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Asymmetric Synthesis of Quaternary α-Amino Phosphonates Using Sulfinimines

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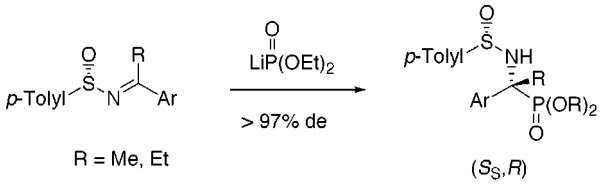
ABSTRACT



The addition of lithium diethylphosphonate to enantiopure ketosulfinimines is highly diastereoselective (>95%), affording the first examples of quaternary α-alkyl α-amino (arylmethyl)phosphonates.

Notwithstanding the fact that the phosphonic and carboxylic acid groups differ substantially with respect to shape, size, and acidity, α-amino phosphonic acids are important structural analogues of α-amino acids.[1] As a consequence they have found widespread use as surrogates for α-amino acids,[1,2] enzyme inhibitors,[3−5] haptens for catalytic antibodies,[6] antibacterial agents,[7,8] anti-HIV agents,[9] and botryticides.[10] The increased importance of unnatural α-amino acids in the modification of peptides to improve bioactivity and stability and their utility in peptide therapeutics make the asymmetric synthesis of α-amino phosphonic acids a significant objective. Although a number of procedures have been described,[11] there are few reports of the asymmetric synthesis of quaternary derivatives. Studer and Seebach reported the synthesis of several 1,2-diaminoalkane-2-phosphonic acids via the alkylation of an enantiopure imidazolidine phosphonate ester,[12] and we prepared (*S*)-(−)-α-methylphosphophenylalanine by a regiocontrolled ring opening of a sulfinimine (*N*-sulfinyl imine)-derived aziridine-2-phosphonate.[13] A rhodium-catalyzed enantioselective Michael addition to vinyl ketones gives a phosphorus-substitute quaternary carbon, which in a series of reactions furnishes α-alkyl α-amino alkylphosphonates.[14] The asymmetric alkylation of α-acetamido *β*-keto phosphonates has recently been described.[15]

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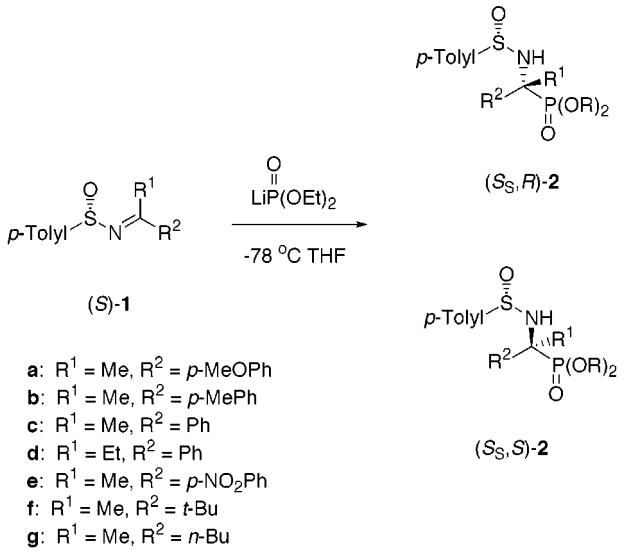
Table 1. Addition of Lithium Diethyl Phosphite to Ketosulfinimines (*S*)-**1**

entry	ketosulfinimine	(*E*:*Z*)[a]	α-amino (S_S,*R*):(S_S,*S*)[b]	phosphonates (**2**) % de	phosphonates (**2**) yield[c] (%)	^{31}P (δ)	$[\alpha]^{20}_D$ ($CHCl_3$)
1	(+)-**1a** Me, *p*-MeOPh	>99:1	99:1	>95	73	22.95	−14.6
2	(+)-**1b** Me, *p*-MePh	>99:1	99:1	>95	91	22.91	−5.8
3	(+)-**1c** Me, Ph	>99:1	99:1	>95	92	22.66	+5.6
4	(+)-**1d** Et, Ph	>99:1	99:1	>95	93	22.55	−2.9
5	(+)-**1e** Me, *p*-NO_2Ph	>99:1	99:1	>95	93	21.36	−45.7
6	+)-**1f** Me, *t*-Bu	>99:1	99:1	>95	97	26.53	+139.0
7	(+)-**1g** Me, *n*-Bu	3:1	82:18	64	71	22.6	+70.3

[a] *E*:*Z* ratio of the ketosulfinimines. [b] From the ^{1}H and ^{31}P of the crude reaction mixture. [c] Yield of major diastereoisomer

Herein we disclose the first asymmetric synthesis of α-alkyl α-amino(arylmethyl)phosphonate derivatives from enantiopure ketosulfinimines **1**.[16] The analogous quaternary α-amino acids are of considerable value because incorporation into peptides has been found to increase rigidity and resistance to protease enzymes and enhance bioactivity.[17] Our process involves the stereoselective addition of 2 equiv of lithium diethyl phosphite, prepared in situ by treatment of diethyl phosphite with LiHMDS, to an enantiopure ketosulfinimine (*S*)-(+)-**1** at −78 °C (Scheme 1). After 1−3 h

Scheme 1

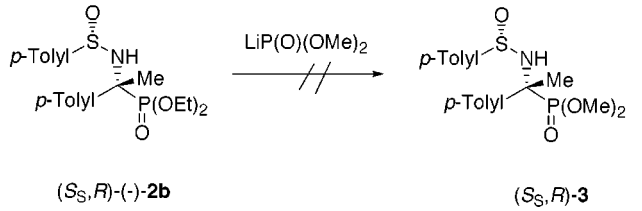


the reaction mixture was quenched with saturated NH_4Cl solution, and the *N*-sulfinyl amino phosphonates **2** were isolated by flash chromatography.

Ketosulfinimines **1** are prepared by condensation of commercially available (*S*)-(+)-*p*-toluenesulfinamide (*p*-TolylS(O)NH_2) with the appropriate ketone in the presence of 10 equiv of $Ti(OEt)_4$.[17,18] Sulfinimines **1a**−**f** were isolated as single *E*-isomers, whereas **1g**, derived from 2-butanone, exists as an inseparable 3:1 mixture of isomers. These results are summarized in Table 1.

The addition of lithium diethyl phosphite to ketosulfinimines (*S*)-(+)-**1a**−**f** is remarkably stereoselective, and only a single isomer was detected in the ^{1}H and ^{31}P NMR spectra of the crude reaction mixtures. This selectivity is independent of electronic factors as long as the ketosulfinimine exists as a single isomer (Table 1, entries 1−6). However, in line with the 3:1 ratio of *E*:*Z* isomers for (+)-**1g** is the 82:12 mixture of diastereoisomers for **2g**, undoubtedly resulting from phosphite addition to both isomers (Table 1, entry 7). Reversibility in the addition of phosphites to sulfinimines is a consideration,[19] and two experiments were designed to reveal whether the addition is under kinetic or thermodynamic control. First, diastereomeric pure (S_S,*R*)-(+)-**2g** was treated, under the reaction conditions, with LiHMDS followed by addition of $LiP(O)(OEt)_2$. The isomeric amino phosphonate (S_S,*S*)-**2g** was not detected, and (S_S,*R*)-(+)-**2g** was recovered unchanged. Next, (S_S,*R*)-(−)-**2b** was treated with lithium dimethyl phosphite. None of the crossover product (S_S,*R*)-**3** was observed, and the substrate was quantitatively recovered (Scheme 2). These experiments

Scheme 2



suggest that addition of metallo phosphites to ketosulfinimines at −78 °C is under kinetic control and may be a consequence of the amino anion stabilizing ability of the *N*-sulfinyl group.[20] However, at higher temperatures reversibility cannot be ruled out since decomposition occurs.

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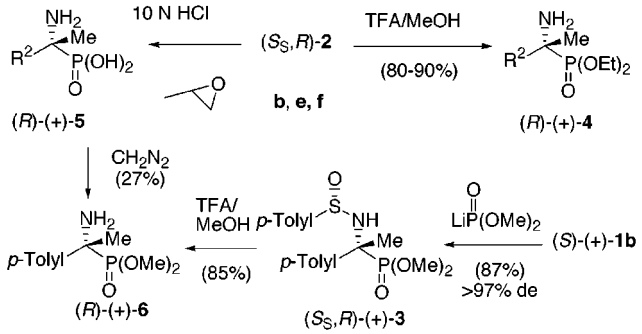
Because there is confusion in the literature regarding the stereochemistry for addition of metallo phosphites to sulfinimines (vide infra) it was necessary to rigorously establish the absolute stereochemistry of our amino phosphonate products **2**. The stereochemistry of (−)-**2d** was determined to be (S_S,*R*) by single-crystal X-ray analysis. The reasonable assumption is that the stereochemistry of **2a**−**c** and **2e**−**g** are also (*R*).

The *N*-sulfinyl group in **2b**, **2e**, and **2f** was selectively removed, in excellent yield, to give the corresponding amino phosphonate esters **4** (Scheme 3). Phosphonate esters are often preferred over the free acids because further elaboration of latter can be problematic; they are insoluble in H_2O and common organic solvents.[2] The acids **5** were obtained by refluxing **2** with 10 N HCl. They were isolated, following concentration, by dissolving the residue in hot EtOH and precipitating the acid with propylene oxide. Racemization is unlikely as a result of the quaternary nature of **4**, and the stereochemistry was confirmed by converting (*R*)-(+)-**5b** into the methyl ester (*R*)-(+)-**6** with diazomethane and comparing it to that prepared independently from (+)-**3** (Scheme 3). Attempts to prepare the Mosher amide of (+)-**5** failed.

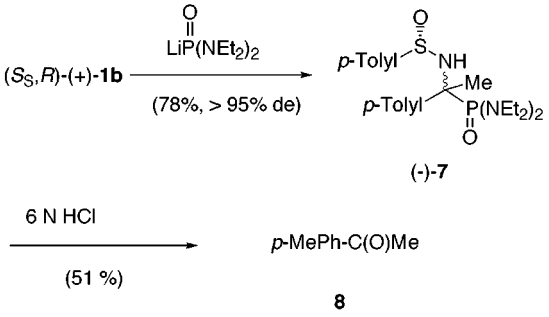
Scheme 3



The opposite sense of stereoinduction is reported to occur on addition of diamido phosphites to aldehyde-derived sulfinimines.[19] Using the standard protocol, (S_S)-(+)-**1b** and lithium bis(*N*,*N*-diethylamino)phosphite afforded (−)-**7** in 78% yield and >95% de (Scheme 4). Unfortunately, attempts to hydrolyze **7** to the acid to establish its absolute configuration was unsuccessful under a variety of conditions, and decomposition occurred. For example, stirring with 6 N HCl for 8 h produced a phosphorous acid and 4′-methylacetophenone (**8**) in 42% and 51% yields, respectively

With regard to the participation of the stereogenic sulfinyl group, steric and chelation-control arguments have been used

Scheme 4



to rationalize the chiral recognition for addition of organometallic reagents to sulfinimines. Enolates, Grignard reagents (allyl and alkyl), DIBAL-H, Et_2AlCN, and lateral lithiated amides and nitriles are all believed to react with sulfinimines via six-membered chairlike transition states where the metal ion is chelated to the sulfinyl oxygen.[21−23] On the other hand, steric arguments have been evoked to explain the stereochemical preference for additions of benzyl Grignard,[24] α-metallo phosphonates,[25] chloromethyl phosphonate anions,[26] 1,3-dipoles,[27] and glycine iminoester enolates[28] to sulfinimines. The situation is less clear for additions of metallo phosphites. For example, Lefebvre and Evans reported that lithium diethyl phosphite affords the (S_S,*S*) diastereoisomer on addition to aldehyde-derived sulfinimines.[29] It was suggested that the preferred product results from coordination of the Li ion to the nitrogen lone pair with delivery of the phosphorus atom to the carbon center from the face opposite the sulfinyl oxygen. For similar substrates Mikolajczyk et al. reported the major diastereoisomer as (S_S,*R*) but gave no rationalization.[19] To resolve these issues we repeated the results of Lefebvre and Evans, adding lithium diethyl phosphite to (*S*)-(+)-*N*-(benzylidene)-*p*-toluenesulfinamide (**9**) and obtained (+)-**10** as described by these authors, to which they had assigned the (S_S,*S*) configuration on the basis of a literature reference (Scheme 5).[2] However, we found that hydrolysis of (+)-**11** with 8 N HCl furnished-(+)-α-amino (phenylmethyl)phosphonic acid (**12**) having the (*R*)-configuration.[30] We conclude that the earlier literature[29]

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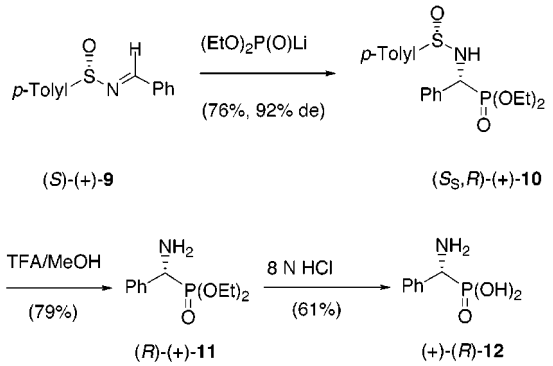
(30) The absolute configuration of (*R*)-(+)-α-amino (phenylmethyl)-phosphoninc acid (**12**) was established by X-ray crystallography: Glowiak, T.; Sawka-Dobrowolski, W.; Kowalik, J.; Mastalerz, P.; Soroka, M.; Zon, J. *Tetrahedron Lett.* **1977**, 3965.

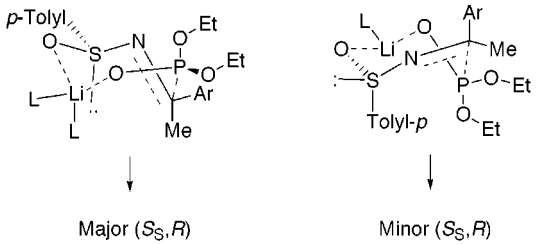
Scheme 5



was in error and that (+)-**10** and (+)-**11** have the (S_S,*R*)- and (*R*)-configuration, respectively.[31]

Resolution of this inconsistency means that metallo phosphite addition to aldehyde- and ketone-derived (*S*)-sulfinimines occurs with the same sense, *re*-face addition, and it is now possible to put forth a unified model for these additions. It is worth noting that this same sense of addition is also observed for the analogous addition of CN in the sulfinimine-mediated Strecker synthesis, as well as for most organometallic reagents. In these examples coordination of the metal ion to the sulfinyl oxygen is thought to play a central role. On the basis of these considerations and assuming that the sulfinimine has the favored *E* geometry,[32] a plausible rationalization for the preferential formation of (S_S,*R*)-**2** is depicted in Scheme 6. In this representation the lithium cation is chelated to the sulfinyl and phosphite

Scheme 6



oxygens in a seven-membered twisted chairlike transition state.[33] By contrast the twisted-chair transition state leading to the minor product has the bulky aryl and *p*-tolyl groups in the energetically unfavorable axial positions. This model can also be extended to the addition of phosphite to aldehyde-derived sulfinimines.

In summary, the first asymmetric synthesis of quaternary α-alkyl α-amino (arylmethyl)phosphonates was accomplished by the highly diastereoselective addition of lithium diethylphosphonate to enantiopure ketosulfinimines. For the addition of metal phosphites to sulfinimines, a unified asymmetric induction model involving coordination of the metal ion to both the sulfinyl and phosphonate oxygens in a seven-membered twisted chairlike conformation is proposed.

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Supporting Information Available: Experimental procedures and spectroscopic data for all compounds and X-ray data for (−)-**2d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(31) Upon re-analysis Smith et al. have confirmed that the configuration assigned to the phospho-phenylglycine derivatives (+)-**12** is indeed *R*. Ambiguous representation of the C1 (α carbon) stereochemistry reported by Soroka and co-workers (ref 30) allowed this error to go previously undetected.

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