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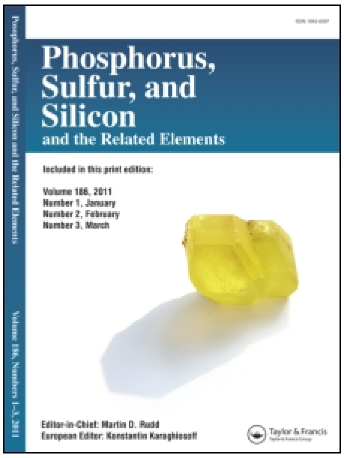

Phosphorus, Sulfur, and Silicon and the Related Elements

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Isabelle M. Lefebvre; Slayton A. Evans

To cite this Article Lefebvre, Isabelle M. and Evans, Slayton A.(1999) 'Asymmetric Synthesis of α-Amino Phosphonic Acids Employing Versatile Sulfinimines and Sulfonimines', Phosphorus, Sulfur, and Silicon and the Related Elements, 144: 1, 397 — 400

To link to this Article: DOI: 10.1080/10426509908546265

URL: http://dx.doi.org/10.1080/10426509908546265

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Phosphorus, Sulfur and Silicon, 1999, Vol. 144-146, pp. 397-400
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Asymmetric Synthesis of α-Amino Phosphonic Acids Employing Versatile Sulfinimines and Sulfonimines

ISABELLE M. LEFEBVRE and SLAYTON A. EVANS

Chemistry Department, The University of North Carolina at Chapel Hill, North Carolina 27599–3290, USA

The addition of metallophosphites to activated imino substrates such as sulfonimine 1 and sulfinimines 4 was successfully achieved. High diastereoselectivities and good yields were obtained with sulfinimine acceptors. The nucleophilic addition was applied to the development of a new methodology for the synthesis of enantiomerically homogeneous α-amino phosphonic acids.

Keywords: α-amino phosphonic acids; sulfinimines; sulfonimines; nucleophilic addition; diastereoselectivity

INTRODUCTION

α-Amino phosphonic acids are well-established antagonists of α-amino carboxylic acids. Because of different acidities of the carboxylic *vs.* phosphonic groups, α-amino phosphonic acids yield peptide analogs with altered isoelectric points and binding properties.[1] α-Amino phosphonic acids exhibit a large spectrum of biological activities: enzyme inhibition, plant growth regulation, and herbicidal, antibacterial, neurological and anticancer activity.[2] Their biological activity is strongly dependent on the stereogenicity at the carbon center α to the phosphorus atom.[3] As a consequence, there is a critical need for enantiomerically homogeneous α-amino phosphonic acids.

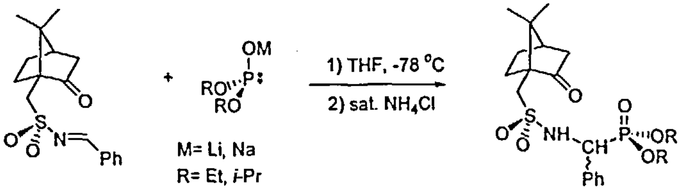
As part of the development of new methodologies for the asymmetric synthesis of α-amino phosphonic acids, the addition of phosphites to a variety of imino-acceptors (*i.e.*, sulfinimines and sulfonimines) has been studied. The new methodology consists of three steps. In the first stage, creation of the P-C bond is achieved *via* the addition of phosphites to activated imine derivatives. Transformation of the adducts into the corresponding α-amino phosphonic acids occurs upon cleavage of the auxiliary and subsequent hydrolysis of the phosphonate moiety.

RESULTS

Addition of Phosphites to Sulfonimines

The first approach to the asymmetric addition of phosphites to activated imines involved the use of *N*-benzylidenecamphor sulfonamide **1**, a chiral sulfonimine bearing a configurationally restricted backbone. The steric hindrance exerted by the camphor auxiliary and the potential for chelation between the Lewis base sites in sulfonimine **1** and a metal ion directly bound to phosphite **2** were expected to create the basis for π-facial discrimination.

Sulfonimine **1** was obtained from the condensation of camphor sulfonamide with benzaldehyde dimethyl acetal at 140 °C.[4] The additions of lithium and sodium dialkyl phosphites **2** to camphor-derived sulfonimine **1** were performed at –78 °C in tetrahydrofuran (Scheme 1). After quenching with ammonium chloride and extracting with ether, *N*-sulfonyl-α-amino phosphonates **3** were obtained. The diastereoselectivity observed during these reactions remained low to moderate, even with the use of a bulkier phosphite (Table 1). Influence of the nature of the metal ion was also studied.



1 **2** **3**

SCHEME 1. Addition of Phosphites to Sulfonimine **1**

R	M	d.e. (%)[a]
Et	Li	20
Et	Na	40
Et	Li[b]	20
i-Pr	Li	20
i-Pr	Na	9

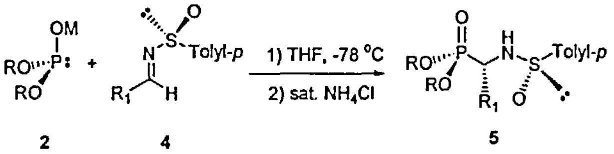
a) Diastereoselectivity determined by integration of ^{31}P NMR resonances from the crude mixture.
b) Addition performed in the presence of 1 equivalent of ZnBr$_2$.

TABLE 1. Diastereoselectivity of the Addition of Phosphites to Sulfonimine **1**

Addition of Phosphites to Sulfinimines

The second approach consisted of the use of enantiomerically homogeneous and configurationally restricted sulfinimines as chiral and activated acceptors in the nucleophilic addition reaction of metallophosphites. Following our earlier investigations[5] and the data reported by Mikolajczyk *et al.*,[6] the scope of this "conjugate addition" was extended to the use of a wider variety of sulfinimines and phosphites.

Chiral sulfinimines were synthesized according to the procedure reported by Davis *et al.*[7] The additions of lithium and sodium dialkyl phosphites to sulfinimines were performed at –78 °C in tetrahydrofuran (Scheme 2). After quenching with a saturated solution of ammonium chloride and extraction with ether, *N*-sulfinyl-α-amino phosphonates were obtained in excellent diastereoselectivities in all cases (Table 2).



R = Et, *i*-Pr; M = Li, Na; R_1 = Ph, *p*-$MeOC_6H_4$, *n*-Pr

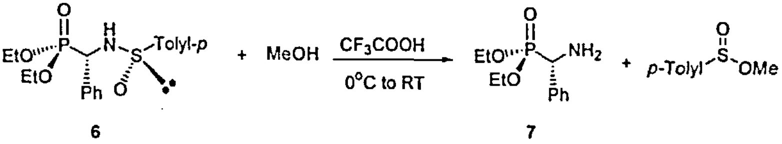
SCHEME 2. Addition of Phosphites to Sulfinimines 4

R_1	R	M	d.e. (%)[a]	Yield
Ph	Et	Li	84	85
Ph	Et	Na	93	80
p-$MeOC_6H_4$	Et	Li	84	50
p-$MeOC_6H_4$	Et	Na	90	50
Ph	*i*-Pr	Li	97	82
p-$MeOC_6H_4$	*i*-Pr	Li	86	55
n-Pr	Et	Li	85	78
n-Pr	*i*-Pr	Na	>98	86

a) Diastereoselectivity determined by integration of ^{31}P NMR resonances from the crude mixture.

TABLE 2. Diastereoselectivity of the Addition of Phosphites to Sulfinimines 4

Removal of the *N*-sulfinyl auxiliary was achieved by acid-promoted methanolysis (Scheme 3). The desulfinylation reaction of compound **6** occurs without epimerization of the stereogenic carbon atom α to the nitrogen atom. Purification *via* flash chromatography afforded homogeneous α-amino phosphonate **7**.



SCHEME 3. Desulfinylation Reaction

Hydrolysis of the phosphonate moiety is known to occur under strongly acidic conditions and without epimerization.[8]

CONCLUSION

The novel method for the asymmetric synthesis of α-amino phosphonic acids employing the nucleophilic addition of phosphites to sulfinimines gives access to different residues, including some with an aliphatic substituent. Due to the highly selective addition process and the favorable reaction conditions, this methodology certainly constitutes one of the best approaches towards enantiomerically homogeneous α-amino phosphonic acids.

ACKNOWLEDGMENTS

We are grateful to the National Science Foundation for support of this research and to Dr. Peter White for collection of X-ray data.

References

[1] D. E. C. Corbridge, *Phosphorus – An Outline of its Chemistry, Biochemistry and Uses, 5th ed.;* (Elsevier: New York, 1995), chapter 3.

[2] P. Kafarski and B. Lejczak, *Phosphorus, Sulfur, Silicon Relat. Elem.*, **63,** 193 (1991).

[3] P. P. Giannousis and P. A. Bartlett, *J. Med. Chem.*, **30,** 1603 (1987).

[4] V. Srirajan, A. R. A. S. Deshmukh, V. G. Puranik and B. M. Bhawal, *Tetrahedron : Asymmetry,* **7,** 2733 (1996).

[5] I. M. Lefebvre and S. A. Evans, Jr., *J. Org. Chem.*, **62,** 7532 (1997).

[6] M. Mikolajczyk, P. Lyzwa and J. Drabowicz, *Tetrahedron: Asymmetry,* **8,** 3991 (1997).

[7] F. A. Davis, R. E. Reddy, J. M. Szewczyk, G. V. Reddy, P.S. Portonovo, H. Zhang, D. Fanelli, R. T. Reddy, P. Zhou and P. J. Carroll, *J. Org. Chem.*, **62,** 2555 (1997).

[8] A. B. Smith, III, K. M. Yager and C. M. Taylor, *J. Am. Chem. Soc.*, **117,** 10879 (1995).