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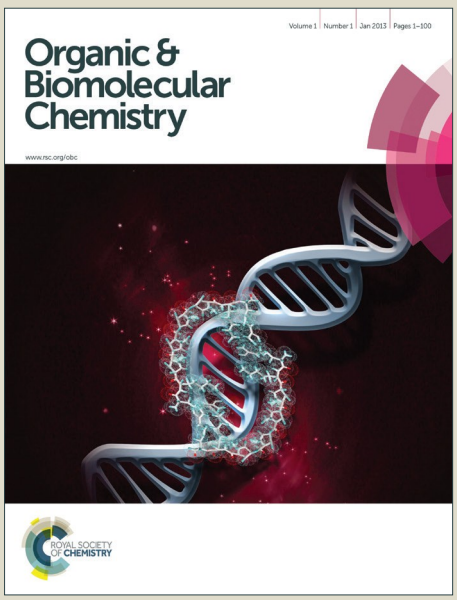

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ARTICLE TYPE

Variable Mechanism of Nucleophilic Substitution of *P*-Stereogenic Phosphoryl Chloride with Alkynyl Metallic Reagents

Lan Yao,[a] Li-Juan Liu,[a] Zhong-Yuan Xu,[a] Shao-Zhen Nie,[a] Xiao-Qing Xiao[a] and Chang-Qiu Zhao*[a]

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The variable mechanism for substitution of *P*-stereogenic phosphoryl chloride with alkynyl metallic reagents, which depended on temperature, stoichiometry of starting materials, structures of nucleophilic reagents, was assumed as S_N2-like and Berry pseudorotation of pentacoordinated phosphorus intermediates, respectively affording inversion and retention products. The formation of inversion product can be controlled to occur predominantly to afford R_P-alkynylphosphinates.

Introduction

The *P*-stereogenic compounds attracted extensive attention because of their various application as precursors of phosphine ligands[1-4] and pharmacological active substances.[5] Traditionally, the C-P bonds can be constructed from nucleophilic substitution of phosphorus-heteroatom species with alkyl metallic reagents.[2a] However, the expansion of this method to the *P*-stereogenic compounds has limited progress, which was restricted not only by the difficulty in acquiring *P*-stereogenic starting materials, but also by the uncertain stereochemistry for *P*-involved reaction, especially for the phosphorus linking to multi heteroatoms. As reported by Mislow and co-workers, the substitution of methylthio from phosphorus afforded *P*-retained or inversed products when it was replaced by methyl or methyloxy anion, respectively.[6a] The *P*-inversion or retention substitution of bromide, as reported by Imamoto and co-workers, depended on the alkynyl lithium or aliphatic alkyl lithium, respectively.[7] However, (S_P)-menthyl phenylphosphonochloridate **1** gave *P*-inversion products when reacted with alkyl metallic reagents, as reported by Han (Chart 1).[8]

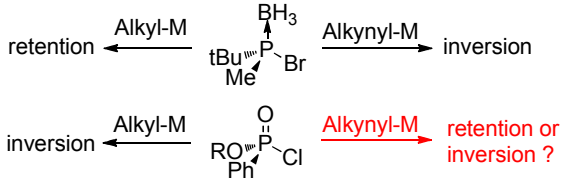


Chart 1. Comparison of reported reactions to our current research.

The uncertain mechanism and stereochemistry for the *P*-centred substitution were summarized in Chart 1. The substitution was also important to the metabolism and degradation of phosphorus derivatives in the organism or the nature.[9] However, beside of the reported reagents-dependence, the variable and controllable mechanism of the substitution has scarcely been studied. As we discussed below, the mechanism and stereochemistry on phosphorus also depend on temperature, stoichiometry of starting materials and the structures of attacking reagents. Ultilizing our discoveries, R_P-alkynylphosphinates were prepared in high to 99:1 dr, which were difficultly obtained through the traditional metal-promoted dehydrogenative coupling reactions between P-H species and terminal alkynes.[10] The compounds have potential but important application as precursors of various (P^O) or (P^N) bidentate ligands.[11]

Results and Discussion

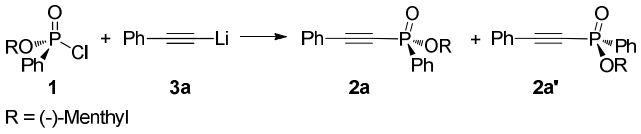
Diastereomeric mixture of (S_P)-**1**/(R_P)-**1'** (ca. 50:50) reacted with phenylethynyl lithium **3a** to form two stereomers of *O*-menthyl phenyl(phenylethynyl) phosphinate **2a** and **2a'**, whose two ^{31}P-NMR signals located at 7.78 and 9.37 ppm (singlet). When the optically pure (S_P)-**1** was used, **2a** and **2a'** were also generated. The dr (ratio of **2a**/**2a'**) was sensitive to stoichiometry of the two starting materials. When **1** was slowly added to **3a** at 0 °C, **2a** was formed in high to 99:1 dr. The reversing addition turn resulted in poor dr (entry 1-3 of Table 1, *vide infra*). In entries 1 to 11, the temperature-dependence of dr was observed. When the reaction was carried out either at rt or –20 °C (entries 4 to 10), the poor dr was obtained. When **1** and **2a** were mixed at –80 °C, then gradually warmed to rt, **2a**/**2a'** were formed still in poor dr (entry 5), which was different to normally thinking that the better selectivity was obtained at low temperature, as seen in the Imamoto's reaction at –78 °C.[7] However, when **1** and **3a** were stirred at –45 °C for enough time (8 h), **2a** was formed in the near quantitative conversion and >99:1 dr (entry 11).

After **1** and **3a** were mixed at –80 °C in ether, the solution was monitored with ^{31}P-NMR spectral at rt. At beginning stage, only the peak of **2a** was observed (Figure 1). The peaks of unconsumed **1**, its epimer **1'**, **2a'** and other *P*-containing species were not detected. The peak of **2a'** started to emerge after five minutes, and gradually increased with prolonged time, until 59:41 dr after an hour.

It looked like that **2a'** was formed later than **2a**, probably in the dilute solution that was developed after formation of **2a**.

However, when both **1** and **3a** were mixed in dilute solution, **2a'** was not dominantly formed (entry 12). The results indicated the dilute solution was not favour for the formation of **2a'**. As reported, halogen-exchange occurred during the similar substitution, and produced the retention product.[7,12] However, in the LiCl-containing solution, no epimerization of **1** was observed. The epimerization was also not detected when the reaction of equal molar **1** and **3a** was quenched at –20 °C. Thus, **2a'** was not produced from chloride-exchange, or the epimerization of **1** during the reaction (*vide infra*).

Table 1. Reaction of **1** with **3a** under various conditions.



entry	temperature/time	yield % (**2a**/**2a'**) (**1**/**1'**) [a]
1	0°C to rt/3 h	>99(89:11)[b]
2	0°C to rt/4 h	**80 (99: 1)**
3	0°C/1 h	96 (68:32)[c]
4	rt/4 h	95 (53:47)
5	–80°C/1 h; to rt/16 h	96 (45:55)[c,d]
6	–20°C/5 min; to rt/5 h	>99 (70:30)[c,d]
7	–20°C/1 h; to rt/16 h	91(40:60)[d]
8	–20°C/9 h; rt/1 h	99 (42: 58)
9	–20°C/9 h; rt/16 h	99 (40: 60)
10	–20°C/9 h	97 (51:49)[e]
11	–45°C/8 h	**99 (>99:1)**
12	–15°C/2.5 h; rt/5 min	99 (51:49)[f]
13	0°C/20 min; rt /2.5 h	37 (69:31) (68:32)[c,g]
14	–15°C /3 h; rt/5 min	63 (80:20) (81:19)[g]
15	–15°C /3 h; rt/16 h	64 (83:17) (50:50)[g]
16	–20°C /3 h; rt/5 min	61 (62:38) (91:9)[g]

[a] In a typical procedure, the powder of **1** was added portionwise within 1 minute to the solution of **3a**. The yields and dr were estimated by the peaks' integrations on ^{31}P and proton NMR spectroscopy. The data in second parentheses was the ratio of unconsumed **1/1'** (if applicable). [b] **3a** was added to the solution of **1** (0.147 M in ether). [c] Solid of **1** added in one portion. [d] The mixture was warmed from an ice-water bath to rt. [e] The mixture was quenched with acetic acid at –20°C. [f] Both two reactants were used in 0.0735 M solution of ether. [g] The ratio of **3a**/**1** was 1:2.

On the basis of the above observations, two routes to form **2a** and **2a'**, respectively, were proposed in Scheme 1. **3a** attacked the phosphorus opposite the chloride via transition state **4** to form *P*-inverted **2a** as in a normal S_N2 substitution (route A). Backside attack opposite the menthoxide formed intermediate **5** which was converted to **6** via a Berry pseudorotation (BPR, route B). The BPR route generated **2a'** that yield retention of configuration upon chloride loss.[13,14]

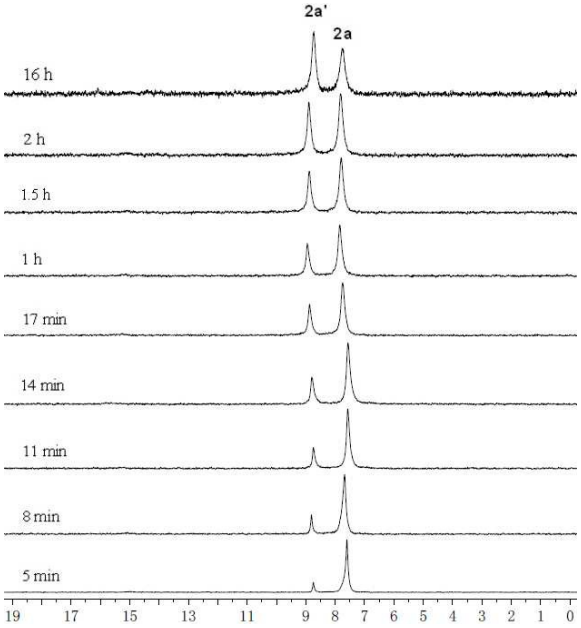
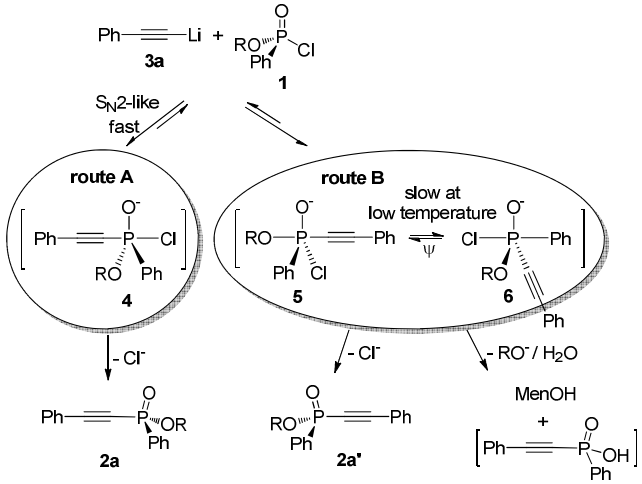


Figure 1. Monitored reaction of **1** with **3a** at rt: the formations of **2a**/**2a'** with time.

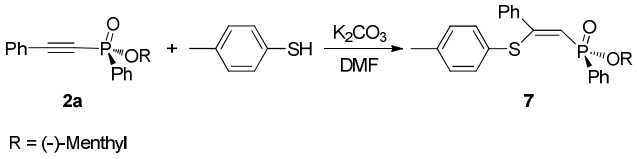


Scheme 1. Proposed mechanism for the reaction of **1** with **3a**.

According to Berry's pseudorotation theory, attacking and leaving groups tend to locate at the apical position of pentacoordinated phosphorus.[14,15] Akiba and coworkers reported the enhanced reactivity of P-O over P-C bond, because of the lower-lying $\sigma^*_{P\text{-}O}$ orbital acted as the reacting LUMO orbital.[13] Similar results could be applied to explain the activities of P-Cl over P-O bond. Route A was considered to take place prior to route B because chloride is a better leaving group than menthoxyl, but was sluggish at temperature lower than –45 °C. Around –45 °C, **2a** could be slowly generated via route A. When **1** and **3a** were warmed from –80°C directly to –20 °C or rt, **2a** was formed incompletely. At a later stage of temperature-increasing, route B

started to take place to generate **2a'** simultaneously (entry 5 and Figure 1). The unsuccessful attempt to prepare **2a'** as sole or major product indicated route B could not take place dominantly (entries 6 to 10).

The hypothesis was supported by the structure of **2a**. When 4-methylbenzenethiol was stirred with **2a** under alkali condition, menthyl (*Z*)-2-(*p*-tolylthio)-2-phenylvinyl(phenyl)phosphinate **7** was afforded, whose S_P configuration was confirmed by X-ray diffraction (Scheme 2 and Figure 2). Because the addition did not involved in phosphorus atom, the R_P configuration of **2a** was thence confirmed, which supplied the evidence to the proposed route A.



Scheme 2. The addition of 4-methylbenzenethiol with **2a** to afford **7**.

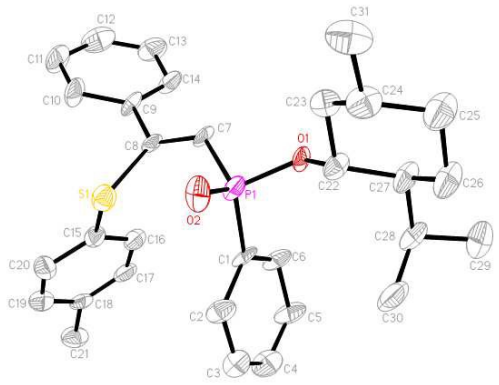


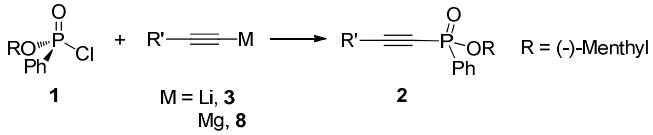
Figure 2. X-Ray diffraction structure of **7** (hydrogen atoms were removed for clarity).

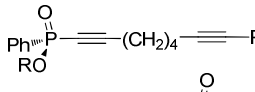
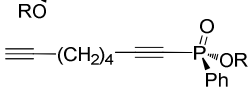
The route A and B were also controlled by the relative amounts of the two starting materials. At 0 °C, **1** was consumed upon being added to **3a** via route A to afford **2a**; meanwhile route B had little chance to occur (entry 2). In the cases of **3a** was added to **1**, or **1** was added to **3a** in one portion (entries 1 and 3), **1** was partially excessive and route B simultaneously occurred. Actually, Figure 1 also indicated that **2a** was formed prior to **2a'** at the starting stage.

In some cases that **2a'** was formed significantly, (–)-menthol was detected by proton NMR spectra, which was probably produced from **5** or **6** with menthoxyl as the leaving group (route B of Scheme 1). When excess **1** was used, the epimerization of unconsumed **1** was observed (entries 13-16). However, no obvious epimerization of **1** was detected when it was stirred in a solution containing 5% menthoxyl lithium at –20 °C for 3 h. We believed **1** was probably epimerized by the reversible equilibrium between **5** or **6** back to **1/1'** and **3a** (entries 13-16).

When the procedure was expanded to 1-hexynyl lithium **3b**, i.e., the solid of **1** was added portionwise to the solution of **3b** at 0 °C, poor dr of **2b**/**2b'** was observed. When the reaction was carried out at –20 °C, the dr was improved to 98:2, as seen in entry 2 of Table 2, Method A. The stronger nucleophilicity of **3b** was proposed to lead to the competition between route B and A at 0 °C. The reaction of less active alkynyl magnesium bromide **8** was less sensitive to temperature (Method B). For example, **8b** (R' = 1-hexynyl) reacted with **1** to afford **2b**/**2b'** in 98:2 dr at 0 °C.

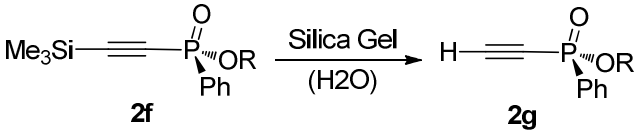
Table 2. Preparation of **2** via reaction of **1** with **3** and/or **8**.



	R'	method and yield (%, dr)[a] A	B	isolated yield
1	R' = Ph, **2a**	99 (99:1)[b]	96 (99:1)	92
2	*n*-Bu, **2b**	94 (98:2)	61 (98:2)	58
3	*t*-Bu, **2c**	91 (65:35)[b]	87 (99:1)	87
4	*n*-BuCH$_2$, **2d**	59 (97:3)	56 (98:2)	53
5	*cyclo*-Pr, **2e**	58 (66:34)	95 (97:3)[c]	93
6	TMS, **2f**	88 (70:30)[b]	97 (96:4)[c]	93
	H, **2g**		96 (96:4)[c]	88
7	Cl(CH$_2$)$_3$, **2h**	51 (89:11)	61 (97:3)[c]	59
8	MeOCH$_2$, **2i**		99 (96:4)	95
9	 **2j**	40 (88:12)	63 (95:5)	61
	 **2k**		35 (92:8)	32

[a] The yields and dr were estimated by the peaks' integrations on ^{31}P and proton NMR spectroscopy, based on **1**. The crude product obtained from method A was isolated with preparative TLC, and the yield was presented. In a typical procedure of Method A, the solution of **1** in ether was added dropwise at –20 °C to the solution of **3** in THF. The procedure of Method B was performed at 0°C with alkynyl Grignard reagents **8** in ether or toluene. [b] The reactions were carried out at 0°C in ether. [c] **1** having the optically purity of 97:3 was used.

Various forms of **2** were prepared in excellent dr from aliphatic and aromatic alkynes according to Method B (Table 2). Some functional groups of alkynes such as cyclopropyl and chloro were tolerated with Grignard reagents. While trimethylsilylethyne and **1** afford **2f** smoothly, C–Si bond cleavage occurred to yield ethynylphosphinate **2g** along with **2f** when purified with preparative TLC on silica gel (Scheme 3). The traditionally de-protection of silylalkynes to generate terminal alkynes was promoted with base. Such readily removal of trimethylsilyl group was rare. This was rationalized from the promotion of electrons from the *p*-orbital of the C-C triple bond to the vacant *d*-orbital of phosphorus that may weaken the C-Si bond to result in the subsequent cleavage. For the reaction of alkadiyne, bis-phosphorylation product **3j** was predominantly afforded in ether (entry 9). In toluene, the mono- and bis-phosphorylation products were generated as a mixture, which can be easily separated by preparative TLC.



2f **2g**

Scheme 3. Hydrolysis of C-Si bond with silica gel.

Conclusions

Although $S_N2(P)$ and BPR mechanisms have been extensively studied for *P*-centered substitutions, to the best of our knowledge, investigations on temperature dependence, stoichiometry and structure-activity-relationships have been scarcely reported. On the basis of the results, R_P-**2** was diastereoselectively prepared by either running the reaction at –45 °C or by slow addition of **1** to the solution of alkynyl metallic reagents at 0 °C. We hoped the research will provide beneficial examples for detailed understanding the mechanism and stereochemistry of the substitution on phosphorus.

Notes and references

Prof. Dr. C.-Q. Zhao, College of Chemistry and Chemical Engineering, Liaocheng University, Liaocheng, Shandong 252059, China, Fax: (+86)6358239121, E-mail: literabc@hotmail.com

† Electronic Supplementary Information (ESI) available: [Experimental procedures, spectral data for products, and crystallographic information are included]. See DOI: 10.1039/b000000x/

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15 According to BPR theory, the apicalphilics of different groups and atoms were discussed in ESI.

