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Stereoselective Synthesis of α-Amino(phenyl)methyl(phenyl)phosphinic Acids with *O*-Pivaloylated D-Galactosylamine as Chiral Auxiliary

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Dedicated to Professor Ruyu Chen on the occasion of her 90th birthday

α-Aminophosphonic and -phosphinic acids are the phosphorus analogues of α-aminocarboxylic acids, and therefore have biological importance both in themselves and as building blocks for peptides.[1] Many natural and synthetic aminophosphonic acids exhibit a variety of biological properties including enzyme inhibitors, such as synthase,[2] HIV protease,[3] renin,[4] phosphatase activity,[5] PTPases,[6] and potent antibiotics.[7] The configuration at the α-carbon atom in the α-aminophosphinic acids plays a decisive role in the biological properties of these types of compound.[8] Numerous optically active aminoalkylphosphonic acids have already been obtained from natural resources and by synthesis. Typical examples include the addition of dialkyl phosphite or its lithium salt to an imine bearing a chiral auxiliary, with or without Lewis acid catalysis, respectively.[9]

Carbohydrates are valuable as enantiomerically pure starting materials in chiral pool syntheses of many chiral natural products and drugs.[10] The polyfunctionality of carbohydrates is useful for binding or coordinating a substrate. Carbohydrate derivatives are efficient auxiliaries for stereodifferentiation in many stereoselective chiral syntheses.[11–12] A notable example is the paper by Kunz, in which the use of carbohydrates as chiral templates to promote Mannich-type reaction and the stereoselective synthesis of α-aminophosphonic acid derivatives is reported.[13] The nucleophilic addition of a dialkyl or diaryl phosphite to imines or oxoiminium derivatives, the Pudovik reaction,[14] is one of the most convenient methods for the preparation of α-aminophosphonates, key intermediates in the synthesis of α-aminophosphonic acids. Chiral auxiliaries proved to be good to excellent in inducing asymmetry on the imine carbon atom resulting in enantiopure α-aminophosphinates. Lewis acid catalysts are required for induction of the enantioselectivity in the phosphorylation reaction.[15] Recently, we reported that β-*N*-glycoside-linked α-aminophosphonic acids derivatives can be synthesized diastereoselectively by the Lewis acid induced addition of diethyl phosphite to Schiff bases of 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosylamine (**1**).[16] We here report on an asymmetric synthesis of α-amino(phenyl)methyl(phenyl)phosphinic acids in which *O*-pivaloylated glycosylamines serve as the stereodifferentiating auxiliaries.

The synthesis of β-*N*-glycoside-linked α-aminophosphonates started with the condensation of amine **1** and arylaldehyde **2**. The formation of the corresponding *N*-galactosylaldimines **3**[17] proceeded smoothly at room temperature under dehydrating conditions. Higher temperatures and longer reaction times led preferentially to the formation of the undesired conjugated enamines. Under these conditions, the Schiff bases **3** of aromatic aldehydes are obtained in crystalline form. The amount of the corresponding α-anomer can be restricted to less than 4%, and imines **3** of aliphatic aldehydes cannot be isolated in a crystalline form by this method. The imines **3** and equivalent amounts of ethyl phenylphosphinate (**4**) were kept at room temperature in THF and the reaction was run until the imine was consumed to furnish the eight diastereomeric *N*-galactosylarylphosphonoglycine esters **5** in high yield. The mixture **5** was treated with 1M hydrogen chloride in methanol at room temperature giving the easily separable carbohydrate template **6** and the α-aminobenzylphosphonate hydrochloride **7** in quantitative yield. Under these conditions, the amount of deglycosylation was minimized, and no loss of anomeric purity was observed (Scheme 1).[18]

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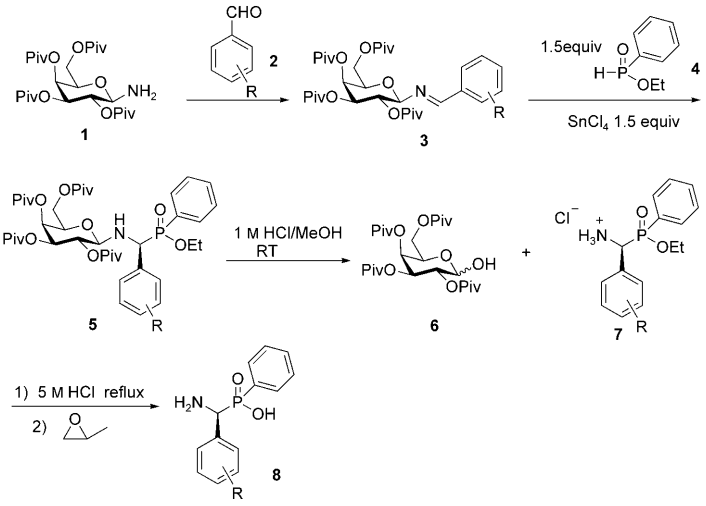


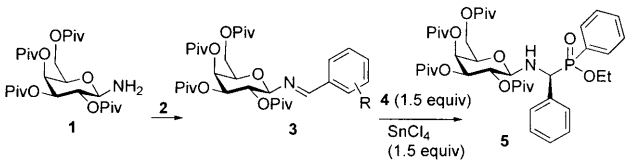
Scheme 1. Synthesis of (*S*)-α-amino(phenyl)methyl(phenyl)phosphinic acids **8**.

We initially investigated the reaction of *O*-pivaloylated *N*-galactosylimine **3a** (R = C_6H_5) with ethyl phenylphosphinate (**4**) in THF without the aid of Lewis acid; no product **5a** was detected. Since the nucleophilicity of ethyl phenylphosphinate **4** is low and the electrophilicity of imines is only moderate, the reaction between these compounds requires activation by a Lewis acid to proceed. In this sense, various Lewis acids were tested in the reaction of the *N*-galactosylimine **3a** with **4** in THF. The results revealed that $AlCl_3$, $SnCl_4$, and $BF_3{\cdot}OEt_2$ were able to promote the addition (Table 1, entries 5–11). Other Lewis acids tested (e.g., $ZnCl_2$, CuBr, CuI) only caused anomerization of the Schiff base **3a**, and no product of **5a** was observed (Table 1, entries 2–4). In addition, the reaction does not work in the absence of Lewis acid if $CHCl_3$ or toluene is used as solvent (Table 1, entries 16 and 17). Since $SnCl_4$ gave the higher diastereoselectivity (d.r. >91%) compared with $BF_3{\cdot}OEt_2$ (d.r. >88%), it was used in further investigations.[13] The ratio of diastereomers **5** was determined by ^{31}P NMR analysis.

To determine the optimal conditions, imine **3a** was reacted with one equivalent of phosphinate **4** in the presence of different concentrations of $SnCl_4$ in THF at 0°C for 1 h, followed by warming to room temperature. An increase in the concentration of Lewis acid (1.5 equiv) resulted in a higher yield of **5a** and a slight increase of the diastereoselectivity. A further increase of the concentration (2 equiv) had no significant effect on the yield or the selectivity. To further demonstrate the scope and flexibility of the present optimized conditions, a wide range of different aromatic aldehydes were then successfully examined with this methodology (Table 2). As expected, a number of *N*-galactosyl α-aminoalkylphosphonates **5a**–**g** were prepared in a Mannich-type reaction. The reaction was conducted in THF at room temperature under mild conditions, in the presence of 1.5 equivalents of $SnCl_4$, and the products **5** were obtained in high yields. Based on these experiments, it was found that the rates of the reaction of the electron-poor aromatic aldehydes were nearly the same as those of the electron-rich aromatic aldehydes. Further more, the reaction of Schiff base **3** of aliphatic aldehydes with ethyl phenylphosphinate **4** under identical conditions did not lead to H-phosphinate addition. Even at low temperature (−78°C), only anomerization and decomposition occurred.

The ratio of the obtained diastereomers **5** was determined by ^{31}P NMR from the crude mixture of the reaction. It should be noted that because of the anomeric carbon and one stereogenic center created at the α-position of the phos-

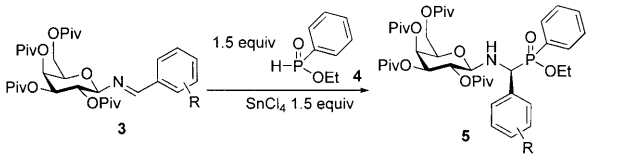
Table 1. Survey of the conditions for the formation of **5a** according to Scheme 1.[a]



	Lewis acid (equiv)	Solvent	*t* [d]	Yields [%][b]	d.r. [%][d]
1	–	THF	3	n.r.[c]	–
2	$ZnCl_2$	THF	3	n.r.	–
3	CuBr (1)	THF	2	n.r.	–
4	CuI (1)	THF	2	n.r.	–
5	$AlCl_3$ (1)	THF	2	49	>73
6	$SnCl_4$ (1)	THF	2.5	89	>85
7	$SnCl_4$ (1.5)	THF	2.5	92	>91
8	$SnCl_4$ (2)	THF	2.5	88	>86
9	$BF_3{\cdot}Et_2O$ (1)	THF	1	80	>87
10	$BF_3{\cdot}Et_2O$ (1.5)	THF	1	83	>88
11	$BF_3{\cdot}Et_2O$ (1.5)	CH_2Cl_2	1	60	>80
12	$SnCl_4$ (1.5)	CH_2Cl_2	3	33	>87
13	$SnCl_4$ (1.5)	$CHCl_3$	3	35	>91
14	$SnCl_4$ (1.5)	$PhCH_3$	3	38	>90
15	–	CH_2Cl_2	3	n.r.	—
16	–	$CHCl_3$	3	n.r.	—
17	–	$PhCH_3$	3	n.r.	—

[a] Unless otherwise noted all the reactions were performed with 3 (0.5 mmol) and diethyl phosphite (0.75 mmol) in solvent (5 mL) at room temperature. [b] Determined from the crude product by ^{31}P NMR spectroscopy. [c] No reaction. [d] Reference [12c].

Table 2. The Mannich-type reaction of imines **5a**–**g** at room temperature.

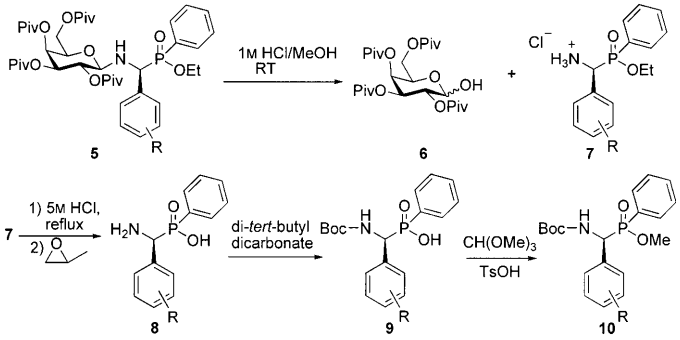


	5	R	*t* [h]	Yield [%][a]	d.r. [%][b]
1	**5a**	H	2	91	>73
2	**5b**	*p*-Br	2	86	>82
3	**5c**	*p*-F	2	92	>76
4	**5d**	*p*-Cl	2.5	84	>86
5	**5e**	*p*-NO_2	3	79	>88
6	**5f**	*p*-OCH_3	2	82	>74
7	**5g**	*p*-CH_3	2	95	>81

[a] After purification by chromatography and recrystallization. [b] Diastereomeric ratio determined from the crude product by ^{31}P NMR spectroscopy.

phonate, the eight diastereomers are β-*S*,*S*, β-*R*,*S*, α-*S*,*S*, α-*R*,*S*, β-*S*,*R*, β-*R*,*R*, α-*S*,*R*, and α-*R*,*R*. Diastereomerically pure compounds **5a–d** and **5f** were obtained by simple recrystallization from *n*-hexane and ethyl ether. In order to assign the configuration of the *N*-galactosyl α-aminoalkylphosphonate **5**, α-aminophosphinate hydrochloride **7** is released from **5** with 1 M HCl in methanol. The diastereomers **7** can be hydrolyzed by using concentrated hydrochloric acid under reflux (Table 3) and the product crystallized spontaneously from propylene oxide to give the α-aminophosphinic acids **8** with (−)-optical rotations (*S*).[19] The deprotection reactions occurred without racemization of the α-carbon atom.[20] Boc-α-aminophosphinic acids **9** can be easily obtained by the reaction of α-amino(phenyl)methyl-(phenyl)phosphinic acids **8** with *di*-tert-butyl dicarbonate in dichloromethane at low temperature. Treatment of compound **9** with trimethyl orthoformate in CH_2Cl_2, gave the *N*-Boc ethylphenyl(benzyl)phosphinate derivatives **10**, which were used for enantioselectivity determination by chiral HPLC.

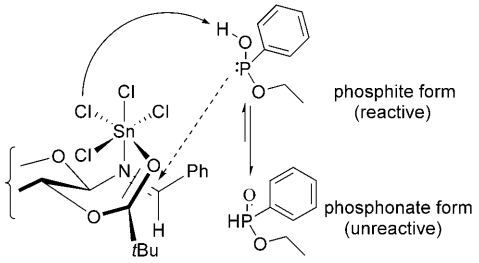
Table 3. Asymmetric Mannich synthesis of α-amino(phenyl)methyl (phenyl)phosphinic acids **8**.[a]



	R	7	*t* [d]	Yield [%][a]	8	*t* [h]	Yield [%][a]	*ee* [%][b]
1	H	**7a**	2	87	**8a**	3	88	84
2	*p*-Br	**7b**	2	90	**8b**	3	87	78
3	*p*-F	**7c**	2	93	**8c**	3	82	90
4	*p*-Cl	**7d**	2	78	**8d**	3	90	94
5	*p*-NO_2	**7e**	2	87	**8e**	3	93	73
6	*p*-OCH_3	**7f**	2	95	**8f**	3	90	88
7	*p*-CH_3	**7g**	2	85	**8g**	3	91	97

[a] Isolated yield. [b] Determined by chiral HPLC analysis.

The proposed mechanism of this catalytic asymmetric hydrophosphonylation is shown in Scheme 2.[21] The preferred formation of the *S*-configured diastereomer of **5** can be rationalized by an attack of ethyl phenylphosphinate from *Si* side of (*E*)-imines **3**. In the transition state, the tin should have octahedral coordination. Two coordination sites of the tin(IV) chloride are occupied by the imine nitrogen and the carbonyl oxygen atoms of the (C-2) pivaloyloxy group. The imine·$SnCl_4$ complex maintains the H-eclipsed conformation, because chelation by the auxiliary's pivaloyl group inhibits rotation along the N−C* bond. Probably, the nonbonding interaction Ph/Cl is relieved by ionic dissociation of the equatorial Sn−Cl bond (*anti* to O), and they would also lead to a more reactive anionic nucleophile. According to this rationalization, the S_N2'-type attack of phosphinate **4** from the back side of the imine is initiated. Based on the results, the OH moiety of the phosphinate **4** is suggested to play an important role in determining the high enantioselectivity, since the required tautomeric equilibrium between the P^V phosphinic and the P^{III} phosphonous forms is still available. The mechanism indicates that the Piv4Gala group plays a significant role in controlling the regio and diastereoselective of ethyl phenylphosphinate to *N*-galactosylimines **3**.



Scheme 2. Plausible reaction mechanism.

In conclusion, we have described a convenient and efficient synthetic protocol for preparation of α-aminophosphinic acid derivatives in high yields and high enantiostereoselectivity, utilizing $SnCl_4$ as the promoter and *O*-pivaloylated D-galactosylamine **1** as chiral auxiliary by means of Mannich-type reactions. The *O*-pivaloylated galactosylamine **1** is an effective chiral template in the synthesis of chiral *N*-galactosyl α-aminoalkylphosphonate **5**. $SnCl_4$ can form the octahedral-coordination intermediate induces the *S* configuration at the Cα center by attack at the *Si* side of the C=N plane of the imine carbon atom. α-Amino(phenyl)methyl (phenyl)phosphinic acids **8** can be detached easily from the carbohydrate template, which can be recollected.

Experimental Section

General procedure for the preparation of *O*-pivaloyiated *N*-galactosylimines 3: To a solution of amine **1** (0.515 g, 1 mmol) and aldehyde **2** (1.3 mmol) in 2-propanol (2.5 mL), 2–3 drops of acetic acid were added and the mixture was stirred at room temperature for about 0.5 h. The appearance of a precipitate from the solution indicated the formation of **3**, after which the precipitate was filtered off, then washed with ice cold 2-propanol and dried in vacuum, *N*-galactosylaldimines **3** were isolated as a colorless solids.

General procedure for the synthesis of *β*-*N*-glycosidic linkages in *α*-aminophosphonic acid derivatives 5: A solution of *N*-galactosylaldimines **3** (0.5 mmol) in THF (5 mL) was cooled to 0 °C, and phosphinate **4** (0.128 g, 0.75 mmol) and $SnCl_4$ (0.087 mL, 0.75 mmol) were added. The mixture was stirred for 2 d at room temperature. The mixture was hydrolyzed with 2 M aqueous NaOH (35 mL) and the mixture was stirred at room temperature for 5 min. The aqueous phase was extracted with $CHCl_3$ (3×25 mL), and the organic layers were dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo to yield the crude products **5**, which were purified by flash column chromatography on silica gel [petroleum ether/ethyl acetate, 2:1(V V)$^{-1}$] to provide pure products **5**.

General procedure for the synthesis of ethyl α-amino(phenyl)methyl-(phenyl)phosphinate hydrochlorides 7: A solution of compound **5** (0.41 mmol) in dry methanol (5 mL) was treated with freshly prepared (1 M) solution of HCl (0.62 mL). The solution was stirred for 2 d (TLC control). Then methanol was evaporated in vacuo and the remaining residue dissolved in 0.5 M HCl (10 mL) and extracted with pentane (3× 10 mL). The aqueous solution was evaporated to dryness and gave **7** as colorless crystals in quantitative yield. From the pentane solution, after drying ($MgSO_4$) and evaporation of the solvent, the *O*-pivaloylated galactopyranose **6** was isolated as colorless crystals in quantitative yield.

General procedure for the synthesis of α-amino(phenyl)methyl-(phenyl)phosphinic acids 8: Hydrochloric acid (1.5 M, 4 mL) was added to compound **7**, and the resultant solution was heated with stirring under reflux for 3 h. The solvent was then evaporated under vacuum to lead to the α-aminophosphinic acid as a white solid. This material was dissolved in refluxing ethanol and treated with propylene oxide at 70–80 °C to precipitate phosphinic acids acid **8** as a white crystalline powders. The product was filtered off, washed with diisopropyl ether, and thoroughly dried at 50 °C under reduced pressure and in the presence of a dehydrating agent (P_2O_5).

General procedure for the synthesis of *N*-boc ethylphenyl-(benzyl)phosphinate derivative 10 for % *ee* determination by chiral HPLC: Triethylamine (0.18 mL, 0.0013 mmol) was added to an ice-cold suspension of **8** (1 mmol) in dichloromethane (2.2 mL). Next, di-*tert*-butyl dicarbonate (0.3 g, 0.0014 mol) in dichloromethane (0.11 mL) was added over 10 min, and the mixture was stirred at 0 °C for overnight. The reaction was discontinued by addition of saturated aqueous citric acid (0.55 mL), and the organic phase was washed with brine (2×0.55 mL) and water (0.55 mL). Removal (in vacuo) of solvent yielded a crude product **9**. Then trialkyl orthoformate (5 mL) was added to the crude product **9** and the resulting mixtures were stirred at 100–110 °C for 2 h, after which time the reaction mixtures were concentrated, then dissolved in CH_2Cl_2 and washed with water, the solution was evaporated to dryness to give the crude products **10**, which were purified by flash chromatography [CH_2Cl_2/MeOH, 50 L (v/v)].

Acknowledgements

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Keywords: aminophosphonic acids · carbohydrates · chiral auxiliaries · Mannich-type reactions · phosphorus

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