Enantioselective Synthesis of α-Aminophosphonates via Organocatalytic Sulfenylation and [2,3]-Sigmatropic Sulfimide Rearrangement

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Received 25 July 2011

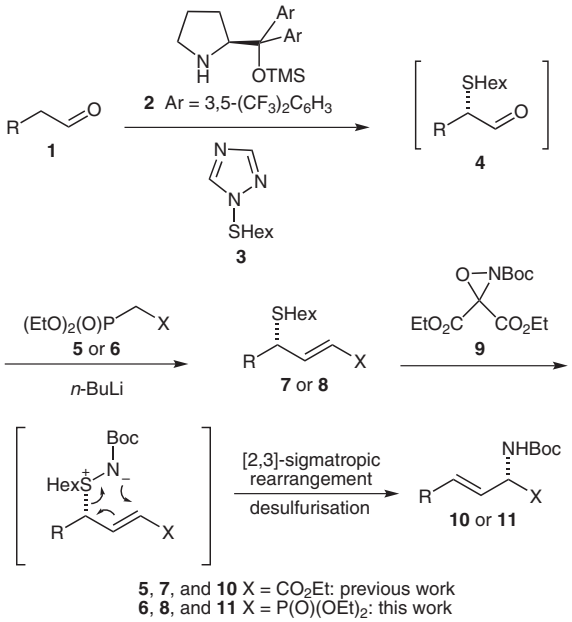
Abstract: β,γ-Unsaturated-α-aminophosphonates are prepared in enantiomerically enriched form via organocatalytic aldehyde α-sulfenylation/olefination followed by oxaziridine-mediated sulfimidation and sulfimide [2,3]-sigmatropic rearrangement. Subsequent N-deprotection and amino acid coupling are also accomplished.

Key words: asymmetric catalysis, amination, rearrangement, organocatalysis, oxaziridine

α-Amino phosphonates have emerged as important molecular targets, due to their bioactivity against protease enzymes which relies on their ability to mimic the tetrahedral transition state of amino acids undergoing hydrolysis. This has led to the application of amino phosphonate derivatives as antibacterial[1] and antifungal agents.[2,3] Syntheses of these compounds[4] are dominated by transition-metal-based catalytic hydrogenation[5] and hydrophosphonylation[6–8] reactions. There are also examples of asymmetric organocatalytic hydrophosphonylation reactions, for instance, Jacobsen's[9] thiourea-catalysed hydrophosphonylation of aldimines and Toru's[10] cinchona alkaloid hydrophosphonylation of a variety of aryl-substituted aldimines. However, there remain a few biologically relevant amino phosphonates that are not available through current methodologies. β,γ-Unsaturated amino phosphonates are one such class whose asymmetric synthesis is limited to a few examples.[11,12] To the best of our knowledge there is no general methodology to access these phosphonates asymmetrically from a broad range of substrates.

Jørgensen and co-workers[13,14] have developed a synthetically useful, organocatalytic α-sulfenylation of aldehydes. Marrying this chemistry with work from this group on amination of sulfur using the oxaziridine **9**[15] led to the strategy of organocatalytic sulfenylation, in situ olefination, and [2,3]-sigmatropic sulfimide rearrangement (Scheme 1) to access a range of vinyl glycines **10** (X = CO_2Et) in good yield and high enantioselectivity.[16,17] Exchanging the phosphonoacetate **5** (X = CO_2Et) for a diphosphonate **6** [X = P(O)$(OEt)_2$] (Scheme 1) was envisaged to give the analogous amino phosphonates **11** [X = P(O)$(OEt)_2$]. In this paper we report the successful realisation of this strategy.

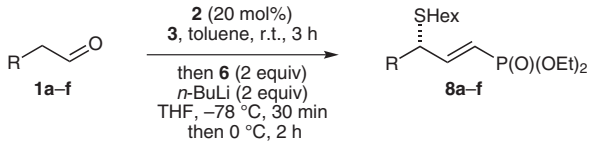
Initially, we applied our previously successful[17a] one-pot sulfenylation–olefination conditions to the phosphonate synthesis. However, the target **8a** [R = Et, X = P(O)$(OEt)_2$] was obtained only in trace yields (<5%). The olefination step was therefore examined in detail starting from isolated samples of the aldehyde rac-**4a** (R = Et). Extensive screening of solvent, temperature, reaction time, and reagent excess gave only modest results. However, application of a method reported by Belakhov et al.[18] which used substoichiometric amounts of *n*-butyllithium and reverse addition (aldehyde added to anion) gave the target phosphonate in 47% yield. Increasing the amount of *n*-butyllithium to a full equivalent provided the target in 87% yield. Utilising these olefinating conditions in the one-pot sulfenylation–olefination procedure, in the first instance, gave again a low yield of 27%, but using 2 equivalents of diphosphonate **6** and 2 equivalents of *n*-butyllithium gave the target in good yield (88%) and ee (87%). With a successful one-pot sulfenylation and olefination in hand the scope was tested with a diverse range of aldehydes bearing alkyl, alkenyl, aromatic, and protect-



Scheme 1

SYNLETT 2011, No. 16, pp 2347–2350
Advanced online publication: 13.09.2011
DOI: 10.1055/s-0030-1260309; Art ID: D23911ST

Table 1 One-Pot Sulfenylation–Olefination with a Diverse Range of Aldehydes



Entry	1	R	Yield of 8 (%)[a]	ee (%)[b]
1	**1a**	Et	**8a** 88	87
2	**1b**	Me	**8b** 79	78
3	**1c**	*i*-Pr	**8c** 73	84
4	**1d**	Bn	**8d** 68	84
5[c]	**1e**	All	**8e** 72	82
6	**1f**	$(CH_2)_2OTBS$	**8f** 65	82

[a] Isolated yield of *E* isomer after flash chromatography.
[b] Determined by HPLC on chiral stationary phase.
[c] Sulfenylation required 24 h.

ed alcohol functional groups (Table 1). In all cases, very high *E*-selectivity was observed (>95:5).

With a successful route to enantiomerically enriched sulfides **8** in hand our attention turned towards the amination at sulfur. While no direct precedent existed, it was hoped that this would lead, in line with the ester series, to a spontaneous [2,3]-sigmatropic rearrangement to furnish the amino phosphonate **11** (Scheme 1). Interestingly, in contrast to the high levels of chemoselectivity in the earlier work,[15a,16,17a] initial results showed significant levels of oxygen transfer from the oxaziridine **9** to sulfide **8a**, giving rise to the unwanted sulfoxide side product **12**. To optimise this process in favour of amination, variation of solvent, temperature, concentration, and reaction time were investigated (Table 2). Desulfurisation with triethyl phosphite was carried out in the same reaction pot to aid ^{1}H NMR analysis of the crude reaction mixture.

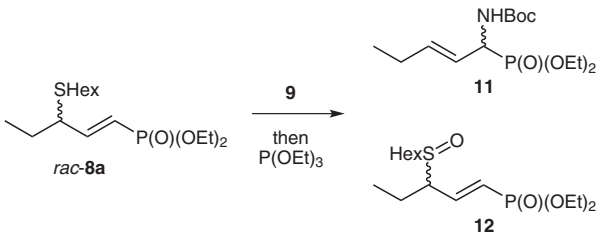
In the first instance the reactions were carried out in a range of solvents at both room temperature and at reduced temperature (Table 2, entries 1–10). In all cases higher temperature gave better conversion but poorer chemoselectivity, as we have noted previously.[15c] This relationship was further studied by investigating a range of temperatures with dichloromethane (Table 2, entries 3, 4, 11, and 12). Dichloromethane at –78 °C gave the best selectivity; increasing the temperature to –40 °C caused a significant decrease in chemoselectivity. Increased concentration (Table 2, entry 13) and reaction time (Table 2, entry 14) were both found to improve conversion without having an adverse effect on selectivity.

In further, preparative experiments, desulfurisation was effected using triphenylphosphine instead of triethylphosphite to aid product purification. The sulfide *rac*-**8a** was again submitted to the optimal amination conditions of entry 14 (Table 2) using the new desulfurisation conditions to afford **11a** in 56% isolated yield. Further increasing the concentration to 0.5 M and using 1.2 equivalents of oxaziridine **9** gave the target in 63% yield. These optimised conditions were then applied to the enantiomerically enriched sulfides **8a–f** (Table 3).

The majority of the examples gave good yields. High *E* selectivity was observed (*Z* isomer not seen by ^{1}H NMR) and there was only minor loss of enantiomeric excess in the rearrangement process. The product configuration is assumed based on the expectation of a suprafacial concerted [2,3]-sigmatropic rearrangement, as in the ester series.[16,17] Two of the substrates gave low yields (Table 3, entries 2 and 5). In the case of R = Me, we were able to isolate side products **15** (30%) and **16** (30%), both presumably originating from the sulfonium ion **14**, which could be formed via elimination from the intermediate sulfimide **13** (Scheme 2).

While the products **11** were obtained in reasonable ee, we wished to improve their enantiomeric purity further. Additionally, we aimed to demonstrate that these motifs could be incorporated into peptide mimetics. Therefore, two of the amino phosphonates (**11a** and **11c**) were depro-

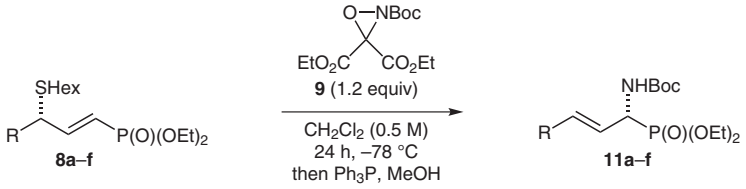
Table 2 Synthesis of Amino Phosphonate **11** and Sulfoxide Side Product **12**



Entry	Solvent	Temp (°C)	Concn (M)	Time (h)	11/12[a]	Conv. (%)[a]
1	MeCN	25	0.1	3	55:45	99
2	MeCN	–40	0.1	3	69:31	91
3	CH_2Cl_2	25	0.1	3	39:61	95
4	CH_2Cl_2	–78	0.1	3	86:14	44
5	PhMe	25	0.1	3	34:66	84
6	PhMe	–78	0.1	3	71:29	19
7	MeOH	25	0.1	3	40:60	81
8	MeOH	–78	0.1	3	0:100	33
9	THF	25	0.1	3	50:50	84
10	THF	–78	0.1	3	71:29	15
11	CH_2Cl_2	0	0.1	3	47:53	77
12	CH_2Cl_2	–40	0.1	3	59:41	44
13	CH_2Cl_2	–78	0.3	3	86:14	55
14	CH_2Cl_2	–78	0.3	24	87:13	80

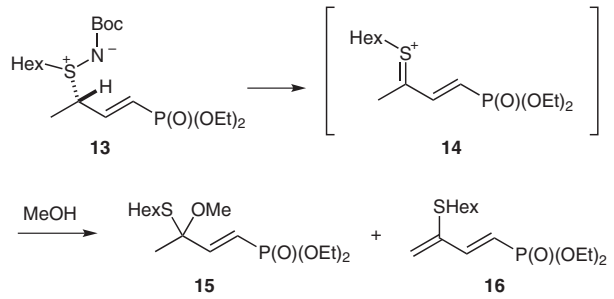
[a] Estimated by ^{1}H NMR integration.

Table 3 Synthesis of Amino Phosphonates **11** under Optimized Conditions

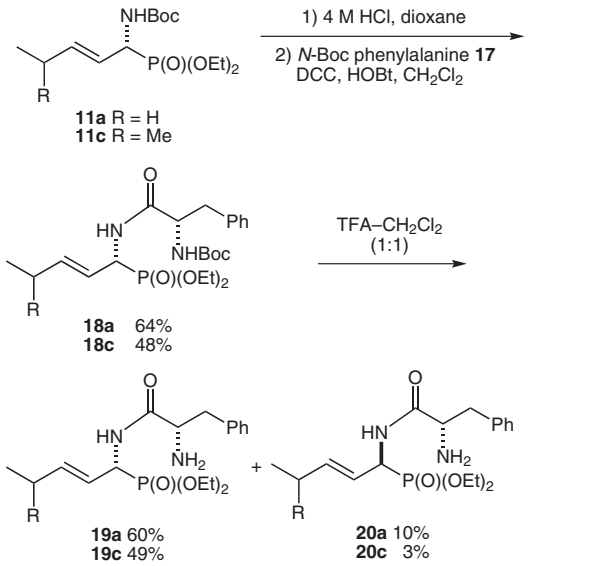


Entry	8	R	ee of **8** (%)	Yield of **11** (%)[a]	ee of **11** (%)[b]
1	**8a**[20]	Et	**8a** 87	**11a**[21] 64	85
2	**8b**	Me	**8b** 79	**11b** 38	79
3	**8c**	*i*-Pr	**8c** 81	**11c** 68	75
4	**8d**	Bn	**8d** 84	**11d** 69	79
5	**8e**	All	**8e** 82	**11e** 35	79
6	**8f**	$(CH_2)_2OTBS$	**8f** 83	**11f** 75	76[c]

[a] Isolated yield after flash chromatography.
[b] Deduced by formation of Mosher's amides[19] and inspection of ^{19}F and ^{1}H NMR.
[c] The silyl protecting group was removed during the formation of this Mosher's amide.



Scheme 2



Scheme 3

tected with HCl in dioxane and coupled with *N*-Boc-phenylalanine using DCC and HOBt to give the corresponding dipeptides **18** in good yield over the two steps. Boc deprotection was then effected with TFA (Scheme 3). Importantly, in both cases the peptide diastereomers **19** and **20** were readily separable by column chromatography, providing an effective means for removing the minor aminophosphonate diastereoisomer.

In conclusion, we have developed a concise route to enantiomerically enriched β,γ-unsaturated α-amino phosphonates by coupling an organocatalytic sulfenylation and olefination procedure to a stereoselective [2,3]-sigmatropic rearrangement. This methodology has provided rapid access to biologically relevant amino acid mimetics. These products have also been shown to undergo coupling to amino acids which also allows purification to afford a single diastereomer. This strategy, in principle, will also furnish alternative amino acid mimetics by varying the coupling partner in the olefination step. Efforts in this area are currently ongoing in this laboratory as well as further investigation into manipulation of the phosphonopeptide products.

Acknowledgment

We gratefully acknowledge AstraZeneca and the EPSRC for funding and L. Challinor for preliminary results.

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(20) **Typical Procedure for One-Pot Sulfenylation–Olefination**
Hexane sulfanyl triazole **3**[17] (480 mg, 2.6 mmol) was added to a solution of aldehyde (2.0 mmol) and catalyst **2** (238 mg, 0.4 mmol) in toluene (1.34 mL). The reaction was allowed to stir for 3 h before addition of THF (7 mL). The mixture was then added dropwise to a prepared solution of tetraethyl methylenediphosphonate (1 mL, 4 mmol) and *n*-BuLi (1.8 mL, 2.22 M, 4 mmol) in THF (7 mL) at –78 °C. After 30 min the reaction was allowed to warm to 0 °C. The reaction was stirred until completion (approx. 1 h). The reaction was taken up in EtOAc (70 mL) and washed with $NaHCO_3$ (sat.), H_2O, and NaCl (sat.) The organics were dried with $MgSO_4$ and concentrated in vacuo. The crude was purified on silica eluting with EtOAc–PE (1:1).
Typical Data for Compound 8a
Colourless oil (0.566 g, 88%). IR (film): ν_{max} = 2962 (s), 2924 (s), 2839 (m), 1624 (m), 1460 (m), 1390 (m), 1248 (s), 1166 (m), 1100 (m), 1054 (s), 1028 (s), 962 (s), 856 (m), 823 (m), 791 (m), 750 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.51 (1 H, ddd, *J* = 20.7, 16.9, 9.2 Hz, SCHC*H*CHP), 5.60 (1 H, dd, *J* = 20.0, 17.2 Hz, SCHCHC*H*P), 4.14–4.05 (4 H, m, $POCH_2CH_3$), 3.17 (1 H, td, *J* = 7.7, 9.2 Hz, SCH), 2.43–2.37 (2 H, m, $SCHCH_2$), 1.73–1.59 (2 H, m, SCH_2), 1.60–1.47 (2 H, m, SCH_2CH_2), 1.34 (6 H, t, *J* = 7.1 Hz, $POCH_2CH_3$), 1.35–1.22 [4 H, m, $S(CH_2)_2CH_2CH_2$], 1.00 (3 H, t, *J* = 7.4 Hz, $SCHCH_2CH_3$), 0.89 [3 H, t, *J* = 7.0 Hz, $S(CH_2)_5CH_3$] ppm. ^{31}P NMR (162 MHz, $CDCl_3$): δ = 17.801 (s)ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.3 (d, *J* = 4.5 Hz) 116.2 (d, *J* = 186.5 Hz), 61.7 (d, *J* = 5.5 Hz), 50.0 (d, *J* = 23.5 Hz), 31.4, 30.6, 29.3, 28.6, 26.7, 22.5, 16.4, 14.0. 11.8. MS (CI): *m/z* = 323 [MH^+], 340 [MNH_4^+]. HRMS: *m/z* calcd for $C_{15}H_{32}O_3SP$: 323.1810, Δ = 1.2 ppm; found: 323.1806 [MH^+]. The enantiomers were separated by HPLC over an AD-H column eluting with 2% 2-PrOH in hexane [t_R = 15 min(major) and 18 min(minor)]; a sample of 87% ee gave $[\alpha]^{24}_D$ –40 (*c* 1, $CHCl_3$).
(21) **Typical Procedure for Amination–Rearrangement–Desulfurisation**
The starting phosphonate (0.62 mmol) in CH_2Cl_2 (0.6 mL) was added to oxaziridine **9** (216 mg, 0.74 mmol) in CH_2Cl_2 (0.6 mL) dropwise at –78 °C. The reaction was stirred for 24 h. To this was added Ph_3P (210 mg, 0.81 mmol) and MeOH (0.1 mL); the reaction was stirred for a further 30 min before being allowed to warm to r.t. The reaction was then concentrated in vacuo. The crude was purified on silica eluting with EtOAc–PE (1:1).
Typical Data for Compound 11a
Clear and colourless oil (127 mg, 64%). IR (film): ν_{max} = 3436 (w), 3156 (w), 2982 (w), 2933 (w), 2361 (w), 2253 (w), 1712 (w), 1496 (w), 1373 (w), 1247 (w), 1166 (w), 1031 (w), 969 (w), 909 (s), 735 (s), 650 (m), 546 (w) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.81 (1 H, m, PCHCHC*H*), 5.51 (1 H, m, PCHC*H*), 4.94 (1 H, br, NH), 4.62 (1 H, br, PCH), 4.19–4.10 [4 H, m, $P(OCH_2CH_3)_2$], 2.15–2.05 (2 H, m, $PCHCHCHCH_2$), 1.47 [9 H, s, $C(CH_3)_3$], 1.33 [6 H, dt, *J* = 1.7, 7.1 Hz, $P(OCH_2CH_3)_2$], 1.01 (3 H, t, *J* = 7.4 Hz, $PCHCHCHCH_2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.8 (d, *J* = 11.6 Hz, CH), 121.5 (CH), 80.2 (CCH_3), 62.9 (d, *J* = 6.7 Hz, CH_2), 62.7 (d, *J* = 6.6 Hz, CH_2), 50.2 (CH), 48.6 (CH), 28.3 (CH_3), 25.4 (CH_2), 16.4 (t, *J* = 7.0 Hz, CH_3), 13.2 (CH_3). MS (CI): *m/z* = 322 [MH^+] 339 [MNH_4^+]. HRMS: *m/z* calcd for $C_{14}H_{29}NO_5P$: 322.1783, Δ = 2.2 ppm; found: 322.1790 [MH^+]; a sample of 85% ee gave $[\alpha]^{24}_D$ –9 (*c* 1, $CHCl_3$).