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Pd-Catalyzed P–C Cross-Coupling Reactions for Versatile Triarylphosphine Synthesis

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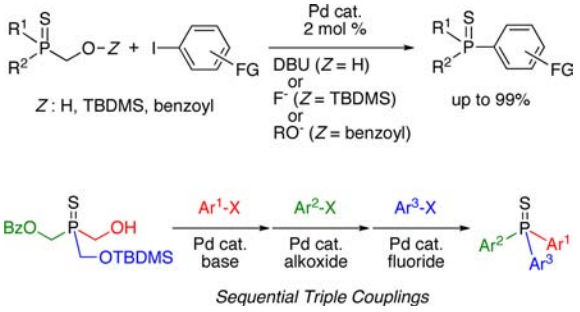
ABSTRACT



Practical and versatile syntheses of tertiary phosphine derivatives have been achieved by palladium-catalyzed deformylative P–C cross-coupling reactions of hydroxymethylphosphine derivatives. Sequential couplings of orthogonally protected precursors provide a simple and practical route toward a variety of tertiary phosphine derivatives having aryl substituents in any combination.

Organophosphorus compounds play important roles in organic synthesis, especially as synthetic reagents and ligands for transition metal catalysis.[1] Much attention has been paid toward the development of functionalized and sophisticated organophosphines for selective transition-metal catalysis because of the high impact of their structure on the reactivity, selectivity, and even the reaction pathway, i.e. products formed, of the catalytic reactions being studied.[2]

In addition to classical nucleophilic P–C bond forming methods,[3] a number of catalytic reactions for the synthesis of organophosphines have also been developed that use various phosphine precursors in nucleophilic addition,[4] hydrophosphination,[5] and P–C cross-coupling reactions.[6,7] In contrast to the classical stoichiometric organometallic reactions for phosphine syntheses, metal-catalyzed P–C bond formations have many advantages due to high functional group tolerance, which is often problematic in the classic methods. However, most of the reported catalytic reactions can construct only one P–C bond, through

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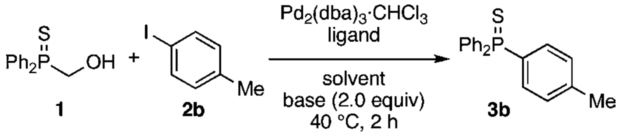
activation of one precursor bond. Moreover, these reactions cannot simply be extended to consecutive multiple coupling sequences in a selective manner because of the unavailability of suitable precursors having more than one functionality on the phosphorus atom being activated, although some nonselective multiple couplings are known.[8] Successful sequential construction of three P−C bonds by using nucleophilic organometallic reagents can be found in the literature, but the problem of functional group tolerance can arise, like in the classical reactions.[9] The sequential synthesis of organophosphines with wide functional group tolerance has yet to be achieved.

Herein we report a novel, practical, and versatile method for organophosphine synthesis based on newly developed palladium-catalyzed deformylative P−C cross-coupling reactions. Successful extension of the strategy provides simple and easy procedures for organophosphine syntheses, which can connect up to three different substituents onto the phosphorus atom, in a selective, actually sequential manner.

A key to success in multiple selective P−C couplings is to develop suitable phosphine precursors for exclusive generation of a reactive site under selective conditions during each step. We have focused on hydroxymethylphosphine derivatives as precursors for P−C cross-coupling reactions, because these compounds generate the parent phosphides through deformylation under mild basic conditions.[10,11] In addition, various kinds of protective groups are available for the hydroxyl group, which can be selectively activated. Selective and stepwise transformation sequences can be realized when bis- and tris-hydroxymethyl derivatives with orthogonal protection are applied in a selective manner.

Prior to attempting multiple couplings, we tried to develop catalytic P−C cross-coupling processes suitable for multiple sequential couplings through deformylation of protected and nonprotected hydroxymethylphosphine precursors, even though a number of catalytic monosubstitutions of phosphine derivatives are known.[6,7] As a model, monohydroxymethylphosphine sulfide **1** was chosen for an initial investigation of our strategy.[12] The reaction of **1** with *p*-iodotoluene **2b** was carried out in toluene at 40 °C in the presence of the Pd catalyst prepared from $Pd_2(dba)_3 \cdot CHCl_3$ and Ph_3P. By using diazabicyclo-[5.4.0]-7-undecene (DBU) as a base to trigger the reaction, **1** actually gave the expected coupling product **3b** in good yield (Table 1, entry 1). A survey of the phosphine ligands revealed that 1,1′-bis(diphenylphosphino)ferrocene (dppf) is particularly suitable for the present coupling reaction (entry 7), whereas the other bidentate phosphine ligands or a sterically hindered ligand gave unsatisfactory results (entries 2−6). Although both the precursor and the product can coordinate to the Pd, and some of phosphine sulfides reported to work as a ligand,[13] the reaction did not proceed in the absence of an additional phosphine ligand (entry 8). DBU was found to be suitable for this reaction. The reactions conducted below 40 °C did not proceed at all, probably because the initial oxidative addition does not occur at that temperature.

Table 1. Ligand/Base Screening for the P−C Coupling of **1**



entry	solvent[a]	base	ligand[b]	yield (%)[c]
1	toluene	DBU	Ph_3P	90
2	toluene	DBU	*t*Bu_3P	3
3	toluene	DBU	dppe	9
4	toluene	DBU	dppp	49
5	toluene	DBU	dppb	40
6	toluene	DBU	(*S*)-BINAP	33
7	toluene	DBU	dppf	99 (99)
8	toluene	DBU	−	0
9	toluene	Et_3N	dppf	7
10	toluene	K_2CO_3	dppf	3
11	THF	K_2CO_3	dppf	1

[a] Conditions: **1** (0.5 mmol), **2b** (1.05 equiv), solvent (5 mL), $Pd_2(dba)_3$ (1 mol %). [b] P/Pd = 2.0. [c] Yield calculated from ^{31}P NMR signal ratio. Isolated yield is shown in parentheses.

Under the optimized conditions, several iodoarenes, **2a**−**o**, with various steric and electronic features, were smoothly coupled with **1** to give the corresponding arylphosphine sulfides **3a**−**o** in excellent yield (Table 2). Although iodoarenes with an electron-donating substituent require a longer reaction time to complete the reaction, the coupling products can be obtained almost quantitatively. Iodobenzenes with other halogens also react without trouble, with the other halogens remaining untouched under the reaction conditions. A sterically hindered substituent engaged in the coupling reaction, but a longer reaction time and/or more severe conditions were required (entries 4, 15−16). Even under elevated temperatures, the reaction of 2,6-disubstituted iodoarene **2p** proceeded slowly to give the coupled product **3p** in a moderate yield (entry 16). Otherwise, the reactions could be readily applied to a wide variety of substrates as shown in the table.

As shown above, **1** acts as a potential masked-phosphine equivalent for the present palladium-catalyzed P−C cross-coupling reaction under basic conditions.

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(11) Some catalytic P−C cross-couplings of hydroxymethylphosphine derivatives are reported, see ref 8.

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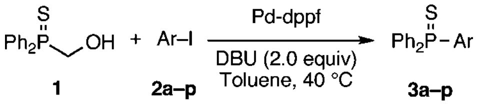
Table 2. Pd-Catalyzed P–C Cross-Coupling of **1** with Various Substrates

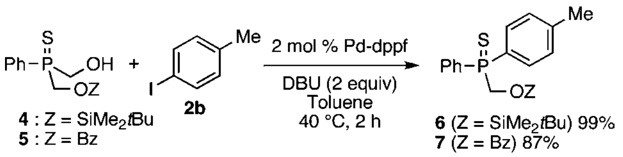


entry	Ar-	time (h)	product	yield (%)[a]
1	Ph- (**2a**)	3	**3a**	99
2	*p*-CH_3-C_6H_4- (**2b**)	3	**3b**	99
3	*m*-CH_3-C_6H_4- (**2c**)	3	**3c**	99
4	*o*-CH_3-C_6H_4- (**2d**)	12	**3d**	86
5	*p*-CH_3O-C_6H_4- (**2e**)	12	**3e**	93
6	*p*-CH_3O_2C-C_6H_4- (**2f**)	3	**3f**	95
7	*p*-F-C_6H_4- (**2g**)	3	**3g**	99
8	*p*-Cl-C_6H_4- (**2h**)	3	**3h**	99
9	*p*-Br-C_6H_4- (**2i**)	3	**3i**	99
10	*p*-NC-C_6H_4- (**2j**)	3	**3j**	99
11	*p*-CF_3-C_6H_4- (**2k**)	3	**3k**	99
12	*p*-NO_2-C_6H_4- (**2l**)	3	**3l**	96
13	*p*-OHC-C_6H_4- (**2m**)	3	**3m**	95
14	*p*-$HOCH_2$-C_6H_4- (**2n**)	3	**3n**	97
15	1-naphthyl- (**2o**)	18	**3o**	97
16	2,6-$(CH_3)_2C_6H_3$- (**2p**)	6	**3p**	32[b]

[a] Isolated yield. Unless otherwise noted, the reaction was conducted at 40 °C for 3 h in the presence of 2 mol % of Pd catalyst and DBU (2 equiv, basic condition). The Pd catalyst was prepared in situ from $Pd_2(dba)_3 \cdot CHCl_3$ (1 mol %) and dppf (2 mol %). [b] The reaction was conducted under reflux. The reaction at temperatures lower than 100 °C did not proceed.

Selective reactions of the hydroxymethyl substrate in the presence of another hydroxy-protected group were checked next for selective multiple couplings. A *tert*-butyldimethylsilyl group and a benzoyl group were chosen for orthogonal protection. Transformations of monoprotected substrates **4** and **5** were examined under basic conditions (Scheme 1). Under the optimized conditions for **1**, silyl ether **4** smoothly reacted with **2b** to give the coupled product **6** in excellent yield. Benzoate **5** also gave the product **7** in good yield, although some byproducts derived from disproportionation of the esters were observed under these conditions. In both cases, only the unprotected part was selectively converted to the aryl group.

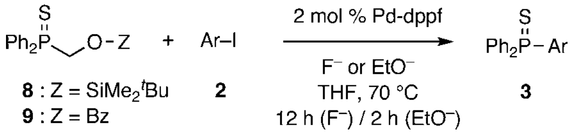
Scheme 1. Selective Coupling of **4** and **5** (Basic Condition)



Although two unique aromatics can be incorporated by using **4** or **5** through repetitive P–C couplings after deprotection, it would be a more straightforward process if the protected side chain could be directly and selectively applied to further P–C cross-couplings. Thus, direct couplings of protected substrates **8** and **9** through *in situ* deprotection were investigated (Table 3). The reaction of TBDMS-protected substrate **8** with iodoarenes was carried out in the presence of fluoride, instead of a base, to trigger the reaction through desilylation. By using CsF in THF at 70 °C, the desired direct cross-coupling reaction proceeded smoothly to give the coupling product in quantitative yields, even though an extended reaction time was required for completion. Benzoyl-protected **9** also reacted with iodoarenes through alcoholysis by using sodium ethoxide in THF at 70 °C, to give the same products. Iodoarenes with an electron-withdrawing substituent reacted slowly under the alcoholytic conditions, and the yields considerably decreased, even though the reactions were extended. Otherwise, coupling through alcoholysis gave the products in excellent yields within 2 h. The results of these direct deprotection–coupling sequences of the protected precursors **8** and **9** are summarized in Table 3.

Selective transformations of unsymmetrically protected diol **10** revealed that each group reacted exclusively to give the corresponding monocoupled product without affecting the other protective group (Scheme 2).

Table 3. Direct P–C Bond Formation by Using Protected Substrates **8** and **9**



entry	Ar–X	results for **8**[a]	results for **9**[a]
1	**2a** (H)	99%	99%
2	**2b** (*p*-Me)	99%	99%
3	**2c** (*m*-Me)	99%	96%
4	**2d** (*o*-Me)	98%	57% (12 h)
5	**2e** (*p*-OMe)	87%	99%
6	**2f** (*p*-CO_2Me)	91%	–[b]
7	**2j** (*p*-CN)	97% (24 h)	32% (24 h)
8	**2l** (*p*-NO_2)	99% (24 h)	38% (6 h)

[a] Isolated yield. Reaction conditions unless otherwise noted; for **8** (fluoride condition): CsF (2 equiv), THF, 70 °C, 12 h; for **9** (alkoxide condition): NaOEt (2 equiv), THF, 70 °C, 2 h. Pd-dppf was prepared same as described in Table 2. [b] Not examined.

An extension of the present strategy to sequential triple couplings would yield phosphines having a variety of structures. For selective triple couplings, we have prepared precursor **13** by selective protections of the two hydroxyl groups of tris(hydroxymethyl)phosphine[14] sulfide which can be easily synthesized from commercially available tetrakis(hydroxymethyl) phosphonium chloride.[15]

Direct triple couplings of **13** were then demonstrated; iterative couplings under the basic, the alkoxide-mediated,

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(14) Tris(hydroxymethyl)phosphine is known as an equivalent of the parent phosphine; see ref 8. Alkylphosphines can be also prepared by alkylation–deformylation processes of this precursor; see ref 3b.

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Scheme 2. Selective Coupling of Unsymmetrically Protected **10**

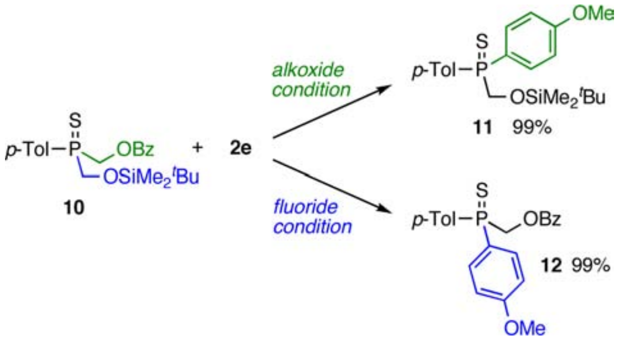
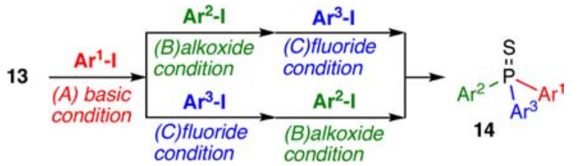


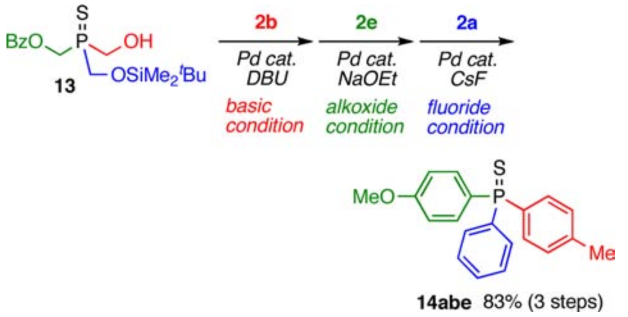
Table 4. Pd-Catalyzed Sequential Multiple P$-$C Couplings of **13**



entry	1st[a]	2nd[a]	3rd[a]	product[b]	yield (%)[c]
1	**2b** (A)	**2e** (B)	**2a** (C)	**14abe**	83
2	**2e** (A)	**2e** (B)	**2e** (C)	**14eee**	85
3	**2b** (A)	**2e** (B)	**2j** (C)	**14bej**	82
4	**2i** (A)	**2e** (B)	**2m** (C)	**14eim**	82
5	**2b** (A)	**2e** (C)	**2a** (B)	**14abe**	80

[a] Substrates in each step were shown. Conditions applied in each step were noted in parentheses: (A) Basic condition same as Table 2; (B) Alkoxide condition same as Table 3; (C) Fluoride condition same as Table 3. Reactions were conducted using **13** (0.5 mmol), **ArI** (1.05 equiv), solvent (5 mL), Pd$_2$(dba)$_3$ (1 mol %), dppf (2 mol %). Intermediates in each step were isolated and used in the next step. [b] Suffixes of the compound number represent the substituents including in the corresponding ArI; see Table 2. [c] Isolated yield for three steps.

Scheme 3. Triarylphosphine Synthesis by Sequential Triple Couplings



and the fluoride-mediated conditions gave the corresponding triarylphosphine sulfide **14abe** in fairly good overall yield in quite a selective manner (Scheme 3). Based on the results of mono- and bis-protected substrates shown above, a variety of aromatic groups can be introduced onto the phosphorus atom via sequential repetitive couplings. Some representative results are summarized in Table 4. In all cases, the triple-coupled triarylphosphine sulfide **14** was isolated in quite good yield in each step, totally over 80%. As shown in Scheme 2, swapping the order of the applied conditions in the second and third steps did not disturb the coupling (entry 5). Some of the products, including a sensitive functional group such as a formyl group and a cyano group, which could not be accessed by other classical organometallic methods, could also be synthesized by the present coupling, without any problem (entries 3 and 4).[16]

In conclusion, we have developed effective P$-$C cross-coupling reactions of hydroxymethylphosphine derivatives, which can be applied in a true sequential synthesis of tertiary phosphine derivatives. The application of this methodology to access synthetically valuable triarylphosphine derivatives in a combinatorial fashion including stereoselectively, using other aryl halides and pseudohalides which are not reactive under the conditions described here, is currently under investigation.

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Supporting Information Available. Reaction procedures and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(16) The products, triarylphosphine sulfides, are known as fine equivalents of the parent trivalent phosphines; they can be easily transformed back to the parent trivalent phosphines, can be handled without care under the air, and can be easily purified due to their low polarity and high tendency to crystallize. See ref 12.