COMMUNICATION

Ph₂PI as a reduction/phosphination reagent: providing easy access to phosphine oxides[†]

Feijun Wang,*^a Mingliang Qu,^a Feng Chen,^a Qin Xu*^a and Min Shi*^{ab}

Received 31st May 2012, Accepted 4th July 2012 DOI: 10.1039/c2cc33908k

The reaction of aldehydes with Ph_2PI provides a facile way to the synthesis of pentavalent phosphine compounds with moderate to good yields.

Phosphorus compounds have emerged as a preeminent class of organic compounds that hold ubiquitous applications serving as versatile ligands for transition metal catalyzed reactions,¹ Lewis basic organocatalysts to promote various organocatalytic transformations, such as Morita–Baylis–Hillman reaction,² and useful reagents in a wide array of organic transformations.³ Therefore, there is a steadily increasing number of reports on the application of phosphorus compounds⁴ and the development of convenient and general protocols for the synthesis of phosphorus compounds.⁵

Compared with the reactivity of Me₃SiCl, Me₃SiI has showed special reactivities to promote a variety of useful synthetic transformations.⁶ For example, Me₃SiI can promote the reaction of salicylic aldehydes with carbonyl compounds providing a facile way to construct 4*H*-benzopyranic scaffold in our previous work.⁷ Therefore, we reasoned that Ph₂PI may also have more special reactivities than Ph₂PCl, which has been widely used as a phosphine reagent in organic synthesis. However, Ph₂PI-mediated reactions received less attention.⁸ Herein, we wish to report a novel and practical synthetic method for the synthesis of phosphorus-containing compounds using Ph₂PI as a multifunctional agent.

The reaction of aldehydes **2** with Ph₂PCl **1** has been a wellknown reaction to give 1-chloroalkylphosphine oxides at elevated temperature (Scheme 1).⁹ However, in order to prepare phosphine oxides, which are key intermediates for the synthesis of *E*-alkenes¹⁰ and tervalent phosphines,^{4,5} these 1-chloroalkylphosphine oxides should be treated with reduction systems, such as NaBH₄/ DMSO.¹¹ Inspired by the reduction of alkyl iodide with I⁻ reagent to give the reductive product with elimination of I₂,⁷ the reaction of aldehydes with Ph₂PI was envisioned to give 1-iodoalkylphosphine



Scheme 1 The reaction of aldehyde with monohalogenophosphine.

oxides, which were further reduced by Ph_2PI to afford phosphine oxides in a one-pot operation.

Initially, the reaction mixture of benzaldehyde **2a** with 3 equiv Ph₂PI generated *in situ* from Ph₂PCl **1a** and NaI in CH₃CN was stirred at 80 °C for 24 h, resulting a brown reaction solution with the formation of I₂. In order to eliminate the I₂ in the work-up procedure, sat. Na₂S₂O₃ solution was added. However, 45% yield of unexpected benzyldiphenylphosphine sulfide **4a** was obtained, and its structure was undoubtedly confirmed by a single-crystal X-ray diffraction.†¹² The formation of **4a** suggested that tervalent benzyldiphenylphosphine should be afforded in this reaction, and subsequently reacted with S derived from the compound **4a**. The formation of tervalent phosphine was further confirmed by mass spectrometry analysis of the reaction mixture (see the ESI†). Therefore, 30% H₂O₂ was used to quench this reaction before the addition of Na₂S₂O₃ solution.

As expected, phosphine oxide **3a** was obtained in 70% yield. Further optimization of the employed amounts of Ph₂PI and reaction temperature was carried out. As shown in Table 1, up to 99% yield of **3a** was obtained in the presence of 4.5 equiv. of Ph₂PCl and NaI at 80 °C (Table 1, entry 3). Using KBr instead of NaI could also afford **3a** in 66% yield (Table 1, entry 7).

Next, we examined the substrate scope of this Ph_2PI -mediated reaction under the optimized conditions (4.5 equiv. of Ph_2PCI and NaI, CH₃CN, 80 °C). The results are shown in Table 2. For aldehydes **2b–d**, the different position of the fluorine substituent on the phenyl ring showed little influence on the yields of corresponding phosphine oxides (Table 2, entries 1–3). However, aldehydes with different electronic properties of substituents showed the significant influence on the reaction outcomes (Table 2, entries 3–8). For instance, aldehydes **2** with electron donating groups, such as Me and OMe, gave higher yields of their corresponding products than those of aldehydes **2** with electron-withdrawing groups, such as F and CF₃. This effect was also found in the oxophilic Lewis acid catalyzed Michaelis–Arbuzov reaction.¹³

^a Key Laboratory for Advanced Materials and Institute of Fine Chemicals, East China University of Science and Technology, and 130 MeiLong Road, Shanghai 200237, P. R. China.

E-mail: feijunwang@ecust.edu.cn, qinxu@ecust.edu.cn ^b State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, P. R. China. *E-mail: meli@mail.sica.com*

E-mail: mshi@mail.sioc.ac.cn

[†] Electronic supplementary information (ESI) available: Experimental procedures, characterization data of new compounds and CCDC 883288. See DOI: 10.1039/c2cc33908k

Table 1 Screening of reaction conditions^a

	CHO Ph_PCI 1a and Ph_PCI 1a an	Nal O PPh 3aa	Ph Ph Ph Ph Ph Ph Ph HS	
Entry	X (equiv.)	$T/^{\circ}\mathrm{C}$	Yield of $3aa^{b}$ (%)	
1	3.0	80	70	
2	1.5	80	8	
3	4.5	80	99	
4	6.0	80	96	
5	4.5	25	25	
6	4.5	50	79	
7^c	4.5	80	66	
^a React	ion conditions: (1) 2 9	(1.0 mmol	1a and NaL (r equiv)	

CH₃CN, 24 h; (2) 30% H₂O₂ used in the work-up procedure. ^b Isolated yield. ^c KBr instead of NaI was used.

Up to 99% yield of 3ai was obtained. 2,4-Dimethyl benzaldehyde 2j and 2,4,6-trimethyl benzaldehyde 2k afforded the corresponding products in up to 99% yield, respectively (Table 2, entries 10-11). In order to synthesize the analogues of these phosphine ligands developed by Buchwald and co-workers,¹⁴ aldehydes **2m** and **2n** with a biaryl framework were used to react with Ph₂PI, affording products 3am and 3an in 99% and 74% yields, respectively (Table 2, entries 12 and 13). Phosphine oxide 3ao containing a ferrocenyl framework was also prepared from aldehyde 20 in 46% yield under the standard conditions (Table 2, entry 14). Salicylic aldehyde 2p also furnished the corresponding functional phosphine oxide **3ap** in 80% yield (Table 2, entry 15). Alkyl aldehyde 2q can also afford the product 3aq in 40% yield (Table 2, entry 16). Moreover, using Et₂PCl 1b as a phosphine reagent could furnish trialkyl phosphine oxides **3ba** and **3bg** in up to 99% yields (Table 2, entries 17 and 18).

Subsequently, different work-up procedures were investigated to prepare other pentavalent phosphines. Benzyldiphenylphosphine sulfide **4a** and selenide **4b** were successfully synthesized (Scheme 2).

Other substrates instead of aldehyde 2 were also examined. As shown in Scheme 3, ketone 5a, benzyl ether 5b, 2-phenyloxirane 5c and benzyloxydiphenylphosphine 5d could also afford their corresponding phosphine oxides in moderate yields. Moreover, the reaction of 5d with Et₂PCl in the presence of NaI afforded the main product 3ba in 60% yield and the minor product 3aa in 6% yield.

In order to further prove the Ph_2PI -mediated reduction of pentavalent phosphine to tervalent phosphine, the mutual transformation between phosphine oxide and sulfide was investigated. With the treatment of Ph_2PI , the transformations of **3aa/4a** into **4a/3aa** can be successfully achieved (Scheme 4). Sulfoxide 7 can also be reduced to sulfur compound **8** by Ph_2PI in 63% yield. Moreover, a deuterium experiment was carried out. Deuterium water was added into this Ph_2PI -mediated reaction and deuterated phosphine oxide **3aa** was formed in 65% yield (D content 48% determined by ESI-MS).

A possible mechanism for the reaction of benzaldehyde and Ph_2PI is proposed in Scheme 5. Like the formation of α -iodo trimethylsilyl ethers from the reaction of Me₃SiI and aldehydes,¹⁵ intermediate **A** was obtained from the addition of Ph₂PI to benzaldehyde, and subsequently reduced by HI to give intermediate **B** with elimination of I₂. Ph₂PI was used as an oxophilic Lewis acid

Table 2 The reaction of Ph₂PI and aldehydes^a

$\begin{array}{c} \text{R}^{1}-\text{CHO} + \text{R}^{2}_{2}\text{PCI} & \stackrel{\text{1}}{\underset{2}{\overset{\text{CH}}}{\overset{\text{CH}}{\overset{\text{CH}}}{\overset{\text{CH}}{\overset{\text{CH}}}{\overset{\text{CH}}{\overset{\text{CH}}}{\overset{\text{CH}}{\overset{\text{CH}}}{\overset{\text{CH}}{\overset{\text{CH}}}{\overset{\text{CH}}{\overset{\text{CH}}}{\overset{\text{CH}}{\overset{\text{CH}}}{\overset{\text{CH}}}{\overset{\text{CH}}}{\overset{\text{CH}}{\overset{\text{CH}}}{\overset{\text{CH}}{\overset{\text{CH}}}{\overset{\text{CH}}{\overset{\text{CH}}}{\overset{\text{CH}}{\overset{\text{CH}}}{\overset{\text{CH}}}{\overset{\text{CH}}}{\overset{\text{CH}}}{\overset{\text{CH}}}{\overset{\text{CH}}}{\overset{\text{CH}}}{\overset{CH}}{\overset{CH}}}{\overset{CH}}{\overset{CH}}{\overset{CH}}}{\overset{CH}}{\overset{CH}}}{\overset{CH}}{\overset{CH}}}{\overset{CH}}{\overset{CH}}}{\overset{CH}}{\overset{CH}}}{\overset{CH}}{\overset{CH}}}{\overset{CH}}{\overset{CH}}}{\overset{CH}}}{\overset{CH}}{\overset{CH}}}{\overset{CH}}{\overset{CH}}}{\overset{CH}}}{\overset{CH}}{\overset{CH}}}{\overset{CH}}{\overset{CH}}}{\overset{CH}}}{\overset{CH}}{\overset{CH}}}{\overset{CH}}{\overset{CH}}}{\overset{CH}}}{\overset{CH}}}{\overset{CH}}}{\overset{CH}}{\overset{CH}}}{\overset{CH}}}{\overset{CH}}}{\overset{CH}}{\overset{CH}}}{\overset{CH}}{\overset{CH}}}{\overset{CH}}}{\overset{CH}}}{\overset{CH}}}{\overset{CH}}}{\overset{CH}}{\overset{CH}}}{\overset{CH}}{\overset{CH}}}{CH$						
Entry	Aldehyde	Chlorophosphine	Product	Yield ^b (%)		
1	CHO 2b F	1a	3ab	76		
2	CHO 2c	1a	3ac	64		
3 4 5 6	2d: $\mathbf{R} = \mathbf{F}$ 2e: $\mathbf{R} = \mathbf{C}\mathbf{I}$ CHO 2f: $\mathbf{R} = \mathbf{B}\mathbf{r}$	1a 1a 1a 1a	3ad 3ae 3af 3ag	66 68 67 60		
7	2g : R = CF ₃ 2h : R = Me	1a	3ah	69		
8	2i : $R = OMe$	1a	3ai	99		
9	Me Me 2j	1a	3aj	99		
10	Me CHO Me CHO	1a	3ak	99		
11		1a	3al	99		
12	CHO 2m	1a	3am	99		
13	CHO 2n	1a	3an	74		
14	СНО Fe 20	1a	3ao	46		
15	CHO OH 2p	1a	3ap	80		
16		1a	3aq	40		
17	CHO 2a	1b : $R^2 = Et$	3ba	95		
18	~(-) ₄ СНО 2q	1b	3bq	99		

^{*a*} Reaction conditions: (1) **2** (1.0 mmol), **1** and NaI (4.5 equiv.), CH₃CN, 24 h; (2) 30% H₂O₂ or air used in the work-up procedure. ^{*b*} Isolated yield.



Scheme 2 The preparation of phosphine sulfide and selenide from 2a.

catalyst to promote the Michaelis–Arbuzov rearrangement of intermediate **B** through a bimolecular process,¹³ affording the corresponding product **3aa**. Ph₂PI with its oxophilic ability further reacted with oxide **3aa** to give zwitterionic



Scheme 3 Ph₂PI promoted the transformations of a series of oxo-containing compounds.



Scheme 4 Controlled experiments in the Ph₂PI-mediated reaction.

Scheme 5 A possible mechanism for the Ph_2PI -mediated reaction.

intermediate C, which was further converted into tervalent phosphine D with the elimination of diphenylphosphinic iodide. Due to the instability of phosphine D for its easy oxidation, oxide **3aa** was obtained in the work-up procedure.

In conclusion, we have developed efficient methods to prepare phosphorus compounds using Ph_2PI as a multifunctional agent. The unusual reactivities of Ph_2PI were disclosed in this work, such as its oxophilic ability to promote the transformations of a series of oxo-containing compounds and reducing ability to achieve the reduction of pentavalent phosphine which usually required more than a stoichiometric amount of expensive, explosive and/or not easy to handle reducing agents. Moreover, a possible mechanism for the reaction of benzaldehyde with Ph_2PI was proposed. Further exploration of Ph_2PI -mediated reactions and the application of phosphorus compounds are ongoing.

Financial support from the Shanghai Municipal Committee of Science and Technology (11JC1402600), the National Natural Science Foundation of China (21072206, 20902019, 20472096, 20872162, 20672127, 21121062 and 20732008), the National Basic Research Program of China (973)-2010CB833302 and the Fundamental Research Funds for the Central Universities is gratefully acknowledged.

Notes and references

- (a) W. Tang and X. Zhang, Chem. Rev., 2003, 103, 3029; (b) V. V. Grushin, Chem. Rev., 2004, 104, 1629; (c) H. Fernández-Pérez, P. Etayo, A. Panossian and A. Vidal-Ferran, Chem. Rev., 2011, 111, 2119.
- 2 For a book, see: M. Shi, F. Wang, M. Zhao and Y. Wei, *The Chemistry of the Morita–Baylis–Hillman Reaction*, RSC Catalysis Series, 2011.
- 3 B. E. Maryanoff and A. B Reitz, Chem. Rev., 1989, 89, 863.
- 4 Selected books: (a) J.-P. Majoral, New Aspects in Phosphorus Chemistry I, Springer, Berlin Heidelberg, 2002; (b) J.-P. Majoral, New Aspects in Phosphorus Chemistry II, Springer, Berlin Heidelberg, 2002. Selected papers: (c) S. Pindi, P. Kaur, G. Shakya and G. Li, Chem. Biol. Drug Des., 2011, 77, 20; (d) P. Kaur, S. Pindi, W. Wever, T. Rajale and G. Li, Chem. Commun., 2010, 46, 4330; (e) A. Kattuboina and G. Li, Tetrahedron Lett., 2008, 49, 1573.
- Selected books: (a) M. L. Clarke and M. J. Williams, in Organophosphorus Reagents, ed. P. J. Murphy, Oxford University Press, New York, 2004, ch. 2; (b) D. G. Gilheany and C. M. Mitchell, in The Chemistry of Organophosphorus Compounds, ed. F. R. Hartley, John Wiley and Sons, Chichester, UK, 1990, vol. 1. Selected papers: (c) H. Ohmiya, H. Yorimitsu and K. Oshima, Angew. Chem., Int. Ed., 2005, 44, 2368; (d) F. Jérôme, F. Monnier, H. Lawicka, S. Dérien and P. H. Dixneuf, Chem. Commun., 2003, 696; (e) A. Caiazzo, S. Dalili and A. K. Yudin, Org. Lett., 2002, 4, 2597.
- 6 (a) G. A. Olah and S. C. Narang, *Tetrahedron*, 1982, **38**, 2225; (b) G. A. Olah, G. K. S. Prakach and R. Krishnamurtiy, *Adv. Silicon Chem*, ed. G. L. Larson, Jai Press, Inc, Greenwich, CT, 1991, vol. 1.
- 7 (a) F. Wang, M. Qu, F. Chen, L. Li and M. Shi, *Chem. Commun.*, 2012, **48**, 437; (b) F. Wang, M. Qu, X. Lu, F. Chen, F. Chen and M. Shi, *Chem. Commun.*, 2012, **48**, 6259–6261.
- 8 Selected papers: (a) V. P. Morgalyuk, P. V. Petrovskii, K. A. Lysenko and E. E. Nifant', *Russ. J. Gen. Chem.*, 2010, 80, 100; (b) A. A. Tolmachev, A. I. Sviridon, A. N. Kostyuk and E. S. Kozlov, *Zh. Obshch. Khim.*, 1992, 62, 2395; (c) A. A. Tolmachev, A. A. Yurchenko and E. S. Kozlov, *Zh. Obshch. Khim.*, 1992, 62, 1667; (d) N. D. Gomelya and N. G. Feshchenko, *Zh. Obshch. Khim.*, 1988, 58, 709.
- Selected papers: (a) K. Sasse, in Methoden der Organischen Chemie, ed. E. Müller, Georg Thieme Verlag, Stuttgart, 1963, vol. 12/1; (b) N. J. De', J. A. Miller, M. J. Nunn and D. Stewart, J. Chem. Soc., Perkin Trans. 1, 1981, 776.
- (a) B. E. Maryanoff and A. B. Reitz, *Chem. Rev.*, 1989, **89**, 863;
 (b) M. D. Wittman and J. Kallmerten, *J. Org. Chem.*, 1987, **52**, 4303;
 (c) C. Palomo, M. Oiarbide, A. Landa, A. Esnal and A. Linden, *J. Org. Chem.*, 2001, **66**, 4180;
 (d) C. Hoarau, A. Couture, E. Deniau and P. Grandclaudon, *Eur. J. Org. Chem.*, 2001, 2559.
- 11 (a) K. M. Brown, N. J. Lawrence, J. Liddle and F. Muhammad, *Tetrahedron Lett.*, 1994, **36**, 6733; (b) N. J. Lawrence, F. A. Ghani, L. A. Hepworth, J. A. Hadfield, A. T. McGown and R. G. Pritchard, *Synthesis*, 1999, 1656.
- 12 CCDC 883288 **4a** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc. cam.ac.uk/data_request/cif.
- 13 (a) P.-Y. Renard, P. Vayron, E. Leclerc, A. Valleix and C. Mioskowski, Angew. Chem., Int. Ed., 2003, 42, 2389; (b) P.-Y. Renard, P. Vayron and C. Mioskowski, Org. Lett., 2003, 5, 1661; (c) W. Dabkowski, A. Ozarek, S. Olejniczak, M. Cypryk, J. Chojnowski and J. Michalski, Chem.-Eur. J., 2009, 15, 1747.
- 14 R. Martin and S. L. Buchwald, Acc. Chem. Res., 2008, 41, 1461.
- 15 M. E. Jung, A. B. Mossman and M. A. Lyster, J. Org. Chem., 1978, 43, 3698.