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[A0045]

ASYMMETRIC SYNTHESIS OF a-AMINO PHOSPHONIC ACIDS *via* THE ADDITION OF PHOSPHITES TO ENANTIOPURE SULFINIMINES.

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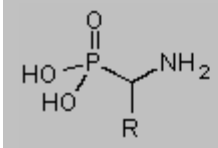
I) OBJECTIVE

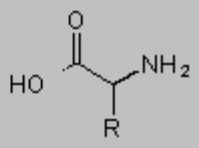
Development of a new, enantiomerically-efficient methodology for the asymmetric synthesis of a-aminophosphonic acids (a-APAs) using a commercially-available chiral auxiliary.

II) INTRODUCTION

a-Aminophosphonic acids **1** serve as important surrogates for a-amino carboxylic acids **2**.



1



2

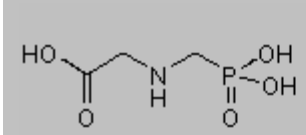
Despite some structural differences between the phosphonic and the carboxylic functional groups (*e.g.*, molecular size and shape, pseudo-tetrahedral array attending the P atom *vs* trigonal array about the C atom, differences in acidity, etc), a-APAs are capable of competing with a-amino carboxylic acids for the active sites of several enzymatic systems. As inhibitors of metabolic processes, a-APAs exhibit:

- neuroactive characteristics

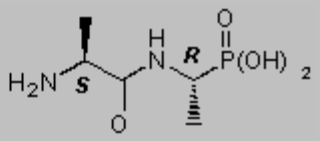
- anticancer activity

- herbicidal activity (*e.g.*, Glyphosate: active ingredient in Roundup®)

- antibacterial activity (*e.g.*, Alafosfalin is an effective inhibitor of bacterial cell wall synthesis).

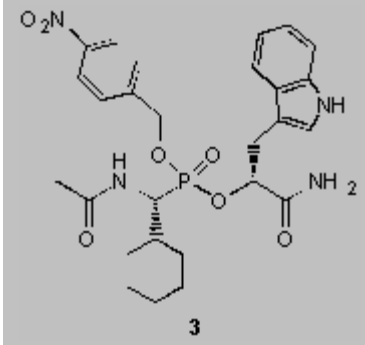


Glyphosate



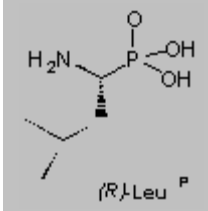
Alafosfalin

a-Aminophosphonic acids are also employed as haptens for the generation of catalytic antibodies (*e.g.*, antibodies capable of catalyzing the formation of a peptide bond were elicited against hapten **3**).



3

The absolute configuration of the stereogenic carbon atom a to the phosphorus atom influences the biological activity of the a-APAs. For example, the (*S*, *R*) diastereomer of Alafosfalin shows significant activity against Gram-positive microorganisms, whereas the other three diastereomers [*i.e.* (*R*, *R*), (*R*, *S*) and (*S*, *S*)] are considerably less potent. The (*R*)-enantiomer of Leucine is a more potent inhibitor of Leucine Aminopeptidase than the (*S*)-isomer; interestingly, this example embodies the L configuration of the encoded a-amino carboxylic acids.



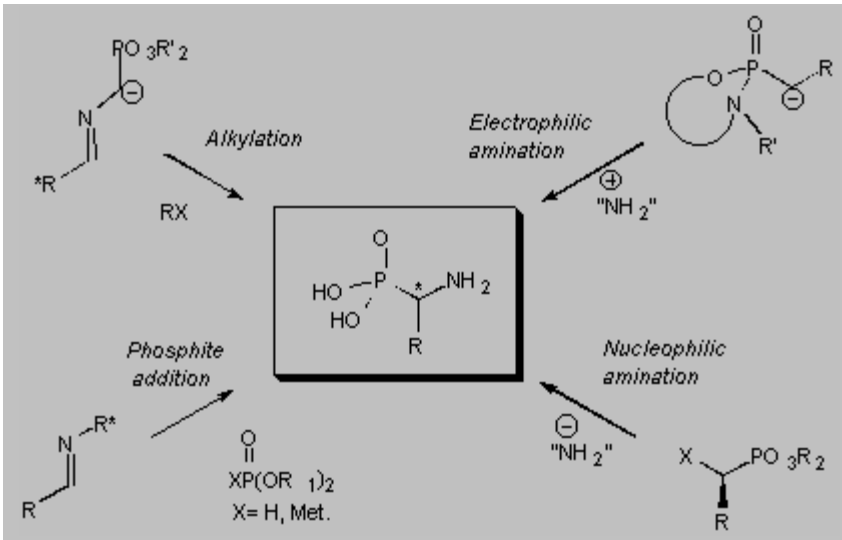
(*R*)-Leu P

III) BACKGROUND

** General Methods for the Synthesis of a-APAs.*

The obvious need for enantiomerically homogeneous a-APAs with established absolute configuration at the stereogenic carbon atom has been realized with the development of several asymmetric syntheses of a-APAs. The most pronounced examples are alkylation of chiral iminophosphonate anions, electrophilic amination of chiral phosphonamide anions, nucleophilic amination, and addition of phosphites to chiral imines or imine derivatives (Scheme 1).

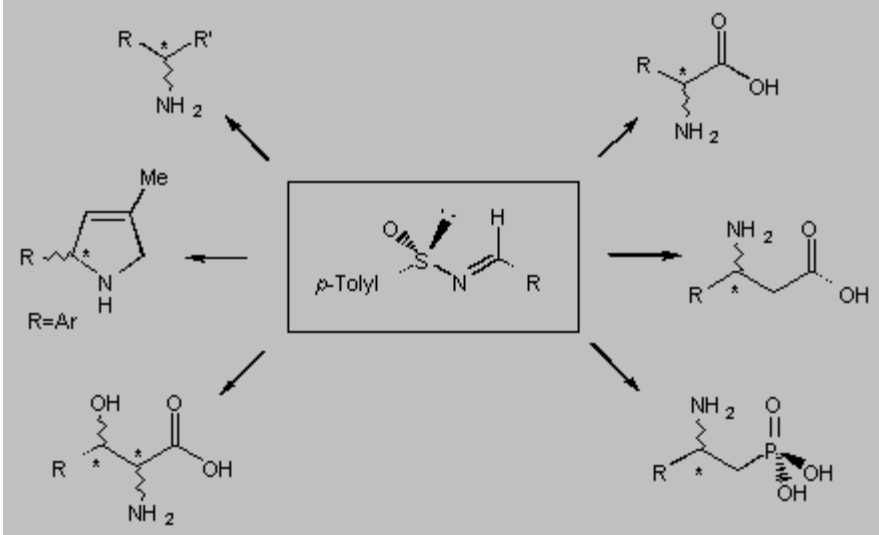
Scheme 1



** Reactivity of Sulfinimines.*

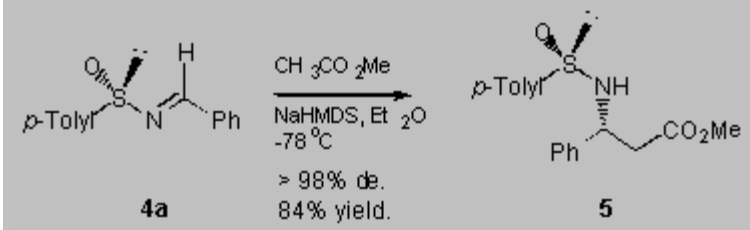
Enantiomerically-homogeneous sulfinimines have been employed as important chiral precursors in the asymmetric synthesis of amine derivatives such as a-amino acids, b-amino acids, b-amino phosphonic acids, b-hydroxy-a-amino acids and 2-arylpyrrolines (Scheme 2).

Scheme 2



The electron-withdrawing sulfinyl auxiliary activates the C-N bond for addition of nucleophiles such as hydrides, Grignard reagents, sulfur ylides, metal enolates and a-phosphonate carbanions. This auxiliary also acts as a powerful stereodirecting group to induce high diastereoselectivities. For instance, the addition of the sodium enolate of methyl acetate to sulfinimine **4a** gave b-amino ester **5** in more than 98% d.e. (Scheme 3).[18]

Scheme 3



4a 5

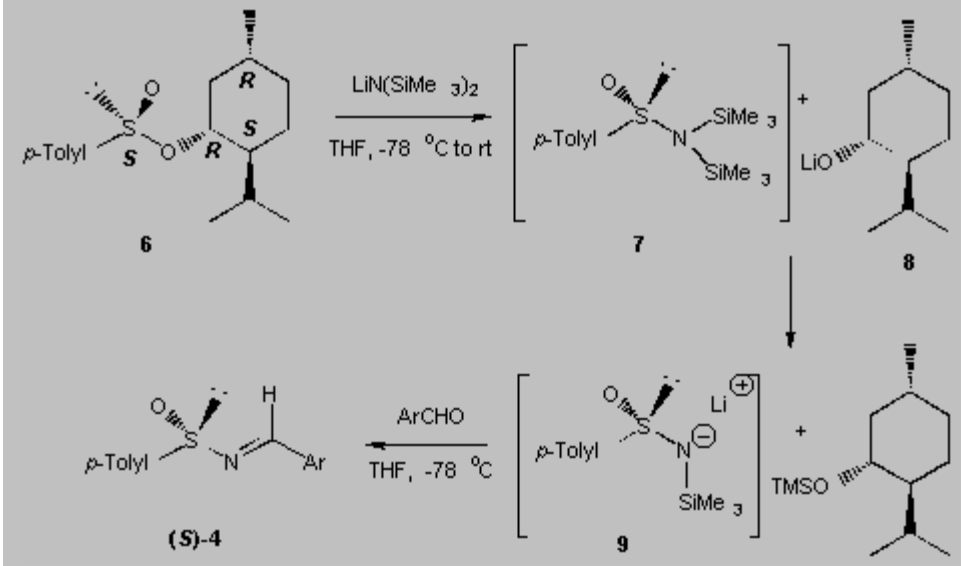
IV) OUR APPROACH

Our goal is to develop a highly selective and efficient asymmetric synthesis of a-APAs with broad application. In this light, the use of sulfinimines as acceptors in the addition reactions of metallophosphites to imine derivatives has 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, and (c) the possibility for recycling the auxiliary.[18]

V) PREPARATION OF SULFINIMINES

Sulfinimines were synthesized according to the procedure reported by Davis *et al.* (Scheme 4).[14] Addition of LiHMDS to the menthol-derived sulfinate **6** presumably generates *N, N*-bis-(trimethylsilyl)-*p*-toluenesulfinamide **7** with inversion of configuration and lithium menthoxide **8**. Sulfinimine **4** arises from a Peterson-type reaction involving reaction of the intermediate silyl sulfinamide anion **9** with an aldehyde.

Scheme 4

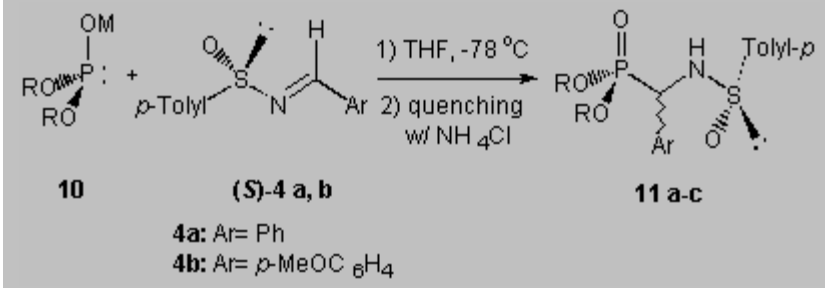


6 7 8 (*S*)-4 9

VI) ADDITION OF PHOSPHITES TO SULFINIMINES

The additions of lithium and sodium phosphites to sulfinimines **4** were performed at -78°C in tetrahydrofuran solvent. After quenching with ammonium chloride and extraction with ether, *N*-sulfinyl-a-aminophosphonates **11** were obtained in excellent diastereoselectivities in all cases (Scheme 5 and Table 1). The major diastereomers **11 a-c** were efficiently separated *via* flash chromatography.

Scheme 5



10 **(*S*)-4 a, b** **11 a-c**

4a: Ar= Ph
4b: Ar= *p*-MeOC $_6$H$_4$

Table 1

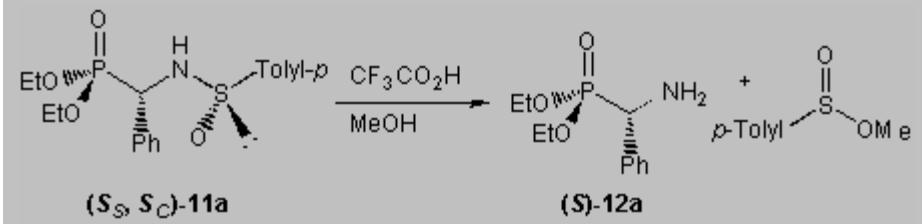
10: R	10: M	(*S*)-4	product	yield (%)	d.e.(%)[a]
Et	Li	**4a**	**11a**	85	84
Et	Na	**4a**	**11a**	80	93
Et	Li	**4b**	**11b**	50	84
Et	Na	**4b**	**11b**	50	90
i-Pr	Li	**4a**	**11c**	82	97

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

VII) DESULFINYLATION OF THE ADDUCT 11a.

Removal of the *N*-sulfinyl auxiliary of diastereomer (S_S, S_C)-**11a** was achieved by acid-catalyzed methanolysis according to the procedure reported by Mikolajczyk *et al.* (Scheme 6). This desulfinylation is known to occur without epimerization of the carbon atom a to the nitrogen atom.

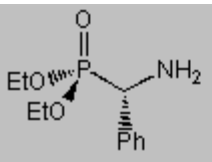
Scheme 6



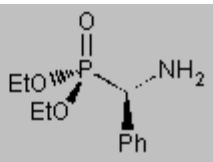
(S_S, S_C)-11a **(*S*)-12a**

VIII) ASSIGNMENT OF STEREOCHEMISTRY

Isolation of the major isomer **11a**, followed by transformation to the targeted a-aminophosphonate **12a** allowed for the assignment of the (*S*)-configuration to the new stereogenic carbon atom, based on the comparison of the sign of the optical rotation of **12a** with the literature value.[13c]



(*S*)-12a



(*R*)-12a

$[\alpha]_D^{25}$ = + 16.45 ° (c 1.9, $CHCl_3$) $[\alpha]_D^{25}$ = -18.73 ° (c 1.9, $CHCl_3$)[13c]

IX) MECHANISM

Configurational Stability of Sulfinimines 4.

Sulfinimines derived from ketones reportedly interconvert rapidly at ambient temperatures (DG= 13-17 kcal/mol).

However, Davies *et al.* reported that sulfinimines derived from aldehydes exist in a single isomeric form: the X-ray crystal structure of **4a** indicated the *E*-configuration of the imino bond, and the assumption was made that all aldehyde-derived sulfinimines possess a similar geometry.[14]

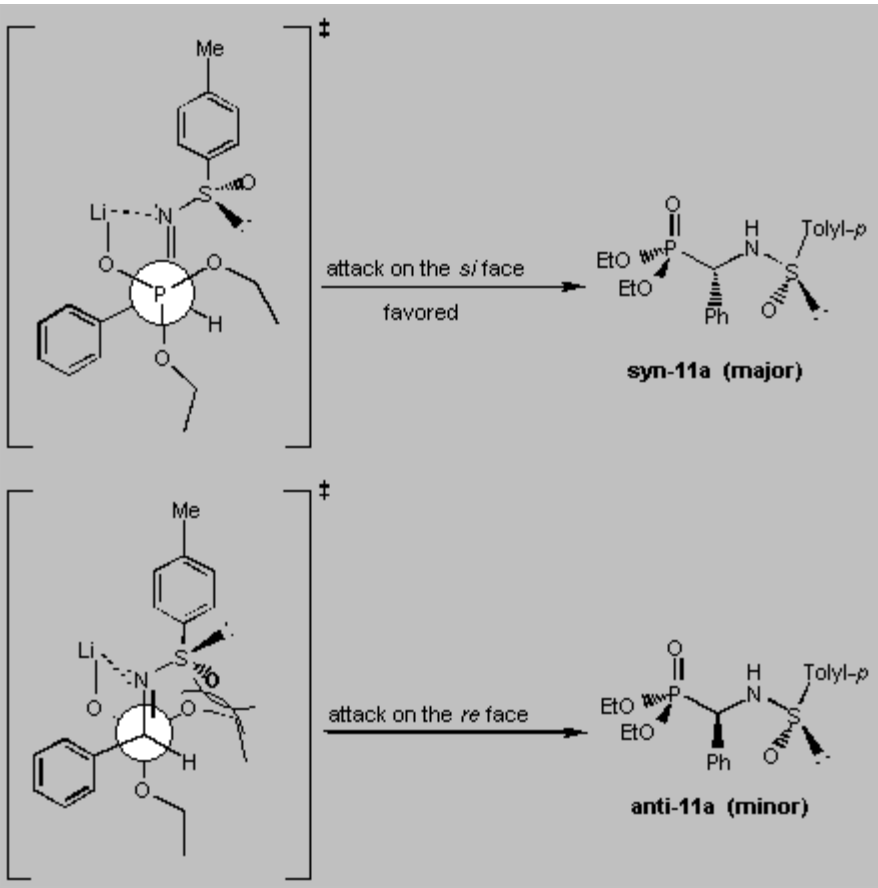
Nevertheless, a thorough investigation of the configurational stability of sulfinimine **4a** seemed appropriate. The dynamic behavior of sulfinimine **4a** was examined at various temperatures using ^{1}H NMR spectroscopy. The ^{1}H NMR resonance of the imino hydrogen (d 8.75 ppm) remained unchanged over the temperature range -66^o to +80^{o}C, suggesting that the barrier attending the *E- vs Z-* equilibration of sulfinimine **4a** was extremely low or that the barrier was quite high and that a single isomer is present. The *E*-isomer is expected to be thermodynamically more stable since the non-bonded interactions between the bulky Ar and the *p*-tolyl-S(O)groups are minimized in this isomer. Consequently, from these limited data we concluded that sulfinimine **4a** exists in the single *E*-isomeric form.

Addition of Phosphites.

While several transition state models may be applicable, the preferred formation of diastereomer (S_S, S_C)-**11a** may be rationalized by assuming a coordination of the metal atom (*e.g.*, Li) to the imino 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.

The proposed transition state models are represented in Scheme 7.

Scheme 7



X) CONCLUSION AND FUTURE WORK

We have devised a highly-efficient protocol for the asymmetric synthesis of a-aminophosphonate esters. Addition of metallophosphites to sulfinimines derived from aromatic aldehydes led to the predominant formation of diastereomers (S_S, S_C)-**11**. Hydrolytic removal of the sulfinyl auxiliary then afforded enantiomerically-enriched a-amino phosphonates.

Our future goal is to extend the versatility of this methodology by studying the addition of phosphites to sulfinimines derived from aliphatic aldehydes.

XI) ACKNOWLEDGMENTS

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