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Bismuth(III)-Catalyzed Sequential Enamine−Imine Tautomerism/2-Aza-Cope Rearrangement of Stable β-Enaminophosphonates: One-Pot Synthesis of β-Aminophosphonates

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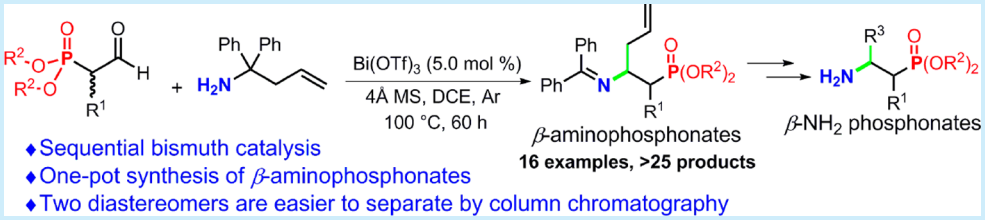

ABSTRACT: A novel catalytic tautomeric transformation of a β-enaminophosphoryl and 2-aza-Cope rearrangement sequence has been successfully applied to the one-pot synthesis of β-aminophosphonates with high efficiency and good tolerance. In this tandem reaction, $Bi(OTf)_3$ exhibits unique activities and promotes both of enamine−imine tautomerism and 2-aza-Cope rearrangement.

β-Aminophosphonic acids,[1] as "phosphorus analogues" of the corresponding amino acids, have widespread applications as antibacterial agents,[2] enzyme inhibitors,[3] haptens for catalytic phosphonate antibodies,[4] and anti HIV agents[5] (Figure 1, A). However, only limited catalytic methods[6] have been established for their preparation. The exploration of novel and versatile protocols which allow easy access to the β-aminophosphonate precursors is in high demand. From the perspective of synthetic potential, catalytic tautomerization of β-enaminophosphoryl to produce active imine[7] intermediates which can go through further functionalizations would provide a concise and general access to β-aminophosphonates. Over the past two decades, a variety of strategies have been developed to drive the tautomerization of enamines to imines in catalytic transformations (Figure 1, B). For example, in 2006, Nagy and Fabian conducted a theoretical study of enol imine−enaminone tautomeric equilibria and found the tautomeric preference changes due to solvent-dependent hydrogen bond interactions.[8] In a host−guest system, Zn^{2+} selectively interacts with anthracenone compounds and induces a metal-mediated imine−enamine tautomerization process, which contributes to the development of a new fluorescence detection method.[9] Moreover, highly Lewis acidic $B(C_6F_5)_3$ can react with equivalent amounts of NH heterocycles to form stable adducts which are useful intermediates in synthesis.[10] Metal ligand cooperation (MLC) catalysis[11] is a new method to drive the tautomerization process, allowing for higher catalytic performance. This strategy has inspired Milstein and co-workers to design new PNN-Ru catalysts[11b] for efficient borrowing hydrogenation reactions. More recently, Luan and co-workers have developed a chiral phosphoric acid catalyzed asymmetric proton transfer reaction in metastable enamines,[12] displaying the practicality of acid-mediated tautomerization of simple enamines to imines. In addition, Hantzsch ester has been widely applied as a hydrogen donor[13] in several transformations, and enamine−imine tautomerism resulting in aromatization is the key to its reactivity. At present, the catalytic transformation of in situ tautomerization of β-enaminophosphoryl species to active imine intermediates is still a challenging process due to the highly stable conjugated NH-C═C−P═O structures. Herein, we have achieved an efficient method for the synthesis of β-aminophosphonates from β-enaminophosphonates by a bismuth-catalyzed tandem enamine−imine tautomerization and 2-aza-Cope rearrangement[14−16] sequence (Figure 1, C).

At the outset, α-phosphoryl formaldehyde **1A** and homoallylic amine **2a** were applied as the model substrates for the tandem reaction (for details, see Supporting Information Table S1). To our delight, the desired product **3A** was detected when $Bi(OTf)_3$ was chosen as the catalyst, albeit in trace yield. Taking into consideration that the effect of steric hindrance was very crucial for the 2-aza-Cope rearrangement step in the formation of the six-membered ring chair transition state, we replaced **1A** (R = Ph) with a more flexible phosphonate **1a** (R = OEt). As a result, this change increased

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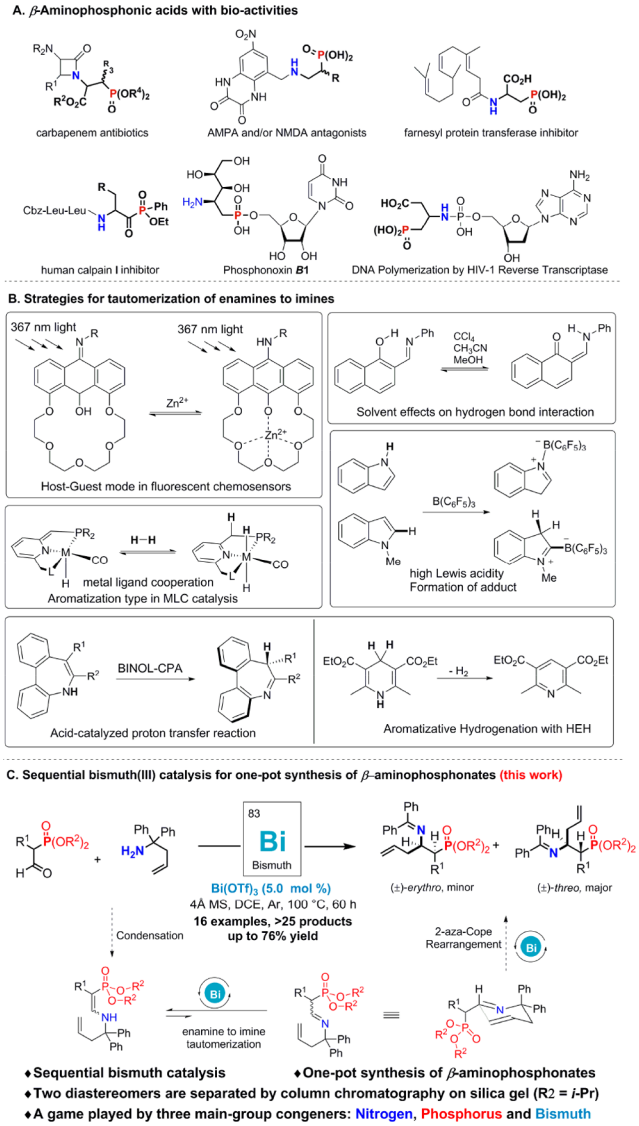

Figure 1. Bioactive β-aminophosphonic acids and strategy for enamine−imine tautomerization.

the yield of the corresponding product **3a** to 55% (Figure 2a). As indicated by Figure 2b, the phosphonate group is more favorable to formation of the six-membered ring transition state. Encouraged by these results, Brønsted acids and other metal catalysts were examined. Chiral phosphonic acids and D-camphorsulfonic acid failed to promote the reaction, as did

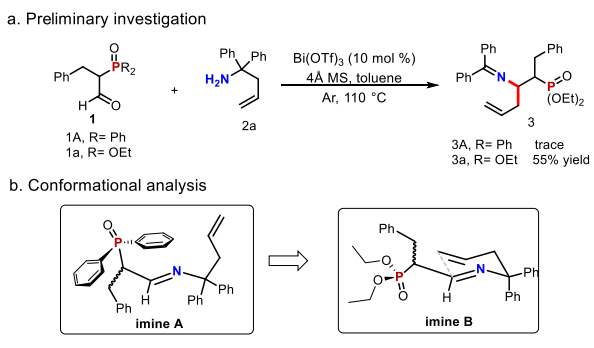

Figure 2. Preliminary results on the tandem reaction.

transition metals including platinum, palladium, rhodium, iridium, and ruthenium complexes. However, metal salts such as bismuth, tungsten, and tin were proven to be effective catalysts. On the basis of these preliminary results, $Bi(OTf)_3$ was chosen as the catalyst for further optimization.

Thereafter, we further investigated the reaction conditions (for details, see Supporting Information Table S2). At first, the temperature was evaluated (entries 1−5). The yield decreased with decreased temperature, and no product was detected below 80 °C. A variety of solvents were then screened at 90 °C (entries 6−13). The reaction did not work in solvents such as CH_3CN, dioxane, and DMAc. Comparatively, the yield was improved to 61% with DCE as the solvent. The effects of antagonistic anions were also investigated through the combination of BiI_3 with different silver salts (entries 14−26). $AgPF_6$ and $AgNTf_2$ showed comparable performance, whereas a sharp decline in yield was observed with $AgBF_4$ additive. Interestingly, the yield increased when the catalyst loading was decreased from 15 to 5.0 mol % (entries 27−29). A diminished yield was observed when the catalyst loading was reduced to 2.5 mol % (entry 30). Then, a secondary investigation on temperature was conducted (entries 31−34) and the yield was further improved to 76% at 100 °C (entry 32). Elevated or reduced concentrations gave no improved results (entries 35−36). An enantioselective variant could not be achieved despite the employment of a variety of chiral ligands.

With the optimal conditions in hand, we set out to explore the scope of this transformation (Scheme 1). Substituents in the phosphonyl group were investigated, giving good reactivity in each case (**3a**−**3c**, 56−72% yields). It should be noted that both diastereoisomers of **3c** were isolated by column chromatography on silica gel. The relative configuration was confirmed by 2D-NOESY analysis, and two isomers were described as (±)-erythro-**3c′** and (±)-threo-**3c′′** (see the SI for details). Substrates with *ortho*-I or *ortho*-Cl in the phenyl groups were well tolerated, albeit in lower yields (**3d** and **3e**, 52−54% yields). Compound **2f** with a $(p\text{-}CF_3)C_6H_4$ group also worked well, giving the product in a satisfactory yield (**3f**, 68% yield). In addition, **2g** bearing a phenolic hydroxyl group could also serve as a reaction partner; however, the two isomers failed to be isolated by column chromatography (**3g**, 40% yield). When the phenolic hydroxyl group was protected with a TBS group, the reaction still proceeded smoothly with the protecting group unaffected (**3h**, 50% yield). Monosubstituted phosphonyl formaldehyde **1i** gave a moderate yield (**3i**, 51% yield), which may derive from more flexible configuration of the corresponding imine intermediate. At this stage, we turned our attention to more general substrates, and a variety of alkyl-substituted α-phosphonyl formaldehydes were tested in the reaction. These reactions all worked smoothly to provide the corresponding β-aminophosphonates with satisfying yields (**3j**−**3o**, 69−75% yields). No isomerization of the olefin or ring-opening of the cyclopropane was observed (**3j**−**3k**, **3o**), indicating excellent tolerance of this bismuth catalysis. Notably, threo-isomers were the major products in the reaction, and the ratio of threo- to erythro-isomer varied from 1.3:1 to 2.8:1 with the change of substrates. However, the reaction did not work with substrates **1r** and **1q**, possibly due to the coordination of nitrile group to the bismuth catalyst and the strong conjugation of the aryl group. In addition, the reaction was incompatible with amines **2b**−**2d**. A possible reason may be that the spatial configurations are

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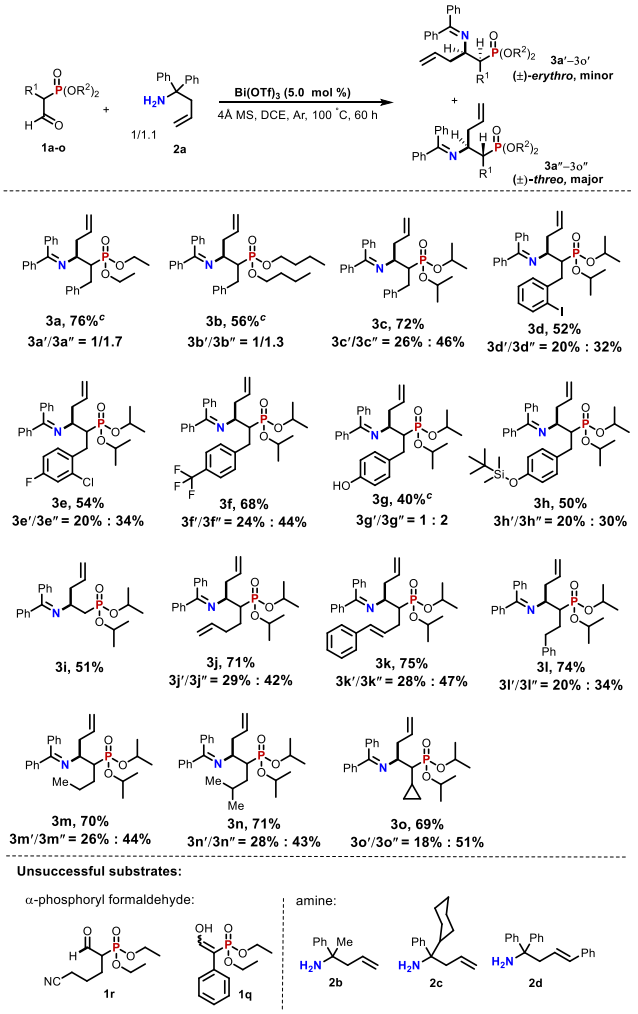
Scheme 1. Reaction Scope[a,b]



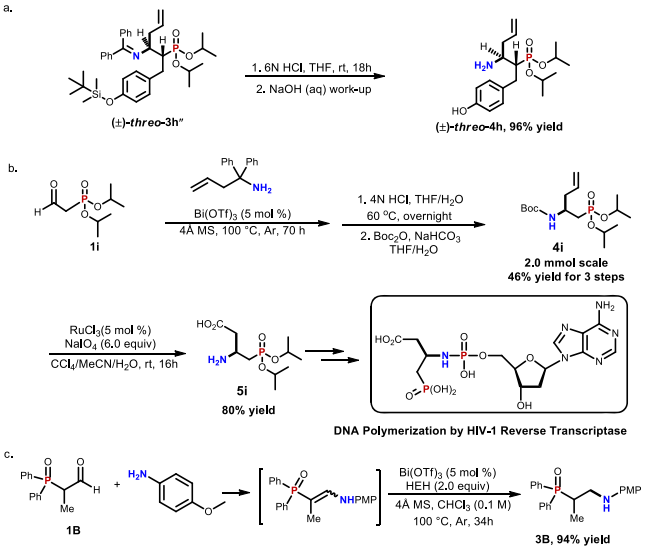
[a]$Bi(OTf)_3$ (0.01 mmol), **1a**−**1o** or **1q**−**1r** (0.10 mmol), **2a**−-**2d** (0.11 mmol), 4 Å MS (50 mg), DCE (1.0 mL), under argon at 100 °C for 60 h. [b]Yield of isolated product. [c]Two diastereomers were not isolated by column chromatography on silica gel, and the ratio was determined by ^{31}PNMR analysis.

changed with different amine substrates, disfavoring the 2-aza-Cope rearrangement processes any further.

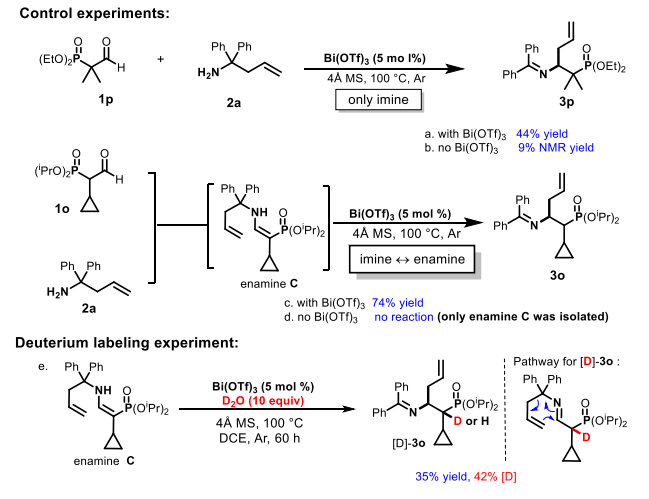
Having establishing the reaction scope, we started to explore the utilities of this method in synthesis. As demonstrated in Scheme 2a, removal of protecting groups in **3h″** was performed with high efficiency, and the corresponding amine **4h** was obtained in excellent yield. Compound **5i**, the precursor of a bioactive molecule,[17] could be easily accessed from simple starting materials with the assistance of this bismuth-mediated tandem reaction (Scheme 2b). Significantly, the current bismuth-catalyzed enamine to imine tautomerization can also cooperate with a successive transfer hydrogenation process, delivering **3B** in 94% yield through a one-pot operation (Scheme 2c).

Subsequently, mechanistic experiments were conducted to obtain more details on this transformation. To verify the role of bismuth catalyst in the reaction, a series of control experiments were performed. The reaction of **1p** and **2a** proceeded in the absence of $Bi(OTf)_3$ at 100 °C to only observe the 9% NMR yield (Schemes 3a). However, the yield was greatly increased to 44% with $Bi(OTf)_3$ as catalyst

Scheme 2. Synthetic Applications



Scheme 3. Mechanism Investigation



(Schemes 3b). These results indicated that $Bi(OTf)_3$ was very effective in prompting the 2-aza-Cope rearrangement process. To further investigate the action of $Bi(OTf)_3$ in the reaction, control reactions of **1o** and **2a** were done under bismuth catalysis, whereas no product was detected without $Bi(OTf)_3$ and only enamine intermediate C was isolated (Schemes 3c and 3**d**), which shows that $Bi(OTf)_3$ could drive the tautomerization of *β*-phosphorylenamine toward *β*-phosphoryl imine and also benefit the subsequent 2-aza-Cope rearrangement process. In addition, monodeuterated product [D]-**3o**, which was generated from the 2-aza-Cope rearrangement of the corresponding imine intermediate, was detected from the deuterium-labeling experiment of enamine **C** in the presence of 10 equiv of D_2O (Scheme 3e), indicating that a proton transfer type tautomerization of enamine **C** took place in the reaction. In conclusion, $Bi(OTf)_3$ acts as a sequential catalyst and promotes both of the two key steps in the tandem reaction: enamine−imine tautomerism and 2-aza-Cope rearrangement of imine intermediate generated in situ.

On the basis of these results and previous reports,[14,18] a plausible reaction pathway was proposed (Scheme 4). Initially, aldehyde **1** and amine **2a** were condensed to provide the

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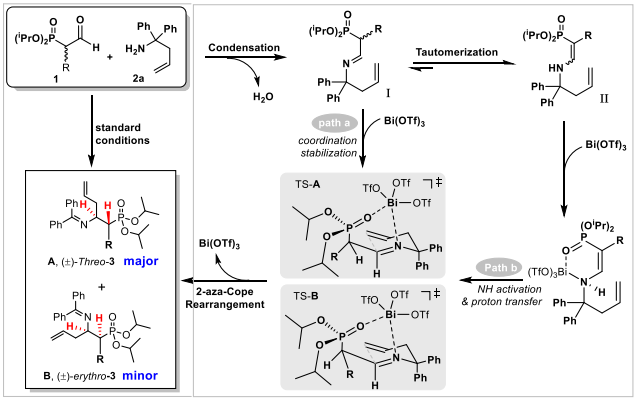
Scheme 4. Mechanistic Rationale



corresponding imine **I**, which tautomerized quickly to a more stable enamine intermediate **II** for the strong electron absorption effect of phosphonate. The bismuth catalyst may prompt this rearrangement in parallel through two possible pathways: (a) coordination stabilization of imine **I** or (b) driving enamine **II** to imine tautomerization with a proton transfer via N−Bi interactions. Subsequently, a tandem 2-aza-Cope rearrangement proceeded efficiently with the assistance of bismuth(III) under heating, furnishing the corresponding *β*-aminophosphonate **3** as a mixture of erythro- and threo-diastereomers. In the second step, TS-A and TS-B may serve as the transition states for the two diastereomers, and (±)-threo-**3** (product A) was generated from a less hindered transition state TS-A, thus providing (±)-threo-**3** as the major diastereomers.

In summary, we have disclosed a general protocol for one-pot synthesis of *β*-aminophosphonates from simple aldehydes and amines under bismuth(III) catalysis. The reaction proceeds through a tandem enamine/imine tautomerism and 2-aza-Cope rearrangement sequence, providing a variety of allylic substituted *β*-aminophosphonates with good yields.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00796.

Experimental details and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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