

Fluoride-catalyzed three-component coupling reaction of a silylphosphine, activated alkenes and aldehydes

Minoru Hayashi,* Yutaka Matsuura and Yutaka Watanabe*

Department of Applied Chemistry, Faculty of Engineering, Ehime University, 3 Bunkyo-cho, Matsuyama 790-8577, Japan

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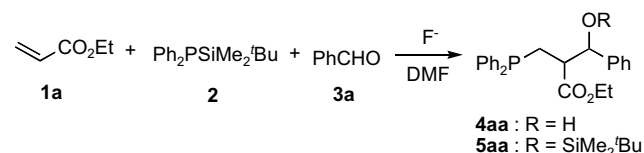
Abstract—A novel CsF-catalyzed three-component coupling reaction of a silylphosphine, activated alkenes and aldehydes is described. Multi-functional phosphines were obtained by forming both carbon–phosphorus and carbon–carbon bonds in good yields under mild conditions.

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A mild and convenient procedure for obtaining a variety of new multi-functional organophosphorus compounds have received great attention due to the wide use of these functional phosphines as ligands in catalysis.¹ Formation of a carbon–phosphorus bond through the phosphination of carbon–carbon unsaturated bonds is of interest in recent times.^{2,3} In addition, a three-component coupling reaction including both carbon–phosphorus and carbon–carbon bond formation is a quite promising method to produce a variety of multi-functional phosphines. We have recently reported a novel phosphination of alkenes and alkynes by use of a fluoride-activated silylphosphine, and a stoichiometric three-component coupling reaction with an aldehyde giving multi-functional phosphines.⁴ In this study, we report a novel catalytic version of the three-component coupling reaction.

We first surveyed the reactivity of several kinds of fluoride source toward silylphosphine in the presence of ethyl acrylate and benzaldehyde as an alkene and an additional electrophile, respectively (Table 1). As already reported, stoichiometric reaction using TASF in DMF proceeded well (entry 1).⁴ The CsF-mediated reaction in DMF also proceeded smoothly, whereas KF did not work probably because of its low solubility. Other solvents, such as CH₂Cl₂, CH₃CN and THF, gave poor results due to low reactivity of the intermediate phos-

Table 1. Fluoride-promoted three-component coupling reaction^a



Entry	Fluoride	Equiv	Time (h)	4aa ^b	5aa ^b
1	TASF	1.2	3	95	— ^c
2		0.1	4	— ^c	— ^c
3	KF	1.2	1	— ^c	— ^c
4	CsF	1.2	2	55	5
5		0.1	3	9	68
6		0.05	4	8	67

^a The reactions were conducted at rt.

^b Isolated yields.

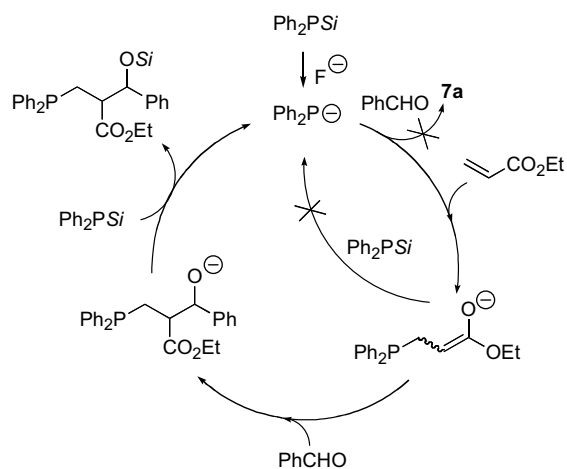
^c Not observed.

phide in these solvents, as seen in the previous Michael addition.⁴

When the reaction was performed with CsF, a small amount of the silyl ether **5aa** was isolated (entry 4). This result clearly showed that a part of the initially formed alkoxide of the adduct **4aa** attacked the silylphosphine and reproduced the nucleophilic phosphide.⁵ Therefore, we next examined the catalytic reactivity of those fluorides, and found that only CsF promoted the reaction in a catalytic way to afford the silyl ether **5aa** as a main product together with the parent alcohol **4aa** in totally good yield (entries 5 and 6).

Keywords: Silylphosphine; Phosphination; Michael addition; Three-component coupling.

* Corresponding authors. Tel.: +81 89 927 9917; fax: +81 89 927 9944; e-mail: hayashi@eng.ehime-u.ac.jp



Scheme 1.

The present catalytic reaction proceeded selectively in one pot because of low reactivity of **2** toward aldehydes and sufficient nucleophilicity of the phosphide derived from **2** toward Michael acceptors, although some silyl-

phosphines easily reacted with aldehydes.⁶ When the reaction was attempted in the absence of aldehyde, CsF did not catalyze the addition; only a trace of the corresponding adduct **6a** was formed instead. Noteworthy was that the enolate formed after Michael addition did not give the silyl enolate, whereas the alkoxide of the aldol-type adduct smoothly attacked the silylphosphine to promote the catalytic cycle (Scheme 1). It is in contrast to the formation of the silyl enolate in the reaction of trimethylsilyldiphenylphosphine and acrolein.⁷ An alkoxide, such as sodium methoxide, reacted with the silylphosphine to produce the corresponding phosphide, and it indeed catalyzed the three-component coupling reaction. However, the results of alkoxide-catalyzed reactions were not satisfactory compared with the present CsF-catalyzed reaction.

The results of the CsF-catalyzed coupling of several alkenes and carbonyl compounds are shown in Table 2.^{8,9}

Since the reaction started with Michael-type phosphination, the alkenes having electron-withdrawing group, such as typical Michael acceptors like α,β -unsaturated carbonyl compounds, reacted smoothly to give the corre-

Table 2. CsF-catalyzed three-component coupling reaction^a

Entry	Acceptor	Electrophile	Products	Yields ^b (%)	dr ^c
1		PhCHO		4aa 88	1:1.5
2		PhCHO		4ba 72 ^d	— ^e
3		PhCHO		4ca 85	1:1.2
4		PhCHO		4da 80	1:1.3
5		PhCHO		4ea 72	1:1.3
6		PhCHO	— ^f	— ^f	—
7		<i>i</i> PrCHO		4ab 76 ^g	1:1.2
8				4ac 67	1:2

^a Unless otherwise noted, the reaction was conducted in DMF at rt for 4 h by using 5 mol% of CsF, an alkene (1.1 equiv) and **2** (1.1 equiv).

^b Yields of the alcohol products isolated after hydrolysis of the initially formed silyl ethers.

^c Diastereomer ratios were determined by ¹H and ³¹P NMR.

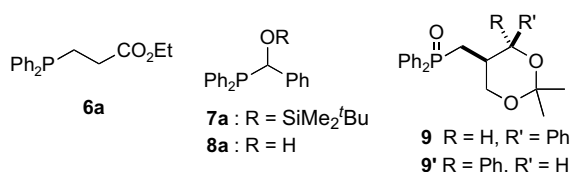
^d The adduct was isolated as its oxide because the initially formed adduct **4ba** readily oxidized in air. The ratio of diastereomers was determined by ³¹P NMR.

^e Not determined.

^f No adduct was formed after 4 h. Extended reaction time resulted in the formation of aldehyde adduct **7a**.

^g The reaction was continued for 6 h.

sponding adducts in fairly good yields (entries 1–5). In contrast, the alkenes having a weak activating group like styrene did not give any adduct (entry 6), although styrene smoothly reacted with stoichiometric TBAF in the presence of proton source to form the corresponding adduct in good yield.⁴ Extended reaction time in the reaction of styrene resulted in the formation of **7a** via direct addition to the aldehyde. Michael acceptors having an acidic proton, such as cyclohexenone, gave no three-component coupling adducts. In these cases, simple Michael adducts were formed instead in good yields.¹⁰ Aromatic and aliphatic aldehydes smoothly reacted as second electrophiles to give the adducts as silyl ethers **5** together with a small amount of the parent alcohols **4**. After hydrolysis of the silyl ethers by means of hydrochloric acid, the parent alcohols were isolated in fairly good yields. In each case, observed stereoselectivity was not satisfactory, in the range of a 1:1–1:2 ratio. The stereochemistry of the major diastereomer of **4aa** was determined as anti by ¹H NMR measurement of the cyclic acetals **9** (from the major isomer) and **9'** (from the minor isomer). When a ketone was applied as a second electrophile, the corresponding three-component adduct was not formed even under more drastic conditions.



No trace of three-component coupling product was observed in the reaction of **1a**, **3a** and diphenylphosphine in the presence of a base;^{3a} the corresponding Michael adduct **6a** (70%) and aldehyde adduct **8a** (26%) were formed instead. This is because of the presence of proton (diphenylphosphine) which readily quenched the intermediate enolate. The following aldol-type reaction did not occur under these conditions. More nucleophilic lithium phosphide reacted preferentially with the aldehyde in comparison to the acrylate, giving **8a** (73%) as a main product together with **6a** (13%). Stepwise addition of ethyl acrylate and benzaldehyde to lithium phosphide gave **4aa** in low yield (38%). From these results, the present CsF-catalyzed reaction of silylphosphine is quite suitable for this three-component coupling reaction.

In conclusion, we have developed the CsF-catalyzed reaction of a silylphosphine, Michael acceptors and carbonyl compounds to produce multi-functionalized phosphines via simultaneous formation of the phosphorus–carbon and the carbon–carbon bonds. Further study of the present reaction to improve the stereoselectivity is now under investigation.

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- Silylphosphine **2** did not silylate alcohols without activation; see Hayashi, M.; Matsuura, Y.; Watanabe, Y. *Tetrahedron Lett.* **2004**, *45*, 1409–1411.
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- Typical procedure: silylphosphine **2** (165 mg, 0.55 mmol) was added to a stirred mixture of cesium fluoride (4 mg, 0.025 mmol), ethyl acrylate **1a** (50 mg, 0.55 mmol) and benzaldehyde **3a** (53 mg, 0.50 mmol) in DMF (3 mL) at rt. After stirring for 4 h at rt, aqueous hydrochloric acid (1 M) was added to hydrolyze the silyl ether and the mixture was extracted twice with CHCl_3 . The combined organic extracts were dried, and the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel (eluent: $\text{AcOEt}/n\text{-hexane} = 1/3$, R_f 0.40) affording **4aa** (172 mg, 88%) as a mixture of diastereomers ($\text{dr} = 1:1.5$).⁴
- Selected data of the products: compound **4ea** ($\text{dr} = 1:1.3$); (major isomer) ¹H NMR δ 0.87 (t, $J = 7.6$ Hz, 3H), 1.16 (s, 3H), 1.18–1.30 (m, 2H), 1.40–1.45 (m, 2H), 2.31 (dd, $J_{\text{P-H}} = 3.2$ Hz, $J_{\text{H-H}} = 14.0$ Hz, 1H), 2.62 (dd, $J_{\text{P-H}} = 1.6$ Hz, $J_{\text{H-H}} = 14.0$ Hz, 1H), 3.30 (br d, 1H), 3.75–3.84 (m, 2H), 5.04 (d, $J = 2.8$ Hz, 1H), 7.24–7.54 (m, 15H); ¹³C NMR δ 13.7, 18.9 (d, $J_{\text{C-P}} = 10.8$ Hz), 19.2, 30.3, 36.6 (d, $J_{\text{C-P}} = 17.2$ Hz), 51.2 (d, $J_{\text{C-P}} = 16.2$ Hz), 64.8, 79.4 (d, $J_{\text{C-P}} = 8.7$ Hz), 127.6, 127.7, 127.8, 128.2 (d, $J_{\text{C-P}} = 6.8$ Hz), 128.3 (d, $J_{\text{C-P}} = 6.8$ Hz), 128.4, 128.6, 132.8 (d, $J_{\text{C-P}} = 12.9$ Hz), 133.0 (d, $J_{\text{C-P}} = 20.1$ Hz), 138.7 (d, $J_{\text{C-P}} = 38.4$ Hz), 139.2 (d, $J_{\text{C-P}} = 31.1$ Hz), 140.0, 175.9 (d, $J_{\text{C-P}} = 1.8$ Hz); ³¹P NMR δ –23.0. (minor isomer) ¹H NMR δ 0.87 (t, $J = 7.6$ Hz, 3H), 1.15 (s, 3H), 1.18–1.30

(m, 2H), 1.40–1.45 (m, 2H), 2.44 (dd, $J_{\text{P-H}} = 4.0$ Hz, $J_{\text{H-H}} = 14.4$ Hz, 1H), 2.81 (dd, $J_{\text{P-H}} = 3.2$ Hz, $J_{\text{H-H}} = 14.4$ Hz, 1H), 3.20 (br, 1H), 3.70–3.82 (m, 2H), 5.02 (br, 1H), 7.24–7.54 (m, 15H); ^{13}C NMR δ 13.7, 19.1 (d, $J_{\text{C-P}} = 12.4$ Hz), 19.2, 30.3, 34.4 (d, $J_{\text{C-P}} = 16.6$ Hz), 51.6 (d, $J_{\text{C-P}} = 16.4$ Hz), 64.9, 78.9 (d, $J_{\text{C-P}} = 7.0$ Hz), 127.6, 127.7, 127.8, 128.2 (d, $J_{\text{C-P}} = 6.6$ Hz), 128.3, 128.4 (d, $J_{\text{C-P}} = 7.6$ Hz), 128.5, 132.8 (d, $J_{\text{C-P}} = 12.9$ Hz), 132.9 (d, $J_{\text{C-P}} = 19.9$ Hz), 138.7 (d, $J_{\text{C-P}} = 14.2$ Hz), 139.2 (d, $J_{\text{C-P}} = 6.2$ Hz), 139.8, 175.8 (d, $J_{\text{C-P}} = 1.1$ Hz); ^{31}P NMR δ –21.4. IR (neat) 3585, 2962, 2877, 1724, 1639, 1454, 1322, 1293, 1164, 1064, 1010, 941, 813, 651 cm^{-1} ; FABMS calcd for $\text{C}_{27}\text{H}_{31}\text{O}_3\text{P}$: 434. Found: 435 (M+H). Compound **4ab** (major isomer) ^1H NMR δ 0.94 (d, $J = 5.5$ Hz, 6H), 1.21 (t, $J = 7.0$ Hz, 3H), 1.89 (m, 1H), 2.33–2.44 (m, 2H), 2.74 (m, 1H), 3.55 (m, 1H), 4.01 (m, 2H), 5.04 (d, $J = 4.4$ Hz, 1H), 7.22–7.35 (m, 10H); ^{13}C NMR δ 14.9, 18.9, 21.4, 25.3 (d, $J_{\text{C-P}} = 12.7$ Hz), 34.7 (d, $J_{\text{C-P}} = 12.5$ Hz), 40.1, 60.4, 73.0 (d, $J_{\text{C-P}} = 10.5$ Hz), 127.4 (d, $J_{\text{C-P}} = 6.7$ Hz), 127.6 (d, $J_{\text{C-P}} = 7.0$ Hz), 127.9, 128.5, 133.3 (d, $J_{\text{C-P}} = 18.5$ Hz), 133.7 (d, $J_{\text{C-P}} = 18.7$ Hz), 137.4 (d, $J_{\text{C-P}} = 11.0$ Hz), 137.8 (d, $J_{\text{C-P}} = 13.5$ Hz), 175.7 (d, $J_{\text{C-P}} = 3.3$ Hz); ^{31}P NMR δ –19.9. (Minor isomer) ^1H NMR δ 0.94 (d, $J = 5.5$ Hz,

6H), 1.21 (t, $J = 7.0$ Hz, 3H), 1.89 (m, 1H), 2.29–2.36 (m, 2H), 2.74 (m, 1H), 3.63 (m, 1H), 4.01 (m, 2H), 4.83 (d, $J = 4.8$ Hz, 1H), 7.22–7.35 (m, 10H); ^{13}C NMR δ 14.8, 15.2 (d, $J_{\text{C-P}} = 17.8$ Hz), 19.1, 25.1, 28.1 (d, $J_{\text{C-P}} = 14.7$ Hz), 49.9 (d, $J_{\text{C-P}} = 16.6$ Hz), 60.9, 75.9 (d, $J_{\text{C-P}} = 11.1$ Hz), 127.4 (d, $J_{\text{C-P}} = 19.8$ Hz), 127.5 (d, $J_{\text{C-P}} = 6.2$ Hz), 128.2, 128.7, 132.7 (d, $J_{\text{C-P}} = 17.8$ Hz), 133.6 (d, $J_{\text{C-P}} = 19.7$ Hz), 136.8 (d, $J_{\text{C-P}} = 13.4$ Hz), 137.9 (d, $J_{\text{C-P}} = 11.7$ Hz), 174.1 (d, $J_{\text{C-P}} = 3.6$ Hz); ^{31}P NMR δ –18.3. IR (neat) 3558, 3022, 2970, 2850, 1604, 1461, 1257, 1133, 1097, 1078, 821, 677 cm^{-1} . Compound **9** (from major isomer of **4aa**) ^1H NMR δ 1.52 (s, 3H), 1.53 (s, 3H), 1.90 (dd, $J_{\text{P-H}} = 9.2$ Hz, $J_{\text{H-H}} = 15.5$ Hz, 1H), 2.11 (br t, 1H), 2.74 (ddd, $J_{\text{P-H}} = 10.9$ Hz, $J_{\text{H-H}} = 12.9$, 15.5 Hz, 1H), 4.19 (d, $J = 12.0$ Hz, 1H), 4.22 (d, $J = 12.0$ Hz, 1H), 5.16 (s, 1H), 7.13–7.64 (m, 15H). Compound **9'** (from minor isomer of **4aa**) ^1H NMR δ 1.42 (s, 3H), 1.55 (s, 3H), 1.80–1.94 (m, 1H), 1.96–2.06 (br, 1H), 2.14–2.32 (m, 1H), 3.86 (t, $J = 11.3$ Hz, 1H), 4.43 (dd, $J = 4.3$, 11.3 Hz, 1H), 4.55 (d, $J = 10.2$ Hz, 1H), 7.18–7.60 (m, 15H).

10. In some cases using a reactive acceptor like methyl vinyl ketone, a complex mixture of the products was formed by multiple addition of the acceptor.