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Phosphorus-Carbon Bond Formation: Palladium-Catalyzed Cross-Coupling of *H*-Phosphinates and Other P(O)H-Containing Compounds

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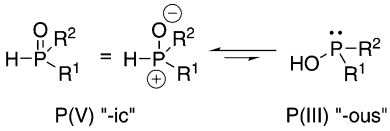
Abstract: Two generally applicable systems have been developed for the cross-coupling of P(O)H compounds with C_{sp2}–X and related partners. Palladium catalysis using a ligand/additive combination, typically either xantphos/ethylene glycol or 1,1′-bis-(diphenylphosphino)ferrocene/1,2-dimethoxyethane, with diisopropylethylamine as the base, proved to be generally useful for the synthesis of numerous P–C containing compounds. Routinely, 2 mol% of catalyst are employed (less than half the amount typically employed in most other literature reports). In most cases, excellent results are obtained with a variety of electrophiles (RX, where R = alkenyl, allyl, alkynyl, etc.). The full account of our studies is disclosed, including tandem hydrophosphinylation/coupling and coupling/coupling for doubly catalytic phosphorus-carbon bond formation. The methodology compares favorably with any existing literature report. The use of an additive appears to be a generally useful strategy to control the reactivity of phosphinylidene compounds.

Keywords: aryl chlorides; cross-coupling; palladium; *H*-phosphinates; phosphinylidenes; tautomerization

Introduction

Phosphorus-carbon bond formation has become a very active research area in modern organophosphorus chemistry due to the importance of the compounds in a variety of fields, from material science to ligands in transition metal-catalyzed reactions, from metal-organic frameworks (MOFs) to biologically active molecules.[1] As a result, intense research has been devoted to this topic in recent years.[2] Over the past decade, our laboratory has reported various synthetic methodologies for the preparation of *H*-phosphinates and disubstituted phosphinates,[3] and we recently disclosed the first general P–C bond formation using the palladium-catalyzed reaction of *H*-phosphinates with aryl chlorides.[4] Below, we are reporting the full account of our studies concerning the palladium-catalyzed cross-coupling of P(O)H compounds with C_{sp2} and related electrophiles.

Phosphinylidene [P(O)H]-containing compounds constitute a significant portion of organophosphorus functionalities, including: phosphinates [$ROP(O)H_2$], *H*-phosphinates [$R^1P(O)(OR)H$], *H*-phosphonates [$(RO)_2P(O)H$], and secondary phosphine oxides [$R_2P(O)H$]. The chemistry of these compounds is largely controlled by the tautomeric equilibrium between the so-called P(V) form [P(O)H] and the P(III) form [P(OH)] [Eq. (1)].[5] An additive (or a catalyst) should be able to affect this equilibrium and increase the concentration of the P(III) tautomer thereby enhancing the scope of various reactions since the availability of this species controls most of the phosphinylidene reactivity.



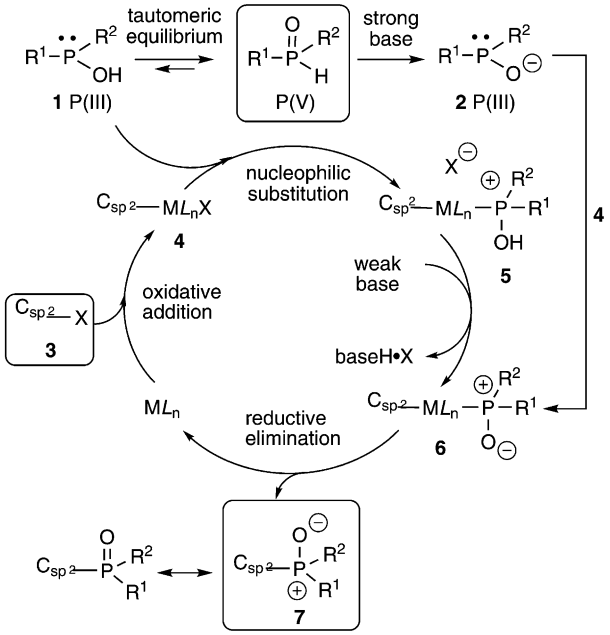
(1)

Numerous reports of metal-catalyzed cross-coupling between a phosphorus reagent and C_{sp2}–X have appeared[6–11] since Hirao's seminal reports.[12] However, to date there is still no truly general set of conditions that are applicable to a broad range of both P(O)H nucleophiles and carbon electrophiles. Our own contributions[13] initially focused on the reactions of phosphinates (pioneered by Schwabacher and Holt),[11a–e] with the added complication that these reagents are

powerful reducing agents so that competing transfer hydrogenation[14] needed to be suppressed. More recently, our focus shifted to *H*-phosphinates.[4,15] Various examples of functionalization of $R^1P(O)(OR)H$ through cross-coupling have been reported in the literature,[11] however, our 2011 communication was the first to offer a general method in which aryl chlorides could be employed, using a broadly applicable set of conditions, lower catalyst loadings, and the use of additives like ethylene glycol (EG).[4] Following this work, we have continued our efforts to develop a synthetic method as generally applicable as possible to any P(O)H reagent, especially *H*-phosphinates, but also *H*-phosphonates, and secondary phosphine oxides. We are now reporting the full study of this reaction.

Our initial cross-coupling of *H*-phosphinates with aryl chlorides can be summarized as follows: a Pd/xantphos (or Pd/dppf) catalyst with a solvent additive (EG) gave excellent results. Nonetheless, EG sometimes gave significant amounts of transesterified product $R^1P(O)(OCH_2CH_2OH)Ar$, thereby decreasing the yield of desired product (unless hydrolysis to the corresponding phosphinic acid is completed). But the study proved that EG could be a general solution for the synthesis of phosphinates $R^1P(O)(OR)Ar$, even with aryl chlorides. Dimethoxyethane (DME) and propylene glycol (PG) were also identified as other promising additives.[4]

A possible mechanistic pathway for the cross-coupling of phosphinylidene compounds [phosphinates, *H*-phosphinates, *H*-phosphonates, and secondary phosphine oxides, $R^1R^2P(O)H$] is summarized in Scheme 1. With phosphinates [$ROP(O)H_2$, R = M, ammonium, H, alkyl], we showed that our metal-catalyzed hydrophosphinylation chemistry [addition of $ROP(O)H_2$ to alkenes and alkynes using Pd and Ni catalysts][16] relies on the suppression of the competing transfer hydrogenation pathway, and that large bite angle ligands slow down the β-hydrogen elimination leading to competing transfer hydrogenation. Transfer hydrogenation with phosphinates $ROP(O)H_2$ is a preparative method, akin to the more usual laboratory-scale reaction using formates.[14] On the other hand, *H*-phosphinates $R^1P(O)(OR)H$ are much less reducing than phosphinates [hypophosphites, $ROP(O)H_2$], however, the P(V) to P(III) tautomeric equilibrium is typically even less favorable, so what is gained on one aspect (less competing reduction) is lost on the other (lower reactivity). The P(III) tautomer **1** is the nucleophile which can either complex to palladium (ligand-like) leading to reduction/hydrophosphinylation pathways, or in cross-coupling reactions displace PdL_nX **4** (formed through insertion into the C–X bond of **3**) producing phosphonium **5**. Deprotonation of **5** into intermediate **6** only requires a weak base, whereas **2** can produce **6** directly from **4**.



Scheme 1. Mechanistic pathways in the cross-coupling of phosphinylidene compounds.

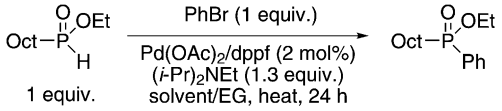
Reductive elimination then gives the coupling product **7** regenerating the metal catalyst. Strong bases (pK_a ~18 or above) can deprotonate the P(O)H compound to form **2** which is an excellent nucleophile. Note that the timing of deprotonation **5**→**6**/reductive elimination **6**→**7** might be reversed (i.e., the phosphonium intermediate could reductively eliminate before deprotonation takes place). Because the reductive elimination of phosphonium ions is known,[17] this must be operating in some cases, however, it is likely that the relative rates of deprotonation and reductive elimination depend on specific cases (and base strength). With relatively weak bases, such as tertiary amines, anion **2** is an unlikely intermediate. In the final analysis, our rationale for successful cross-coupling of *H*-phosphinates and related P(O)H compounds was therefore based on using an additive to promote the P(V) to P(III) equilibrium [Eq. (1)] and increase the concentration of **1**, and/or to stabilize the palladium catalyst.

Results and Discussion

General Conditions

An investigation on the role of additives in the cross-coupling of *H*-phosphinates followed from the discovery of EG as an additive in the hydrophosphinylation of *H*-phosphinic acids with alkenes and alkynes.[18] As a model system, the cross-coupling between equimolar amounts of OctP(O)(OEt)H and bromobenzene

Table 1. Role of solvent and EG in *H*-phosphinate cross-coupling.[a]



Entry	Solvent	^{31}P NMR yield [%][b] without EG	with EG
1	EG	–	(59)
2	EtOH	30	69 (7)
3	*t*-AmOH	30	72 (7)
4	CH_3CN	0	63 (16)
5	DMF	5	71 (1)
6	toluene	7	80 (7)

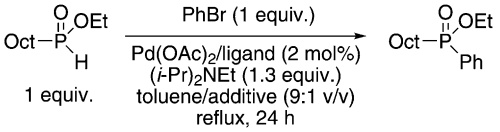
[a] *Conditions:* the reactions were conducted at reflux using solvent or solvent/EG (9:1 v/v), or at 115 °C with neat EG or DMF.

[b] Determined after addition of EtOH to obtain a homogeneous mixture. In a few cases, some 2-hydroxyethyl ester also formed and the yield is indicated in parentheses.

was chosen. Table 1 shows the role of the solvent in the absence or presence of EG. For these initial studies, $(i\text{-Pr})_2$NEt and dppf were selected as ligand and base, respectively, based on our earlier work on the cross-coupling of $(i\text{-PrO})_2$P(O)H. Regardless of the solvent, addition of EG consistently gives outstanding increases in yields. Small and variable amounts of transesterification to the 2-hydroxyethyl ester are also observed. Using neat EG (entry 1) instead of as an additive with other solvents does not give a higher yield of cross-coupling product. The effect is seen even with other protic solvents (entries 2 and 3), in which case the yields are doubled. The effect of EG is even more dramatic with non-protic solvents (entries 4–6).

Because toluene gave the best results in the above study, the role of other parameters was examined next with this solvent (Table 2). With EG as the additive, the yields were consistently high, regardless of the ligand employed, and even successful in the absence of ligand (entry 2). Nonetheless xantphos gave the best results (entry 5). When the additive was switched from EG to PG the yield decreased a little (entry 11 *versus* entry 4). Using DME (entry 12) also gave satisfactory results and prevented transesterification, but was completely ineffective in the absence of ligand (entry 12a), but dppf was excellent (entry 12b), and the product was isolated in 87% yield. With xantphos as the ligand, EG remained a better additive (entry 12c *versus* entry 5). Clearly, significant differences can be observed depending on the additive and ligand combination that is selected. Nonetheless, one conclusion is that additives play a critical role in the cross-coupling of OctP(O)(OEt)H with PhBr, where-

Table 2. Role of ligand and additive in *H*-phosphinate cross-coupling in toluene.[a]



Entry	Cosolvent additive	Ligand	^{31}P NMR yield [%][b]
1	none	dppf	7
2	EG	none	70
3	EG	PPh_3	85
4	EG	dppf	80
5a	EG	xantphos	90
5b			96[c]
6	EG	dppe	65
7	EG	dppp	84
8	EG	DBFphos	81
9	EG	BINAP	83
10a	EG	PS-nixantphos	84
10b			74[d]
11	PG	dppf	72
12a		none	0
12b	DME	dppf	96
12c		xantphos	81

[a] *Conditions:* the reactions were conducted at reflux using toluene/additive (9:1 v/v). 2.2 mol% of bidentate ligands, or 4.4 mol% for PPh_3.

[b] Determined after addition of EtOH to obtain a homogeneous mixture.

[c] $PdCl_2$ was used instead of $Pd(OAc)_2$.

[d] Obtained after reusing the catalyst from entry 10a.

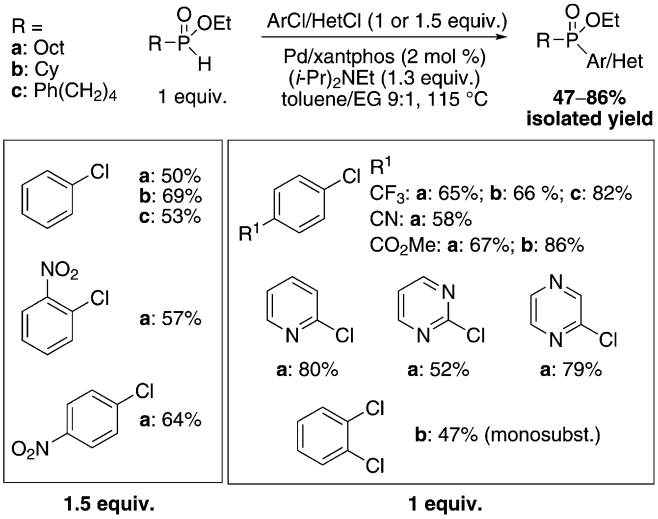
as the nature of the ligand has a significant but smaller effect.

Scope of the Reaction

At this point, the scope of the reaction was explored. Bromobenzene is a moderately challenging substrate in cross-coupling reactions. As we reported in the communication, even aryl and heteroaryl chlorides were successfully coupled to various ethyl alkyl-*H*-phosphinates [RP(O)(OEt)H, R = Oct, Cy, 4-phenylbutyl] in moderate to good isolated yields. Scheme 2 summarizes these results.[4]

In all cases, the EG/xantphos system was employed with toluene as the solvent, and in some cases, the use of 1.5 equiv. of ArCl gave improved yields. Regardless, this was the first general method to cross-couple phosphorus nucleophiles with C_{sp2}–Cl electrophiles.[4]

Continuing these studies, other electrophiles and *H*-phosphinates combinations were studied. Table 3 summarizes the results. Not surprisingly, the cross-coupling of ethyl octyl-*H*-phosphinate takes place as expected with additional electrophiles (entries 1–4).



Scheme 2. Isolated yields for the cross-coupling of RP(O)(OEt)H with ArCl/HetCl, using Pd/xantphos (2 mol%), (*i*-Pr)$_2$NEt (1.3 equiv.) in refluxing toluene/EG (9:1 v/v).[4]

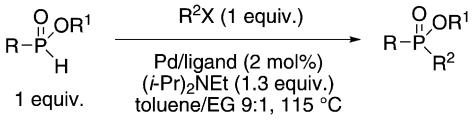
More interestingly, cross-couplings also took place satisfactorily with a broad range of electrophiles, such as benzylic (entry 5), alkenyl (entries 6 and 7), allylic (entries 8 and 9), and even alkynyl (entries 10 and 11) substrates. Gaumont and co-workers recently demonstrated the cross-coupling of secondary phosphine-boranes with alkynyl bromides as a useful method for the preparation of alkynyl-phosphorus compounds.[8a] Butyl cinnamyl- and methyl-*H*-phosphinates also reacted uneventfully with aryl bromides (entries 12 and 13). The product of entry 13 can be converted into the corresponding phosphindolin-3-one heterocycle (LDA, 2 equiv., THF, −78 °C to room temperature, 89% yield).[19]

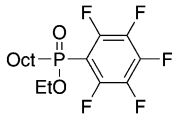
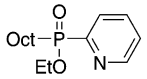
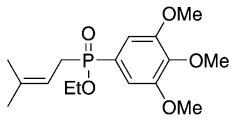
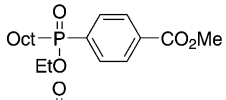
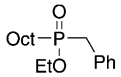
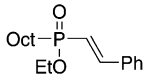
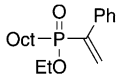
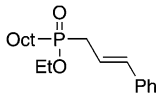
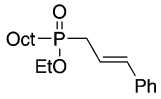
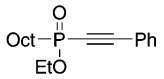
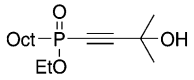
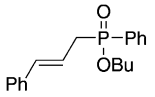
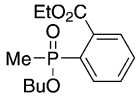
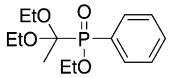
Even the "Ciba-Geigy reagent" MeC(OEt)$_2$P(O)(OEt)H could be coupled with chlorobenzene, however the conditions needed to be adjusted in this case (entry 14b) as although the standard conditions were successful in terms of overall P−C bond formation, elimination to PhP(O)(OEt)C(OEt)=CH$_2$ was the major product (entry 14a). Replacing (*i*-Pr)$_2$NEt with K_2CO_3 prevented the side reaction. This is an important reaction because the acetal is a protected version/precursor of the corresponding *H*-phosphinate ester. Hall and co-workers nicely demonstrated this approach through the cross-coupling of aryl bromides under Hirao-type conditions [ArBr (1 equiv.), Et_3N (2 equiv.), 10 mol% Pd(PPh$_3$)$_4$, 7 examples, 65–89%].[11z]

Cross-Coupling of Aryl-*H*-phosphinate Esters

Early on, Schwabacher reported the formation of Ar$_2$P(O)(OR) through Pd-catalyzed coupling between

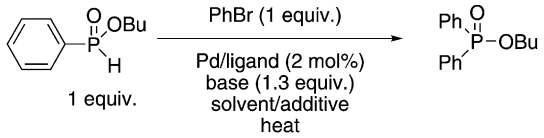
Table 3. Scope of the *H*-phosphinate cross-coupling with various electrophiles.[a]



Entry	X	Product	Isolated yield [%] (^{31}P NMR yield)
1	Cl		78 (85)
2	Br		93 (96)[b]
3	Br		61 (83)
4	OTf		89 (91)
5	Cl		85 (89)
6	Br		80 (82)
7	Br		76 (79)
8	OAc		87 (94)
9	OCO_2Et		78 (90)
10	Br		62 (75)
11	Br		43 (52)
12	Br		84 (89)[c]
13	Br		83 (85)[d]
14a 14b	Cl		(33)[e] 64 (73)[f]

[a] See the Supporting Information for details: electrophile (1 equiv.), (*i*-Pr)$_2$NEt (1.3 equiv.), Pd(OAc)$_2$/xantphos (2 mol%), toluene/EG (9:1, v/v), 115 °C, 24 h.
[b] Microwave heating.
[c] PdCl$_2$/2 PPh$_3$ (2 mol%).
[d] BuOH was used instead of EG.
[e] Also contains 59% of PhP(O)(OEt)C(OEt)=CH$_2$.
[f] K_2CO_3 (0.65 equiv.) was used instead of (*i*-Pr)$_2$NEt.

Table 4. Optimization study for the cross-coupling of PhP(O)(OBu)H with bromobenzene.[a]



Entry	Solvent	Base	Additive	Ligand	^{31}P NMR yield [%][b]
1	toluene	(i-Pr)$_2$NEt	none	xantphos	71
2	toluene	(i-Pr)$_2$NEt	EG	xantphos	80
3	**toluene**	**pyridine**	**EG**	**xantphos**	**92**[c]
4	toluene	(i-Pr)$_2$NEt	DME	xantphos	77
5	toluene	(i-Pr)$_2$NEt	BuOH	xantphos	84
6	toluene	(i-Pr)$_2$NEt	1,3-diphenylurea	xantphos	86
7	toluene	(i-Pr)$_2$NEt	methylcellulose	xantphos	68
8	toluene	(i-Pr)$_2$NEt	PEG	xantphos	71
9	toluene	(i-Pr)$_2$NEt	diglyme	xantphos	64
10	BuOH	(i-Pr)$_2$NEt	none	xantphos	77
11	**DME**	**(i-Pr)$_2$NEt**	**none**	**xantphos**	**94**
12	**DME**	**(i-Pr)$_2$NEt**	**none**	**dppf**	**92**
13	toluene	pyridine	DME	dppf	30
14	DMF	pyridine	DME	dppf	45
15	CH_3CN	pyridine	DME	dppf	21
16	CH_3CN	propylene oxide	DME	dppf	62
17	**toluene**	**propylene oxide**	**DME**	**dppf**	**96**[d]

[a] *Conditions:* the reactions were conducted at reflux using toluene, BuOH, DME or CH_3CN, and at 115 °C with DMF. Liquid additives were used as 10 % v/v.
[b] Determined after addition of EtOH to obtain a homogeneous mixture.
[c] 84% isolated yield.
[d] 94% isolated yield.

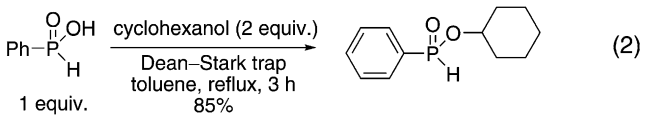
ArI and ROP(O)H$_2$, but the less reactive bromides and triflates failed.[11a] Thus, the cross-coupling between PhP(O)(OBu)H and bromobenzene was investigated next in some detail (Table 4).

Even in the absence of any additive (entry 1), the yield was acceptable. This should be compared with Table 1, entry 6, which shows a very low yield of cross-coupling for OctP(O)(OEt)H in the absence of additive. And so, with PhP(O)(OBu)H, the addition of EG improved the yield only slightly (entry 2). The reason is likely related to the intrinsically higher concentration of P(III) tautomer in the case of phenyl-*H*-phosphinate, so that cross-coupling is faster (see also Scheme 1) and less sensitive to the role of an additive. Indeed, in aryl-*H*-phosphinates the P(III) tautomer [Eq. (1)] is stabilized by the electron-withdrawing aryl moiety (lone pair delocalization) while the phosphonium form is simultaneously destabilized.[18] Electron-donating substituents (such as alkyl) have the opposite effect: destabilization of the P(III) form and stabilization of the phosphonium. However, oxidative addition into the P(O)H (potentially leading to transfer hydrogenation) is also easier, as well as other competitive and undesired side-reactions associated with the P(III) tautomer, such as: air oxidation, transesterification, and base-promoted ester dealkylation.[13c] Presumably because of the latter side reaction, switching the base from (i-Pr)$_2$NEt to pyridine resulted in a larger improvement (entry 3).

Several additives were considered beyond EG and DME (entries 4–9). As expected based on the discussion above, only a moderate (+10%) or no improvement was observed when (i-Pr)$_2$NEt is the base. On the other hand, DME as a solvent gave excellent results with both xantphos and dppf (entries 11 and 12). But as an additive using dppf, the results were disappointing (entries 13–16). Finally, using propylene oxide as the HBr scavenger resulted in a nearly quantitative yield (entry 17, 94 % isolated).

Unfortunately, attempted reactions with chlorobenzene gave disappointing results. No matter what the conditions [base: (i-Pr)$_2$NEt, pyridine, tetramethylpiperidine, DABCO, Cy$_2$NMe, *N*-methylmorpholine, K_3PO_4, K_2CO_3, zinc powder, etc.] or solvent, ligand, and additive: the best yield remained below 30 %. This clearly points to the fact that the slower oxidative addition into PhCl leads to dominant competing side reactions associated with P(III) PhP(OBu)(OH) resulting in poor yields. The most pronounced side-reactions were air oxidation to the phosphonate monoester and dealkylation. While freeze-degas-thaw conditions helped slightly with the former, the latter re-

mained a major issue. We therefore reasoned that changing the ester group to cyclohexyl might solve this problem. It is standard knowledge that the rate of S_N2 decreases significantly from primary to secondary alkyls, and by another two orders of magnitude from isopropyl to cyclohexyl. Also, cyclohexyl *H*-phosphinates can be prepared easily through Dean–Stark esterification of the corresponding acid with cyclohexanol [Eq. (2)].

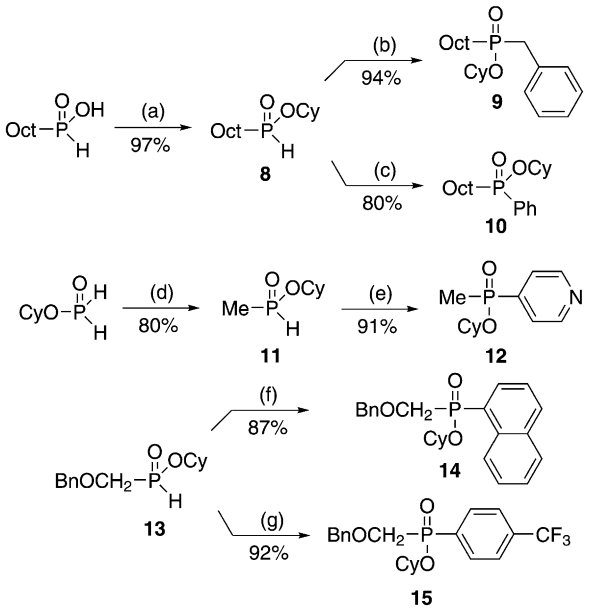


(2)

The cross-coupling of PhP(O)(OCy)H with aryl chlorides was therefore examined next (Table 5). As expected, the cyclohexyl ester more resistant to dealkylation gave much better results. Isolated yields of cross-coupling with activated $CF_3C_6H_4Cl$ (entry 4), unactivated chlorobenzene (entry 6), and deactivated 2-iodoaniline (entry 7), or 2-bromoaniline (entry 8) were 95%, 77%, 59%, and 70%, respectively. Even the sterically hindered 2-iodomesitylene reacts successfully (entry 9, 61% isolated yield). This is noteworthy because the cross-coupling of PhP(O)(OMe)H with iodomesitylene was reported previously [10 mol% $Pd(PPh_3)_4$, propylene oxide, CH_3CN] to proceed in less than 18% yield![11w]

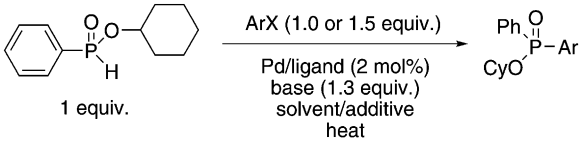
In contrast, our conditions use 5-times less palladium and result in a better than 3-fold improvement in yield.

The use of the cyclohexyl ester can also be applied to other cases (Scheme 3). For example, cross-coupling of cyclohexyl octyl-*H*-phosphinate **8** with benzyl



Scheme 3. Preparation of RP(O)(OCy)H and cross-coupling using Pd/ligand (2 mol%). All specified yields are for isolated products. (a) cyclohexanol (2 equiv.), toluene, Dean–Stark trap, 3 h. (b) BnCl (1 equiv.), $Pd(OAc)_2$ (2 mol%), xantphos (2.2 mol%), $(i\text{-Pr})_2NEt$ (1.3 equiv.), toluene/EG (9:1, v/v), reflux, 24 h. (c) chlorobenzene (3 equiv.), $Pd(OAc)_2$ (2 mol%), xantphos (2.2 mol%), K_2CO_3 (0.65 equiv.), DMF/DME (9:1, v/v), 115 °C, 48 h. (d) MeI (1.1 equiv.), DBU (1.1 equiv.), toluene, 0 °C to room temperature, 16 h. (e) 4-bromopyridine hydrochloride (1 equiv.), $Pd(OAc)_2$ (2 mol%), dppf (2.2 mol%), $(i\text{-Pr})_2NEt$ (2.3 equiv.), DMF/DME (9:1, v/v), 115 °C, 24 h. (f) 1-bromonaphthalene (1 equiv.), $Pd(OAc)_2$ (2 mol%), dppf (2.2 mol%), propylene oxide (1.3 equiv.), DMF/DME (9:1, v/v), 115 °C, 24 h. (g) 4-$CF_3C_6H_4Cl$ (1.5 equiv.), $Pd(OAc)_2$ (2 mol%), dppf (2.2 mol%), propylene oxide (1.3 equiv.), DMF/DME (9:1, v/v), 115 °C, 24 h.

Table 5. Cross-coupling of PhP(O)(OCy)H with aryl halides.[a]



Entry	Solvent/additive	Base	Ligand	ArX (equiv.)	Isolated yield [%] (^{31}P NMR yield)[b]
1	toluene/EG	pyridine	xantphos	$CF_3C_6H_4Cl$ (1.5)	– (87)
2	DMF/EG	pyridine	xantphos	$CF_3C_6H_4Cl$ (1.5)	– (90)
3	toluene/EG	propylene oxide	dppf	$CF_3C_6H_4Cl$ (1.5)	– (97)
4	DMF/DME	propylene oxide	dppf	$CF_3C_6H_4Cl$ (1.5)	95 (100)
5	DMF/DME	propylene oxide	dppf	PhCl (1.5)	– (46)
6	DMF/DME	$(i\text{-Pr})_2NEt$	dppf	PhCl (1.5)	77 (80)
7	DMF/DME	$(i\text{-Pr})_2NEt$	dppf	2-$H_2NC_6H_4I$ (1.0)	59 (65)
8	DMF/DME	$(i\text{-Pr})_2NEt$	dppf	2-$H_2NC_6H_4Br$ (1.0)	70 (89)
9	DMF/DME	propylene oxide	dppf	MesI (1.5)	61 (65)[c]

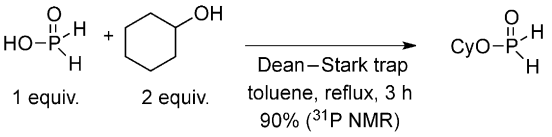
[a] *Conditions:* the reactions were conducted at reflux using toluene, and at 115 °C with DMF. Liquid additives were used as 10% v/v; with base or HX scavenger (1.3 equiv.).

[b] Determined after addition of EtOH to obtain a homogeneous mixture when EG was used.

[c] Contains an additional 23% of transesterification due to iodopropanol.

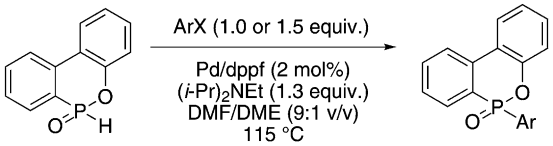
chloride gives the corresponding product **9** in excellent yield (also compare with Table 3, entry 5 for the ethyl ester). Similarly, a significant yield improvement is obtained for cross-coupling with chlorobenzene to form **10**.

Scheme 3 shows several other examples. Cross-coupling of methyl-*H*-phosphinate **11** with bromopyridine gives **12.** Cristau and co-workers reported the cross-coupling of ethyl benzyloxymethyl-*H*-phosphinate with several aryl halides (no chloride) using Hirao conditions [10 mol% $Pd(PPh_3)_4$, 3 equiv. Et_3N, toluene, reflux] and obtained the corresponding products in 27–70% isolated yield (50% with 1-bromonaphthalene).[11u] Using cyclohexyl benzyloxymethyl-*H*-phosphinate **13**, compounds **14** and **15** are obtained in excellent yields. Clearly, the combination of our cross-coupling conditions with the more resistant cyclohexyl ester delivers much better results (87% isolated yield of **14** versus 50% reported by Cristau). Cyclohexyl phosphinate [$CyOP(O)H_2$] can also be prepared in excellent yield through the Dean–Stark esterification of H_3PO_2 [Eq. (3)]. As usual, the phosphinate is not isolated but instead the solution (typically 0.5 M) in which it is generated, is used directly.[20]



(3)

Table 6. Cross-coupling of DOPO with aryl halides.[a]



Entry	Time [h]	ArX (equiv.)	Yield [%] (^{31}P NMR yield)
1	48	4-NCC_6H_4Br (1.0)	68 (83)
2a	24	4-$CF_3C_6H_4Cl$ (1.5)	– (49)
2b	48		59 (70)
3	48	4-$EtO_2CC_6H_4Cl$ (1.5)	65 (75)
4	48	PhCl (3.0)	55 (56)[b]

[a] *Conditions*: the reactions were conducted at 115 °C.
[b] K_2CO_3 (0.65 equiv.) was used instead of $(i\text{-Pr})_2NEt$.

6*H*-Dibenzo[*c*,*e*][1,2λ^5]oxaphosphinine 6-Oxide (DOPO)

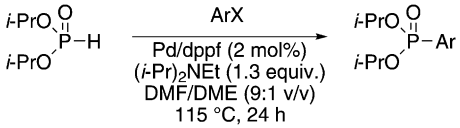
DOPO is an important *H*-phosphinate used in the flame-retardant industry. Beletskaya and co-workers studied the arylation of DOPO with iodides and bromides and 5 mol% palladium. The isolated yields were in the 75% range with iodides, and 50% with 4-NCC_6H_4Br.[11t] Using our conditions, DOPO reacts uneventfully in moderate yields, as shown in Table 6. The reactions were slow so extended times (48 h) resulted in improved yields (entry 2a versus 2b). This constitutes the first cross-coupling of DOPO with any aryl chloride.

H-Phosphonate Diester Cross-Coupling

As mentioned in the introduction, the metal-catalyzed cross-coupling of *H*-phosphonate diesters has been extensively studied.[2,6,12] We were the first to report the successful use of aryl chlorides in low to moderate yields.[6c] Addition of DME as the additive results in significant improvements (Table 7).

Interestingly, the reaction of 3-amino-2-bromopyridine (entry 6) worked very well, whereas Heinicke studied a broad range of conditions and obtained only 26% yield with 10 mol% palladium and $P(OEt)_3$ while Hirao-type conditions or stoichiometric nickel were reported to fail completely.[21]

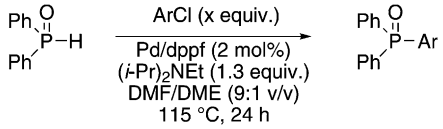
Table 7. Cross-coupling of $(i\text{-PrO})_2P(O)H$ with aryl chlorides.[a]



Entry	ArX (phosphite:ArX equivalent ratio)	Isolated yield [%] without DME[b]	Isolated yield [%] (^{31}P NMR yield) with DME
1	4-NCC_6H_4Cl (1.2:1.0)	57	61 (64)
2	4-$CF_3C_6H_4Cl$ (1.0:1.0)	22	52 (68)
3	4-$CF_3C_6H_4Cl$ (1.2:1.0)	–	61 (70)
4	4-$EtO_2CC_6H_4Cl$ (1.2:1.0)	44[c]	63 (78)
5	PhCl (1.2:1.0)	– (22)	– (42)
6	3-amino-2-bromopyridine (1.2:1.0)	–	87 (100)

[a] *Conditions:* the reactions were conducted at 115 °C. [b] From ref.[6c] The ratio $(i\text{-PrO})_2P(O)H$:ArCl was 1.2/1.0.
[c] With 4-$MeO_2CC_6H_4Cl$.

Table 8. Cross-coupling of $Ph_2P(O)H$ with aryl chlorides.



Entry	ArCl (equiv.)	Isolated yield [%] (^{31}P NMR yield)
1	4-NCC_6H_4Cl (1.5)	96 (97)
2	4-$CF_3C_6H_4Cl$ (1.5)	93 (94)
3	4-$EtO_2CC_6H_4Cl$ (1.5)	96 (100)
4	PhCl (1.5)	– (36)
5	PhCl (3.0)	78 (81)[a]

[a] K_2CO_3 (0.65 equiv.) was used instead of $(i\text{-Pr})_2$NEt.

Diphenylphosphine Oxide Cross-Coupling

To the best of our knowledge, a successful Pd-catalyzed cross-coupling of $Ph_2P(O)H$ with ArCl has not been reported previously. Table 8 summarizes our results. Activated (electron-poor) chlorides reacted in excellent yields, but chlorobenzene was unsatisfactory unless an excess was employed (entry 5).

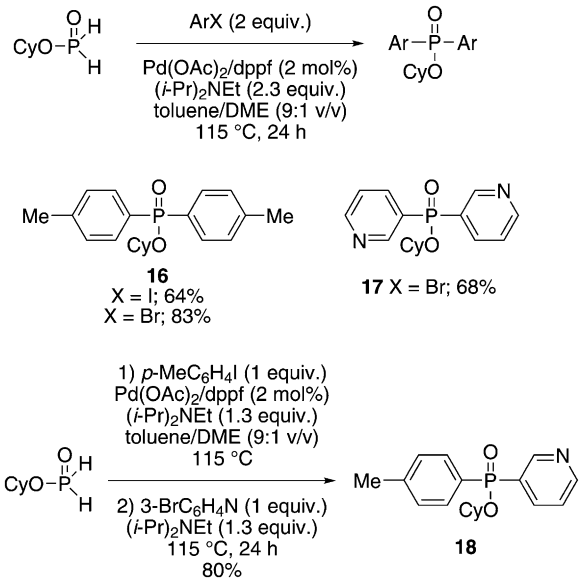
Tandem Reactions

Our laboratory has reported a variety of methods for the preparation of *H*-phosphinate esters.[3,13,16] Therefore, some tandem reaction sequences were investigated next. First, the cross-coupling/cross-coupling reaction was studied (Scheme 4).

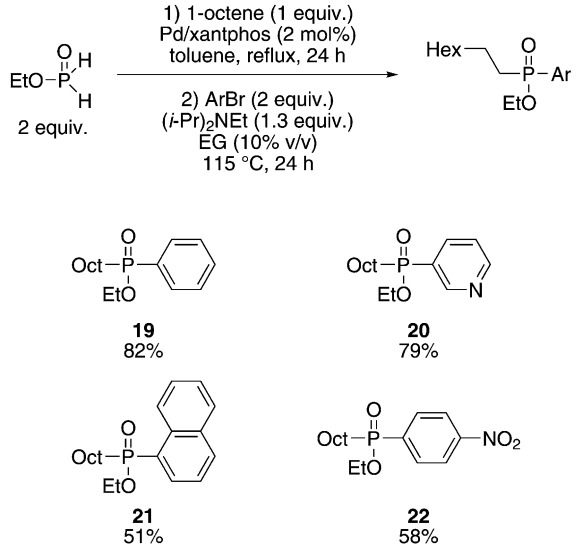
Cross-coupling of $CyOP(O)H_2$ to form symmetrically disubstituted $Ar_2P(O)(OCy)$ **16** and **17** worked well using toluene/DME as the solvent (64–83%). Schwabacher reported the synthesis of $(p\text{-}MeC_6H_4)_2P(O)(OMe)$ in 55% yield using 4-iodotoluene (but bromides failed).[11a] Unsymmetrical diarylphosphinate **18** could also be synthesized without any difficulty. Here, the use of the cyclohexyl ester is important to minimize side reactions as was discussed above.

Second, the tandem palladium-catalyzed hydrophosphinylation/cross-coupling was briefly investigated (Scheme 5). The hydrophosphinylation of 1-octene was conducted in toluene (in order to avoid a solvent switch) as described previously using $EtOP(O)H_2$ (2 equiv.) with Pd/xantphos (2 mol%). Cross-coupling was conducted directly on the crude reaction mixtures. Ethyl aryl-octylphosphinates **19**–**22** were obtained in moderate to good overall yield (51–82%), with the same palladium catalyzing both steps.

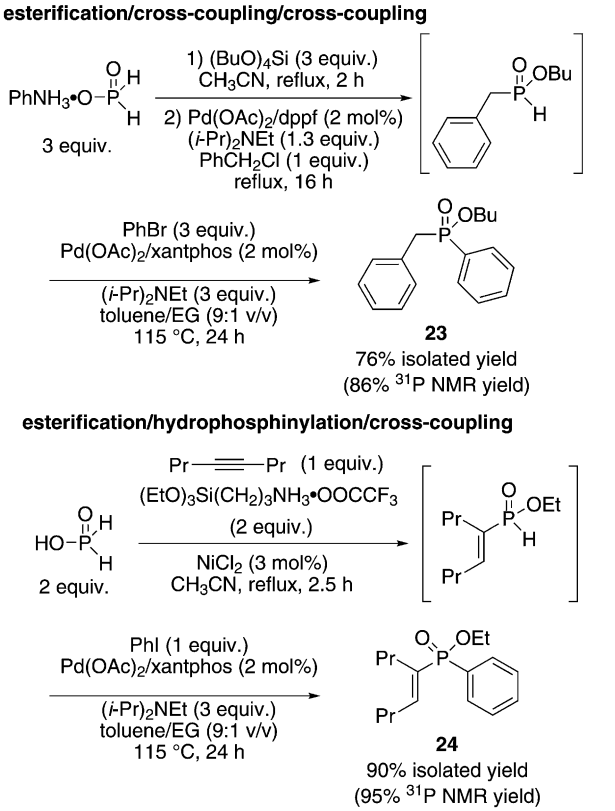
Other tandem sequences can be employed for dual P–C bond formation of unsymmetrically substituted phosphinates without intervening purification of both the phosphinate ester and the intermediate *H*-phosphinate (Scheme 6). Cross-coupling of anilinium hypophosphite as we described previously,[13] produces butyl benzyl-*H*-phosphinate, which is then coupled under our present conditions to form butyl benzylphenylphosphinate **23** in good combined yield. Similarly, our nickel-catalyzed hydrophosphinylation[16b] of 4-octyne can be followed by cross-coupling to form ethyl phenyl-(1-propylpent-1-enyl)phosphinate **24** in 90% isolated yield. Notably, we originally reported the preparation of **24** in 58% isolated yield, but using Hirao-type conditions [2 mol% $Cl_2Pd(PPh_3)_2$ with Et_3N as base] for the cross-coupling step.[16b] Once again, this illustrates the very significant improvement that additives offer.



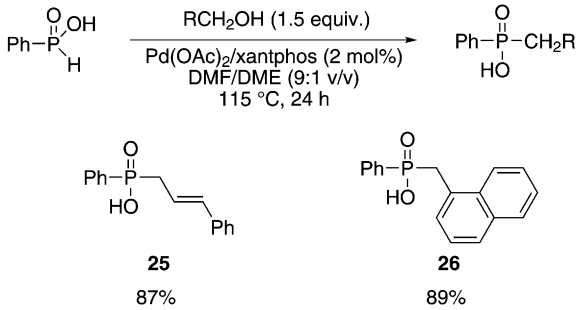
Scheme 4. Tandem cross-coupling/cross-coupling.



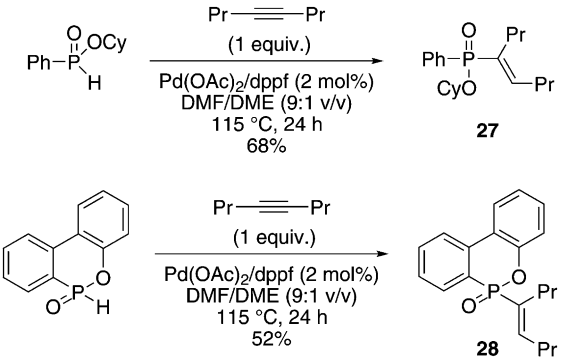
Scheme 5. Tandem hydrophosphinylation/cross-coupling.



Scheme 6. Tandem esterfication/P–C/P–C bond formations without intermediate purification.



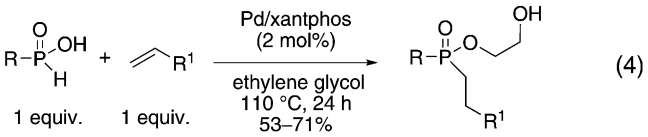
Scheme 7. Cross-coupling of phenyl-*H*-phosphinic acid with allylic or benzylic alcohols.



Scheme 8. Hydrophosphinylation reactions with Pd/dppf and DMF/DME.

Miscellaneous Applications

The use of an additive is not limited to the cross-coupling of C_{sp2}–X (and related) electrophiles with phosphinylidene P(O)H nucleophiles. The present studies were prompted by the discovery that EG allowed the hydrophosphinylation of *H*-phosphinic acids with alkenes [Eq. (4)].[9]

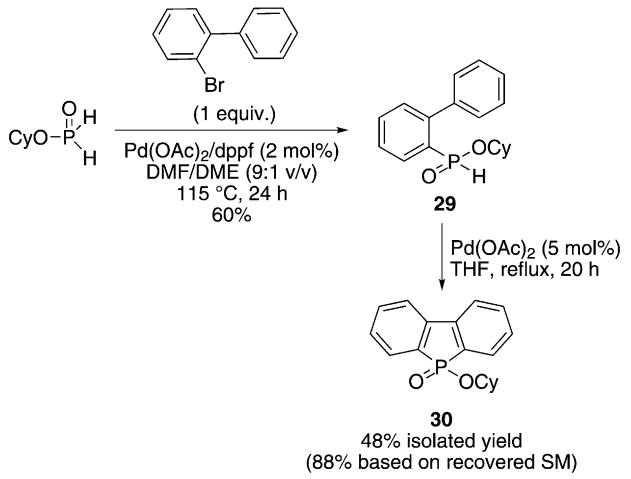


(4)

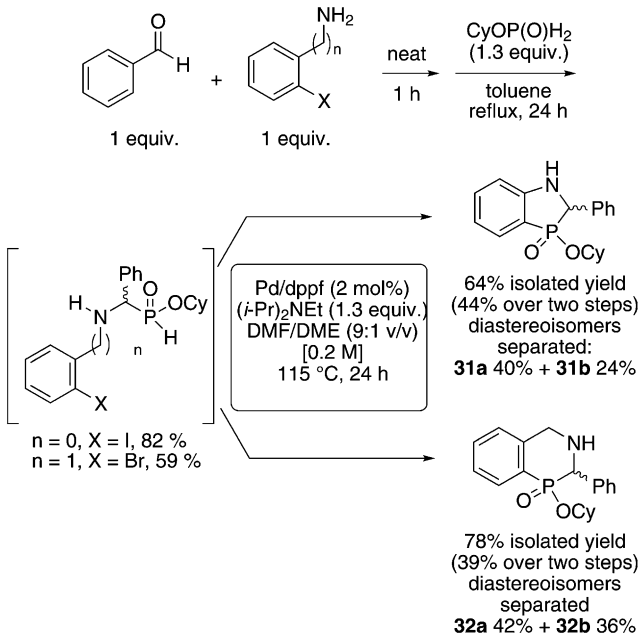
However, it was clear that EG played an active role as the intermediate 2-hydroxyethyl ester. Based on the present work, a few reactions were investigated using DME to see if promotion of the tautomerization to the P(III) tautomer and/or stabilization of the palladium catalyst was in fact a generally applicable strategy. Previously, we reported the direct cross-coupling of hypophosphorous acid and *H*-phosphinic acids with allylic and benzylic alcohols.[15] For the second P–C bond formation from the *H*-phosphinic acid, *t*-AmOH was found to be superior to DMF, presumably because of stabilization of the P(III) tautomer through hydrogen bonding, but also drying through the use of a Dean–Stark trap or molecular sieves was necessary. Therefore, phenyl-*H*-phosphinic acid was reacted with cinnamyl alcohol and 1-naphthylmethanol, respectively, using DMF/DME in the absence of any drying process (Scheme 7). In the case of cinnamyl alcohol, our original conditions gave a higher yield of product **25** (100%). On the other hand, with 1-naphthylmethanol, the present conditions give a significantly improved yield of **26** (89% *versus* 71%).

Other reactions are shown in Scheme 8. Whereas a few hydrophosphinylation reactions of terminal alkynes have been described with ArP(O)(OR)H,[22] the addition to internal alkynes, and the use of inexpensive dppf are unprecedented. The preparation of addition products **27** and **28** illustrates the importance of the additive (DME) in the tautomerization of the starting *H*-phosphinates.

The broad scope of the present cross-coupling also has implications in the synthesis of *P*-heterocycles. Kuninobu, Yoshida, and Takai, reported recently the formation of dibenzophosphole oxides through the Pd-catalyzed cyclization of substituted 1-biphenylphosphine oxides (the precursors were synthesized using Grignard reagents and Cl_2PR).[23] In order to ex-



Scheme 9. Cross-coupling of 1-bromobiphenyl with Pd/dppf and DMF/DME followed by Pd-catalyzed oxidative cyclization.



Scheme 10. Synthesis of *P,N*-heterocycles *via* tandem Kabachnick–Fields/Pd-catalyzed cross-coupling.

amine if *H*-phosphinate **29** can also undergo the analogous cyclization, the sequence shown in Scheme 9 was accomplished. Whereas the yield of the corresponding heterocycle **30** was moderate, this kind of process can now be investigated in more details.

Finally, in keeping with our ongoing interest in *P,N*-heterocycles,[24] P(O)H cross-coupling was briefly investigated as the key ring-closing step as shown in Scheme 10.

The substrates were synthesized through the Kabachnick–Fields reaction (phospha-Mannich),[25] then subjected to our cross-coupling conditions. Notably, the cyclizations were conducted at the same concentration as in the intermolecular cases (0.2 M) with good results. In both cases **31** and **32** the respective diastereoisomers (**a** and **b**) could be separated readily by simple chromatography on silica gel. The 6-membered heterocycle **32** appears to be a novel type of *P,N*-heterocyclic ring system.

The role of the additive can be two-fold: (i) stabilization of the palladium catalyst over time (slow-down of decomposition pathways to metallic palladium), and (ii) promotion of the P(V) to P(III) tautomeric equilibrium [Eq. (1)]. At the very least, the latter must be operative, and although it is a largely neglected phenomenon in the literature concerning phosphinylidenes P(O)H, we believe that the control of the tautomeric equilibrium is a major option to improve upon known reactions or to develop new reactivity as shown in Scheme 8. Other designed tautomerization catalysts could be even more powerful even in reduced quantities, and this will be a major focus of our laboratory's future studies.

Conclusions

Generally useful sets of conditions are described for the palladium-catalyzed cross-coupling of phosphinylidene compounds P(O)H with various electrophiles, including activated and unactivated aryl chlorides. While aryl chlorides have previously been used on very rare occasions, the present work provides a broadly successful cross-coupling methodology. Additionally, even other electrophiles have not always led to very high yields before, and several examples where our conditions offer significant improvements over literature procedures are provided. In particular, ethylene glycol (EG) is a successful solvent additive, especially with xantphos as ligand, or with 1,2-dimethoxyethane (DME) in combination with dppf. The latter is probably the ideal option since transesterification is totally avoided, and dppf is one of the cheapest and broadly available ligands. Both bisphosphine ligands (xantphos and dppf) are readily available and inexpensive, and even other ligands like the ubiquitous triphenylphosphine look promising. For cross-coupling reactions, the base was generally $(i\text{-Pr})_2$NEt, or in a few cases propylene oxide or potassium carbonate, and employing strong bases, such as *t*-BuOK, is completely avoided. All reactions were conducted with 2 mol% palladium, which is also an improvement over other literature methods. Various examples were provided where the use of the additive offers very significant improvements over other procedures. The use of an additive in the reactions of *H*-phosphinates, *H*-phosphonates, and diphenylphosphine oxide promises to extend the range of organophosphorus synthesis. The use of cyclohexyl *H*-phosphinate esters is also de-

scribed as a general and convenient solution to various problems associated with the chemistry of alkyl *H*-phosphinate esters (such as competing dealkylation).

The generality of our reaction, along with its use in tandem processes, provides a significant leap over the current "state-of-the-art" methodologies in P–C cross-coupling reactions. Overall, the present work is the first truly general method for the synthesis of various organophosphorus compounds *via* Pd-catalyzed P–C bond formation.

Future studies from our laboratory will focus on the design of P(V) to P(III) phosphinylidene tautomerization catalysts, since this will likely lead to general improvements not just for metal-catalyzed reactions, but for organophosphorus synthesis in general, since the P(III) tautomer is the key reactive species in the vast majority of cases.

Experimental Section

Representative Procedure for Cross-Coupling

Procedure A: To a tube was added *H*-phosphinate (1 mmol, 1 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 2.0 mol%), xantphos (12.7 mg, 0.022 mmol, 2.2 mol%), toluene and ethylene glycol (4.5 mL:0.5 mL), DIPEA (0.23 mL, 1.3 mmol, 1.3 equiv.) and the electrophile (1 mmol, 1 equiv.). The heterogeneous mixture was stirred under a flow of N_2 for 10 min and then heated at 115 °C for 24 h. After cooling to room temperature, the mixture was diluted with *ca.* 2.5 mL EtOH until homogeneous for ^{31}P NMR spectroscopy of the crude material. The solvent was then removed under vacuum and the resulting residue was dissolved in EtOAc and washed with $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under vacuum. The crude obtained was purified by column chromatography using mixtures of hexanes and EtOAc.

Procedure B: To a tube was added *H*-phosphinate (1 mmol, 1 equiv.), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 2.0 mol%), dppf (12.2 mg, 0.022 mmol, 2.2 mol%), DMF and 1,2-dimethoxyethane (4.5 mL:0.5 mL), DIPEA (0.23 mL, 1.3 mmol, 1.3 equiv.) and the electrophile (1 mmol, 1 equiv.). The mixture was stirred under a flow of N_2 for 10 min and then heated at 115 °C for 24 h before cooling to room temperature. The solvent was then removed under vacuum and the resulting residue was dissolved in EtOAc and washed with $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under vacuum. The crude obtained was purified by column chromatography using mixtures of hexanes and EtOAc.

Representative Procedure for Tandem Hydrophosphinylation/Cross-Coupling

To a solution of ethyl phosphinate (4.0 mL, 2 mmol, 2 equiv., 0.5 M in toluene) under N_2 were added 1-octene (0.16 mL, 1 mmol, 1 equiv.), $PdCl_2$ (3.55 mg, 0.02 mmol, 2 mol%) and xantphos (12.7 mg, 0.022 mmol, 2.2 mol%). After 24 h at reflux, the electrophile (2 mmol, 2 equiv.), DIPEA (0.23 mL, 1.3 mmol, 1.3 equiv.), toluene (0.5 mL) and ethylene glycol (0.5 mL) were added. After 24 h at reflux, the mixture was allowed to cool down to room temperature and the solvent was then removed under vacuum. The residue obtained was dissolved in EtOAc and washed with $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under vacuum. The crude obtained was purified by column chromatography.

Acknowledgements

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