Communications

Studies toward the Asymmetric Synthesis of α-Amino Phosphonic Acids via the Addition of Phosphites to Enantiopure Sulfinimines

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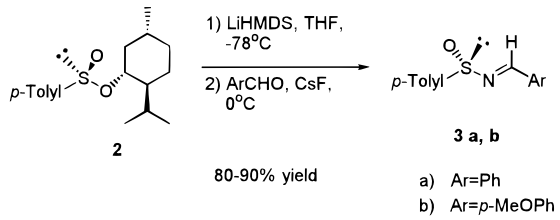
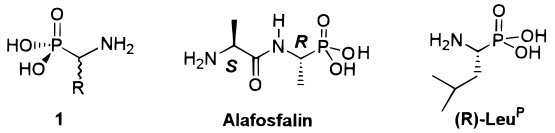
α-Amino phosphonic acids **1** serve as important surrogates for α-amino carboxylic acids and therefore exhibit a range of intriguing biological attributes.[1] They usually act as antagonists in the metabolism of amino acids. Furthermore, α-amino phosphonic acids are potential antibacterial agents,[2] exhibit neuroactive characteristics,[3] and have been employed as anticancer drugs[4] and pesticides.[5] Generally, the biological activities of α-amino phosphonic acids strongly depend on the stereogenicity at the carbon center α to the phosphorus atom. One such example is the high antibacterial activity of alafosfalin, [*N*-(L-alanyl)-L-1-aminoethyl]phosphonic acid [(*S*,*R*) diastereomer], as compared to that of the other diastereoisomers [*i.e.*, (*R*,*R*), (*S*,*S*), and (*R*,*S*)].[2] Also, the (*R*)-enantiomer of the phosphonic acid analog of leucine (*i.e.*, (*R*)-Leu^P) is a more potent inhibitor of leucine aminopeptidase than the (*S*)-isomer.[6] As a consequence, considerable research has been devoted to the asymmetric synthesis of α-amino phosphonic acids during the past decades.[7]

Our synthetic strategy illustrating an enantioselective approach to α-amino phosphonic acids involved the addition of metallo phosphites to enantiomerically homogeneous and configurationally restricted sulfinimines. Enantiopure sulfinimines have found wide utility as precursors in the asymmetric synthesis of amines[8] and, particularly, α-amino acids by utilizing the stereodirecting capability of the chiral sulfinyl moiety. They were used as activated imine acceptors in the "conjugate addition" of various nucleophiles (*e.g.*, hydrides,[9] organoaluminum reagents,[10] Grignard reagents,[11] and sulfur ylides[12]). Among the most recent and stereochemically illustrative examples, lithium ester enolates were added to sulfinimines to form β-amino esters in high diastereoselectivities and excellent yields.[13] In addition, the reactions of α-metallo phosphonates with sulfinimines have exhibited high diastereoselectivities as well.[14]

Scheme 1





These intriguing findings prompted us to study the asymmetric synthesis of α-amino phosphonic acids *via* the addition of metallo phosphites **4** to enantiopure sulfinimines **3**. The use of chiral sulfinimines as acceptors presented several unique advantages: (a) commercial availability of the chiral auxiliary, (b) diverse electronic and steric properties of the chiral sulfinyl auxiliary which may encourage metal binding and unique organizational requirements for substrate/reagent approach (*i.e.*, stereodirecting functional group), and (c) the possibility for recycling the auxiliary.[13a]

Chiral sulfinimines **3** were synthesized according to the procedure reported by Davis *et al.* (Scheme 1).[8]

The additions of lithium and sodium dialkyl phosphites **4** to sulfinimines **3** were performed at −78 °C in tetrahydrofuran (THF) solvent. After quenching with a saturated solution of ammonium chloride and extraction with ether, *N*-sulfinyl-α-amino phosphonates[15] **5** were obtained in excellent diastereoselectivity in all cases (Scheme 2 and Table 1).

Isolation of the major isomer **5a** followed by transformation to the target α-amino phosphonate **6a** allowed for the assignment of the (*S*)-configuration to the new stereogenic carbon center. Removal of the *N*-sulfinyl auxiliary of diastereomer **5a** was achieved by acid-promoted methanolysis according to the procedure re-

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(15) The structures of products **5a**−**c** have been assigned by ^{1}H, ^{13}C, and ^{31}P NMR spectroscopic techniques. The diastereoselectivities were determined by ^{31}P NMR. All products **5a**−**c** gave satisfactory elemental analysis.

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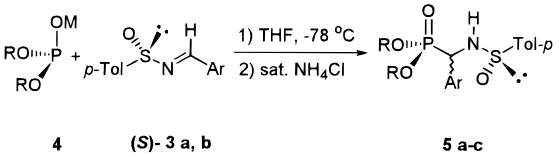
Table 1. Diastereoselective Additions of Metallo Phosphites 4 to Sulfinimines 3 at − 78 °C in THF

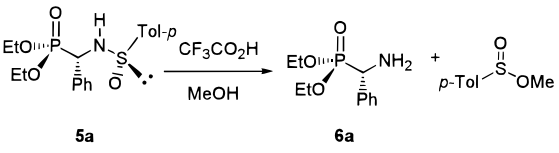
entry	phosphite **4**: R	phosphite **4**: M	sulfinimine **3**	product	yield (%)	de[a] (%)
1	Et	Li	**3a**	**5a**	85	84
2	Et	Na	**3a**	**5a**	80	93
3	Et	Li	**3b**	**5b**	50	84
4	Et	Na	**3b**	**5b**	50	90
5	*i*-Pr	Li	**3a**	**5c**	82	97

[a] All diastereoselectivities were determined by ^{31}P NMR.

Scheme 2

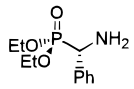


Scheme 3



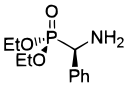
ported by Mikolajczyk *et al.* (Scheme 3).[16] The desulfinylation reaction occurs without epimerization of the stereogenic carbon atom α to the nitrogen atom in **5a**.[16] Purification *via* flash chromatography afforded homogeneous α-amino phosphonate **6a**.

The absolute configuration of α-amino phosphonate **6a** was established *via* the comparison of the sign of its optical rotation with that reported in the literature.[7c]



(*S*)-6a

$[\alpha]_D^{25}$ = + 16.45° (c 1.9, $CHCl_3$)

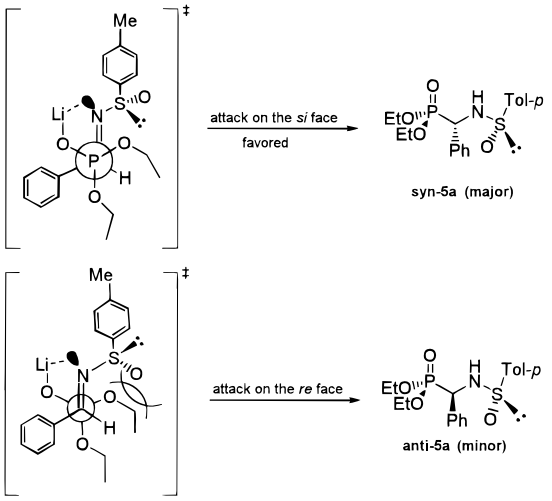


(*R*)-6a

$[\alpha]_D^{25}$ = -18.73° (c 1.9, $CHCl_3$)[7c]

Mechanistic Rationale. Sulfinimines derived from ketones reportedly interconvert rapidly at ambient temperatures ($\Delta G^{\ddagger} = 13-17$ kcal/mol).[17] However, Davis *et al.*[8] reported that sulfinimines derived from aldehydes exist in a single isomeric form. The *E*-configuration of the imino bond in **3a** was established by single-crystal X-ray analysis, and the assumption was made that all aldehyde-derived sulfinimines possessed a similar geometry. While this generalization may be valid, it seemed appropriate to establish the boundaries for considering the relevance of *E*- *vs.* *Z*-configurational lability[18] under the reaction conditions. The ^{1}H NMR resonance of the imino proton (δ 8.75 ppm) of sulfinimine **3a** was invariant between −66 °C and +80 °C, suggesting that the barrier attending the *E* to *Z* equilibration of sulfinimine **3a** was greater than that for the sulfinimine derived from 4,4′-dimethylbenzophenone, assuming that both have similar transition-state energies. On the basis of the potentially higher steric hindrance between the bulky Ar and the S(O)-*p*-tolyl substituents in the *Z*-isomer, one might anticipate that the *E*-isomer would be thermodynamically more stable since these interactions are minimized in this isomer. Consequently, from these limited data we concluded that sulfinimine **3a** exists in the single *E*-isomeric form, and the same conclusion was drawn for compound **3b**.

Scheme 4



While several transition-state models may be applicable, the preferred formation of diastereomer (S_S, S_C)-**5a** may be rationalized by assuming a coordination of the metal atom (*i.e.*, Li) to the nitrogen lone pair, facilitating the delivery of the phosphorus atom to the prochiral trigonal carbon center from the face opposite to the sulfinyl oxygen atom (Scheme 4). Such a transition-state model rationalizes the greater diastereoselectivity observed in the addition of diisopropyl phosphite to sulfinimine **3**, relative to diethyl phosphite.

In conclusion, we reported that the addition of metallo phosphites to chiral sulfinimines occurs with high diastereoselectivity. The application of this novel reaction has been demonstrated with the asymmetric synthesis of α-amino phosphonate esters.

Acknowledgment. We are grateful to the National Science Foundation for support of this research.

Supporting Information Available: Experimental procedure and compound characterization data for compounds **5a**−**c** (20 pages).

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