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# Synthesis of Unsymmetrical Tertiary Phosphine Oxides via Sequential Substitution Reaction of Phosphonic Acid Dithioesters with Grignard Reagents

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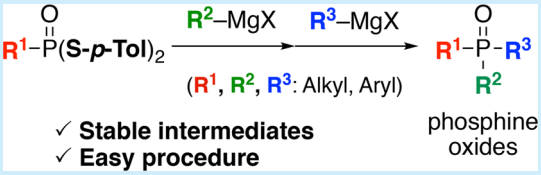
Supporting Information

**ABSTRACT:** A facile synthetic method for unsymmetrical tertiary phosphine oxides is reported. Sequential treatment of phosphonodithioic acid *S*,*S*-di(*p*-tolyl) esters with two Grignard reagents enabled the stepwise introduction of different carbon substituents on the phosphorus atom. The chemical stability of dithioesters and monosubstituted thioesters has enhanced the utility of this method, rendering a wide range of organophosphorus compounds easily available.




Organophosphorus compounds play significant roles in synthetic organic chemistry, and they have a wide range of applications in various fields, including organometallic chemistry,[1] medicinal chemistry,[2] chemical biology,[3] and materials science.[4] To prepare useful organophosphorus compounds, numerous carbon−phosphorus (C−P) bond-forming reactions have been developed.[5−13] For the synthesis of unsymmetrical tertiary phosphines or phosphine oxides, which have three different substituents on the phosphorus atom, a sequential substitution reaction of an organodichlorophosphorus compound with organometallic reagents, which involves the formation of C−P bonds via cleavage of phosphorus−chlorine (P−Cl) bonds, has been conventionally employed (Figure 1A).[6] However, this approach requires the experiment to be conducted under precisely controlled conditions. In particular, the addition of exactly 1 equiv of an organometallic reagent is necessary during the first substitution reaction (**A** to **B**) to avoid the overreaction that affords the undesired product **F**, which made the method difficult to apply to the synthesis of unsymmetrical phosphines especially in a small laboratory scale. Therefore, for convenience, an alternative method was developed that uses a secondary amino group as a temporary protective group (**A** to **D**).[7,8] However, this approach necessitates the regeneration of the P−Cl bond via chlorination under acidic conditions (**E** to **B**). Moreover, starting materials and intermediates used and produced in these conventional methods are unstable phosphorus electrophiles, which contain P−Cl and/or phosphorus−nitrogen bonds and are difficult to purify by silica-gel column chromatography. In this context, a more convenient method for the synthesis of organophosphorus compounds is required. Herein, we report an efficient synthetic method for unsymmetrical tertiary phosphine oxides through a sequential substitution reaction of stable phosphonic acid dithioesters, which can be readily prepared from phosphonic dichlorides (Figure 1B, **A** to **1**), with Grignard reagents (**1** to **3** via **2**).

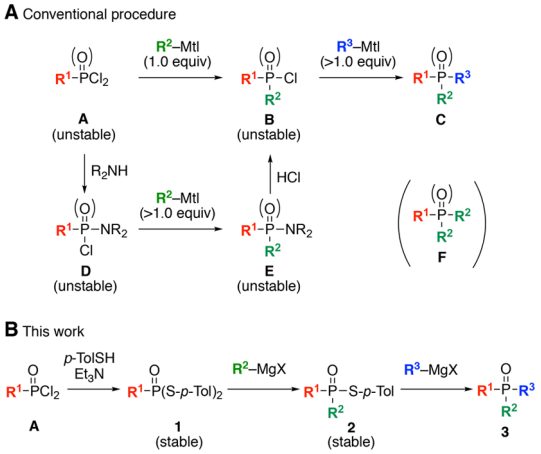



**Figure 1.** Synthetic methods for unsymmetrical tertiary phosphines and phosphine oxides. (A) Conventional methods. (B) Our method reported herein.

Screening of several phenylphosphonic acid ester derivatives **1** in the reaction with a phenyl Grignard reagent indicated that di(*p*-tolyl)thioester **1a**[14] suited our purpose in terms of chemical stability[15] and reactivity (Table 1). Treatment of a solution of **1a** in tetrahydrofuran (THF) with 2 equiv[16] of phenylmagnesium bromide at −40 °C for 1 h afforded the desired monosubstituted compound **2a** in high yield (entry 1). In this reaction, formation of only a small amount of undesired diphenylated product **3a**, resulting from the overreaction of the Grignard reagent with **2a**, was observed. By contrast, when *S*,*S*-dialkyl phenylphosphonodithioate **1b** was used, a large amount of the starting material **1b** remained unreacted (entry 2). Replacing the leaving group of **1a** with a bulky *o*-tolylthio or an electron-deficient *p*-

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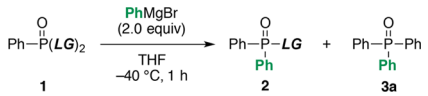
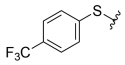
**Table 1. Leaving Group (LG) Screening**




| entry | *LG* | 1 | 2 | yield (%)[a] 2 | yield (%)[a] 3a | recovery of 1 (%)[a] |
|---|---|---|---|---|---|---|
| 1 | *p*-TolS | **1a** | **2a** | 85 (77)[b] | 11 | N.D. |
| 2 | *n*-$C_{12}H_{25}S$ | **1b** | **2b** | 39 | N.D. | 60 |
| 3 |  | **1c** | **2c** | 71 | 30 | N.D. |
| 4 |  | **1d** | **2d** | 28 | 70 | N.D. |
| 5 | *p*-TolO | **1e** | **2e** | N.D. | N.D. | 94 |
| 6[c] | *p*-TolO | **1e** | **2e** | 24 | 16 | 15 |

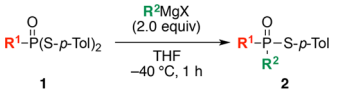
[a]Yields determined by $^1$H NMR analysis unless otherwise noted. N.D. = not detected. [b]Isolated yield in parentheses. [c]The reaction was performed at 0 °C for 2 h using 3.0 equiv of PhMgBr.

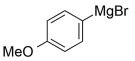
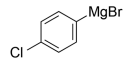
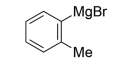
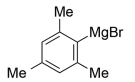
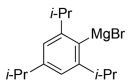
(trifluoromethyl)phenylthio group resulted in the increase of the amount of undesired diphenylated compound **3a** (entries 3 and 4). In sharp contrast to *S*,*S*-diaryl phenylphosphonodithioates, which reacted smoothly with a phenyl Grignard reagent at −40 °C (entries 1, 3, and 4), the reaction of the same Grignard reagent with di-*p*-tolyl phenylphosphonate (**1e**) did not proceed at all at −40 °C (entry 5) and proved sluggish even at a higher temperature (0 °C) to nonselectively give a mixture of products in low yields (entry 6).[17] These results clearly demonstrated the advantage of using the *p*-tolylthio group as a leaving group for the monoselective substitution reaction.

Various phosphinic acid thioesters **2** were prepared by the monoselective substitution reaction of phosphonodithioic acid *S*,*S*-di(*p*-tolyl) esters **1** with slight modifications of the reaction conditions depending on the substrates (Table 2). Various Grignard reagents were utilized in the monosubstitution reaction of phenylphosphonodithioate **1a**. For example, *p*-methoxy-, *p*-chloro-, and *o*-methylphenylation took place to yield the monosubstituted products **2f**–**h**, respectively, using the corresponding Grignard reagents (entries 1–3). Notably, the introduction of bulky mesityl and 2,4,6-triisopropylphenyl groups could also be achieved by increasing the reaction temperature and reaction time to afford **2i** and **2j** in high yields (entries 4 and 5). Various alkyl groups, including primary, secondary, tertiary, and cyclic alkyl groups, could also be introduced to give **2k**–**n**, demonstrating the remarkable leaving ability of the *p*-tolylthio group (entries 6–9). Moreover, monophenylation of arylphosphonodithioates, such as **1f** and **1g**, which bear either an electron-donating or an electron-withdrawing group, and alkylphosphonodithioate **1h** proceeded smoothly to afford the corresponding phosphinic acid thioesters **2f**, **2o**, and **2k**, respectively (entries 10–12). All phosphinic acid thioesters **2f**–**o** prepared by this method were sufficiently stable to be purified by standard silica-gel column chromatography without special care.

Further substitutive arylation or alkylation of phosphinic acid thioesters using the remaining *p*-tolylthio group as a leaving group enabled the synthesis of a wide range of tertiary phosphine oxides (Figure 2). For example, upon treatment of phosphinic acid thioester **2g** with a phenyl Grignard reagent at room temperature, the second substitution reaction proceeded smoothly to afford phosphine oxide **3b** in high yield. By

**Table 2. First Substitution Reaction of Phosphonodithioic *S*,*S*-Di(*p*-tolyl) Esters**




| entry | $R^1$ | 1 | $R^2$MgX | 2 | yield (%)[a] |
|---|---|---|---|---|---|
| 1 | Ph | **1a** |  | **2f** | 85 |
| 2 | Ph | **1a** |  | **2g** | 71 |
| 3[b] | Ph | **1a** |  | **2h** | 90 |
| 4[b] | Ph | **1a** |  | **2i** | 93 |
| 5[c] | Ph | **1a** |  | **2j** | 79 |
| 6 | Ph | **1a** | *n*-BuMgCl | **2k** | 79 |
| 7[b] | Ph | **1a** | *i*-PrMgCl | **2l** | 74 |
| 8[b] | Ph | **1a** | *t*-BuMgCl | **2m** | 40 |
| 9[b] | Ph | **1a** | *c*-HexMgCl | **2n** | 92 |
| 10 | 4-(MeO)$C_6H_4$ | **1f** | PhMgBr | **2f** | 75 |
| 11 | 4-$CF_3C_6H_4$ | **1g** | PhMgBr | **2o** | 48 (81)[d] |
| 12 | *n*-Bu | **1h** | PhMgBr | **2k** | 59 (81)[d] |

[a]Isolated yields. [b]The reaction was performed at room temperature for 2 h. [c]The reaction was performed at room temperature for 12 h. [d]Yields using 1.2 equiv of Grignard reagents in parentheses.

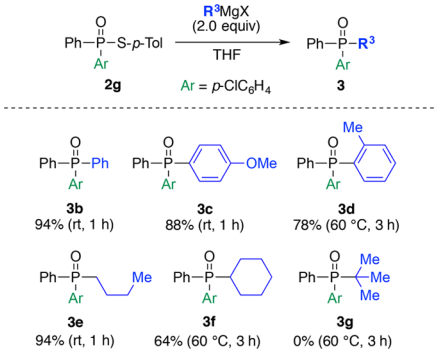



**Figure 2.** Synthesis of various tertiary phosphine oxides by second substitution reaction.

changing the Grignard reagent, other substituents, such as *p*-methoxyphenyl, bulky *o*-tolyl, acyclic alkyl, and cyclic alkyl groups, could also be installed to efficiently afford unsymmetrical tertiary phosphine oxides **3c**–**f**, which are difficult to synthesize by the conventional methods. The second substitution reaction using significantly bulky Grignard reagents such as *tert*-butylmagnesium chloride did not proceed at all even when the reaction temperature was increased. This could be attributed to the sterically hindered character of phosphinic acid thioesters when compared with phosphonic acid dithioesters.

Synthesis of a phosphine oxide bearing a bulky substituent was achieved by performing the reactions with the relevant Grignard reagents in the appropriate order. In particular, the bulky Grignard reagent needs to be used in the first substitution reaction, and then the less sterically hindered counterpart must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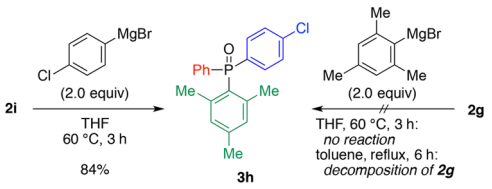
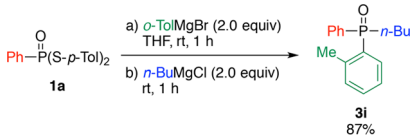
be used in the second substitution reaction. For example, although phosphine oxide **3h** was prepared efficiently by the reaction of **2i**, which has a preinstalled mesityl group, with a *p*-chlorophenyl Grignard reagent, **3h** was not obtained from the reaction of **2g** with a bulky mesityl Grignard reagent even performing the reaction at a higher temperature (Scheme 1).[18]

**Scheme 1. Changing the Order of Addition of Grignard Reagents**




The large difference in reactivity between phosphonic acid dithioesters and phosphinic acid thioesters toward Grignard reagents enabled the preparation of tertiary phosphine oxides in a simple one-pot reaction (Scheme 2). For example, treatment of

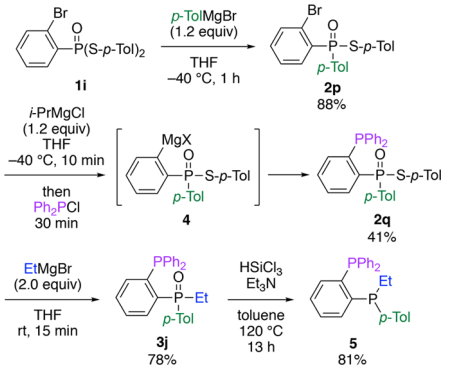
**Scheme 2. One-Pot Synthesis of an Unsymmetrical Tertiary Phosphine Oxide**




**1a** with 2 equiv of *o*-tolylmagnesium bromide at room temperature followed by the addition of the more reactive *n*-butylmagnesium chloride at the same temperature selectively afforded the unsymmetrical tertiary phosphine oxide **3i** in high yield.

Use of phosphinic acid thioesters with moderately reactive phosphorus−sulfur bonds enabled the synthesis of various types of organophosphorus compounds via the generation of a carbanion species (Scheme 3 and Figure 3). For example,

**Scheme 3. Synthesis of Unsymmetrical *o*-Diphosphinobenzene Derivative**




unsymmetrical *o*-diphosphinobenzene derivative **5** was easily prepared from *o*-bromophenylphosphonic acid dithioester **1i** via the formation of three new C−P bonds (Scheme 3). Treatment of **1i** with a *p*-tolyl Grignard reagent afforded the monosubstituted phosphinic acid thioester **2p**, which includes an untouched bromo group that proved susceptible to a halogen−

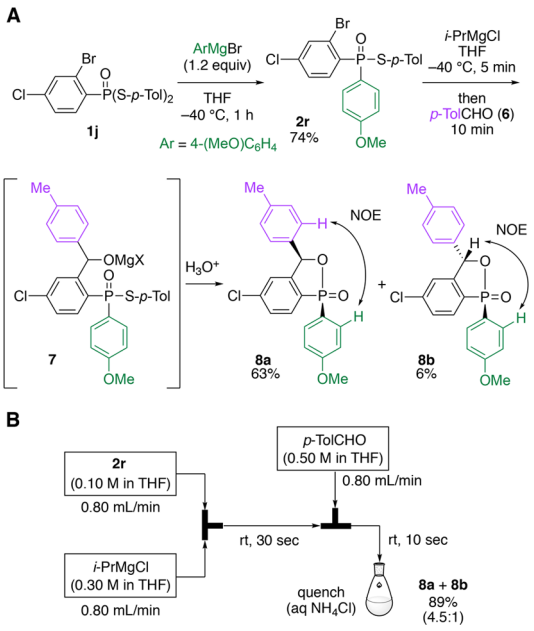



**Figure 3.** Synthesis of phosphinate analogues of phthalides. (A) Two-step synthesis by batch reactions. (B) Synthesis using a flow microreactor system for the second reaction.

magnesium exchange reaction with an isopropyl Grignard reagent at −40 °C. This enabled the selective generation of the aryl anion **4** that proceeded without a second substitution reaction taking place on the phosphorus atom. Subsequent treatment of the reaction mixture with chlorodiphenylphosphine afforded *o*-phosphanylphenylphosphinic acid thioester **2q**. Further treatment of **2q** with an ethyl Grignard reagent afforded phosphine oxide **3j**, which was successfully reduced by a conventional method[19] to give diphosphinobenzene derivative **5**.

Trapping an *o*-magnesiated phenylphosphinic acid thioester with an aldehyde afforded a unique multisubstituted cyclic phosphinic acid ester (Figure 3A). Indeed, treatment of phosphinic acid thioester **2r**, which was prepared from dithioester **1j** and *p*-methoxyphenylmagnesium bromide, with an isopropyl Grignard reagent, followed by the addition of *p*-tolualdehyde (**6**) and acidic workup, afforded a mixture of cyclic phosphinic acid esters[20] **8a** and **8b**, which are phosphorus analogues[21] of phthalides, with high diastereoselectivity. Furthermore, conducting this transformation using a flow microreactor system[22] improved the total yield of **8a** and **8b** (Figure 3B). This is probably because the unstable carbanion species,[23] generated from **2r** via a bromo−magnesium exchange reaction, was rapidly trapped by the aldehyde. Notably, using the flow system, the reaction could be conducted in a shorter period of time at room temperature, thus making the process more practical.

In summary, we have developed a facile synthetic method for unsymmetrical tertiary phosphine oxides using phosphonodithioic acid *S*,*S*-di(*p*-tolyl) esters. The two *p*-tolylthio groups of dithioesters served as suitable leaving groups in a sequential substitution reaction that proceeded in a stepwise manner through treatment with two Grignard reagents, allowing for the sequential introduction of different carbon substituents on the phosphorus atom. The chemical stability of thioester intermediates rendered the method practical, enabling the synthesis of a broad range of organophosphorus compounds. Further



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application studies using this method are currently underway in our group.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01796.

Experimental procedures, characterization for new compounds including copies of NMR spectra (PDF)

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### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES


(1) (a) *Phosphorus Ligands in Asymmetric Catalysis*; Börner, A., Ed.; Wiley: New York, 2008. (b) *P-Stereogenic Ligands in Enantioselective Catalysis*; Grabulosa, A., Ed.; Royal Society of Chemistry: Cambridge, 2011.

(2) Demkowicz, S.; Rachon, J.; Daśko, M.; Kozak, W. *RSC Adv.* **2016**, *6*, 7101.

(3) van Berkel, S. S.; van Eldijk, M. B.; van Hest, J. C. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 8806.

(4) (a) Baumgartner, T.; Réau, R. *Chem. Rev.* **2006**, *106*, 4681. (b) Queffélec, C.; Petit, M.; Janvier, P.; Knight, D. A.; Bujoli, B. *Chem. Rev.* **2012**, *112*, 3777.

(5) For reviews of the recent C−P bond-forming reactions, see: (a) Yorimitsu, H. *Beilstein J. Org. Chem.* **2013**, *9*, 1269. (b) Wauters, I.; Debrouwer, W.; Stevens, C. V. *Beilstein J. Org. Chem.* **2014**, *10*, 1064.

(6) Clarke, M. L.; Williams, M. J. The Synthesis and Applications of Phosphines. In *Organophosphorus Reagents*; Murphy, P. J., Eds.; Oxford University Press: Oxford, 2004; pp 15−50.

(7) Bestmann, H. J.; Lienert, J.; Heid, E. *Chem. Ber.* **1982**, *115*, 3875.

(8) Singh, S.; Nicholas, K. M. *Chem. Commun.* **1998**, 149.

(9) (a) Neuffer, J.; Richter, W. J. *J. Organomet. Chem.* **1986**, *301*, 289. (b) Kawashima, T.; Kojima, S.; Inamoto, N. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2603. (c) Langer, F.; Knochel, P. *Tetrahedron Lett.* **1995**, *36*, 4591. (d) Langer, F.; Püntener, K.; Stürmer, R.; Knochel, P. *Tetrahedron: Asymmetry* **1997**, *8*, 715. (e) Miyaji, T.; Xi, Z.; Ogasawara, M.; Nakajima, K.; Takahashi, T. *J. Org. Chem.* **2007**, *72*, 8737. (f) Hosein, A. I.; Caffyn, A. J. M. *Dalton Trans.* **2012**, *41*, 13504. (g) Gregson, A. M.; Wales, S. M.; Bailey, S. J.; Willis, A. C.; Keller, P. A. *J. Org. Chem.* **2015**, *80*, 9774. (h) Murai, T.; Maekawa, Y.; Hirai, Y.; Kuwabara, K.; Minoura, M. *RSC Adv.* **2016**, *6*, 15180. (i) Maekawa, Y.; Maruyama, T.; Murai, T. *Org. Lett.* **2016**, *18*, 5264. (j) Maekawa, Y.; Kuwabara, K.; Sugiyama, A.; Iwata, K.; Maruyama, T.; Murai, T. *Chem. Lett.* **2017**, *46*, 1077. (k) Unoh, Y.; Hirano, K.; Miura, M. *J. Am. Chem. Soc.* **2017**, *139*, 6106.

(10) (a) Hirao, T.; Masunaga, T.; Yamada, N.; Ohshiro, Y.; Agawa, T. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 909. (b) Andaloussi, M.; Lindh, J.; Sävmarker, J.; Sjöberg, P. J. R.; Larhed, M. *Chem. - Eur. J.* **2009**, *15*, 13069. (c) Hayashi, M.; Matsuura, T.; Tanaka, I.; Ohta, H.; Watanabe, Y. *Org. Lett.* **2013**, *15*, 628. (d) Yang, J.; Chen, T.; Han, L.-B. *J. Am. Chem. Soc.* **2015**, *137*, 1782. (e) Yu, R.; Chen, X.; Martin, S. F.; Wang, Z. *Org. Lett.* **2017**, *19*, 1808.

(11) (a) Rémond, E.; Tessier, A.; Leroux, F. R.; Bayardon, J.; Jugé, S. *Org. Lett.* **2010**, *12*, 1568. (b) Yoshida, S.; Hosoya, T. *Chem. Lett.* **2013**, *42*, 583. (c) Dhokale, R. A.; Mhaske, S. B. *Org. Lett.* **2013**, *15*, 2218. (d) Shen, C.; Yang, G.; Zhang, W. *Org. Lett.* **2013**, *15*, 5722. (e) Lopez-Leonardo, C.; Raja, R.; López-Ortiz, F.; del Águila-Sánchez, M. Á.; Alajarin, M. *Eur. J. Org. Chem.* **2014**, 1084. (f) Bhunia, A.; Roy, T.; Gonnade, R. G.; Biju, A. T. *Org. Lett.* **2014**, *16*, 5132. (g) Ueta, Y.; Mikami, K.; Ito, S. *Angew. Chem., Int. Ed.* **2016**, *55*, 7525. (h) Qi, N.; Zhang, N.; Allu, S. R.; Gao, J.; Guo, J.; He, Y. *Org. Lett.* **2016**, *18*, 6204.

(12) (a) Lopin, C.; Gouhier, G.; Gautier, A.; Piettre, S. R. *J. Org. Chem.* **2003**, *68*, 9916. (b) Sato, A.; Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1694. (c) Wada, T.; Kondoh, A.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2008**, *10*, 1155. (d) Lamas, M.-C.; Studer, A. *Org. Lett.* **2011**, *13*, 2236. (e) Fisher, H. C.; Berger, O.; Gelat, F.; Montchamp, J.-L. *Adv. Synth. Catal.* **2014**, *356*, 1199. (f) Yang, J.; Chen, T.; Han, L.-B. *J. Am. Chem. Soc.* **2015**, *137*, 1782. (g) Sato, Y.; Kawaguchi, S.-i.; Nomoto, A.; Ogawa, A. *Angew. Chem., Int. Ed.* **2016**, *55*, 9700.

(13) (a) Sadow, A. D.; Togni, A. *J. Am. Chem. Soc.* **2005**, *127*, 17012. (b) Feng, J.-J.; Chen, X.-F.; Shi, M.; Duan, W.-L. *J. Am. Chem. Soc.* **2010**, *132*, 5562. (c) Sun, W.; Hong, L.; Liu, C.; Wang, R. *Org. Lett.* **2010**, *12*, 3914. (d) Chen, Y.-R.; Duan, W.-L. *Org. Lett.* **2011**, *13*, 5824. (e) Nogi, K.; Yorimitsu, H. *Chem. Commun.* **2017**, *53*, 4055.

(14) (a) Sekine, M.; Hamaoki, K.; Hata, T. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3815. (b) Sekine, M.; Hata, T. *Yuki Gosei Kagaku Kyokaishi* **1986**, *44*, 229.

(15) The stability of phosphonic acid dithioester **1a** was checked under various conditions. See the Supporting Information for details.

(16) From the reaction of **1a** using 1.2 equiv of PhMgBr were obtained **2a**, **3a**, and unreacted **1a** in 66%, 3%, and 25% yields, respectively. We generally used 2.0 equiv of Grignard reagents to consume phosphonic acid dithioesters smoothly.

(17) Recently, nonselective substitution reactions using two alkoxy groups as leaving groups have been reported; see: Kendall, A. J.; Salazar, C. A.; Martino, P. F.; Tyler, D. R. *Organometallics* **2014**, *33*, 6171.

(18) As shown in Table 2 and Figure 2, bulky groups are introducible to phosphonic acid dithioesters, whereas they are difficult to introduce to phosphinic acid thioesters. This difference in reactivity could be explained by the length of a P−S bond that is longer than a P−C bond, which makes bulky nucleophiles more accessible to phosphonic acid dithioester with two P−S bonds than phosphinic acid thioesters bearing only one P−S bond.

(19) (a) Fritzsche, H.; Hasserodt, U.; Korte, F. *Chem. Ber.* **1965**, *98*, 171. (b) Hérault, D.; Nguyen, D. H.; Nuel, D.; Buono, G. *Chem. Soc. Rev.* **2015**, *44*, 2508.

(20) For an example of synthesis of cyclic phophinic acid esters, see: Ryu, T.; Kim, J.; Park, Y.; Kim, S.; Lee, P. H. *Org. Lett.* **2013**, *15*, 3986.

(21) Phosphonates are regarded as bioisosteres of carboxylic acid. For example, see: Ballatore, C.; Huryn, D. M.; Smith, A. B., III *ChemMedChem* **2013**, *8*, 385.

(22) For reviews of flow chemistry, see: (a) Yoshida, J.-i.; Suga, S.; Nagaki, A. *Yuki Gosei Kagaku Kyokaishi* **2005**, *63*, 511. (b) Porta, R.; Benaglia, M.; Puglisi, A. *Org. Process Res. Dev.* **2016**, *20*, 2.

(23) For an example of flow chemistry using an unstable intermediate at higher temperature, see: Kawaguchi, T.; Miyata, H.; Ataka, K.; Mae, K.; Yoshida, J.-i. *Angew. Chem., Int. Ed.* **2005**, *44*, 2413.




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