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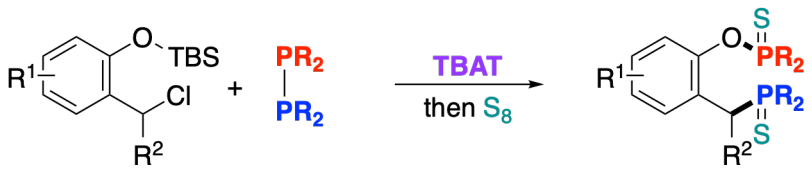

Tetrahedron Letters
journal homepage: www.elsevier.com

Diphosphination of *ortho*-quinone methide precursors with diphosphines

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ARTICLE INFO

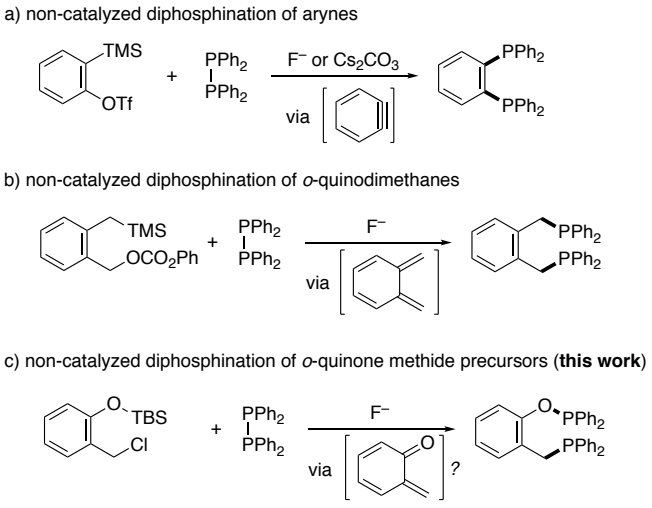
Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
C–P bond formation
Diphosphination
Diphosphines
o-Quinone methides

ABSTRACT

A fluorine anion-mediated diphosphination of *ortho*-quinone methide precursors (2-(chloromethyl)silyloxybenzenes) with diphosphines has been developed. The reaction proceeds smoothly under mild conditions (CH_2Cl_2 solvent, 0 ˚C) to form the corresponding 2-(phosphinomethyl)oxyphosphinobenzenes, which are potential bidentate ligands in metal catalysis. Additionally, some mechanistic investigations are also performed.

Bisphosphines are now indispensable materials in organic synthetic chemistry because they are among representative bidentate ligands in metal catalysis, which can promote otherwise challenging organic transformations with high efficiency and selectivity.[1] Accordingly, considerable attention has been focusing on the rapid and concise synthesis of the bisphosphines. In addition to the classical substitution-type reaction, addition reaction of phosphino groups to C–C multiple bonds has recently received attention because relatively simple molecules can be used as the starting platforms.[2] In particular, our group and others focused on the unique reactivity of diphosphines ($R_2P–PR_2$) and developed diphosphination reactions of alkenes,[3] alkynes,[4] and dienes[5] under radical conditions or transition metal catalysis to deliver the corresponding bisphosphine products in one synthetic operation. Additionally, we found that in-situ generated, certain strained molecules such as arynes and *ortho*-quinodimethanes underwent the non-catalyzed diphosphination with the diphosphine to furnish the targeted diphosphinated compounds directly (Scheme 1a, b).[6] In our continuing interest in this chemistry, we envisioned the direct diphosphination of *ortho*-quinone methides, which would be generated from the corresponding 2-(chloromethyl)silyloxybenzenes upon treatment with an appropriate fluorine anion (Scheme 1c).[7] In this letter, we wish to report a fluorine anion-mediated diphosphination of *ortho*-quinone methide precursors with diphosphines. Detailed optimization studies, substrate scope, and mechanistic insights are described herein.



Scheme 1. Non-catalyzed diphosphination of strained molecules such as a) arynes, b) *ortho*-quinodimethanes, and c) *ortho*-quinone methides with diphosphines.

Our optimization studies commenced with the *ortho*-quinone methide precursor **1a** bearing the phenyl group at the benzylic position and tetraphenyldiphosphine ($Ph_2P–PPh_2$; **2a**) to identify a suitable fluoride (Table 1). On the basis of our previous work,[6] treatment of **1a** (0.25 mmol) with **2a** (1.6 equiv) in the presence of tetrabutylammonium difluorotriphenylsilicate ($Bu_4NPh_3SiF_2$; TBAT) and MS 4A (200 mg) in CH_2Cl_2 at 0 ˚C was followed by quenching with elemental sulfur S_8 (5.0 equiv, based on S) to

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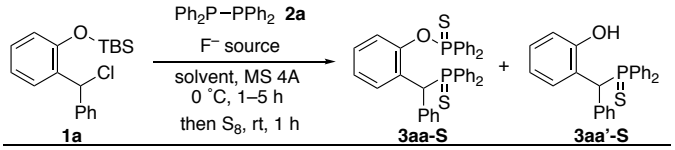
afford the desired diphosphinated product **3aa-S** in 91% NMR yield (76% isolated yield; entry 1). We tested some fluorine anion sources including Bu_4NF (TBAF), Me_4NF (TMAF), KF, and CsF (entries 2–8), but only the combination of CsF and 18-crown-6 promoted the reaction with a comparable efficiency (78%; entry 8). Without any fluorine anion sources, no reaction occurred (entry 9). Additionally, the addition of MS 4A was also essential for acceptable yield of **3aa-S**; a significant amount of monophosphinated side product **3aa'-S** was formed in the absence of MS 4A (entry 10).[8] Screening of solvents proved CH_2Cl_2 to be best (entries 11–15). We also investigated the reaction temperature, but neither increase nor decrease improved the yield of **3aa-S** (entries 16 and 17).

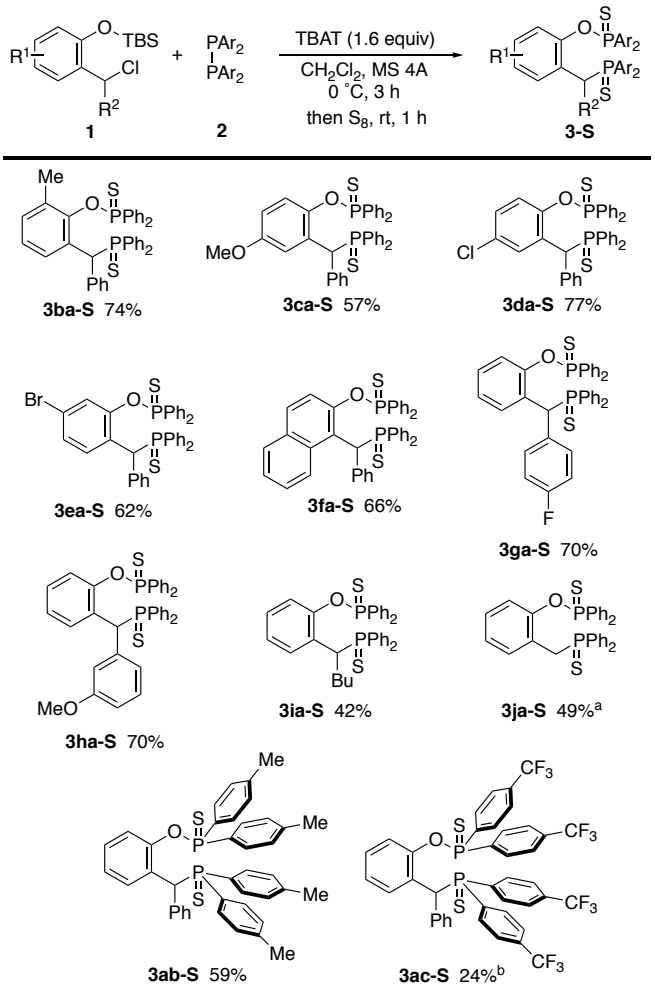
Table 1. Optimization studies for diphosphination of *ortho*-quinone methide precursor **1a** with tetraphenyldiphosphine (**2a**)[a]



entry	F⁻ source	Solvent	Yield (%)[b]	
			3aa-S	**3aa'-S**
1	TBAT	CH_2Cl_2	91 (76)	6
2	TBAF (silica support)	CH_2Cl_2	45	6
3	TBAF	CH_2Cl_2	18	14
4	TMAF	CH_2Cl_2	27	0
5	KF	CH_2Cl_2	0	0
6	KF/18-crown-6	CH_2Cl_2	0	0
7	CsF	CH_2Cl_2	0	0
8	CsF/18-crown-6	CH_2Cl_2	78 (71)	trace
9	none	CH_2Cl_2	0	0
10[c]	TBAT	CH_2Cl_2	45	34
11	TBAT	THF	51	12
12	TBAT	DMF	59	13
13	TBAT	MeCN	34	25
14	TBAT	toluene	6	1
15	TBAT	$ClCH_2CH_2Cl$	74	13
16[d]	TBAT	CH_2Cl_2	49	19
17[e]	TBAT	CH_2Cl_2	63	9

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.40 mmol), F⁻ source (0.40 mmol), MS 4A (200 mg), solvent (1.5 mL), 0 °C, 1–5 h, N_2 then S_8 (1.3 mmol based on S), rt, 1 h, N_2. TBS = t*ert*-butyldimethylsilyl. [b] ^1H NMR yields for **3aa-S** and ^{31}P NMR yields for **3aa'-S**. Isolated yields in parentheses. [c] Without MS 4A. [d] At rt. [e] At –20 °C.

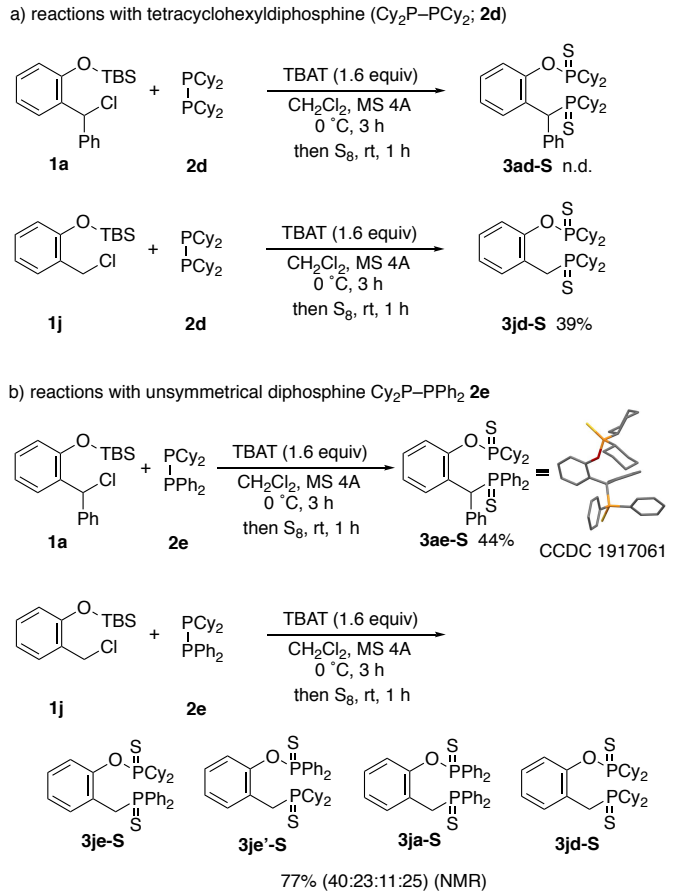
With the optimal conditions in hand (Table 1, entry 1), we examined the scope of *ortho*-quinone methide precursors **1** (Scheme 2). The electron-donating and electron-withdrawing groups on the benzene ring were equally tolerated under the standard conditions to form the corresponding diphosphinated products **3ba-S**–**3ea-S** in good yields. Particularly, the reaction occurred with the Ar-Br moiety left intact (**3ea-S**), which can be a synthetic handle for additional functionalization. The fused naphthalene system was also accommodated (**3fa-S**). The effects of substituents at the benzylic position were next investigated. Whereas both the electron-poor and -rich aromatic groups gave almost no influence on the reaction efficiency (**3ga-S** and **3ha-S**), the alkyl- and non-substituted substrates resulted in somewhat lower yields (**3ia-S** and **3ja-S**). The functionalized tetraaryldiphosphines **2** other than the parent **2a** were easily prepared from the corresponding chlorophosphines and hydrophosphines and thus tested in the reaction: electron-donating methyl and electron-withdrawing trifluoromethyl groups were easily incorporated into the products, thus readily giving the electronically tuned bisphosphines **3ab-S** and **3ac-S** in acceptable yields.



Scheme 2. TBAT-mediated diphosphination of various *ortho*-quinone methide precursors **1** with tetraaryldiphosphines **2**. Isolated yields are shown. Conditions: **1** (0.25 mmol), **2** (0.40 mmol), TBAT (0.40 mmol), MS 4A (200 mg), CH_2Cl_2 (1.5 mL), 0 °C, 3 h, N_2 then S_8 (1.3 mmol based on S), rt, 1 h, N_2. [a] At – 5 °C. [b] On a 0.10 mmol scale with CsF (0.16 mmol) and 18-crown-6 (0.16 mmol) instead of TBAT at – 10 °C.

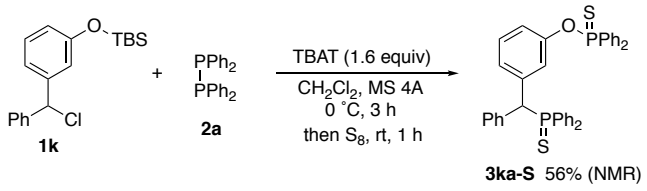
Some unique phenomena were observed in the reaction with alkyl-substituted diphosphines **2** (Scheme 3). Tetracyclohexyldiphosphine (Cy_2P–PCy_2; **2d**) did not react with **1a** at all (Scheme 3a). On the other hand, the non-substituted **1j** was successfully coupled with **2d** to form the corresponding diphosphinated product **3jd-S** in 39% yield. The observed difference is attributed to steric factors. The unsymmetrical Cy_2P–PPh_2 **2e** showed the more salient reactivity: the reaction with **1a** gave the coupling product **3ae-S** as the single isomer, where the PCy_2 and PPh_2 groups are attached to the O and C atoms, respectively (Scheme 3b). The structure of **3ae-S** was unambiguously confirmed by X-ray analysis (CCDC 1917061). The observed high regioselectivity can stem from steric factors: the bulkier PCy_2 group is selectively introduced at the more

sterically accessible O atom. On the other hand, the reaction of **1j** with **2e** formed a mixture of possible four isomers, including the regioisomers (**3je-S** and **3je'-S**) and phosphine scrambling isomers (**3ja-S** and **3jd-S**). The latter findings suggest that the reaction mechanism is more complicated than our initial working hypothesis in Scheme 1c.



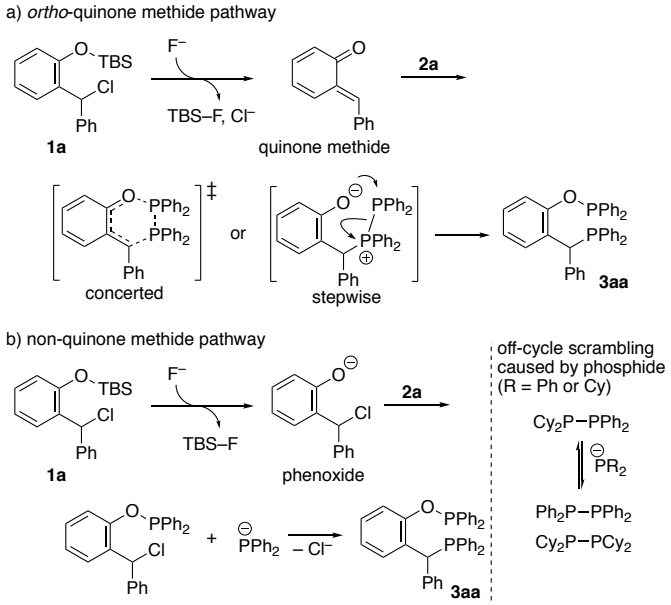
Scheme 3. Attempts to apply alkyl-substituted diphosphines **2d** and **2e**.

Inspired by the results obtained in Scheme 3b, we prepared the 3-(chloromethyl)silyloxybenzene **1k** and tried the reaction with **2a**, where any quinone methide cannot be formed (Scheme 4). To our surprise, the corresponding diphosphinated product **3ka-S** was obtained albeit in 56% NMR yield. Thus, under current TBAT-mediated conditions, a non-quinone methide pathway may also be operative.



Scheme 4. Attempt to apply 3-(chloromethyl)silyloxybenzene **1k**.

On the basis of the above outcomes, we propose the two reaction mechanisms of the *ortho*-quinone methide precursor **1a** and diphosphine **2a** (Scheme 5). One is the initially hypothesized, quinone methide pathway that includes the fluorine anion-mediated simultaneous elimination of TBS-F and chlorine anion (Scheme 5a). The formed *ortho*-quinone methide undergoes a concerted or stepwise cycloaddition-type reaction with **2a**[9] to afford the observed diphosphinated product **3aa**. Another is a phenoxide-initiated pathway, in which the initially formed phenoxide anion attacks at the phosphorus of diphosphine **2a** to cleave the P–P bond (Scheme 5b). The corresponding O–P bond is formed, but concurrently the free phosphide anion is generated. The phosphide then undergoes the nucleophilic substitution at the benzylic chloride moiety to produce **3aa**. The free phosphide anion is known to cause the scrambling of unsymmetrical diphosphines,[10] and thus the proposed mechanism in Scheme 5b well explains the result of the reaction of **1j** and **2e** (Scheme 3b). However, the formation of single isomer **3ae-S** in Scheme 3b is better consistent with the quinone methide pathway described in Scheme 5a. At this stage, we believe that both mechanisms in Scheme 5 are competitive and somewhat dependent on the substrates used. Further efforts are essential for clarification of the detailed reaction mechanism.



Scheme 5. Plausible reaction mechanisms.

In conclusion, we have developed a fluorine anion-mediated diphosphination reaction of *ortho*-quinone methide precursors, 2-(chloromethyl)silyloxybenzenes, with diphosphines. The reaction proceeds under mild, transition-metal-free conditions to form the corresponding diphosphinated products, which can be of potent interest in transition metal catalysis. Further development of related phosphination reactions with uniquely reactive diphosphines is now ongoing in our laboratory.

Acknowledgments

This work was supported by JSPS KAKENHI Grant nos. JP 15H05485 (Grant-in-Aid for Young Scientists (A)) and 18K19078 (Grant-in-Aid for Challenging Research (Exploratory)) to K.H. and JP 17H06092 (Grant-in-Aid for Specially Promoted Research) to M.M. We thank Mitsuhiro Ikeda (Osaka University) for his assistance in obtaining X-ray diffraction data.

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