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One-pot synthesis of α-aminophosphonates catalyzed by antimony trichloride adsorbed on alumina

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Abstract

$SbCl_3$ adsorbed on Al_2O_3 is found to be an efficient and recyclable catalyst in promoting three-component coupling reactions of aldehydes (aromatic and aliphatic), amines (aryl amines, aliphatic amines and esters of *S*-α-amino acids) and dialkylphosphites to afford the corresponding α-aminophosphonates in high yields. The ethyl ester of *S*-phenylalanine was observed to yield the corresponding α-aminophosphonate with *S*,*S*-diastereoisomer formed in dominance over the *S*,*R*-diastereoisomer.
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Keywords: $SbCl_3/Al_2O_3$; α-Amino acid; α-Aminophosphonate; Solid supported reagents; Recyclability

α-Aminophosphonates have been the focus of attention in recent years because of their structural analogy to the corresponding α-amino acids as well as heterocyclic phosphonates[1] and ω-aminophosphonates.[2] They act as peptide mimics,[3] antibiotics, herbicides,[4] pharmacological agents[5] and enzyme inhibitors.[6] In addition, α-aminophosphonates have broad application due to their antifungal[7] and antibacterial activities.[8] There are two main pathways for the synthesis of α-aminophosphonates:

(a) *Kabachnik–Fields* three-component reaction in which an amine, an aldehyde and a di- or trialkylphosphite are reacted in a single-pot in the presence of a catalyst such as $LiClO_4$,[9,10] $TaCl_5$–SiO_2,[11] $InCl_3$,[12] $Sc(O_3SOC_{12}H_{25})_3$,[13] SiO_2/NH_4HCO_3,[14] lanthanide–triflate,[15] CF_3CO_2H,[16] $Mg(ClO_4)_2$,[17] $TiCl_4$,[18] $PhMe_3NCl$[19] and $In(OTf)_3$.[20]

(b) *Pudovik reaction*, where dialkylphosphites are added to imines using either a base[21–23] or a Lewis acid such as $AlCl_3$,[24] Me_2AlCl,[25] BF_3,[26] $SnCl_4$,[27] *t*-PcAlCl[28] and $ZrCl_4$.[29]

However, in spite of their potential utility, these methods typically suffer from one or more disadvantages such as high cost, use of a stoichiometric amount of catalyst, moisture sensitivity, specialized handling, tedious work-up and non-recyclability of the catalyst. The use of reagents impregnated on inorganic supports[11,14,30] offers advantages in preparative procedures, such as simple work-up, easy handling, mild reaction conditions, cleaner products, enhanced selectivity, reduction of by-products and produced waste, much improved reaction rates and recyclability of the catalyst. In continuation of our ongoing studies[30b,31] into the applications of $SbCl_3$ impregnated on inorganic supports as a post transitional Lewis acid in organic synthesis, we wished to explore the usage of $SbCl_3/Al_2O_3$ for the synthesis of a-aminophosphonates and α-aminophosphonates of the esters of α-amino acids (*S*-phenylglycine and *S*-phenylalanine).

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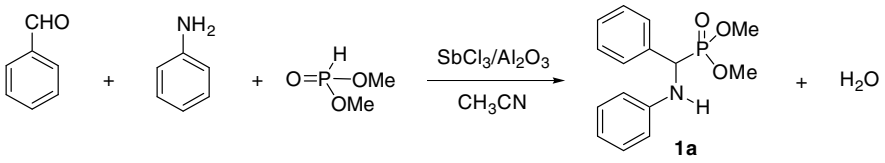


Scheme 1. Preparation of α-aminophosphonate **1a** in the presence of $SbCl_3/Al_2O_3$.

A mixture of benzaldehyde (10 mmol), aniline (10 mmol) and dimethylphosphite (12 mmol) in acetonitrile (65 mL) was stirred at room temperature in the presence of 5 mol % of $SbCl_3/Al_2O_3$ and 5 Å molecular sieves (Scheme 1) to yield the expected α-aminophosphonate **1a**[10] in 3 h.

The above experiment was carried out with 5 mol % of $SbCl_3$ and it was found that the reaction took longer (5 h) to reach completion. No product formation was observed in the presence of Al_2O_3 even after 8 h of stirring at room temperature. It seems that Al_2O_3 acts only as a support for the reaction. It was considered appropriate to employ $SbCl_3/Al_2O_3$ in future studies in view of the recyclability of $SbCl_3$ adsorbed on an inorganic support (hydroxyapatite, HAP).[30b] In order to investigate the recyclability, $SbCl_3/Al_2O_3$ was recovered, activated at 110 °C in an oven and reused ten times, successively, for the reaction of benzaldehyde, aniline and dimethylphosphite; no significant decrease in its activity was noticed (Fig. 1).

A range of aldehydes underwent reactions with aromatic and aliphatic amines including a secondary amine (entry 16) to give the corresponding α-aminophosphonates. The results are summarized in Table 1.

We next focused our attention on the esters of α-amino acids (Scheme 2). For the ethyl esters of *S*-phenylglycine and *S*-phenylalanine, the formation of 9:1 and 3:2 mixtures of diastereoisomers was evident upon analyzing the ^1H NMR spectra of the viscous oils obtained by column chromatography over silica gel. Interestingly, in all the cases, the major diastereoisomer crystallized from the viscous oil on cooling in a refrigerator. The crystalline product **1z** obtained in the reaction between *S*-phenylalanine ethyl ester and *p*-chlorobenzaldehyde was assigned the *S*,*S*-configuration on the basis of X-ray analysis.[32c] (Fig. 2).

The structure is stabilized by two hydrogen bonds (Fig. 3) between the hydrogen attached to the amine nitrogen (N1) and the phosphonate oxygen ($O1^i$) belonging to the symmetry related molecule (where $i = -x+1, -y, -z$). The N1–H1···$O1^i$ distance is 2.053(4) Å and the N1–H1···O1 angle is 168.1(2)°. The amine hydrogen of this symmetry related molecule forms an identical H-bond with molecule (x, y, z) to give a tight H-bonded dimer (Fig. 3).

In summary, $SbCl_3/Al_2O_3$ is found to be an efficient catalyst for the synthesis of α-aminophosphonates. $SbCl_3/Al_2O_3$ is stable, easy to handle, recoverable by simple filtration and is recyclable.

General procedure: A mixture of amine (10.0 mmol), aldehyde (10.0 mmol), dialkylphosphite (12.0 mmol), 5 Å molecular sieves (200 mg) and $SbCl_3/Al_2O_3$[31] (3.1 g, 5 mol % with respect to the amount of $SbCl_3$) in CH_3CN (65 mL) was stirred at room temperature for the appropriate amount of time (Table 1). After completion of the reaction (TLC), CH_3CN was distilled off under reduced pressure and the residue was diluted with EtOAc (70 mL) and filtered to remove solid materials. The filtrate was washed with water (2 × 20 mL) and brine (20 mL). The organic layer was dried over anhydrous Na_2SO_4 and con-

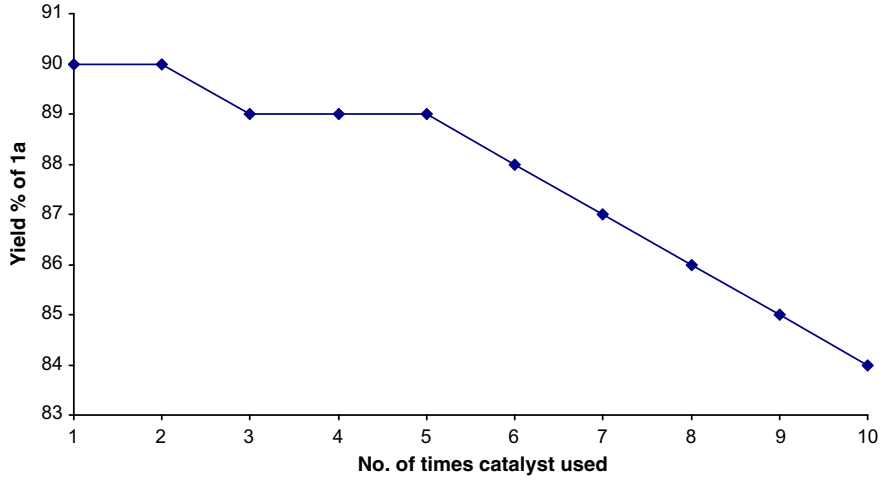
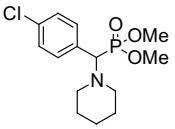


Fig. 1. Results of recycling the catalyst.

Table 1
One-pot synthesis of α-aminophosphonates catalyzed by $SbCl_3/Al_2O_3$

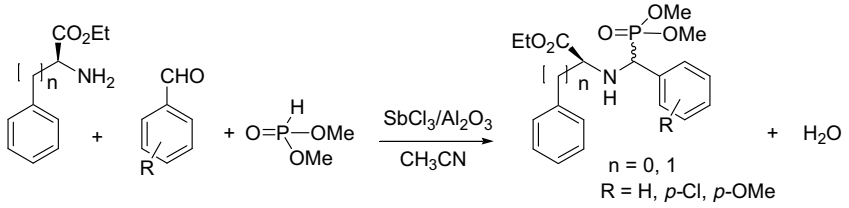
Entry	Aldehyde	Amine	Phosphite[a]	Product[b]	Time (h)	Yield (%)
1	Benzaldehyde	Aniline	DMP	**1a**[10]	3	90
2	Benzaldehyde	Aniline	DEP	**1b**[17]	3	91
3	*p*-Tolualdehyde	Aniline	DEP	**1c**	3.5	90
4	3,4,5-Trimethoxybenzaldehyde	Aniline	DEP	**1d**	4	82
5	*p*-Nitrobenzaldehyde	Benzylamine	DEP	**1e**	2.5	83
6	*trans*-Cinnamaldehyde	Aniline	DEP	**1f**	5	75
7	Benzaldehyde	Benzylamine	DEP	**1g**	3	90
8	*p*-Anisaldehyde	Aniline	DEP	**1h**[17]	3.5	92
9	*p*-Anisaldehyde	*p*-Toluidine	DMP	**1i**	3.5	84
10	*p*-Tolualdehyde	*p*-Toluidine	DEP	**1j**	3.5	86
11	Butyraldehyde	Aniline	DMP	**1k**	7.0	49
12	*p*-Tolualdehyde	Aniline	DMP	**1l**	4.5	88
13	*p*-Tolualdehyde	Benzylamine	DMP	**1m**	4.5	83
14	*p*-Anisaldehyde	2-Aminopyridine	DEP	**1n**	5.0	77
15	*m*-Anisaldehyde	Aniline	DMP	**1o**	3.0	89
16	*p*-Chlorobenzaldehyde	Piperidine	DMP	 **1p**	4.0	84
17	*o*-Chlorobenzaldehyde	Aniline	DMP	**1q**	3.0	92
18	*o*-Chlorobenzaldehyde	Aniline	DEP	**1r**	3.5	90
19	*p*-Chlorobenzaldehyde	Aniline	DMP	**1s**[17]	2.5	91
20	*p*-Chlorobenzaldehyde	Aniline	DEP	**1t**	2.5	91
21	*p*-Tolualdehyde	2-Aminobenzothiazole	DMP	**1u**	5	65
22	Benzaldehyde	Ethyl ester of *S*-phenylglycine[c]	DMP	**1v**[d]	4.5	74
23	*p*-Chlorobenzaldehyde	Ethyl ester of *S*-phenylglycine[c]	DMP	**1w**[d]	5	78
24	*p*-Anisaldehyde	Ethyl ester of *S*-phenylglycine[c]	DMP	**1x**[d]	4.5	73
25	Benzaldehyde	Ethyl ester of *S*-phenylalanine[c]	DMP	**1y**[e]	5.5	68
26	*p*-Chlorobenzaldehyde	Ethyl ester of *S*- phenylalanine[c]	DMP	**1z**[e]	5	65

[a] DMP = dimethyl phosphite and DEP = diethyl phosphite.
[b] All new compounds gave satisfactory spectral data (^1H and ^{13}C NMR, MS).
[c] Reactions (entries 22–26) were carried out at reflux.
[d] 9:1 mixture of diastereoisomers as calculated from the ^1H NMR spectrum of the crude product.
[e] 3:2 mixture of diastereoisomers as calculated from the ^1H NMR spectrum of the crude product.

centrated under reduced pressure to afford a crude product, which on passing through a silica (60–120 mesh) column using EtOAc–petroleum ether as an eluent gave the pure α-aminophosphonates. The structures of the products were established by spectroscopy.

For the esters of α-amino acids: To a solution of 10.0 mmol of the ester of the α-amino acid hydrochloride in 80 mL of water at 0 °C was added aqueous ammonia solution (25% NH_3) dropwise with stirring until the solution became neutral. The mixture was extracted with $CHCl_3$ (4 × 30 mL) and the combined $CHCl_3$ layers were washed with brine (40 mL), dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure to afford the ester of the α-amino acid, which was converted to the corresponding aminophosphonates following the general procedure.

With α-amino acid esters, better yields were obtained using 1.1 equiv of the aldehyde with respect to the amount



Scheme 2. α-Aminophosphonates of the esters of α-amino acids in the presence of $SbCl_3/Al_2O_3$.

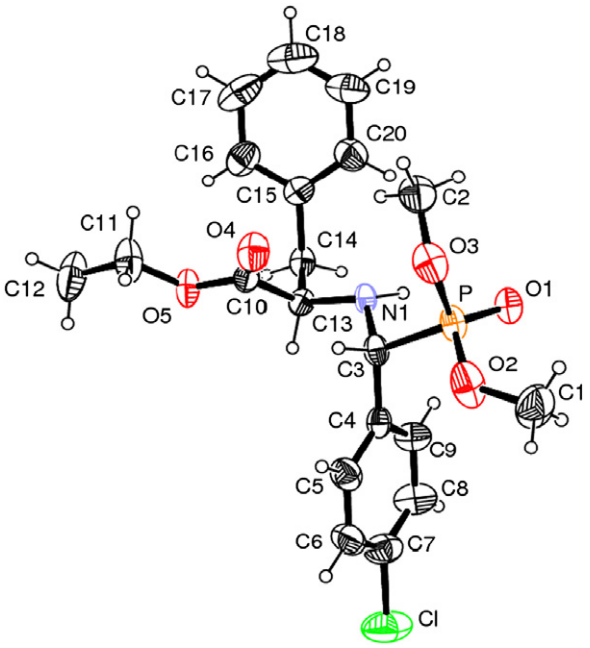


Fig. 2. ORTEP drawing of **1z**.

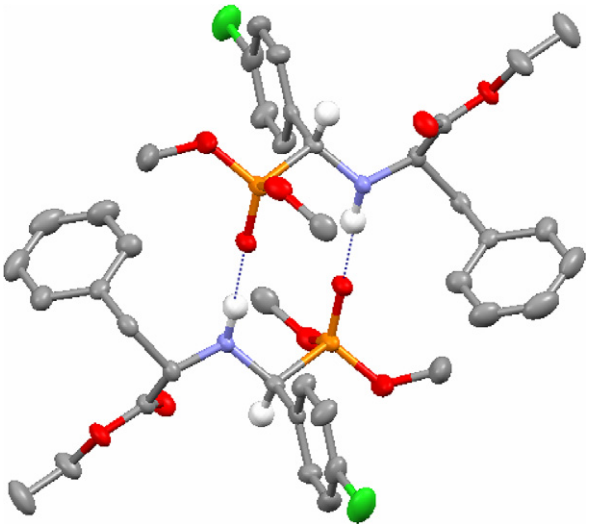


Fig. 3. H-bonding between phosphonate oxygen (O1) and the amino hydrogen (H1) attached to nitrogen (N1). Hydrogen atoms attached to carbon atoms are not shown.

of ester. MeOH–$CHCl_3$ was used as an eluent for column chromatography of the products in these cases.

Acknowledgement

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32. The physical and spectroscopic data of the selected compounds is as follows:
(a) Compound **1u**: Yellowish, crystalline; mp: 174–175 °C. IR, ν_{max}/cm^{-1} (KBr): 3217, 3016, 1596, 1538, 1443, 1250. ^1H NMR: ($CDCl_3$, 300 MHz) δ 2.31 (s, 3H, CH_3), 3.55 (d, 3H, $^3J_{HP} = 10.5$ Hz, OCH_3), 3.81 (d, 3H, $^3J_{HP} = 10.8$ Hz, OCH_3), 5.58 (d, 1H, $^2J_{HP} = 21.9$ Hz, C*H*), 7.02–7.22 (m, 4H, Ar-*H*), 7.33–7.54 (m, 4H, Ar-*H*). ^{13}C NMR: ($CDCl_3$, 75 MHz) δ 21.7, 54.6, 56.6, 119.8, 121.2, 122.3, 126.3, 127.6, 128.8, 129.9, 131.7, 132.4, 138.6, 152.5, 166.4. Anal. Calcd for $C_{17}H_{19}N_2O_3PS$ (362.384): C, 56.35: H, 5.28: N, 7.73: S, 8.85. Found: C, 56.35: H, 5.29: N, 7.72: S, 8.84. MS (ESI) *m*/*z*: 362.9 $(M+H)^+$.
(b) Compound **1v**: White, crystalline; mp: 76–78 °C. IR, ν_{max}/cm^{-1} (KBr): 3267, 2954, 1738, 1599, 1490, 1454, 1243. ^1H NMR: ($CDCl_3$, 200 MHz) δ 1.15 (t, 3H, $^3J_{HH} = 7.1$ Hz, CH_3), 3.62 (d, 3H, $^3J_{HP} = 11.5$ Hz, OCH_3), 3.75 (d, 3H, $^3J_{HP} = 10.5$ Hz, OCH_3),

4.10–4.31 (m, 4H, C*H*CO_2Et, C*H*PO_3Me_2, CH_2), 7.27–7.41 (m, 10H, Ar-*H*). ^{13}C NMR: ($CDCl_3$, 50 MHz) δ 13.2, 53.1, 56.5, 59.3, 60.3, 61.9, 126.3, 126.7, 127.0, 127.3, 127.5, 133.5, 133.7, 136.2, 171.8. Anal. Calcd for $C_{19}H_{24}NO_5P$ (377.371): C, 60.47: H, 6.41: N, 3.71. Found: C, 60.47: H, 6.40: N, 3.72.

MS (ESI) *m*/*z*: 378.2 $(M+H)^+$.

(c) Compound **1z**: White, crystalline mp: 65 °C; $[\alpha]_D^{20}$ 0, *c* 1 in chloroform X-ray crystallographic details: $C_{20}H_{25}ClNO_5P$, formula weight = 425.83, $\lambda = 0.71069$ Å, triclinic, $P\bar{1}$ (number 2), $a = 10.256(5)$ Å, $b = 10.583(5)$ Å, $c = 11.097(5)$ Å, $\alpha = 81.940(5)°$, $\beta = 78.030(5)°$, $\gamma = 67.740(5)°$, $V = 1087.9(9)$ Å^3, $Z = 2$, $\rho_{calc} = 1.300$ Mg/m^3, $\mu = 0.279$ mm^{-1}, $F(000) = 448$, reflections collected = 4308, full-matrix least-squares on F^2, parameters = 253, $R_1 = 0.0807$, $wR_2 = 0.1987$, largest difference in peak and hole (0.475 and −0.336 e Å^{-3}). CCDC number: 662851; IR, ν_{max}/cm^{-1} (KBr): 3259, 2959, 1736, 1597, 1492, 1458, 1247. ^{1}H NMR: ($CDCl_3$, 200 MHz) δ 1.20 (t, 3H, $^3J_{HH} = 7.1$ Hz, C*H*$_3$), 2.79 (dd, 1H, $J_{HH} = 13.5$ Hz, 8.8 Hz, CH_aH$_b$Ph), 2.98 (dd, 1H, $J_{HH} = 13.5$ Hz, 5.2 Hz, CH$_a$*H*$_b$Ph), 3.22 (dd, 1H, $^3J_{HH} = 8.7$ Hz, 5.3 Hz, C*H*CO_2Et), 3.61 (d, 3H, $^3J_{HP} = 10.5$ Hz, OC*H*$_3$), 3.69 (d, 3H, $^3J_{HP} = 10.6$ Hz, OC*H*$_3$), 4.10 (d, 1H, $^2J_{HP} = 18.2$ Hz, C*H*PO_3Me_2), 4.13 (q, 2H, $^3J_{HH} = 7.1$ Hz, CH_2CH$_3$), 6.95–7.27 (m, 9H, Ar-*H*). ^{13}C NMR: ($CDCl_3$, 50 MHz) δ 14.3, 39.7, 53.8, 57.7, 58.9, 59.9, 61.0, 126.9, 128.4, 128.7, 129.5, 130.0, 133.1, 133.9, 137.3, 173.6. Anal. Calcd for $C_{20}H_{25}ClNO_5P$ (425.843): C, 56.41: H, 5.92: N, 3.29. Found: C, 56.42: H, 5.93: N, 3.28. MS (ESI) *m*/*z*: 428.1 (30) and 426.1 (100) $(M+H)^+$.

2nd diastereoisomer: Viscous oil; $[\alpha]_D^{20}$ −23.54, *c* 1 in chloroform; IR, ν_{max}/cm^{-1} (neat): 3259, 2959, 1736, 1597, 1492, 1458, 1247. ^{1}H NMR: ($CDCl_3$, 200 MHz) δ 1.02 (t, 3H, $^3J_{HH} = 7.1$ Hz, C*H*$_3$), 2.87 (m, 2H, CH_2Ph), 3.48 (d, 3H, $^3J_{HP} = 10.5$ Hz, OC*H*$_3$), 3.56 (dd, 1H, $^3J_{HH} = 5.9$ Hz, 7.8 Hz, C*H*CO_2Et), 3.60 (d, 3H, $^3J_{HP} = 10.6$ Hz, OC*H*$_3$), 3.87 (q, 2H, $^3J_{HH} = 7.1$ Hz, CH_2CH$_3$), 3.88 (d, 1H, $^2J_{HP} = 19.7$ Hz, C*H*PO_3Me_2), 6.96–7.27 (m, 9H, Ar-*H*). ^{13}C NMR: ($CDCl_3$, 50 MHz) δ 13.9, 39.2, 53.6, 58.8, 59.8, 60.9, 61.6, 126.9, 128.4, 128.6, 129.5, 129.9, 133.1, 133.9, 137.2, 173.6. Anal. Calcd for $C_{20}H_{25}ClNO_5P$ (425.843): C, 56.41: H, 5.92: N, 3.29. Found: C, 56.42: H, 5.93: N, 3.28. MS (ESI) *m*/*z*: 428.1 (30) and 426.1 (100) $(M+H)^+$.