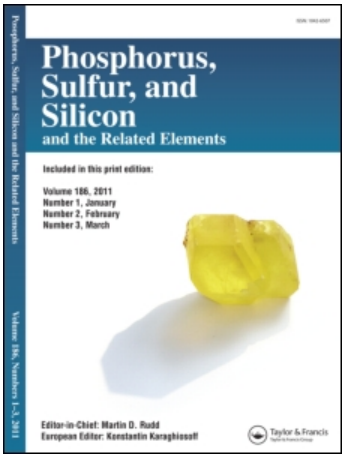

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Asymmetric Synthesis of Aminophosphonic Acids and Trifluoromethylated Derivatives Thereof

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ASYMMETRIC SYNTHESIS OF AMINOPHOSPHONIC ACIDS AND TRIFLUOROMETHYLATED DERIVATIVES THEREOF

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Various approaches leading to chiral aminophosphonic acids were described. Catalytic asymmetric-induced addition of dialkylphosphite to chiral aldimine gives low ee. value. The diastereoselective alkylation of bicyclic phosphonamide derived from anilinomethylpyrrolidine and followed by subsequent reactions provide much better results. 1,3-Proton Schiff reaction was applied successfully for chiral trifluoromethylated α- and/or β-aminophosphonic acids.

Keywords: Aminophosphonic acids; asymmetric synthesis; 1,3-PSR; trifluoromethylated derivatives

INTRODUCTION

Aminophosphonic acids constitute an important group of biologically active organophosphorus compounds. Asymmetric synthesis of these molecules aroused interests of organic chemists. Gilmore announced the first synthesis of optically active α-aminophosphonic acid based on the addition of diethylphosphite to Schiffs base, which resulted from condensation of benzaldehyde with either (R)(+) or (S)(−) α-methylbenzylamine.[1] This method does not seem to be as good as an asymmetric synthesis due to the harsh reaction conditions that required heating at 140°C for 1 hr.

RESULTS AND DISCUSSION

As reported by us with the aid of Lewis acids even proton acids as catalysis in appropriate solvent, this asymmetric-induced nucleophilic

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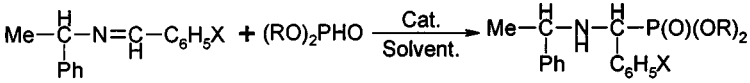
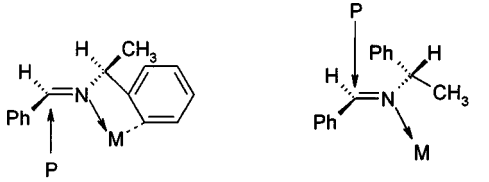
addition of dialkylphosphite to aldimine with sp^2C atom can be achieved at room temperature.[2] Our experimental result demonstrated that both electronic and steric effects, either from nuclear substituents or from ester alkyl groups, have no significant influence on the chemical yield and ee. value of this reaction.



X=H, Me, MeO, Cl, Br, F; R=Me, Et, iPr, n-Bu, i-Bu, Ph
Cat.=$AlCl_3$, $BF_3{\cdot}OEt_2$, $ZnCl_2$, TsOH; Solvent.=CH_2Cl_2

The absolute configuration of the resulting product is controlled by the catalyst used. This phenomenon could be rationalized by the fact that the empty *d* orbital of the central atom of $AlCl_3$ or BF_3 coordinates with the benzene ring of the Schiff base to form complex with

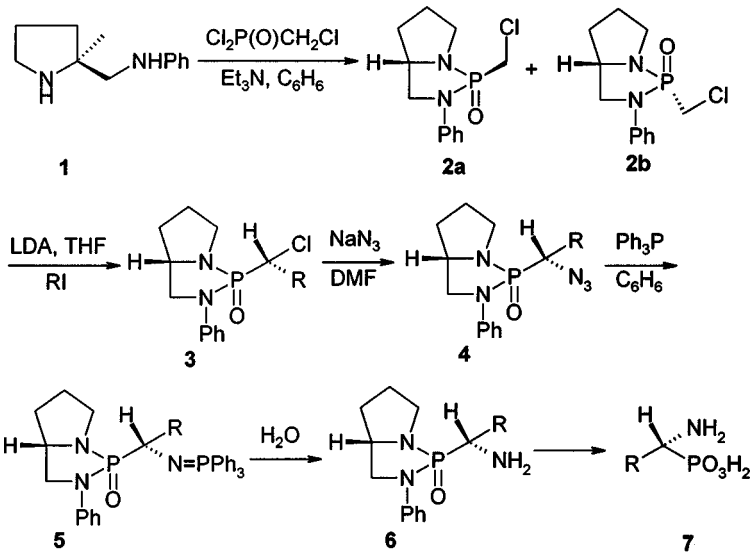


Conformation A (S) Conformation B (R)

conformer A that give product with S configuration since dialkylphosphite is favorable to be added from the bottom of the conformer. While $ZnCl_2$ or proton acid TsOH can only form conformer B, that allows top attack of phosphorus reagent to sp^2C of the conformer; consequently, only R configuration could be provided. This prediction was fully supported by molecular mechanics calculation based on energy differences.[3]

A more convenient and efficient synthesis of chiral aminophosphonic acid with high optical activity is based on the use of (S)-2-anilinomethylpyrrolidine as chiral auxiliary[4,5] that is obtained by reduction of (S) 5-oxopyrrolidine-2-carboxanilide.[6] The latter was prepared conveniently by heating L-glutamic acid with aniline in 46%. As demonstrated by us, the yield of this reaction can be markedly increased to 94% by refluxing mixture around 190°C using Dean-Stack trap. Reaction of **1** with choromethanephosphonyl dichloride gave a mixture of bicyclic chloromethylphosphonamide **2a** and **2b**

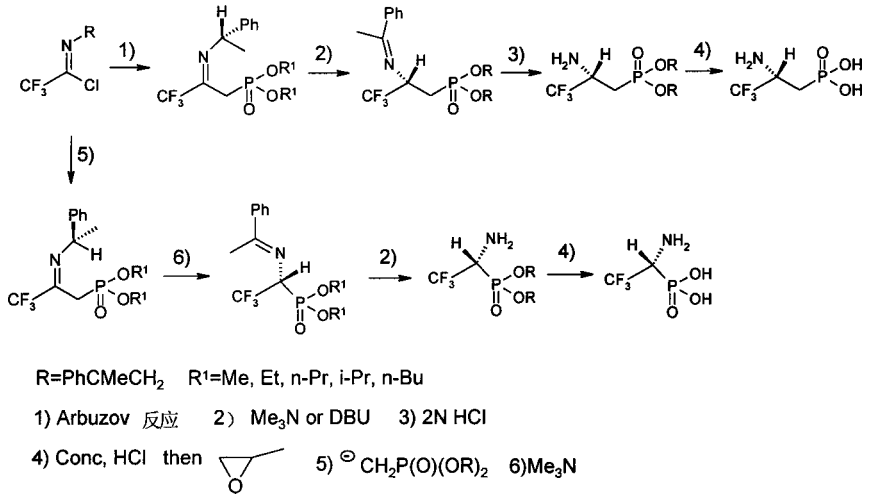
namdy (2S,5S) and (2R,5R)-2-chloromethyl-2-oxo-3-phenyl-1,3-diaza-2-phospha-bicyclo-[3,3,0]-octane.



Diastereoselective alkylation is the key step in this synthetic route. The isolated **2a** was alkylated with appropriate alkyl iodide at –78°C in THF using LDA as base **3** was obtained in high yield (74–82%) and excellent optical purity (>95%). Nucleophilic displacement with azide ion gave the azido compounds. The latter gave corresponding amino derivative by Staudinger reaction. Upon acid hydrolysis, free aminophosphonic acid were obtained. The chiral auxiliary was recovered in 85% yield.

Starting from trifluoromethylated (N—)(—)α-methylbenzylacetimidoyl chloride as building block, an asymmetric synthesis of trisfluoromethylated α- or β-aminoalkane phosphonic acid was developed based on [1,3]-proton shift reaction—a reducing agent-free biomimetic reductive amination using triethylamine as a base and solvent.

The resulting α-amino-β,β,β-trifluoroethanephosphonic acids give positive Cotton effect in the CD curve for the compound; however, we described a practical and effective asymmetric synthesis of β-amino-γ,γ,γ-trifluoromethylpropanephosphonic acid with high chemical purity by a [1,3] proton shift reaction.



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