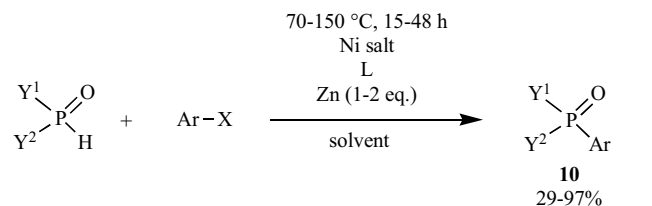
Y^1	OEt	OEt	4-MeOC$_6$H$_4$	3,5-diMeOC$_6$H$_3$	4-MeC$_6$H$_4$	4-F$_3$CC$_6$H$_4$
Y^2	OEt	Ph	4-MeOC$_6$H$_4$	3,5-diMeOC$_6$H$_3$	4-MeC$_6$H$_4$	4-F$_3$CC$_6$H$_4$

Ar = Ph, 4-MeOC$_6$H$_4$, 3-MeOC$_6$H$_4$, 4-HOC$_6$H$_4$, 4-H$_2$NC$_6$H$_4$,
3-H$_2$NC$_6$H$_4$, 2-H$_2$NC$_6$H$_4$, 4-MeC$_6$H$_4$, 3-MeC$_6$H$_4$, 2-MeC$_6$H$_4$,
4-PhC$_6$H$_4$, 4-MeO(O)CC$_6$H$_4$, 4-Me(O)CC$_6$H$_4$,
1,3-benzodioxol-5-yl, naphthyl

X = I, Br, OMs, OTs

Ni salt: NiCl$_2$, Ni(OAc)$_2$, Ni(NO$_3$)$_2$

L: dppf, pyridine, byp, dibenzylethylenediamine, dianilinoethane,
tetramethylethylenediamine

solvent: DMF, H$_2$O

Scheme 17.

1.2.3. Environmental-friendly Approaches

Over the past few years, "green" techniques including phase transfer catalysis (PTC) and microwave (MW) irradiation came into fashion.

The PTC-promoted Hirao reaction employing triethylbenzyl-ammonium chloride (TEBAC) was developed by *Beletskaya et al.* (Scheme **18**) [146-149]. The reaction of diethyl phosphite and bromoarenes performed in the presence of Pd(OAc)$_2$ gave better results using tris(2-furyl)phosphine as the *P*-ligand, as compared to the case applying triphenylphosphine [146, 147]. 6-Aryl-6*H*-dibenzo[*c*,*e*][1,2]oxaphosphorine 2-oxides were prepared by both Pd- and Ni-catalyzed PTC-assisted coupling reactions [148]. It is noteworthy that the solid-liquid phase coupling of "phosphorylated"

monosaccharides could also be performed under PTC conditions [149].
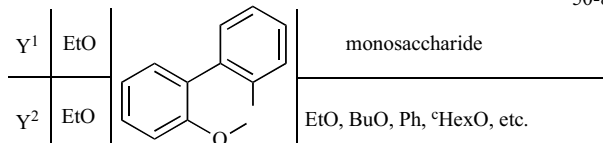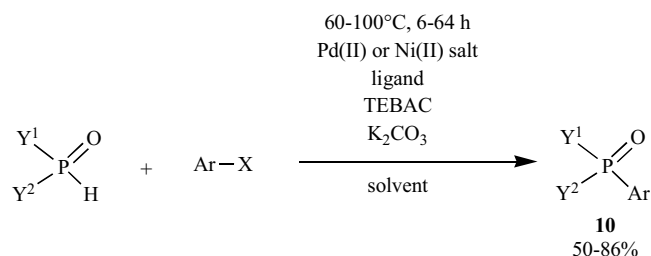
Ar = Ph, 4-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-EtO(O)CC$_6$H$_4$,
   4-HO(O)CC$_6$H$_4$, 4-NCC$_6$H$_4$, anthracenyl
X = I, Br
Pd(II) or Ni(II) salt: Pd(OAc)$_2$, PdCl$_2$, NiCl$_2$
ligand: PPh$_3$, P(2-furyl)$_3$
solvent: MeCN, 1,4-dioxane

Scheme 18.

The use of the MW technique in organic chemistry has spread. In this way, the yields and selectivity could be improved, the needless excess of reagents could be eliminated, and the catalytic-systems could be simplified [150]. In 1997, a Pd(PPh$_3$)$_2$Cl$_2$-catalyzed P-C coupling reaction performed in a Teflon autoclave placed in a kitchen MW oven was reported [151]. Ten years later, *Stawinski* et al. developed a general MW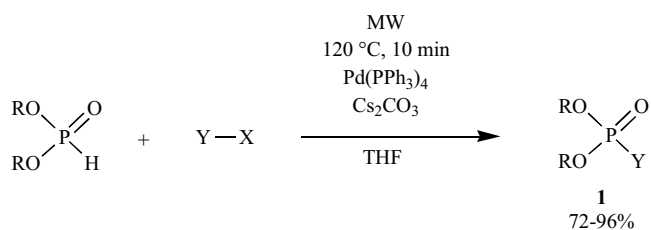-assisted method for the P-C coupling of dialkyl phosphites and substituted aryl, hetaryl and vinyl reagents in the presence of Pd(PPh$_3$)$_4$ as the catalyst, Cs$_2$CO$_3$ as the base, and THF as the solvent using a dedicated MW oven (Scheme **19**) [152].

R = Me, Et, ^{i}Pr, Bn
Y = Ph, 4-MeOC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$, naphthyl, phenanthryl,
   pyridyl, vinyl, 1-methylvinyl, 2-methylvinyl
X = I, Br, OTf

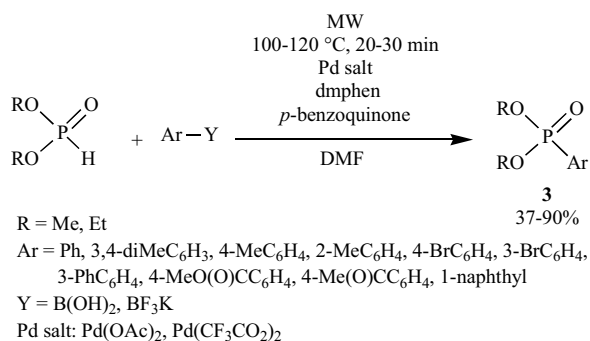**Scheme 19.**

Later on, the reaction of a wide range of substrates was carried out under MW irradiation. For example, the coupling of aryl boronic acids or aryltrifluoroborates and dialkyl phosphites was performed employing Pd salts as the catalyst precursor and dmphen as the ligand (Scheme **20**) [153].

Water-soluble tertiary phosphine oxides were prepared by the Pd/C catalyzed coupling reaction of halobenzoic acids and diphenylphosphine oxide in water (Scheme **21**) [154].

2. NOVEL DEVELOPMENTS ON THE HIRAO REACTION

Extensions and novel advances on the Hirao reaction attained in the last four years are presented in this chapter.

R = Me, Et
Ar = Ph, 3,4-diMeC$_6$H$_3$, 4-MeC$_6$H$_4$, 2-MeC$_6$H$_4$, 4-BrC$_6$H$_4$, 3-BrC$_6$H$_4$,
   3-PhC$_6$H$_4$, 4-MeO(O)CC$_6$H$_4$, 4-Me(O)CC$_6$H$_4$, 1-naphthyl
Y = B(OH)$_2$, BF$_3$K
Pd salt: Pd(OAc)$_2$, Pd(CF$_3$CO$_2$)$_2$

Scheme 20.

X = I, Br, Cl
Y = H, 4-Me, 4-MeO, 3-H$_2$N
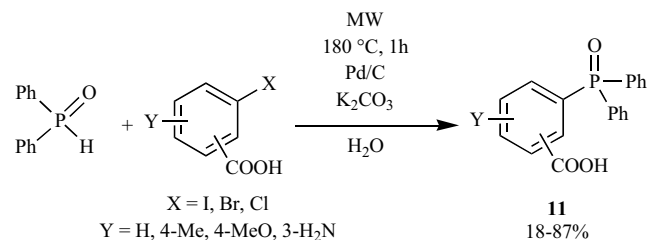
Scheme 21.

2.1. Extensions of the Pd-catalyzed Hirao Reaction

Optically active P(V) derivatives, the precursors of P(III) ligands are of importance. Beside resolution [155], enantioselective syntheses may also lead to optically active phosphine oxides [156-158]. Transition-metal-catalyzed cross-coupling reactions may also be suitable for the preparation of optically active phosphine oxides. The Pd(PPh$_3$)$_4$-catalyzed coupling of aryl halides and enantio-merically pure *tert*-butylphenylphosphine oxide carried out in the presence of K$_2$CO$_3$ as the base and toluene as the solvent afforded enantiomerically enriched (ee>78%) tertiary phosphine oxides in yields of 63-96% (Scheme **22**) [159].

Ar = Ph, 4-MeOC$_6$H$_4$, 2-Me$_2$NC$_6$H$_4$, 2-H$_2$NC$_6$H$_4$, 3-H$_2$NC$_6$H$_4$,
   4-H$_2$NC$_6$H$_4$, 4-^{t}BuC$_6$H$_4$, 2-HOCH$_2$C$_6$H$_4$, 4-F$_3$CC$_6$H$_4$,
   2-O$_2$NC$_6$H$_4$, 1-naphtyl, 2-thiophenyl, 3-thiophenyl,
   2-pyridyl, 9-anthracenyl
X = I, Br

Scheme 22.

Ar = Ph, 3,4-di(MeO)C$_6$H$_3$, 4-MeOC$_6$H$_4$, 2-MeOC$_6$H$_4$, 4-ClC$_6$H$_4$,
   1-(2-MeO-naphtyl)
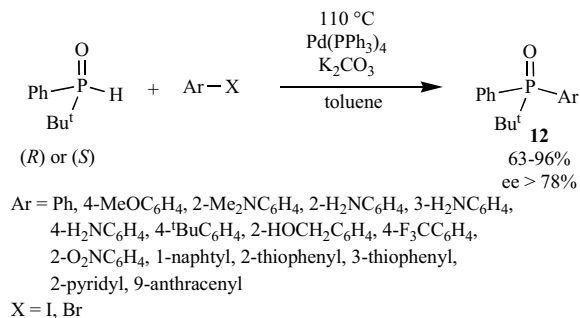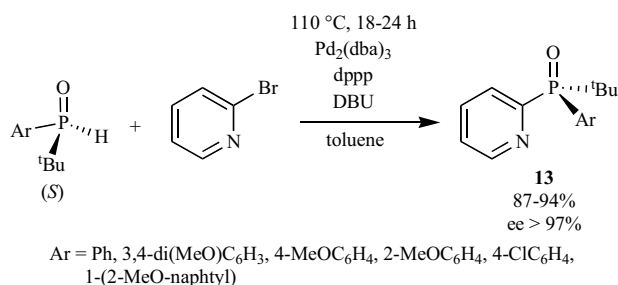
Scheme 23.

(*S*)-*Tert*-butyl-aryl phosphine oxides were coupled with 2-bromopyridine using Pd$_2$(dba)$_3$ as the catalyst, dppp as the ligand, and DBU as the base to give products **13** with excellent selectivity

Scheme 24.

Scheme 25.

R = Et, ^{i}Pr, Bu

Ar = Ph, 4-MeOC$_6$H$_4$, 3-MeOC$_6$H$_4$, 4-F$_3$COC$_6$H$_4$, 4-MeC$_6$H$_4$, 2-MeC$_6$H$_4$,
3,4-diFC$_6$H$_3$, 4-FC$_6$H$_4$, 3-FC$_6$H$_4$, 2-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 3-ClC$_6$H$_4$,
4-PhC$_6$H$_4$, 2-PhC$_6$H$_4$, 4-MeO(O)CC$_6$H$_4$, 4-Me(O)CC$_6$H$_4$, 4-F$_3$CC$_6$H$_4$,
3-F$_3$CC$_6$H$_4$, 2-F$_3$CC$_6$H$_4$, 4-NCC$_6$H$_4$, 1,3-benzodioxol-5-yl,
2,3-dihydro-1,4-benzodioxin-6-yl, 2$^-$(7-MeO)naphtyl, 2-thiophenyl

R'		Ms	Ts	Ts
R"		Ph	Ph	Me

base: Et$_3$N, Na$_2$CO$_3$, ^{i}Pr$_2$NEt

Scheme 26.

Y^1 = Me, 2-MeOC$_6$H$_4$, 3,5-di^{t}BuC$_6$H$_3$, 2-MeC$_6$H$_4$, 2-PhC$_6$H$_4$, 1-naphtyl
Y^2 = C(O)^{t}Bu, C(O)Me, C(O)CF$_3$, SO$_2$Ph
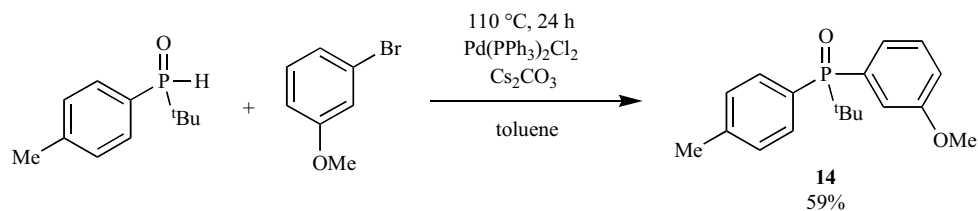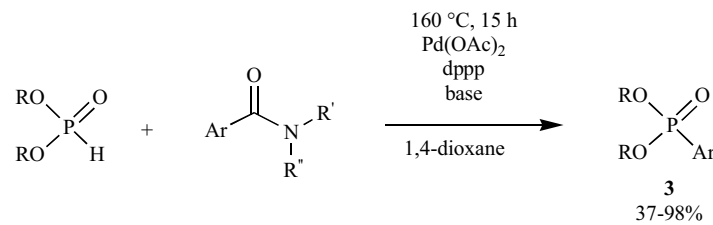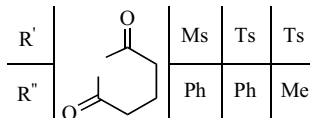Z = H, MeO, H$_2$N, Me, F, Cl, Br, MeO(O)C, O$_2$N

L*:
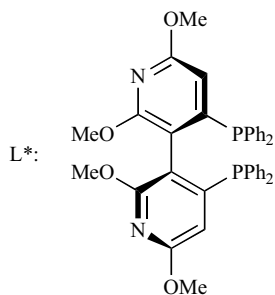
(ee>97%) (Scheme **23**) [160]. The retention of the *P*-atom was proved by single-crystal X-ray analysis.

Stankevič et al. prepared the *m*-anisyl-*t*-butyl-*p*-tolylphosphine oxide (**14**) by the Pd(PPh$_3$)$_2$Cl$_2$-catalyzed reaction of *t*-butyl-*p*-tolylphosphine oxide and 3-bromoanizole (Scheme **24**) [161].

The palladium-catalyzed Hirao reaction was extended to the phosphorylation of aryl amides (Scheme **25**) [162]. Substrates containing acyclic and cyclic *N*-activating groups were reacted with dialkyl phosphites. Mechanistic studies suggested that the course of

the reaction is similar to that of the original Hirao reaction of aryl halides, and the key step of the catalytic cycle is the insertion of the metal into the C-N bond.

A method for the arylation of *P*-stereogenic secondary phosphine oxides was developed to provide optically active tertiary phosphine oxides (**15**) (Scheme **26**) [163]. The P-C coupling of *ortho*-substituted aryl iodides carried out applying Pd(CF$_3$CO$_2$)$_2$ as the precursor for Pd(0) and a chiral ligand (**L***) furnished the target tertiary phosphine oxides (**15**) in moderate to good enantio-selectivities (ee: 19-83%).

Scheme conditions (top reaction):

100 °C, 2 h
PdCl$_2$
PPh$_3$
Ag$_2$O (2 eq.)
DMA

16
51-95%

R = Et, ^{i}Pr, ^{n}Bu, ^{s}Bu
Y = H, PrO, PhO, BnO, Me$_2$N, Me, F, Cl, Ph, Me(O)CHN, F$_3$C
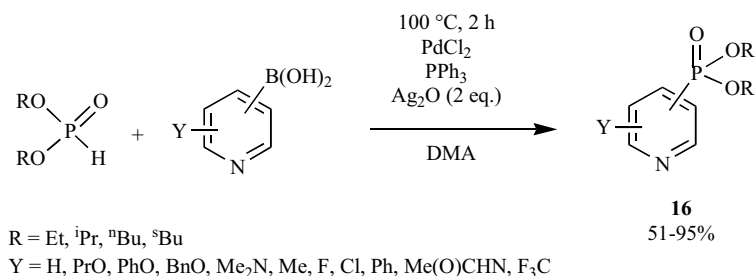
Scheme 27.

Chinese researchers reported a protocol for the P-C coupling of heteroaryl boronic acids and dialkyl phosphites in the presence of PdCl$_2$ and PPh$_3$, and in the absence of any base (Scheme **27**) [164]. At the same time, Ag$_2$O was needed as an additive, whose role has not been clarified.

Arylphosphonates (**3**) were prepared *via* C-Si bond cleavage by the reaction of arylsilanes and dialkyl phosphites performed in the presence of Pd(PPh$_3$)Cl$_2$ as the catalyst (Scheme **28**) [165]. Potassium fluoride is necessary to activate the arylsilane before its entering the catalytic cycle. Ag$_2$CO$_3$ was assumed as a reoxidant at the end of the catalytic cycle, however, this has not been proved.

Scheme conditions (Scheme 28 reaction):

80-100 °C, 12 h
Pd(PPh$_3$)$_2$Cl$_2$
KF (4 eq.)
Ag$_2$CO$_3$
DMF

ArSi(OEt)$_3$

3
31-94%

R = Me, Et, ^{i}Pr, Bu
Ar = Ph, 4-MeOC$_6$H$_4$, 3-MeOC$_6$H$_4$, 3,5-diMeC$_6$H$_3$, 4-^{t}BuC$_6$H$_4$,
  4-MeC$_6$H$_4$, 3-MeC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$,
  4-PhC$_6$H$_4$, 4-F$_3$CC$_6$H$_4$, 1,3-benzodioxol-5-yl, 1-thiophenyl,
  1-naphtyl

Scheme 28.

New magnetically recoverable heterogeneous palladium catalysts were developed to make the Hirao reaction environmentally more capable (Scheme **29**) [166-168]. At first, the Pd complex of an "*NNN*" princer ligand (BIP) supported on nanomagnetic γ-Fe$_2$O$_3$@SiO$_2$ was prepared, which proved to be a good catalyst in the cross-coupling reaction of diethyl phosphite and iodobenzene under solvent-free conditions [166]. The Pd complex of 2-aminothiophenol (Pd-2-ATP-γ-Fe$_2$O$_3$) [167] and DABCO (Pd-DABCO-γ-Fe$_2$O$_3$) [168] could be used 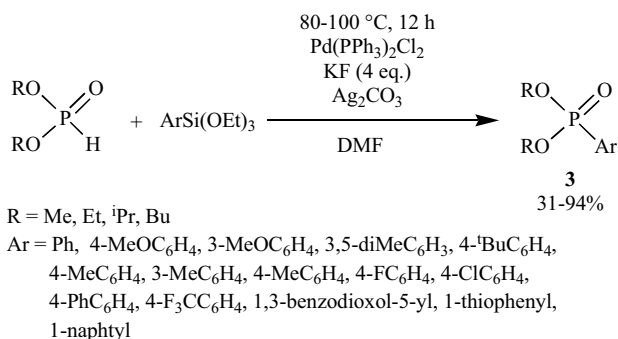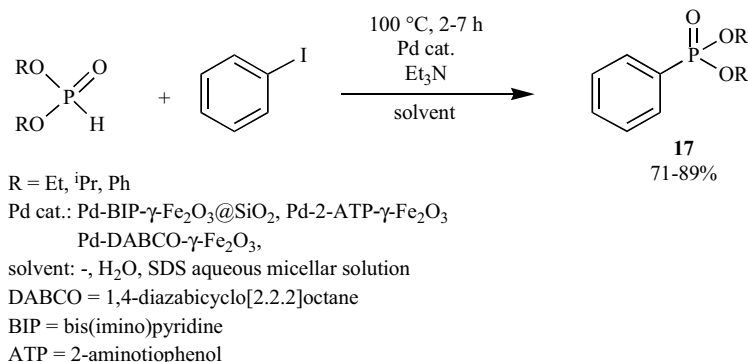as a catalyst in pure water, or in sodium dodecyl sulfate (SDS) aqueous micellar solution. The heterogeneous catalysts could be reused in five or six consecutive cycles, without any significant loss in their catalytic activity.

2.2. Nickel-catalyzed P-C Coupling Reactions

In the last years, the Ni-catalyzed P-C bond formation was also developed. *Han* and his co-workers elaborated the *P*-arylation of different >P(O)H compounds with aryl triflates in the presence of Ni(cod)$_2$ as the Ni(0) precursor and dppf as the *P*-ligand (Scheme **30**) [169].

Scheme conditions (Scheme 30 reaction):

80-120 °C, 20 h
Ni(cod)$_2$
dppf
Na$_2$CO$_3$
1,4-dioxane

Ar—OTf

10
56-96%

Y^1	Ph	Ph	^{n}Bu	Cy	O^{i}Pr
Y^2	Ph	^{t}Bu	^{n}Bu	Cy	O^{i}Pr

Ar = Ph, 4-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$, 3-MeC$_6$H$_4$, 2-MeC$_6$H$_4$,
  4-FC$_6$H$_4$, 4-PhC$_6$H$_4$, 4-F$_3$CC$_6$H$_4$, 4-NCC$_6$H$_4$,
  2-naphtyl, 3-piridyl
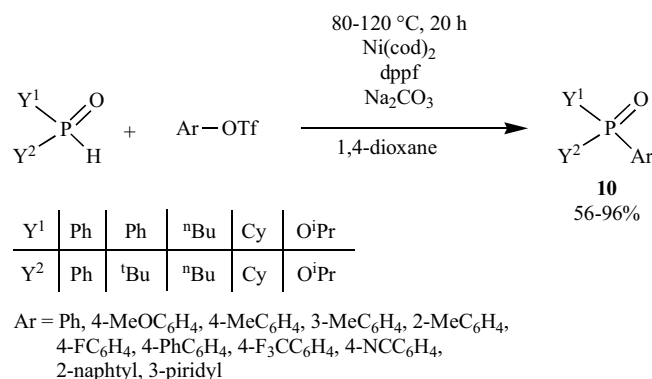
Scheme 30.

The same research group also used aryl pivalates as C-O bond activated substrates for coupling reactions with >P(O)H reagents (Scheme **31**) [170, 171]. Application of the Ni(cod)$_2$/dcype catalyst system led to the corresponding P=O derivatives (**10**) in good yields (50-98%). Beside phenol esters, benzylic and allylic esters could also be phosphorylated.

The combination of Ni- and photoredox catalysis allowed the cross-coupling of "C-O-S" containing aryl- and vinyl compounds (tosylates, sulfonates and sulfamates) with >P(O)H reagents under mild conditions (Scheme **32**) [172]. In this case, Ni(cod)$_2$ applied together with *N*-ligands, *eg*. 1,10-phenanthroline or dtbbyp, served as the catalyst.

The use of Ni(cod)$_2$ as the Ni-source, and 8-hydroxyquinoline as the *N*-ligand allowed the synthesis of tertiary phosphine oxides

Scheme conditions (Scheme 29 reaction):

100 °C, 2-7 h
Pd cat.
Et$_3$N
solvent

17
71-89%

R = Et, ^{i}Pr, Ph
Pd cat.: Pd-BIP-γ-Fe$_2$O$_3$@SiO$_2$, Pd-2-ATP-γ-Fe$_2$O$_3$
    Pd-DABCO-γ-Fe$_2$O$_3$,
solvent: -, H$_2$O, SDS aqueous micellar solution
DABCO = 1,4-diazabicyclo[2.2.2]octane
BIP = bis(imino)pyridine
ATP = 2-aminotiophenol

Scheme 29.

80-120 °C, 18-46 h
Ni(cod)$_2$
dcype
base

solvent

10
50-98%
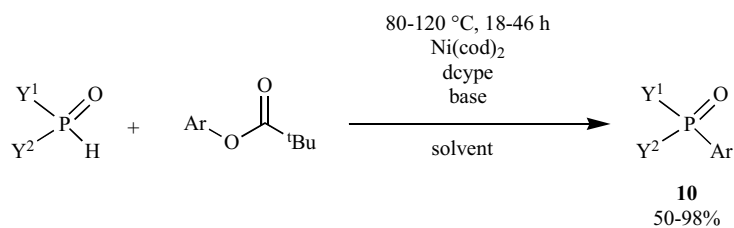
Y^1	Ph	^{n}Bu	^{n}Bu	^{t}Bu	Cy	OEt	OEt	O^{i}Pr
Y^2	Ph	^{n}Bu	Ph	Ph	Cy	Ph	OEt	O^{i}Pr

Ar [170] = Ph, 4-MeOC$_6$H$_4$, 4-^{n}BuC$_6$H$_4$, 4-MeC$_6$H$_4$, 3-MeC$_6$H$_4$, 2-MeC$_6$H$_4$, 4-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-PhC$_6$H$_4$,
2-PhC$_6$H$_4$, 2-^{t}Bu(O)COC$_6$H$_4$, 4-^{t}Bu(O)CHNC$_6$H$_4$, 4-Me(O)CC$_6$H$_4$, 4-F$_3$CC$_6$H$_4$, 4-NCC$_6$H$_4$

Ar [171] =

Y^3 = H, MeO, ^{t}BuC(O)NH, ^{t}BuC(O)O,
Br, H(O)C, NC
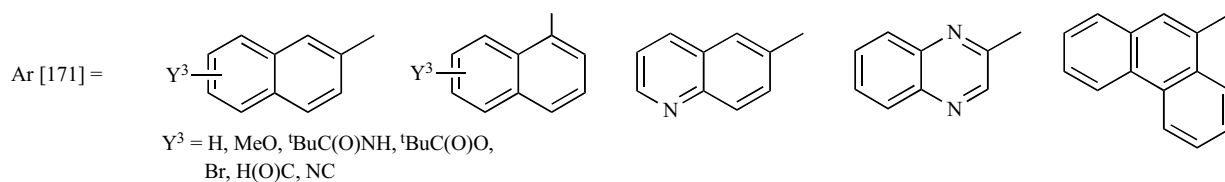
base: K$_2$CO$_3$, Cs$_2$CO$_3$
solvent: toluene, 1,4-dioxane

Scheme 31.

25 °C, 12-24 h, 10 W blue LED
Ni(cod)$_2$
ligand
[Ru(byp)$_2$Cl$_2$]*6H$_2$O
DBU

solvent

18
51-97%
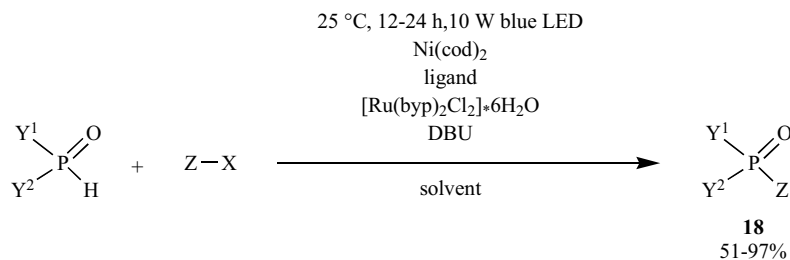
Y^1	OEt	OBu	Ph	Ph	4-MeC$_6$H$_4$	Me$_3$C-CMe$_3$
Y^2	OEt	OBu	OEt	Ph	4-MeC$_6$H$_4$	

Z =

Y^3 = Me, Ph, C(O)OEt

Q = O, NBoc

Y^4 = Ph, Br, MeO
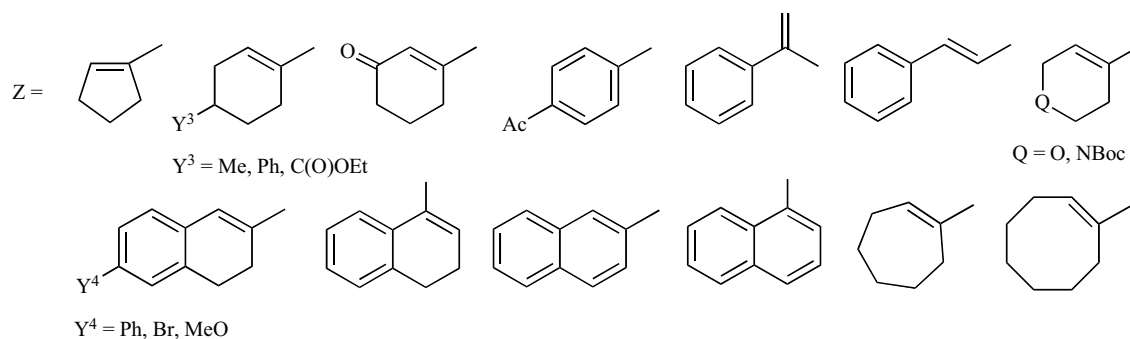
X = OTs, OMs, OSO$_2$NMe$_2$
ligand: 1,10-phenanthroline, dtbbyp
solvent: MeCN, DMA

Scheme 32.

Scheme 33.

Ar[1] = Ph, 4-MeOC$_6$H$_4$, 4-H$_2$NC$_6$H$_4$, 4-MeC$_6$H$_4$, 3-MeC$_6$H$_4$,
2-MeC$_6$H$_4$, 4-PhC$_6$H$_4$, 1-naphtyl, 2-naphtyl,
2-(7-MeO)naphtyl, 9-phenantryl, 3-(*N*-metyl)indolyl

Ar[1]	Ph	4-MeC$_6$H$_4$	Ph	Ph	^{n}Bu
Ar[2]	Ph	4-MeC$_6$H$_4$	^{n}Bu	^{t}Bu	^{n}Bu

Scheme 34.

R = Et, ^{i}Pr, Bu
Ar = Ph, 4-MeOC$_6$H$_4$, 3-MeOC$_6$H$_4$, 4-F$_3$COC$_6$H$_4$, 4-MeC$_6$H$_4$, 2-MeC$_6$H$_4$,
3,4-diFC$_6$H$_3$, 4-FC$_6$H$_4$, 3-FC$_6$H$_4$, 2-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 3-ClC$_6$H$_4$,
4-PhC$_6$H$_4$, 2-PhC$_6$H$_4$, 4-MeO(O)CC$_6$H$_4$, 4-Me(O)CC$_6$H$_4$, 4-F$_3$CC$_6$H$_4$,
3-F$_3$CC$_6$H$_4$, 2-F$_3$CC$_6$H$_4$, 4-NCC$_6$H$_4$, 1,3-benzodioxol-5-yl,
2,3-dihydro-1,4-benzodioxin-6-yl, 2-(7-MeO)naphtyl, 2-thiophenyl

R'		Ms	Ts	Ts
R"		Ph	Ph	Me

base: Et$_3$N, Na$_2$CO$_3$, ^{i}Pr$_2$NEt

Scheme 35.

(**19**) from aryl nitriles and secondary phosphine oxides (Scheme **33**) [173].

The coupling of amides with dialkyl phosphites described in subchapter 2.1, Scheme **25** was also accomplished using Ni(dppp)Cl$_2$ as the catalyst (Scheme **34**) [162].

An example for the application of Ni(OAc)$_2$ together with a tiophene-based diphosphine ligand (dcypt) using the esters of aromatic carboxylic acids as the substrate is shown in Scheme **35** [174]. Utilizing NaF as an additive increased the efficiency of the coupling, although its exact role is unknown.

Y[1]	Ph	OEt	O^{n}Bu	O^{i}Bu	OEt
Y[2]	Ph	OEt	O^{n}Bu	O^{i}Bu	Ph

Ar = 4-MeO(O)CC$_6$H$_4$, 4-F$_3$CC$_6$H$_4$, 3-F$_3$CC$_6$H$_4$, 4-NCC$_6$H$_4$,
1,3-benzodioxol-5-yl, 1-naphtyl, 2-naphtyl, 4-pyridyl, 3-pyridyl,
3-(6-trifluoromethyl)pyridyl, 2-pyrazinyl, 2-thiophenyl, 3-thiophenyl,
2-benzothiophenyl, 2-furanyl, 1-isoquinolinyl, 4-(2-phenyl)quinolinyl,
2-quinolinyl
additive: -, NaF

According to a recent study, the Ni-catalyzed P-C coupling reaction of aryl bromides and dialkyl phosphites was performed under electrochemical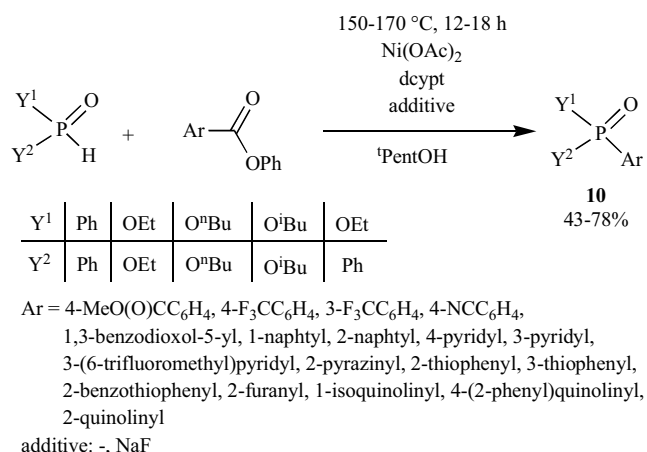 conditions to provide the corresponding aryl phosphonates (**3**) in moderate to good yields (15-91%) (Scheme **36**) [175].

R = Me, Et, Bu
Ar = Ph, 4-MeOC$_6$H$_4$, 3-MeOC$_6$H$_4$, 2-MeOC$_6$H$_4$, 4-MeSC$_6$H$_4$, 4-Me$_2$NC$_6$H$_4$,
4-MeC$_6$H$_4$, 3-MeC$_6$H$_4$, 4-FC$_6$H$_4$, 3-FC$_6$H$_4$, 3-ClC$_6$H$_4$, 4-EtO(O)CC$_6$H$_4$,
3-EtO(O)CC$_6$H$_4$, 4-F$_3$CC$_6$H$_4$, 3-F$_3$CC$_6$H$_4$, 2-F$_3$CC$_6$H$_4$,
1,3-benzodioxol-5-yl, 1-naphtyl, 3-thiophenyl, 3-pyridyl
TBAB = tetrabutylammonium bromide
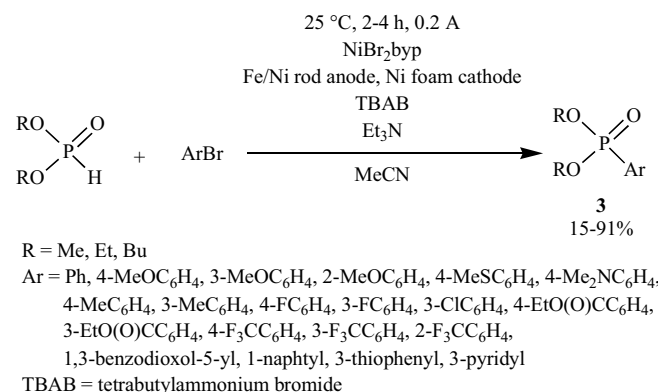
Scheme 36.

2.3. Copper-catalyzed P-C Couplings

The application of Cu as the catalyst is by far less investigated, thus it is a more challenging field. Cu-catalyzed methods for C-P bond formation were summarized in a recent review [176]. Since then, just a few methods have been described for the coupling of >P(O)H reagents and aryl halides using Cu(I) or Cu(II) precursors and *N*-ligands [177-182]. A novel method involves the reaction of

aryl boronic acids and dialkyl phosphites performed in the presence of a Cu(II) complex, (Benz-bpa)Cu(CF$_3$SO$_3$)$_2$ as the catalyst, and KOAc as an additive (Scheme **37**) [183].

$R = {}^i$Pr, Me, Et
Ar = Ph, 4-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$, 3-MeC$_6$H$_4$, 2-MeC$_6$H$_4$,
    4-FC$_6$H$_4$, 4-MeO(O)CC$_6$H$_4$, 4-F$_3$CC$_6$H$_4$, 4-NCC$_6$H$_4$,
    1-naphtyl
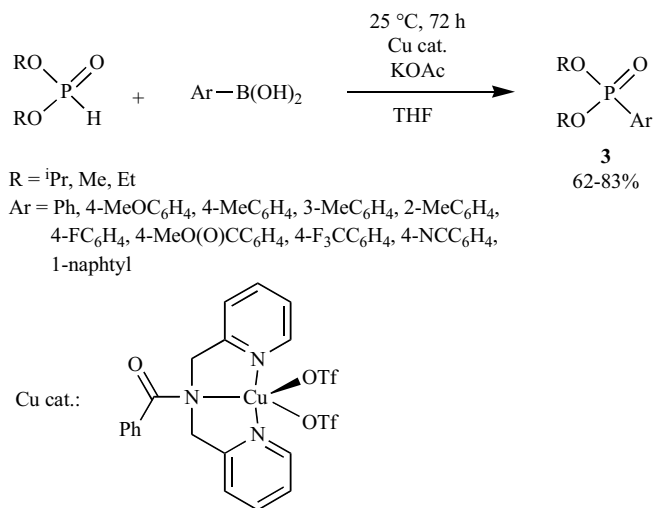
Scheme 37.

The enantioselective Cu-catalyzed P-C coupling reactions represent a new trend (Scheme **38**) [184]. Optically active tertiary phosphine oxides (**20**) could be prepared from racemic secondary

phosphine oxides and diaryliodonium tetrafluoroborate salts in the presence of Cu(II) triflate as the metal source, (*S,S*)-PhPyBox as the chiral *N*-ligand, and K$_2$HPO$_4$ as the base in acetonitrile-water mixture, in mostly high enantioselectivities (ee: 50-98%). The role of water has not been mentioned.
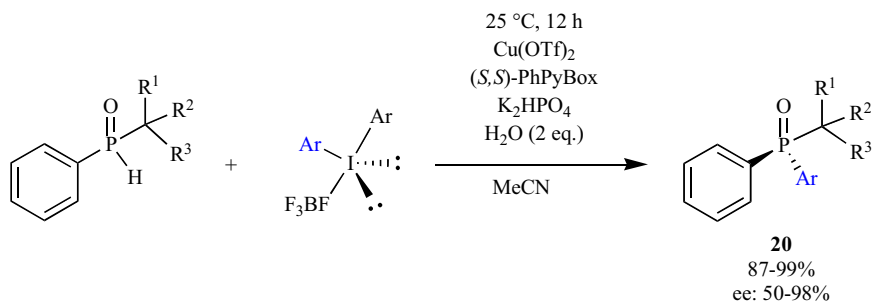
2.4. Other Methods

Special catalytic systems have also been developed. Visible light photoredox catalysis was combined with an Au catalyst to promote the reaction of aryldiazonium salts with *H*-phosphinates and *H*-phosphonates (Scheme **39**) [185]. In this way, the reactions could be carried out at room temperature, without the addition of any base. However, the synthesis of the starting diazonium salts from commercially available anilines means an extra step.

A similar Au(I)-assisted redox catalytic coupling using diethyl phosphite and aryldiazonium salts was also developed (Scheme **40**) [186]. In this case, 3-chloropyridine served as the base.

3. HIRAO REACTIONS WITHOUT THE ADDITION OF USUAL *P*-LIGANDS

Keglevich and his co-workers found that the Hirao reaction of bromoarenes with dialkyl phosphites, *H*-phosphinates or secondary phosphine oxides may take place without the addition of usual *P*-ligands, but using the >P(O)H reactant in excess under MW conditions (Scheme **41**) [187, 188]. It was found that both electron-donating and electron-withdrawing substituents of the aromatic ring

R^1	^{t}Bu	H	Me(CH$_2$)$_2$	(4-MeOC$_6$H$_4$)CH$_2$	Me$_2$CH	Cy	Me	Me	2-MeC$_6$H$_4$	Me$_3$Si		
R^2	H	H	H	H	H	H	Me	Me	H	H		
R^3	H	H	H	H	H	H	Me	H	H	H		

Ar = 4-F$_3$COC$_6$H$_4$, 2-F$_3$COC$_6$H$_4$, 3,5-diMeC$_6$H$_3$, 4-^{t}BuC$_6$H$_4$, 3-^{t}BuC$_6$H$_4$, 4-MeC$_6$H$_4$, 3-MeC$_6$H$_4$,
    2-MeC$_6$H$_4$, 3,5-diFC$_6$H$_3$, 3,4-diClC$_6$H$_3$, 4-FC$_6$H$_4$, 3-FC$_6$H$_4$, 2-FC$_6$H$_4$, 4-ClC$_6$H$_4$, 3-ClC$_6$H$_4$,
    2-ClC$_6$H$_4$, 4-BrC$_6$H$_4$, 3-BrC$_6$H$_4$, 2-BrC$_6$H$_4$, 4-EtO(O)CC$_6$H$_4$, 3-EtO(O)CC$_6$H$_4$, 4-F$_3$CC$_6$H$_4$,
    3-F$_3$CC$_6$H$_4$

Scheme 38.
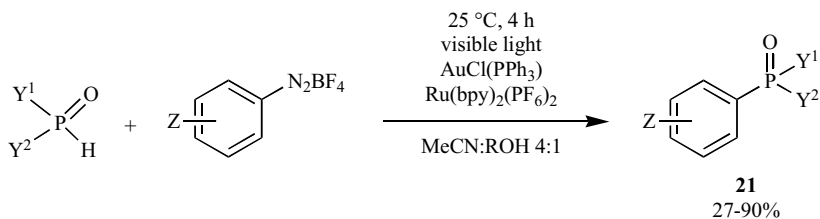
Y^1	OEt	OMe	O^{i}Pr	OBn	OPh	OEt
Y^2	OEt	OMe	O^{i}Pr	OBn	OPh	Ph

Z = H, MeO, Me, F, Br, Ph, MeO(O)C, F$_3$C, O$_2$N, ethynyl
R = Me, Et, ^{i}Pr

Scheme 39.

50 °C, 5 h
AuCl(PPh₃)
3-chloropyridine

MeCN

22
51-87%
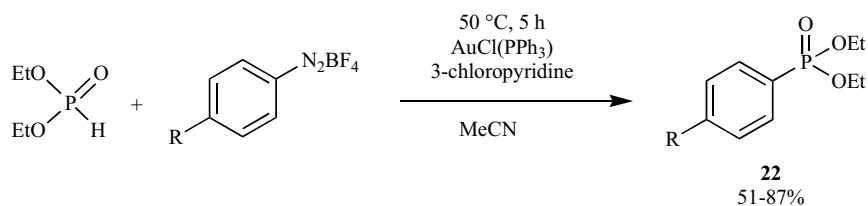
R = MeO, Me, F, Br, Cl, I, Me(O)C, Ph(O)C, TMS-ethylnyl,
2-EtO(O)C-vinyl, 2-Me-phenyldiazenyl

Scheme 40.

MW
120-200 °C, 2 min-1.5 h
Pd(OAc)₂
Et₃N

no solvent

1.5 eq.

23
41-95%
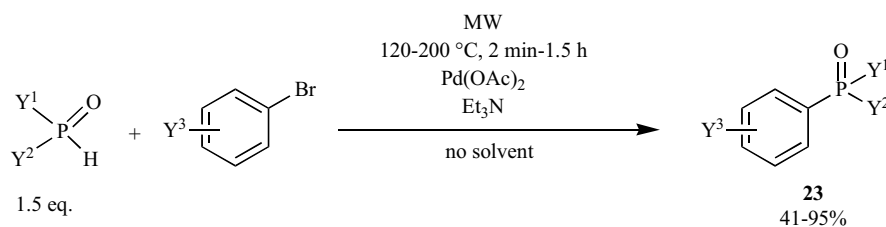
Y¹	OEt	OBu	OEt	OⁿPr	OⁱPr	OⁿBu	OⁱBu	OⁱPent	Ph	ⁿPr	ⁿBu	Bn
Y²	OEt	OBu	Ph	Ph	Ph	Ph	Ph	Ph	Ph	ⁿPr	ⁿBu	Bn

Y³ = H, 4-MeO, 3-MeO, 4-Pr, 4-Et, 4-Me, 4-F, 3-F, 4-Cl, 3-Cl, 4-EtO(O)C,
3-EtO(O)C, 4-Me(O)C, 3-Me(O)C

Scheme 41.

MW
120°C, 30-60 min
Pd(OAc)₂ (2.5-10%)
Et₃N (1.1 eq.)

EtOH or MeCN
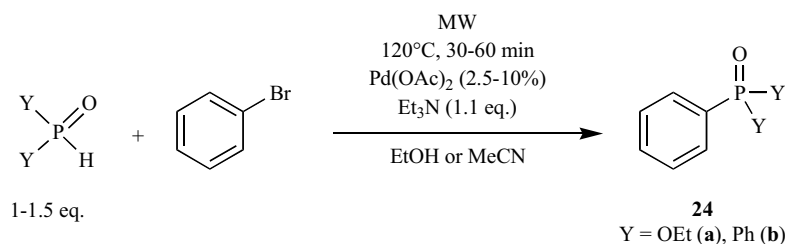
1-1.5 eq.

24
Y = OEt (**a**), Ph (**b**)

Scheme 42.

decrease the reactivity dictating harsher reaction conditions (175-200°C).

Our assumption was that in the Pd(OAc)₂-catalyzed "*P*-ligand-free" Hirao reactions the trivalent tautomeric form of the excess of the >P(O)H reactant may serve as the *P*-ligand. To justify this, the reaction of bromobenzene with diethyl phosphite and diphenyl-phosphine oxide was investigated in detail (Scheme **42**) [189].

Experiments showed that the use of only 1 equivalent of diethyl phosphite or diphenylphosphine oxide was not enough, as the yields were only 54% (**24a**) and 54% (**24b**), respectively. In the presence of 10% of Pd(OAc)₂, the optimal amount of the >P(O)H reagent was 1.3 equivalents, leading to yields of 74% (**24a**) and 84% (**24b**), respectively. Theoretical calculations were in accord with the preparative results, and suggested that the >P(O)H reagents have a triple role in the cross-coupling process: 1 equivalent of it serves as the reactant, 10% of the >P(O)H species ensures the reduction of Pd(II) to Pd(0), while 20% of the reagent provides the *P*-ligand of the Pd-complexes of type (HO)Y₂P···Pd···PY₂(OH).

The formation of the active catalyst (PdP₂) in the Hirao reaction of bromobenzene and diaryl phosphine oxides was studied in detail (Scheme **43**). Quantum chemical calculations revealed that the activity of the PdP₂ catalyst has a greater impact on the P-C coupling, than the intrinsic reactivity of the Ar₂P(O)H compound. Hence, the catalyst containing (2-MeC₆H₄)POH as the ligand is more efficient, than that with Ph₂POH ligand [190].

Later on, *Hirao et al.* have also studied a "*P*-ligand-free" P-C coupling reaction. Diethyl (4-methoxy-3-nitrophenyl)phosphonate (**26**) was synthetized from 4-bromo-1-methoxy-2-nitrobenzene applying only Pd(OAc)₂ as the catalyst, and Na₂CO₃ as the base in xylene as the medium (Scheme **44**) [191].

Recently, 2- and 4-phosphonated 13α-estrones (**27** and **28**) have been prepared by MW-assisted P-C coupling reactions [192]. Although the best results (yields of 66-93%) were obtained in the presence of Pd(PPh₃)₄, Pd(OAc)₂ together with the excess of the Y₂P(O)H reagent could also be used as the catalyst (to afford yields of 58-77%) (Scheme **45**). The products proved to be potent estron-based OATP2B1 inhibitors.

A "ligand-free" MW-promoted desulfitative coupling of arylsulfinate salts with dialkyl phosphites was performed using PdCl₂ as the catalyst under MW irradiation (Scheme **46**) [193]. Ag₂CO₃ was assumed to be involved in the oxidation of the arylsulfinate substrate, but this has not been proved.

The *Keglevich* group also developed a Ni-catalyzed "*P*-ligand-free" P-C coupling process (Scheme **47**) [194]. During the arylation of the >P(O)H compounds, NiCl₂ was applied as the catalyst and triethylamine or potassium carbonate as the base under MW irradiation.

The coupling of aryl sulfides, sulfoxides or sulfones with >P(O)H reagents was carried out in the presence of Ni(cod)₂ without the use of conventional ligands (Scheme **48**) [195]. The

ligation & reduction

Ar = Ph, 4-MeC$_6$H$_4$, 2-MeC$_6$H$_4$, 3,5-diMeC$_6$H$_3$

Scheme 43.

26
69%

Scheme 44.

Y = EtO, Ph
R = H, Me, Bn
X = I, Br
Pd catalyst: Pd(OAc)$_2$, Pd(PPh$_3$)$_4$
base: Et$_3$N, K$_2$CO$_3$
solvent: MeCN, toluene

27, 58-93%

28, 71-83%

Scheme 45.

MW
120 °C,10 min
PdCl$_2$
Ag$_2$CO$_3$

DMF-DMSO

29
31-96%

R = Me, Et, ^{n}Pr, ^{i}Pr, ^{n}Bu, ^{i}Bu, MeOCH$_2$CH$_2$
M = Na, Li, K, Ag, Zn, Cu

Scheme 46.

MW
150 °C, 30 min-2 h
NiCl$_2$
base

solvent

23
67-94%

Y^1	OEt	OBu	OEt	O^{n}Pr	O^{i}Pr	O^{n}Bu	O^{i}Bu	O^{i}Pent
Y^2	OEt	OBu	Ph	Ph	Ph	Ph	Ph	Ph
Y^1	Ph	4-MeOC$_6$H$_4$	4-^{t}BuC$_6$H$_4$	4-MeC$_6$H$_4$		3-MeC$_6$H$_4$	4-FC$_6$H$_4$	4-ClC$_6$H$_4$
Y^2	Ph	4-MeOC$_6$H$_4$	4-^{t}BuC$_6$H$_4$	4-MeC$_6$H$_4$		3-MeC$_6$H$_4$	4-FC$_6$H$_4$	4-ClC$_6$H$_4$

Y^3 = H, 4-MeO, 3-MeO, 4-^{t}Bu, 4-Pr, 4-Et, 4-Me, 3-Me, 4-F, 3-F, 3-Cl

base: Et$_3$N, K$_2$CO$_3$
solvent: -, MeCN

Scheme 47.

reaction of diphenylphosphine oxide and thioanisol could be catalyzed by NiCl$_2$.

100-120 °C, 18-24 h
Ni cat.
KO^{t}Bu

1,4-dioxane

10
30-98%
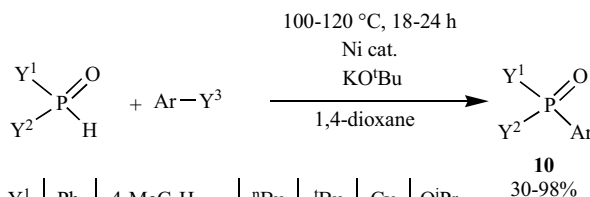
Y^1	Ph	4-MeC$_6$H$_4$	^{n}Bu	^{t}Bu	Cy	O^{i}Pr
Y^2	Ph	4-MeC$_6$H$_4$	^{n}Bu	Ph	Cy	O^{i}Pr

Y^3 = SMe, SPh, S(O)$_2$Me
Ar = 4-MeOC$_6$H$_4$, 3-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-PhC$_6$H$_4$, 4-F$_3$CC$_6$H$_4$,
    4-NCC$_6$H$_4$, 2-naphtyl, 2-piridyl, 2-pyrimidyl, 2-thiophenyl,
    3-quinolinyl, 4-(2-methylprop-1-en-1-yl)phenyl
Ni cat.: Ni(cod)$_2$, NiCl$_2$

Scheme 48.

A heterogeneous Ni-catalyst supported by CeO$_2$ or Al$_2$O$_3$ was utilized in the P-C coupling of aryl halides and secondary phosphine oxides without any added ligand (Scheme **49**) [196]. However, the catalyst used in the reaction of 1-bromonaphthalene and diphenylphosphine oxide, and separated from the mixture by filtration practically lost its activity in the second load.

Chinese researchers published the Cu-catalyzed "ligand-free" coupling reaction of >P(O)H compounds and aryl bromides or iodides to give the 2-phosphorylated phenolic derivatives (**28**) (Scheme **50**) [197]. The reaction of (-)-menthyl phenylphosphinate and (-)-menthyl benzylphosphinate occurred with the retention of

configuration at the *P*-atom. According to the plausible mechanism, the oxidative addition may take place *via* a "Cu-phenolate" intermediate, although the mechanism was not proved.

The reaction of vinyl or aryl halides with dialkyl phosphites was studied by applying excess of Cu(I)-iodide and the base (Scheme **51**) [198]. The best results (yields of 78-99%) could be obtained in the presence of KH/HMPA system, but the results with triethylamine as the base and THF as the solvent also deserve attention providing product **1** in yields of 24-76%.

A Co-catalyzed and Cu-assisted P-C coupling of aryl/vinyl bromides and dialkyl phosphites or diphenylphosphine oxide was also described in the absence of any added ligand (Scheme **52**) [199]. The corresponding products (**2** and **31**) were obtained in good yields (60-91%). The authors suggested that Co(I) formed from Co(II) by reduction with acac in the first step of the catalytic cycle may be the active form. At the same time, the transmetallation step is supported by Cu(I). It is noteworthy that the >P(O)H reactant was used in excess, so the participation of the >POH form cannot be excluded in the process.

Regarding the Ni-, Cu- or even the co-catalyzed "ligand-free" coupling protocols, it should be emphasized that these reactions may be of a complex nature, therefore further investigations are necessary to understand the mechanism of each system.

Nowadays, metal-free catalysis is of great importance. For this purpose, the P-C coupling of diaryl phosphine oxides with iodo-, or bromobenzoic acids was performed in the absence of any catalyst in water as the solvent under MW conditions (Scheme **53**) [200]. Unfortunately, this method is limited only to the reaction of halobenzoic acids, but may be regarded as the "greenest" accomplishment that has been so far elaborated.

8
3-86%

R^1	Ph	4-MeOC$_6$H$_4$	3-MeOC$_6$H$_4$	3,5-diMeC$_6$H$_3$	4-MeC$_6$H$_4$	Ph	^{n}Bu
R^2	Ph	4-MeOC$_6$H$_4$	3-MeOC$_6$H$_4$	3,5-diMeC$_6$H$_3$	4-MeC$_6$H$_4$	^{t}Bu	^{n}Bu

Ar = 4-PhC$_6$H$_4$, 2-MeC$_6$H$_4$, 4-HOCH$_2$C$_6$H$_4$, 4-MeOC$_6$H$_4$, 3-MeOC$_6$H$_4$,
    2-MeOC$_6$H$_4$, 3,5-di(MeO)C$_6$H$_3$, 4-H$_2$NC$_6$H$_4$, 4-FC$_6$H$_4$, 4-IC$_6$H$_4$,
    2-BrC$_6$H$_4$, 4-Me(O)CC$_6$H$_4$, 4-F$_3$CC$_6$H$_4$, 4-(Ph$_2$(O)P)C$_6$H$_4$, 1-naphthyl,
    2-naphthyl, 2-(7-MeO-naphthyl), 9-phenantryl
X = Br, I
nanoparticle: CeO$_2$, Al$_2$O$_3$

Scheme 49.

30
57-99%

Y^1	O^{i}Pr	OEt	OBu	Ph	Ph	Ph	Bn
Y^2	O^{i}Pr	OEt	OBu	^{t}Bu	Ph	O-(-)-menthyl	O-(-)-menthyl

X = I, Br
Y^3 = H, 4-MeO, 2,6-diBr, 4-F

Scheme 50.

1
15-99%

R = Me, Et, ^{i}Pr, Ph
base: KH, Et$_3$N
solvent: HMPA, tetrametylcarbamide, THF, DMF

Z^1, Z^2 = H, OMe, Z^3 = H, Me$_2$N, Ph$_2$N, MeS, Ph$_2$P, Cl

Scheme 51.

Y = OEt, O^{i}Pr, Ph
Ar = 2,6-di(MeO)C$_6$H$_3$, 4-MeOC$_6$H$_4$, 4-IC$_6$H$_4$, 4-EtO(O)CC$_6$H$_4$,
     4-Me(O)CC$_6$H$_4$, 4-F$_3$CC$_6$H$_4$, 4-NCC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$,
     2-(CH=CHCH$_2$)C$_6$H$_4$, 2-naptyl, 2-pyridyl, 3-pyridyl
R = 2,5-di(MeO)C$_6$H$_3$, 3-MeO-4-BnOC$_6$H$_3$, 4-F$_3$COC$_6$H$_4$,
     4-^{t}BuC$_6$H$_4$, 3,4-diClC$_6$H$_3$, 4-FC$_6$H$_4$, 4-BrC$_6$H$_4$,3-BrC$_6$H$_4$,
     2-BrC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-MeO(O)CC$_6$H$_4$, 2-naphtyl,
     3-thiophenyl, 2-furyl, heptyl, 1,2-diphenylvinyl
X = I, Br

Scheme 52.

Ar = Ph, 4-MeC$_6$H$_4$
X = I, Br
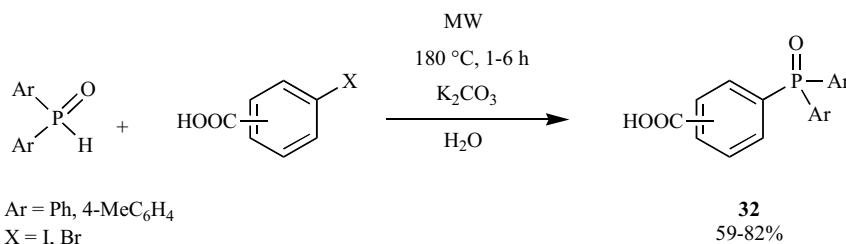
Scheme 53.

CONCLUSION

These days, the Hirao reaction is an important synthetic tool to provide phosphonates, phosphinates and tertiary phosphine oxides as useful intermediates. Toluene, DMSO, acetonitrile, 1,4-dioxane, THF, DMF, EtOH (or other alcohols) are the typical solvents used in the Hirao reaction. The selection of the solvent should also depend on the catalyst/catalyst precursor. Pd(PPh$_3$)$_4$ is, in most cases, applied together with toluene, while with Pd(OAc)$_2$ as the catalyst precursor, DMSO is the most often used solvent. The best medium for the Ni-catalyzed P-C couplings is 1,4-dioxane, and sometimes acetonitrile. One can see that mainly aprotic solvents are applied, but protic solvents may also emerge. Both organic and ionic bases may be used in the Hirao reaction. Regarding the Pd-catalysts, triethylamine and diisopropylethylamine are the most often used tertiary amines, but the use of pyridine, DBU and *N*-methylmorpholine was also described. In certain cases, K$_2$CO$_3$, Cs$_2$CO$_3$ and Na$_2$CO$_3$ played the role of the deprotonating agent. In the Ni-catalyzed cases, all bases mentioned were used. The originally applied Pd(PPh$_3$)$_4$

catalyst may be replaced by Pd(OAc)$_2$ used together with mono- and bidentate *P*-ligands. The best protocol is when the >P(O)H reagent serves not only as the reactant, but, *via* its tautomeric form (>P-OH), also as the *P*-ligand. In this "green" approach, the >P(O)H species have to be measured in a suitable excess (in three equivalents to the catalyst precursor), and MW-assistance is needed. The optimum temperature may be in the range of 120-150 °C. Ethanol and acetonitrile may be the best solvents, but in special cases, there is no need for any solvent. Triethylamine seems to be the best base. Other metals, such as Ni and Cu may also be used as catalysts. The environmentally-friendly variations of the P-C coupling reactions offer newer possibilities. Evaluation of the mechanism of the Hirao reaction has had a positive impact on finding the optimum conditions. The reactivity of the Hirao reaction is, of course, influenced by the substituent in the aromatic ring. Both the electron-donating and the electron-withdrawing groups decrease the reactivity. On the other hand, the P-C coupling reactions remained chemoselective also in the presence of different substituents, like halogeno-, ethoxycarbonyl- and acetyl groups.

LIST OF ABBREVIATIONS
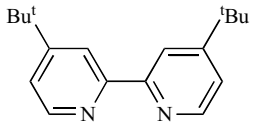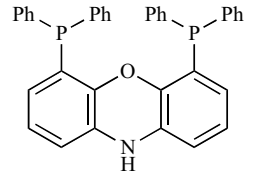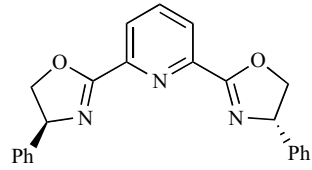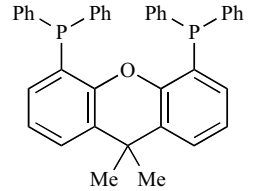
acac   acetylacetone

BINAP   2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
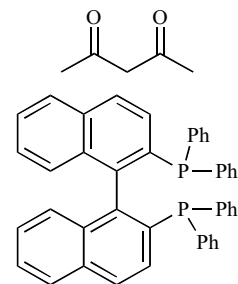
byp	2,2'-bipyridine	
cod	1,5-cyclooctadiene	
CM-Phos	2‑(2‑(dicyclohexylphosphino)phenyl)‑1‑methyl‑1*H*‑indole	
dba	dibenzylideneacetone	
DBFphos	4,6-bis(diphenylphosphino) dibenzofuran	
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene	
dcype	1,2-bis(dicyclohexylphosphino)ethane	
dcypt	3,4-bis(dicyclohexylphosphino)thiophene	
dppb	1,4-bis(diphenylphosphino)butane	
dppe	1,2-bis(diphenylphosphino)ethane	
dppf	1,1'-bis(diphenylphosphino)ferrocene	
dppp	1,3-bis(diphenylphosphino)propane	

dtbbyp	4,4′-di-tert-butyl-2,2′-dipyridyl
PS-nixantphos	polystyrene-supported 4,6-bis(diphenylphosphino)-10*H*-phenoxazine
(*S*,*S*)-PhPyBox	(*S*,*S*)-2,6-Bis(4,5-dihydro-4-phenyl-2-oxazolyl)pyridine
Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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