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P-Arylation: Arynes to Aryl-Phosphonates, -Phosphinates, and -Phosphine Oxides

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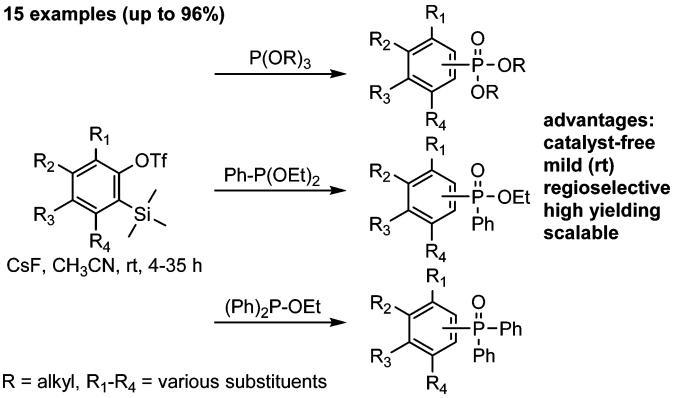
ABSTRACT



Synthesis of organo-phosphorus compounds and their application in organic synthesis and life sciences has been a topic of contemporary interest. Michaelis–Arbuzov reaction is the most extensively utilized method for their preparation, which works well only with aliphatic halides. Hence, relatively harsh reaction conditions using transition-metal-catalyzed P-arylation (Arbuzov/Hirao reaction) are used for the preparation of aryl-phosphorus compounds. Presented herein is a competent process for the synthesis of aryl-phosphonates, -phosphinates, and -phosphine oxides by making an efficient use of arynes for C–P bond construction.

Organo-phosphorus compounds represent an important class of chemicals, which are most extensively used[1] in organic synthesis as well as pharmaceuticals, agrochemicals, and poultry chemicals and in the preparation of materials with desired properties. Particularly aryl-phosphorus compounds find prime application as ligands[2] in metal-catalyzed reactions in addition to other well-known organic transformations.[3] The classical Michaelis–Arbuzov reaction provides an easy access to alkyl-phosphorus compounds;[4] however, the synthesis of aryl-phosphorus compounds posed a major challenge.[5] They are usually prepared by a transition-metal-catalyzed Arbuzov or Hirao C–P bond construction reaction, which

(1) (a) Corbridge, D. E. C. *Phosphorus: Chemistry, Biochemistry and Technology*, 6th ed.; CRC Press: London, 2013. (b) Demmer, C. S.; Krogsgaard-Larsen, N.; Bunch, L. *Chem. Rev.* **2011**, *111*, 7981. (c) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338. (d) Kolio, D. T. *Chemistry and Application of H-Phosphonates*; Elsevier Science: Oxford, 2006. (e) Bialy, L.; Waldmann, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 3814. (f) Erion, M. D.; Reddy, K. R.; Boyer, S. H.; Matelich, M. C.; Gomez-Galeno, J.; Lemus, R. H.; Ugarkar, B. G.; Colby, T. J.; Schanzer, J.; van Poelje, P. D. *J. Am. Chem. Soc.* **2004**, *126*, 5154. (g) Mathey, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1578. (h) Quin, L. D. *A Guide to Organophosphorus Chemistry*; Wiley-Interscience: Hoboken, NJ, 2000. (i) Consiglio, G. A.; Failla, S.; Finocchiaro, P.; Siracusa, V. *Phosphorous, Sulfur Silicon Relat. Elem.* **1998**, *134*, 413.

(2) (a) *Phosphorus(III) Ligands in Homogeneous Catalysis: Design and Synthesis*; Kamer, P. C. J., van Leeuwen, P. W. N. M., Eds.; Wiley-VCH: Chichester, U.K., 2012. (b) *Phosphorus Ligands in Asymmetric Catalysis-Synthesis and Application*; Börner, A., Ed.; Wiley-VCH: Weinheim, 2008. (c) Charles, M. D.; Schultz, P.; Buchwald, S. L. *Org. Lett.* **2005**, *7*, 3965. (d) *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004.

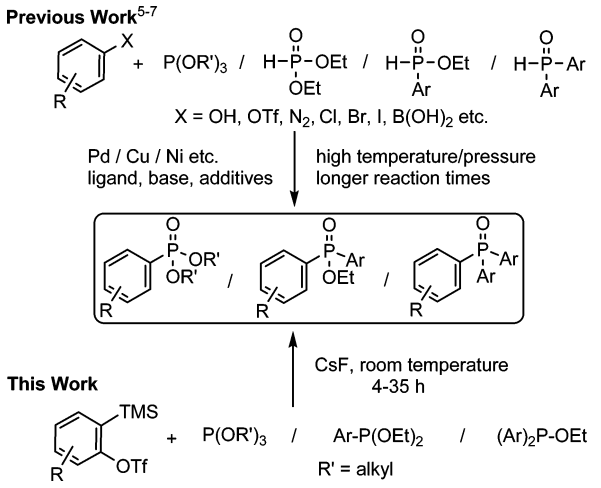
(3) McClure, C. K. *Phosphorus in Organic Chemistry*; Wiley-VCH: Weinheim, 2012.

(4) (a) Renard, P.-Y.; Vayron, P.; Leclerc, E.; Valleix, A.; Mioskowski, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 2389. (b) Bhattacharya, A. K.; Thyagarajan, G. *Chem. Rev.* **1981**, *81*, 415. (c) Arbuzov, B. A. *Pure Appl. Chem.* **1964**, *9*, 307.

(5) (a) Hayashi, M.; Matsuura, T.; Tanaka, I.; Ohta, H.; Watanabe, Y. *Org. Lett.* **2013**, *15*, 628. (b) Bloomfield, A. J.; Herzon, S. B. *Org. Lett.* **2012**, *14*, 4370. (c) Effenberger, F.; Kottmann, H. *Tetrahedron* **1985**, *41*, 4171.

10.1021/ol400780f

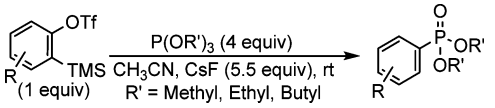
Scheme 1. Previous Methods of P-Arylation and This Work

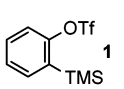
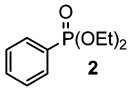
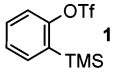
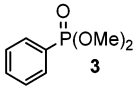
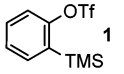
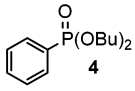
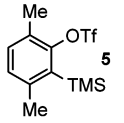
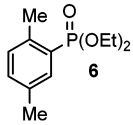
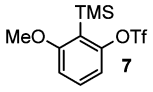
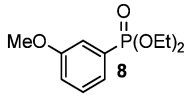
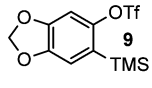
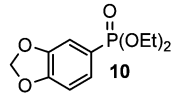
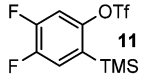
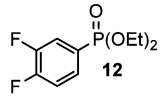
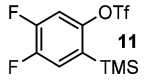
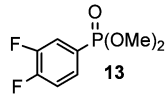
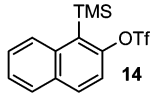
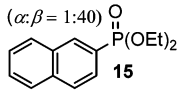


requires a high temperature, high pressure, and longer reaction times (Scheme 1).[6] With the broad application of aryl-phosphorus compounds considered, the development of novel and more efficient synthetic methods for P-arylation has been a topic of extensive research interest.[7] Recently, we[8] and others[9] have demonstrated a transition-metal-free C-arylation at room temperature using arynes. In continuation of our research interest in the development and application of aryne chemistry, we envisioned an efficient C−P bond forming reaction to access various aryl-phosphorus compounds utilizing the very high reactivity of arynes toward nucleophiles (Scheme 1, this work).

We envisaged that the treatment of alkyl-phosphites with arynes might furnish corresponding P-arylated products at much milder reaction conditions. It is important to note that in the meantime Jugé et al. reported[10] the

Table 1. Synthesis of Various Phosphonates



entry	silyl triflate	phosphonate	time	yield
1	 **1**	 **2**	20 h	96%
2	 **1**	 **3**	16 h	90%
3	 **1**	 **4**	24 h	72%
4	 **5**	 **6**	35 h	87%
5	 **7**	 **8**	24 h	74%
6	 **9**	 **10**	16 h	85%
7	 **11**	 **12**	04 h	78%
8	 **11**	 **13**	04 h	71%
9	 **14**	(α:β = 1:40)  **15**	24 h	82%

formation of phosphonium salts on treatment of arynes with several other phosphorus compounds. Our first attempt was a reaction of silyl triflate **1** (1 equiv) with triethyl phosphite (1 equiv) and cesium fluoride (1.2 equiv) in acetonitrile at room temperature for 24 h. To our delight we obtained the expected product 'diethyl phenylphosphonate (**2**)' in 47% yield. We report here the optimization and application of the P-arylation protocol for an efficient synthesis of aryl-phosphonates, -phosphinates, and -phosphine oxides.

The protocol was first optimized on simple silyl triflate **1** using several permutations and combinations of triethyl phosphite, fluoride-ion sources, and solvents. Phosphonate **2** was obtained in a maximum 92% yield when silyl triflate **1** (1 equiv, 0.084 mmol) and triethyl phosphite (4 equiv) were treated with cesium fluoride (5.5 equiv) in acetonitrile at room temperature for 20 h. The same

(6) (a) Xu, K.; Hu, H.; Yang, F.; Wu, Y. *Eur. J. Org. Chem.* **2013**, 319. (b) Shen, C.; Yang, G.; Zhang, W. *Org. Biomol. Chem.* **2012**, *10*, 3500. (c) Yang, G.; Shen, C.; Zhang, L.; Zhang, W. *Tetrahedron Lett.* **2011**, *52*, 5032. (d) Rao, H.; Jin, Y.; Fu, H.; Jiang, Y.; Zhao, Y. *Chem.—Eur. J.* **2006**, *12*, 3636. (e) Gelman, D.; Jiang, L.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 2315.

(7) (a) Han, Z. S.; Goyal, N.; Herbage, M. A.; Sieber, J. D.; Qu, B.; Xu, Y.; Li, Z.; Reeves, J. T.; Desrosiers, J.-N.; Ma, S.; Grinberg, N.; Lee, H.; Mangunuru, H. P. R.; Zhang, Y.; Krishnamurthy, D.; Lu, B. Z.; Song, J. J.; Wang, G.; Senanayake, C. H. *J. Am. Chem. Soc.* **2013**, *135*, 2474. (b) Nakano, K.; Oyama, H.; Nishimura, Y.; Nakasako, S.; Nozaki, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 695. (c) Zhao, Y.-L.; Wu, G.-J.; Han, F.-S. *Chem. Commun.* **2012**, *48*, 5868. (d) Xiang, C.- B.; Bian, Y.-J.; Mao, X.-R.; Huang, Z.-Z. *J. Org. Chem.* **2012**, *77*, 7706. (e) Zhuang, R.; Xu, J.; Cai, Z.; Tang, G.; Fang, M.; Zhao, Y. *Org. Lett.* **2011**, *13*, 2110. (f) Andaloussi, M.; Lindh, J.; Sävmarker, J.; Sjöberg, P. J. R.; Larhed, M. *Chem.—Eur. J.* **2009**, *15*, 13069. (g) Kalek, M.; Ziadi, A.; Stawinski, J. *Org. Lett.* **2008**, *10*, 4637. (h) Stadler, A.; Kappe, C. O. *Org. Lett.* **2002**, *4*, 3541. (i) Griffin, C.; Castellucci, N. *J. Org. Chem.* **1961**, *26*, 629.

(8) Dhokale, R. A.; Thakare, P. R.; Mhaske, S. B. *Org. Lett.* **2012**, *14*, 3994.

(9) Mohanan, K.; Coquerel, Y.; Rodriguez, J. *Org. Lett.* **2012**, *14*, 4686.

(10) (a) Rémond, E.; Tessier, A.; Leroux, F. R.; Bayardon, J.; Jugé, S. *Org. Lett.* **2010**, *12*, 1568. (b) Bayardon, J.; Laureano, H.; Diemer, V.; Dutartre, M.; Das, U.; Rousselin, Y.; Henry, J.-C.; Colobert, F.; Leroux, F. R.; Jugé, S. *J. Org. Chem.* **2012**, *77*, 5759. (c) Diemer, V.; Berthelot, A.; Bayardon, J.; Jugé, S.; Leroux, F. R.; Colobert, F. *J. Org. Chem.* **2012**, *77*, 6117.

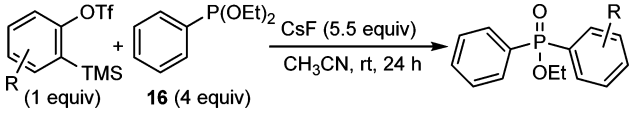
reaction at a higher scale (**1**, 1.68 mmol) furnished phosphonate **2** with a 96% yield (Table 1, entry 1).

During optimization studies we also tried the reaction using diethyl phosphite $H(O)P(OEt)_2$; however a complex TLC pattern was observed, and the expected product was obtained only in trace amounts. Use of other trialkyl phosphites provided the expected phosphonates in good to excellent yields.

Thus, treatment of trimethyl phosphite and tributyl phosphite (Table 1, entries 2 and 3) with silyl triflate **1** using the optimized protocol furnished the corresponding phosphonates **3** and **4** in 90% and 72% yields respectively. The scope of the protocol for the synthesis of aryl-phosphonates was validated on various 2-(trimethylsilyl)aryl triflates (Table 1, entries 4–9). Treatment of the symmetrically substituted aryne precursor **5** with triethyl phosphite provided phosphonate **6** (Table 1, entry 4) in 87% yield, but the reaction required more time (35 h) for completion as compared to other silyl triflates, most probably due to steric reasons. The strong electronic and steric effects were observed in the unsymmetrically substituted electron-rich aryne precursor **7**, which showed excellent regioselectivity and furnished phosphonate **8** as the only regioisomer in 74% yield (Table 1, entry 5). The highly electron-rich substrate **9** also gave the corresponding phosphonate **10** (Table 1, entry 6) in good yields (85%) in 16 h. This result confirms that the presence of electron-donating groups on the aromatic ring does not affect the yield of such reactions or the time required for their completion. The aryne precursor **11** smoothly reacts with triethyl phosphite and trimethyl phosphite to obtain phosphonates **12** and **13** in 78% and 71% yields respectively in a short time (4 h), as expected (Table 1, entries 7 and 8). The presence of fluorines on the aromatic ring further enhances the overall electrophilicity of the aryne thus making it more reactive, which results in a shorter reaction time. The steric and electronic factors also predominate in the case of silyl triflate **14**, which provides regioisomer **15** as the major product (Table 1, entry 9). The obtained product was an inseparable mixture of regioisomers (α:β = 1:40) as revealed from the ^{1}H NMR spectra.

The generalization studies (Table 1, entries 1–9) on various aryl triflates to obtain corresponding arylphosphonates worked very well, which prompted us to study further application of the protocol to obtain arylphosphinates. The aryne precursor **1** was treated with diethyl phenylphosphonite (**16**) under the standardized protocol to obtain the expected product ethyl diphenylphosphinate (**17**) in 76% yield (Table 2, entry 1). Similarly, treatment with silyl triflate **5** smoothly furnished phosphinate **18** in 62% yield (Table 2, entry 2).

Table 2. Synthesis of Phosphinates



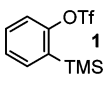
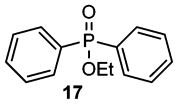
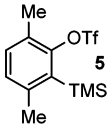
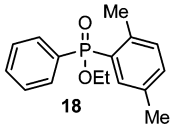
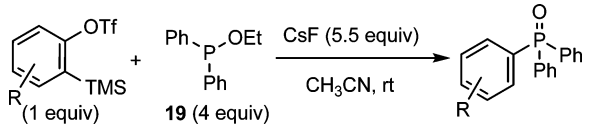
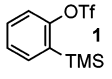
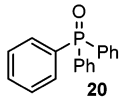
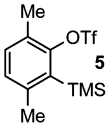
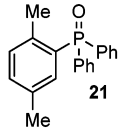
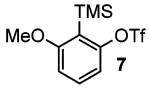
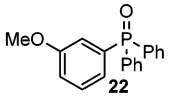
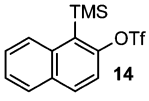
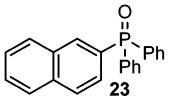
entry	silyltriflate	phosphinate	time	yield
1		 **17**	24 h	76%
2		 **18**	32 h	62%

Table 3. Synthesis of Various Phosphine Oxides



entry	silyltriflate	phosphine oxide	time	yield
1	 **1**	 **20**	16 h	75%
2	 **5**	 **21**	30 h	81%
3	 **7**	 **22**	20 h	68%
4	 **14**	 **23**	16 h	83%

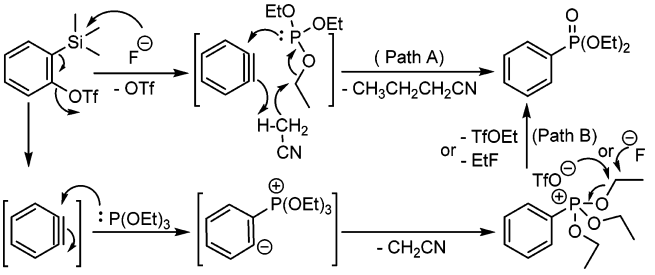
These intriguing results (Tables 1 and 2) impelled us to explore the applicability of the methodology for the preparation of very interesting and important compounds, the 'phosphine oxides'. They are considered as vital precursors in the preparation of various aryl-phosphine ligands, which are highly useful in organic synthesis. Toward this direction, we first treated the simplest aryne precursor **1** with ethyl diphenylphosphinite (**19**) using the standardized protocol, and to our immense interest the predicted product triphenyl phosphine oxide (**20**) was obtained in 75% yield (Table 3, entry 1). The substrate scope was studied by treating various silyl triflates with ethyl diphenyl phosphinite (**19**) to satisfyingly obtain corresponding phosphine oxides in good yields (Table 3, entries 2–4). The steric effect on the reaction time as observed in the case of entry 4 (Table 1) was also observed here (Table 3, entry 2) to obtain phosphine oxide **21** with 81% yield in 30 h. The high regioselectivity observed on substrate **7** (Table 1, entry 5) was retained during the formation of corresponding phosphine oxide **22** as well (Table 3, entry 3). Interestingly the

regioselectivity noticed during the reaction of silyl triflate **14** with triethyl phosphite (Table 1, entry 9) was found to be enhanced with ethyl diphenylphosphinite (**19**), as expected, due to the bulkier nucleophile (Table 3, entry 4). Only one regioisomer, naphthalen-2-yldiphenylphosphine oxide (**23**), was observed in this case. Several other phosphine oxides can be easily prepared following this process. Use of varyingly substituted aromatic/heteroaromatic, or aryl-alkyl ethylphosphinate, should provide an easy access to interesting phosphine oxides with three different substituents attached to phosphorus. This process will be also useful to generate chiral phosphine oxides under very mild conditions. These products will serve as precursors to obtain novel phosphine ligands. The conversion of phosphine oxides to phosphines is considered as the best method for their preparation among the others,[11] and recently Beller et al. reported an efficient method for this useful transformation.[11]

The methodology developed herein works well to furnish several aryl-phosphorus compounds as demonstrated in Table 1−3. A plausible mechanism for the observed transformation has been depicted in Scheme 2. 'Path A' which follows a concerted type of mechanism and 'Path B' which follows a Michaelis−Arbuzov type of mechanism are two probable ways. 'Path B' involving fluoride ion participation appears more appropriate (Scheme 2); however, a detailed study on the mechanism is warranted.

In conclusion a mild and convenient aryl-C−P bond forming reaction protocol has been demonstrated using facile aryne reactivity. The scope of the reaction has been extended to the synthesis of aryl-phosphonates, -phosphinates, and -phosphine oxides. Notable features of the process developed herein are as follows: a metal-free straightforward approach to a variety of aryl-phosphorus compounds, efficiency, regioselectivity, convenient reaction conditions, and generality. This finding opens whole new possibilities, and the utility of the process developed herein for the synthesis of various aryl-phosphorus compounds is vast. We believe that this might become one of the leading methods for their preparation in the near future. Further investigations are focused on the application of the process to synthesize complex bioactive molecules as well as chiral aryl-phosphorus compounds.

Scheme 2. Proposed Mechanism



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Supporting Information Available. Experimental details, characterization data, and copies of spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(11) Li, Y.; Das, S.; Zhou, S.; Junge, K.; Beller, M. *J. Am. Chem. Soc.* **2012**, *134*, 9727.