

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

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Abstract

SbCl₃ adsorbed on Al₂O₃ 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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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 phosphonates¹ and ω -aminophosphonates.² They act as peptide mimics,³ antibiotics, herbicides,⁴ pharmacological agents⁵ and enzyme inhibitors.⁶ In addition, α -aminophosphonates have broad application due to their antifungal⁷ and antibacterial activities.⁸ There are two main pathways for the synthesis of α -aminophosphonates:

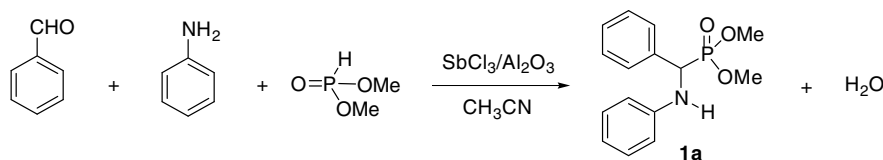
- (a) *Kabachnik–Fields* three-component reaction in which an amine, an aldehyde and a di- or trialkylphosphite are reacted in a single-pot in the presence of a catalyst such as LiClO₄,^{9,10} TaCl₅–SiO₂,¹¹ InCl₃,¹² Sc(O₃SOC₁₂H₂₅)₃,¹³ SiO₂/NH₄HCO₃,¹⁴ lanthanide–triflate,¹⁵ CF₃CO₂H,¹⁶ Mg(ClO₄)₂,¹⁷ TiCl₄,¹⁸ PhMe₃NCl¹⁹ 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 AlCl₃,²⁴ Me₂AlCl,²⁵ BF₃,²⁶ SnCl₄,²⁷ *t*-PcAlCl²⁸ and ZrCl₄.²⁹

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 SbCl₃ impregnated on inorganic supports as a post transitional Lewis acid in organic synthesis, we wished to explore the usage of SbCl₃/Al₂O₃ for the synthesis of α -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 $\text{SbCl}_3/\text{Al}_2\text{O}_3$.

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 $\text{SbCl}_3/\text{Al}_2\text{O}_3$ 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 $\text{SbCl}_3/\text{Al}_2\text{O}_3$ 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, $\text{SbCl}_3/\text{Al}_2\text{O}_3$ 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 (O1ⁱ) belonging to the symmetry related molecule (where $i = -x + 1, -y, -z$). The N1–H1 $\cdots$ O1ⁱ distance is 2.053(4) Å and the N1–H1 $\cdots$ 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, $\text{SbCl}_3/\text{Al}_2\text{O}_3$ is found to be an efficient catalyst for the synthesis of α -aminophosphonates. $\text{SbCl}_3/\text{Al}_2\text{O}_3$ 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 $\text{SbCl}_3/\text{Al}_2\text{O}_3$ 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-

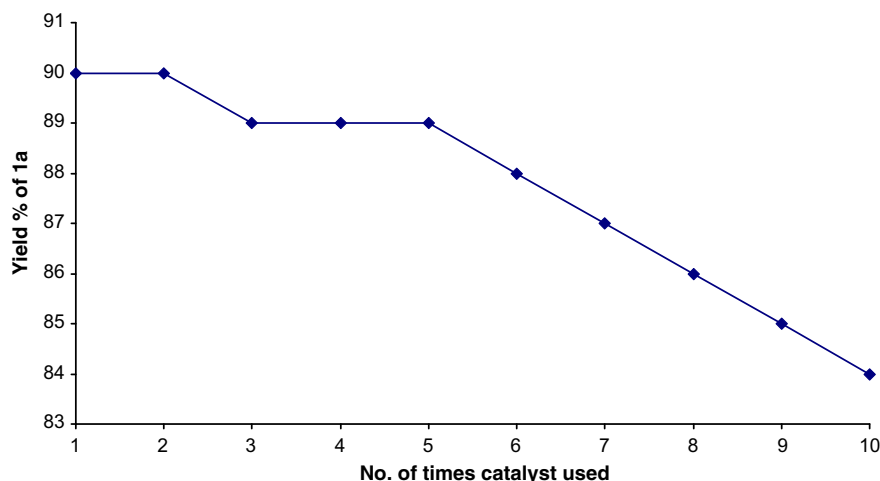
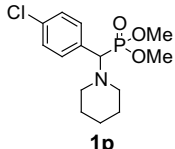


Fig. 1. Results of recycling the catalyst.

Table 1
One-pot synthesis of α -aminophosphonates catalyzed by $\text{SbCl}_3/\text{Al}_2\text{O}_3$

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

^a DMP = dimethyl phosphite and DEP = diethyl phosphite.

^b All new compounds gave satisfactory spectral data (¹H and ¹³C 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.

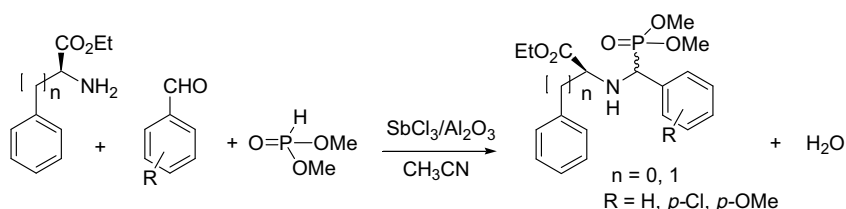
^e 3:2 mixture of diastereoisomers as calculated from the ¹H NMR spectrum of the crude product.

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 solu-

tion became neutral. The mixture was extracted with CHCl_3 (4 $\times$ 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 $\text{SbCl}_3/\text{Al}_2\text{O}_3$.

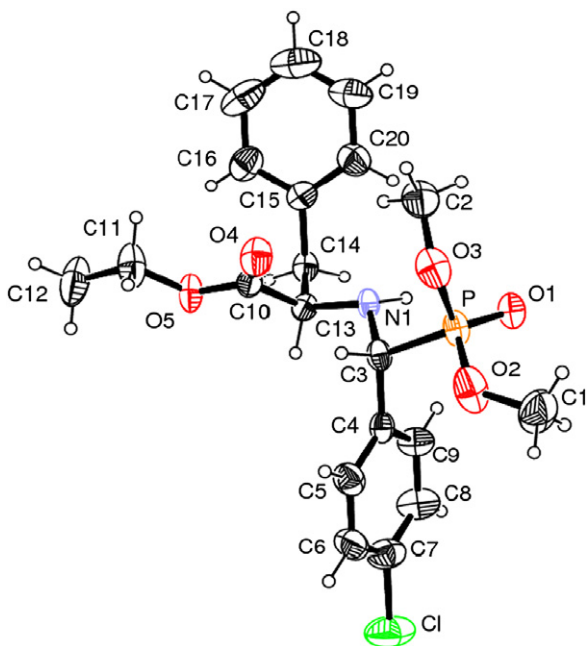
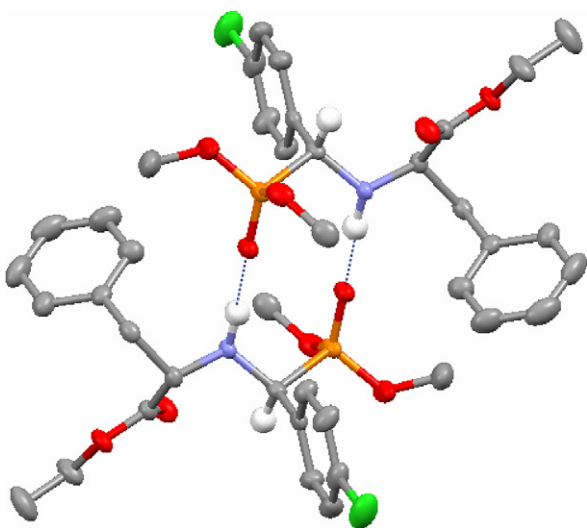
Fig. 2. ORTEP drawing of **1z**.

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–CHCl₃ was used as an eluent for column chromatography of the products in these cases.

Acknowledgement

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References and notes

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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, $\nu_{\max}/\text{cm}^{-1}$ (KBr): 3217, 3016, 1596, 1538, 1443, 1250. ¹H NMR: (CDCl₃, 300 MHz) δ 2.31 (s, 3H, CH₃), 3.55 (d, 3H, ³J_{HP} = 10.5 Hz, OCH₃), 3.81 (d, 3H, ³J_{HP} = 10.8 Hz, OCH₃), 5.58 (d, 1H, ²J_{HP} = 21.9 Hz, CH), 7.02–7.22 (m, 4H, Ar-H), 7.33–7.54 (m, 4H, Ar-H). ¹³C NMR: (CDCl₃, 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 C₁₇H₁₉N₂O₃PS (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, $\nu_{\max}/\text{cm}^{-1}$ (KBr): 3267, 2954, 1738, 1599, 1490, 1454, 1243. ¹H NMR: (CDCl₃, 200 MHz) δ 1.15 (t, 3H, ³J_{HH} = 7.1 Hz, CH₃), 3.62 (d, 3H, ³J_{HP} = 11.5 Hz, OCH₃), 3.75 (d, 3H, ³J_{HP} = 10.5 Hz, OCH₃),

4.10–4.31 (m, 4H, CHCO_2Et , CHPO_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 $\text{C}_{19}\text{H}_{24}\text{NO}_5\text{P}$ (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 ($\text{M}+\text{H}$) $^+$.

(c) Compound **1z**: White, crystalline mp: 65 °C; $[\alpha]_{\text{D}}^{20}$ 0, c 1 in chloroform X-ray crystallographic details: $\text{C}_{20}\text{H}_{25}\text{ClINO}_5\text{P}$, 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, $\alpha = 81.940(5)^\circ$, $\beta = 78.030(5)^\circ$, $\gamma = 67.740(5)^\circ$, $V = 1087.9(9)$ Å 3 , $Z = 2$, $\rho_{\text{calc}} = 1.300$ 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, $\nu_{\text{max}}/\text{cm}^{-1}$ (KBr): 3259, 2959, 1736, 1597, 1492, 1458, 1247. ^1H NMR: (CDCl_3 , 200 MHz) δ 1.20 (t, 3H, $^3J_{\text{HH}} = 7.1$ Hz, CH_3), 2.79 (dd, 1H, $J_{\text{HH}} = 13.5$ Hz, 8.8 Hz, $\text{CH}_a\text{H}_b\text{Ph}$), 2.98 (dd, 1H, $J_{\text{HH}} = 13.5$ Hz, 5.2 Hz, $\text{CH}_a\text{H}_b\text{Ph}$), 3.22 (dd, 1H, $^3J_{\text{HH}} = 8.7$ Hz, 5.3 Hz, CHCO_2Et), 3.61 (d, 3H,

$^3J_{\text{HP}} = 10.5$ Hz, OCH_3), 3.69 (d, 3H, $^3J_{\text{HP}} = 10.6$ Hz, OCH_3), 4.10 (d, 1H, $^2J_{\text{HP}} = 18.2$ Hz, CHPO_3Me_2), 4.13 (q, 2H, $^3J_{\text{HH}} = 7.1$ 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 $\text{C}_{20}\text{H}_{25}\text{ClINO}_5\text{P}$ (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) ($\text{M}+\text{H}$) $^+$.

2nd diastereoisomer: Viscous oil; $[\alpha]_{\text{D}}^{20} -23.54$, c 1 in chloroform; IR, $\nu_{\text{max}}/\text{cm}^{-1}$ (neat): 3259, 2959, 1736, 1597, 1492, 1458, 1247. ^1H NMR: (CDCl_3 , 200 MHz) δ 1.02 (t, 3H, $^3J_{\text{HH}} = 7.1$ Hz, CH_3), 2.87 (m, 2H, CH_2Ph), 3.48 (d, 3H, $^3J_{\text{HP}} = 10.5$ Hz, OCH_3), 3.56 (dd, 1H, $^3J_{\text{HH}} = 5.9$ Hz, 7.8 Hz, CHCO_2Et), 3.60 (d, 3H, $^3J_{\text{HP}} = 10.6$ Hz, OCH_3), 3.87 (q, 2H, $^3J_{\text{HH}} = 7.1$ Hz, CH_2CH_3), 3.88 (d, 1H, $^2J_{\text{HP}} = 19.7$ Hz, CHPO_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 $\text{C}_{20}\text{H}_{25}\text{ClINO}_5\text{P}$ (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) ($\text{M}+\text{H}$) $^+$.