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Phosphorus−Carbon Bond Formation by Lewis Acid Catalyzed/Mediated Addition of Silylphosphines

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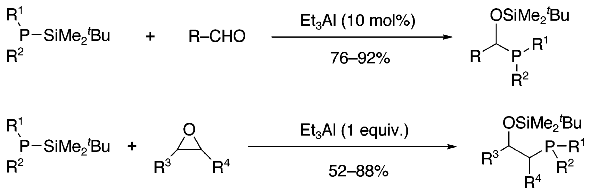
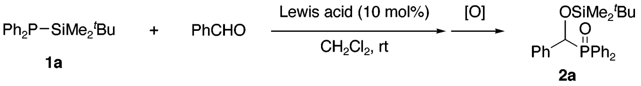


Triethylaluminum-catalyzed/mediated addition of a silylphosphine to aldehydes and epoxides is described. Organophosphines containing a silyloxy group at the α- or β-position on the alkyl substituent are successfully prepared in good yields.

Syntheses of organophosphorus compounds have received much attention due to their essential roles in various fields of chemistry, especially as ligands in transition-metal catalysis.[1] In most of the synthetic methods of trivalent organophosphines, the formation of the carbon−phosphorus(III) bond is usually achieved by a classical phosphination procedure using highly reactive organometallic reagents under severe conditions or via reduction of P(V) derivatives. Recent reports have described mild phosphination procedures, such as transition-metal-catalyzed hydrophosphinations,[2] base-catalyzed addition of phosphide equivalents,[3] among other reactions. In contrast to the wide scope of those basic phosphinations, limited examples have been reported on the phosphination under acidic conditions,[4] primarily due to a drawback in loss of the reactivities of both the acid and the phosphine precursor. We wish to report herein a successful Lewis acid catalyzed/mediated carbon−phosphorus bond forming reaction using a silylphosphine, yielding phosphines with a variety of functionalities.

TABLE 1. Survey of Lewis Acid Catalyst for the Addition of 1a to Benzaldehyde[a]



entry	Lewis acid	time (h)	yield (%)[b]
1	−	12	31
2	$BF_3{\cdot}OEt_2$	8	57
3	$TiCl_4$	4	52
4	$Ti(O^iPr)_4$	5	80
5	Et_2AlCl[c]	3	72
6	Et_3Al[c]	3	92

[a] Each reaction was continued until the silylphosphine was completely consumed. [b] Isolated yield after oxidation in the presence of air. [c] Added as a solution in *n*-hexane.

We have recently reported that sterically protected *tert*-butyldimethylsilyldiphenylphosphine **1a** serves as a synthetic equivalent of reactive diphenylphosphino group source,[2a,5] especially in the presence of Lewis acid.[5a] Increasing the electrophilicity of carbon electrophiles by a suitable Lewis acid would give rise to carbon−phosphorus bond formation by using the silylphosphine in a controlled manner. Therefore, we set out to investigate Lewis acid mediated reaction of silylphosphines to α- and β-hydroxyalkylphosphines, by the reactions with aldehydes and epoxides, respectively.

Addition of **1a** to benzaldehyde is our first attempt to evaluate the suitability of Lewis acids and conditions. Several Lewis acids listed in Table 1 were surveyed to conduct the addition to the aldehyde.

As shown in Table 1, silylphosphine **1a** slowly reacted with benzaldehyde without any catalyst (entry 1).[6] However, the yield of adduct **2a** was low (31%) even when the reaction continued for 12 h. Additions of a Lewis acid (10 mol %) remarkably accelerated the addition in all cases, giving adduct **2a** in higher yields. In addition, the silyl group was transferred to the adduct

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(1) (a) Clarke, M. L.; Williams, M. J. In *Organophosphorus Reagents*; Murphy, P. J., Ed.; Oxford University Press: New York, 2004; Chapter 2. (b) Gilheany, D. G.; Mitchell, C. M. In *The Chemistry of Organophosphorus Compounds*; Hartley, F. R., Ed.; John Wiley and Sons: Chichester, UK, 1990; Vol. 1, pp 151−190.

(2) For Rh-catalyzed hydrophosphination, see: (a) Hayashi, M.; Matsuura, Y.; Watanabe, Y. *J. Org. Chem.* **2006**, *78*, 9248−9251. For Ni- and Pd-catalyzed reactions, see: (b) Kazankova, M. A.; Efimova, I. V.; Kochetkov, A. N.; Afanas'ev, V. V.; Beletskaya, I. P. *Russ. J. Org. Chem.* **2002**, *38*, 1465−1474. (c) Kazankova, M. A.; Efimova, I. V.; Kochetkov, A.N.; Afanas'ev, V. V.; Beletskaya, I. P.; Dixneul, P. H. *Synlett* **2001**, 497−500. For a Co-catalyzed reaction, see: (d) Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 2368−2370. For Ru-catalyzed reaction, see: (e) Jérôme, F.; Monnier, F.; Lawicka, H.; Dérien, S.; Dixneuf, P. H. *Chem. Commun.* **2003**, *9*, 696−697. For Yb-catalyzed reactions, see: (f) Komeyama, K.; Kobayashi, D.; Yamamoto, Y.; Takehira, K.; Takaki, K. *Tetrahedron* **2006**, *62*, 2511−2519. (g) Takaki, K.; Komeyama, K.; Kobayashi, D.; Kawabata, T.; Takehira, K. *J. Alloys Compd.* **2006**, *408−412*, 432−436. (h) Komeyama, K.; Kawabata, T.; Takehira, K.; Takaki, K. *J. Org. Chem.* **2005**, *70*, 7260−7266. (i) Takaki, K.; Koshoji, G.; Komeyama, K.; Takeda, M.; Shishido, T.; Kitani, A.; Takehira, K. *J. Org. Chem.* **2003**, *68*, 6554−6565. (j) Takaki, K.; Takeda, M.; Koshoji, G.; Shishido, T.; Takehira, K. *Tetrahedron Lett.* **2001**, *42*, 6357−6360.

(3) (a) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079−3159. (b) Wicht, D. K.; Glueck, D. S. In *Catalytic Heterofunctionalization*; Togni, A., Grützmacher, H., Eds.; Wiley-VCH Verlag GmbH: Weinheim, Germany, 2001; pp 143−170. (c) Tanaka, M. *Top. Curr. Chem.* **2004**, *232*, 25−54.

(4) (a) Hirano, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2004**, *6*, 4873−4875. (b) Caiazzo, A.; Dalili, S.; Yudin, A. K. *Org. Lett.* **2002**, *4*, 2597−2600.

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(6) (a) Epstein, M.; Buckler, S. A. *Tetrahedron* **1962**, *18*, 1231−1242. (b) Petrov, K. A.; Parshina, V. A. *Zh. Obshch. Khim.* **1961**, *5*, 3417. (c) Becker, G.; Mundt, O. Z. *Anorg. Allg. Chem.* **1980**, *462*, 130−142. (d) Kolodiazhnyi, O. I. *Tetrahedron Lett.* **1982**, *23*, 4933−4936. (e) Kolodiazhnyi, O. I.; Guliaiko, I. V.; Kolodiazhna, A. O. *Tetrahedron Lett.* **2004**, *45*, 6955−6957. (f) Kolodiazhnaya, A. O.; Kukhar', V. P.; Kolodyazhnyi, O. I. *Russ. J. Gen. Chem.* **2004**, *74*, 965−966.

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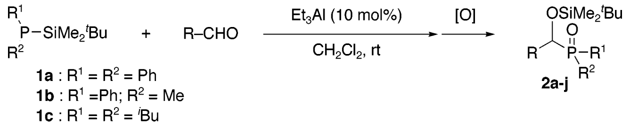
TABLE 2. Et_3Al-Catalyzed Silylphosphination of Several Aldehydes



entry	silylphosphine	R		time (h)	yield (%)[a]
1	**1a**	C_6H_5-	**2a**	3	92
2	**1a**	p-$Cl-C_6H_4-$	**2b**	3	92
3	**1a**	p-$NO_2-C_6H_4-$	**2c**	1	90
4	**1a**	p-$CH_3O-C_6H_4-$	**2d**	5	86
5	**1a**	$C_6H_5CH_2CH_2-$	**2e**	6	76
6	**1a**	$CH_3(CH_2)_4-$	**2f**	8	66
7	**1a**	$(CH_3)_2CH-$	**2g**	3	88
8	**1a**	$(CH_3)_3C-$	**2h**	16	28
9	**1b**	C_6H_5-	**2i**	5	69
10	**1c**	C_6H_5-	**2j**	4	55

[a] Isolated yield of the corresponding oxide after oxidation in the presence of air.

to give the silyl ether of the α-hydroxyalkylphosphine. Although the α-hydroxyalkylphosphines are reported to isomerize to alkylphosphine oxide under acidic conditions via dehydration–hydration,[7] the initial adducts, protected as the silyl ether, should be stable under the Lewis acidic conditions. Triethylaluminum gave rise to the best result among the Lewis acids tested (entry 6). Poor yields of the product in entries 2 and 3 are caused by decomposition of the starting silylphosphine under the reaction conditions. Dichloromethane was determined as the solvent of choice.

The results of the Et_3Al-catalyzed addition of silylphosphines to various aldehydes are summarized in Table 2.

In all cases, the aluminum catalyst accelerates the reaction. In the absence of the catalyst, a trace amount of the corresponding adduct was formed under the same conditions. Several aryl aldehydes gave the corresponding α-silyloxyalkylphosphines in high yields (entries 1–4). The addition to primary and secondary alkyl aldehydes also proceeded smoothly (entries 5–7). A tertiary alkyl aldehyde, pivalaldehyde, also gave the adducts, though the yield was poor even when the reaction continued for 16 h (entry 8). Silylphosphines **1b** and **1c**, bearing alkyl group(s) on the phosphorus atom, also reacted to give the corresponding adducts (entries 9 and 10). Although the product was isolated as the phosphine oxide in all cases, the initially formed adduct in the reaction was identified as the trivalent silyloxyalkylphosphine by ^1H and ^{31}P NMR spectra.[8] The initial adduct could be trapped as its borane complex by addition of BH_3-THF after the initial reaction was completed.[9]

The silyl ether was subsequently cleaved during the formation of the borane complex. Fortunately, deprotection of the silyl ether did not cause the reverse reaction;[6e] therefore, α-hydroxyphosphine derivative **3** could be obtained in stable form (Scheme 1).

Organophosphonates containing a hydroxy group(s) at the α-position have received much attention because of the biological importance of these compounds.[10] Thus, stereoselective addition of a phosphonate diester to an aldehyde has been studied to achieve the asymmetric synthesis of these hydroxyphosphonates.[11] In contrast, trivalent organophosphines having a similar structure receive less attention. The rate enhancement in the presence of Lewis acid shown above provides a promising route toward various trivalent organophosphines having chirality at the α-position through the stereocontrolled synthesis of the α-hydroxyalkylphosphines. The stereoselective version of the present reaction is now under investigation and will be reported elsewhere.

SCHEME 1. Isolation as the Borane Complex 3

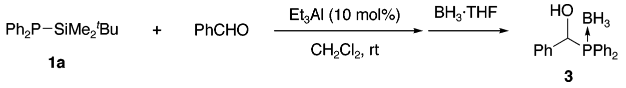
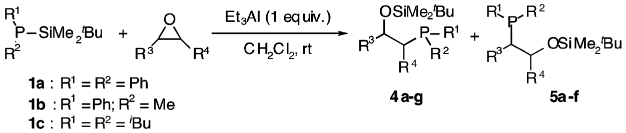
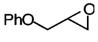
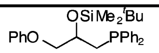
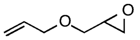
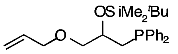
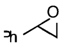
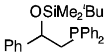
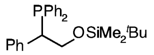
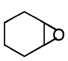
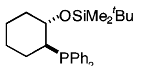
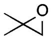
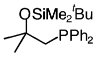
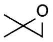
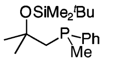
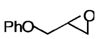
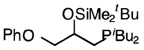


TABLE 3. Lewis Acid Catalyzed Phosphination of Epoxides[a]



Entry	1	Epoxide	Time (h)	Products		Yield (%)[b]
1	**1a**		3		**4a**	78
2			1.5		**4b**	75
3			1.5		**4c**	66[c]
					**5c**	
4			1		**4d**	84
5			1		**4e**	86
6	**1b**		1		**4f**	88
7	**1c**		3		**4g**	57

[a] The reaction was quenched by addition of MeOH before isolation by chromatography on silica gel. [b] Isolated yield. [c] The products were completely oxidized during workup and isolated as oxides in the ratio of 22:78 (**4c**/**5c**).

It is well-known that epoxides are successfully activated by the action of a suitable Lewis acid, resulting in acid-mediated nucleophilic addition with ring opening. Thus, we have extended the scope of the present silylphosphination toward epoxides. After several attempts, the reaction with an epoxide proceeded smoothly in the presence of a stoichiometric amount of Et_3Al.[12] Successful results are summarized in Table 3.

As shown in Table 3, the β-hydroxyalkylphosphine derivatives were formed in good yields and excellent regioselectivities.

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(7) Quin, L. D. *A Guide to Organophosphorus Chemistry*; John Wiley and Sons: New York, 2000; Chapter 3, pp 81–82.

(8) For example, the trivalent adduct of benzaldehyde with **1a** was observed in the ^{31}P NMR (δ −5 ppm) spectrum of the reaction mixture, which was completely converted to the oxide (δ +30 ppm) in the presence of air; see Supporting Information for detail.

(9) For example, the borane complex of the benzaldehyde adduct was isolated in 58% yield; see Supporting Information for detail.

(10) Kolodiazhnyi, O. I. *Tetrahedron: Asymmetry* **2005**, *16*, 3295–3340.

(11) (a) Sasai, H.; Bougauchi, M.; Arai, T.; Shibasaki, M. *Tetrahedron Lett.* **1997**, *38*, 2717–2720. (b) Yokomatsu, T.; Yamagishi, T.; Shibuya, S. *Tetrahedron: Asymmetry* **1993**, *4*, 1779–1782. (c) Yokomatsu, T.; Yamagishi, T.; Shibuya, S. *Tetrahedron: Asymmetry* **1993**, *4*, 1783–1784. (d) Yokomatsu, T.; Yamagishi, T.; Shibuya, S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1527–1534.

(12) The use of a catalytic amount of Et_3Al gave unreproducible results with variable regioselectivity. The factor of the reproducibility of the catalytic reactions could not be found.

In most cases, formation of less substituted phosphines **4** predominated, showing that the selectivity depends primarily on the steric hindrance during nucleophilic attack by the phosphorus than Lewis acid mediated ring opening. The other regioisomers **5** could not be isolated in most cases. The reaction of phenyl glycidyl ether (entry 1) gave the regioisomer as the oxide in less than 1%.

Ring opening at benzylic carbon proceeded with the reversed regioselectivity to give the more substituted phosphine **5** as its oxide (entry 3). This result clearly indicated that the reaction proceeded by a nucleophilic addition of a silylphosphine to the epoxide activated by a Lewis acid. By using other silylphosphines with alkyl substituent(s) on the phosphorus atom, various organophosphorus compounds with silyloxy functionality could be successfully obtained (entries 6 and 7). In addition, availability of optically active epoxides via asymmetric epoxidation makes this process effective for the preparation of optically active organophosphines. Moreover, this methodology represents a new entry for the synthesis of functional phosphines with various alkyl groups, which are difficult to prepare other phosphination procedure.

In conclusion, we have developed new synthetic procedures for α- and β-hydroxyalkylphosphine derivatives by Lewis acid catalyzed and mediated reactions of silylphosphines with aldehydes and epoxides in the preparation of functionalized phosphines. Further application of this methodology and stereoselectivity of the reaction is now under investigation and will be reported elsewhere.

Experimental Section

General Procedure for the Addition to Aldehydes: To a solution of Et_3Al in *n*-hexane (1.0 M, 52 μL, 0.05 mmol) and an aldehyde (0.5 mmol) in anhydrous CH_2Cl_2 (3 mL) was added silylphosphine **1a** (0.6 mmol) under argon. The resulting mixture was stirred at ambient temperature until the aldehyde was consumed (ca. 3−5 h), then quenched by addition of methanol (0.5 mL). After the reaction mixture was concentrated, purification of the crude product by column chromatography on silica gel afforded the corresponding α-*tert*-butyldimethylsilyloxyalkyldiphenylphosphine, which was isolated in the oxide form.

General Procedure for the Reaction with Epoxides: To a solution of silylphosphine **1a** (0.36 mmol) and an epoxide (0.3 mmol) in anhydrous CH_2Cl_2 (3 mL) was added Et_3Al in *n*-hexane (1.0 M, 0.3 mL, 0.3 mmol) under argon. The resulting mixture was stirred at ambient temperature until the epoxide was consumed (ca. 1−3 h), then quenched by addition of methanol (0.3 mL). After the reaction mixture was concentrated, purification of the crude product by column chromatography on silica gel afforded the corresponding β-hydroxyalkyldiphenylphosphines.

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Supporting Information Available: Experimental details and characterization data for **2a**−**2j**, **3**, **4a**−**4g**, and **5c** and ^1H, ^{13}C, and ^{31}P NMR spectra of **2a**−**2j**, **3**, **4a**−**4g**, and **5c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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