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One-pot Synthesis of α-Aminophosphonates via Cascade Sequence of Allylamine Isomerization/Hydrophosphonylation

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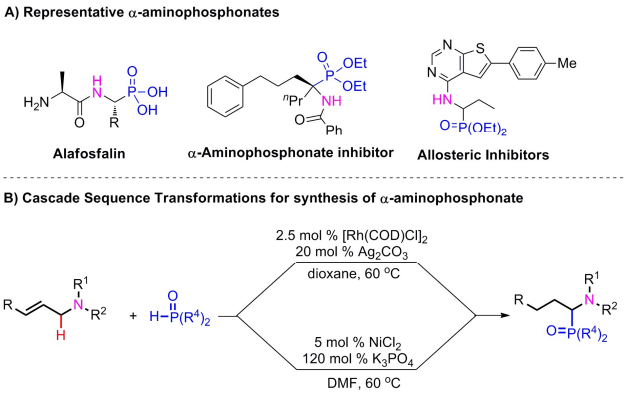
A Rh/Ni-catalyzed cascade sequence of allylamine isomerization and hydrophosphonylation to synthesis α-aminophosphonates has been disclosed. This method, not only allows the generation of widespread valuable α-aminophosphonates under simple systems and mild condition, but also enriches the process of olefin isomerization-addition both in catalytic system and reaction type variedly.

α-Aminophosphonates and α-aminophosphonic acids have received enormous attention owing to their potential biological activities in various natural products and pharmaceutical compounds.[1] Representative compounds such as the antibacterial agent alafosfalin,[2] hapten for the generation of catalytic antibodies B,[3] and the allosteric inhibitors of hFPPS (**A, Scheme 1**).[4] Among the existing methods for the preparation of α-aminophosphonates, one of the most convenient approach is the nucleophilic addition of H-phosphonates to imines to construct the C-P bond, that is, the Pudovik reaction.[5] Another important approach is the the Kabachnik–Fields reaction,[6] which involes three-component reaction between amines, carbonyl compounds, and H-phosphonates. At the same time, transition-metal-catalyzed hydrogenation[7] and phase transfer catalysis system[8] have also been used in preparation of α-aminophosphonates derivartives. However, these process usually suffers from serious limitations on substrates scope and/or reaction applicability due to the poor stability and availability of imines, To overcome these limitations, Li's CDC reaction provide a new strategy which take the advantage of an in-situ oxidative generated imine from simple amine and then reacted with H-phosphonates by nucleophilic addition to obtain the α-aminophosphonates.[9] However, base on these methodology, the examples of transition-metal-catalyzed the nucleophilic addition of allylamine isomerization to in-situ generate imine or enamine intermediate is very rare,[10] only few representative works have been reported by Terada[11] and Nielsen's groups.[12] Therefore, the development of a facile and efficient protocol toward α-aminophosphonates from the combination of stable and accessible allylamine and enamine intermediate is still highly desirable.

Herein, for the first time, we report an one-pot synthesis of α-aminophosphonates via cascade sequence transformations of allylamine isomerization and hydrophosphonylation[13] (**B, Scheme 1**). Notable features of this methodology include (a) direct hydrophosphonylation of enamine intermediate with high atom economy; (b) both terminal and unterminal allylic compound can be applied in reaction system, and the catalytic process of allylamine isomerisation to enamine intermediate which goes through the π-allyl mechanism;[14] (c) the reaction substrate is stable and accessible.



Scheme 1. Cascade Sequence Transformations of Allylamine for the Synthesis of α-Aminophosphonates

To begin our study, we chose Bz-protected allylamine and diphenylphosphine oxide as the model substrates to examine different catalysts such as $[RuClH(CO)(PPh_3)_3]$, $Pd(PPh_3)_4$, $Ni(COD)_2$, $[Ir(COD)Cl]_2$, $[Rh(COD)Cl]_2$, by using Ag_2CO_3 as the

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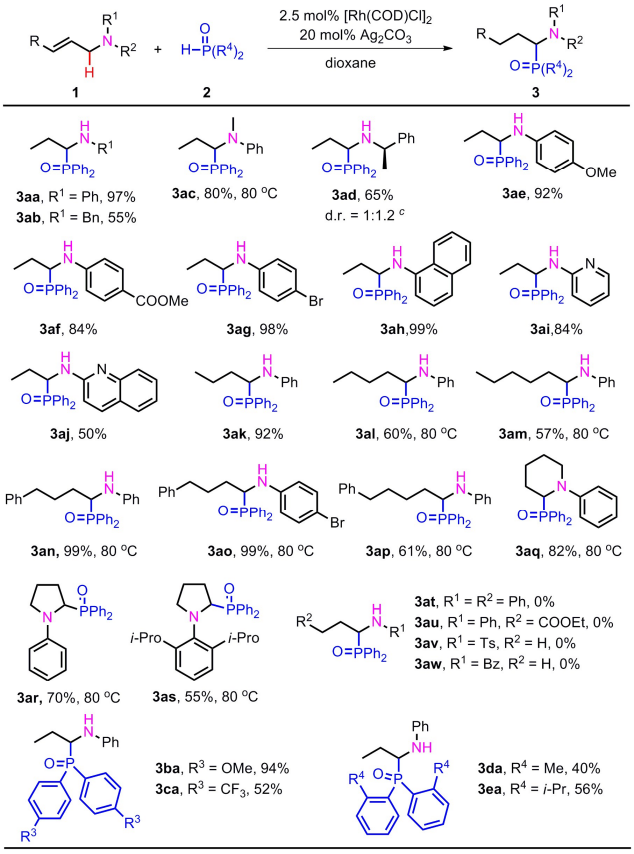
oxidant, Although α-aminophosphonates was not obtained as the desired product, we got the significant amount of isomerization product enamine when using $[Rh(COD)Cl]_2$ as the catalyst. Then, we investigated a range of *N*-protecting groups for allylamine, including Ts, Bz, Boc, Ph. Fortunately, we detected the desired product **3aa** in a yield of 91% with phenyl as *N*-protecting group by using $[Rh(COD)Cl]_2$ as catalyst and Ag_2CO_3 as additive in toluene under 60 ˚C. These results showed that the existence of phenyl group is the key to the hydrophosphonylation process. Subsequently, different solvents and additives examinations indicated that dioxane and Ag_2CO_3 were the best choices (for details see Supporting Information). Finally, we got our best result with 2.5 mol % $[Rh(COD)Cl]_2$, 20 mol % Ag_2CO_3 in dioxane at 60 °C for 16 h under Argon, and the desired product was formed in 97 % yield.

Table 1. Rh(I)-catalyzed Cascade Sequence Transformations of Allylamine with Different Phosphates[a,b]

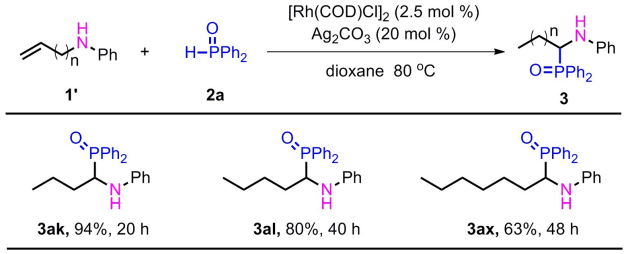


[a] All the reactions were carried out in the presence of 0.3 mmol of **1**, 1.5 equiv **2**, 2.5 mol % $[Rh(COD)Cl]_2$ and 20 mol % Ag_2CO_3 in dioxane under Ar. [b] Isolated yields based on **1**. [c] The d.r. value was determined by ^{31}P NMR.

With the optimal condition in hand, we then investigated reactivity of different allylamines (Table 1). First, we tested differnt *N*-protecting groups effect(**3aa**-**3ab** and **3av**-**3aw**) and found that the desired product could be obtained in an excellent yield by using Ph or Bn as protecting group. When we use *N*-methyl-phenyl allylamine as substrate, the reaction required a higher temperature to produce desired product in excellent yield (**3ac**). When chiral benzyl group was used to protect amino group, we got the product in a yield of 65% with low diastereoselectivity (**3ad**). Next, the investigation of different aromatic *N*-protecting groups (**3ae**-**3aj**) showed that electron-rich aromatic substituents are more conducive to produce final products. The (*E*)-typed alkyl substituted *N*-phenyl allylamine all worked well, in general, the longer alkyl chain substrates require a harsher reaction condition (**3ak**-**3am**). Also, the (*Z*)-typed substrates need a harsher reaction condition to generate the final product(**3an-3as**). When using phenyl, carbonyl or other groups that can conjugate with C-C double bond as the substution on olefin, no product was obtained (**3at-3au**). Finally, we tested different phosphorus source in the reaction (**3ba-3ea**) and found that diarylphosphoryl oxygen could well tolerate under reaction condition, with both electron-rich or electron-deficient substitution on the aromatic ring.

Beside allylamines derivities, we wanted to extend our substrates scope to other types of olefin amines. To our delight, Isomerization and hydrophosphonylation were successfully achieved over a 4/5/7-carbon chain, and the corresponding desired products were obtained in moderate to good yields by using longer reaction time, this result highlighted the universality and scope of this cascade reaction (entries 1-3, Table 2).

Table 2. Isomerization-Hydrophosphonylation with Special Vinyl amines[a,b]



[a] The reaction was carried out with $[Rh(COD)Cl]_2$ 2.5 mol %, **1** (0.30 mmol), **2a** (1.5 equiv.) and 20 mol % Ag_2CO_3 in dioxane (1.5 mL) under argon. [b]Isolated yields of **3** based on **1'**.

Unfortunately, under above system, phosphite ester was not an efficient phosphorus source for Rh(I)-catalyzed the allylamine isomerization and hydrophosphonylation reaction. After a massive screening on different metal catalysts, base, ligand, and solvent, we finally found the best conditions for using phosphite ester as phosphorus source on this cascade reaction:5 mol % $NiCl_2$, 120 mol % K_3PO_4, DMF as solvent at 60 °C for 10 h under Ar, and the desired product diethyl (1-(4-methylphenylsulfonamido)propyl) phosphonate (**6aa**) was obtained in an excellent yield of 91% (Table S2, see Supporting Information). Then a variety of phosphite esters were evaluated with *N*-allyl-4-methylbenzenesulfonamide under this Ni-system, and desired α-aminophosphonate products was obtained in good to excellent yields (**6aa-6ae**, Table 3). Different *N*-protecting groups were also examined, and methanesulfonyl, *P,P*-diphenylphosphoryl, (S)-(-)-*t*-butylsulfinyl,

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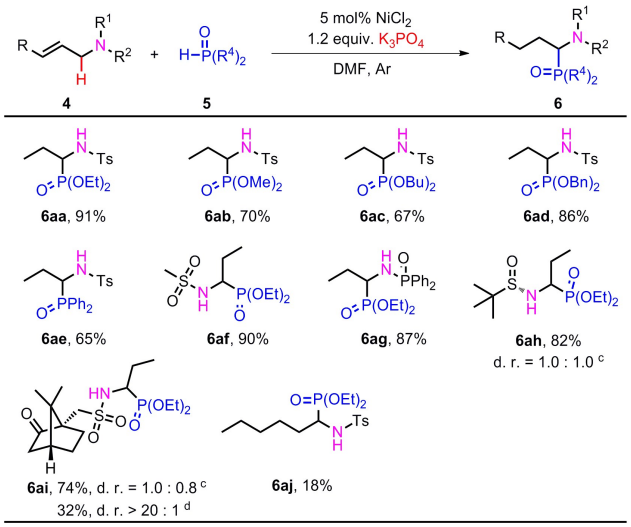
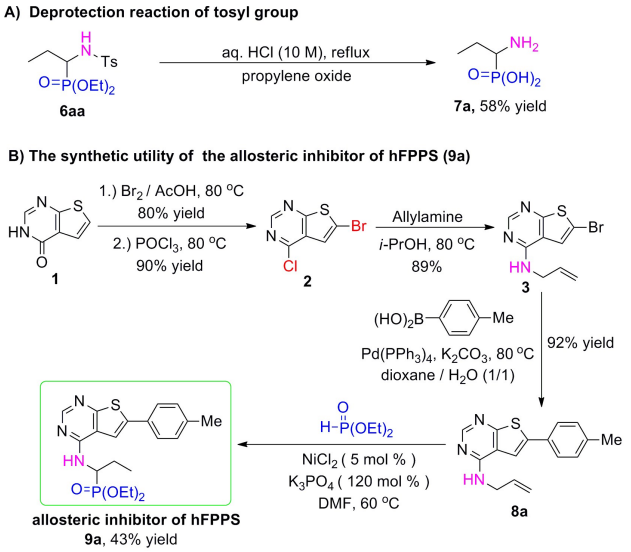
and D(+)-10-Camphorsulfonyl were proven to be suitable protecting groups for this reaction and the corresponding products were produced in good yields (**6af-6ai**). (*E*)-*N*-(hex-2-en-1-yl)-4-methylbenzenesulfonamide could also be used as substrate, although the desired product was obtained in a low yield (**6aj**).

Table 3. Ni(II)-catalyzed Cascade Sequence Transformations of Allylamine with Different Phosphates[a,b]



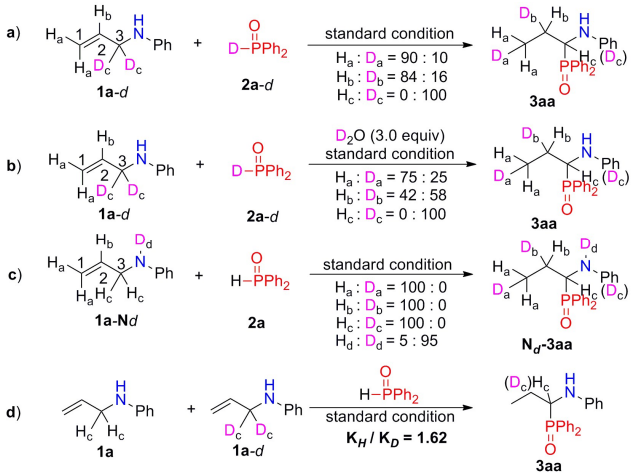
[a]All the reactions were carried out in the presence of 0.2 mmol of **4**, 1.5 equiv **5**, 5 mol % $NiCl_2$ and 120 mol % K_3PO_4 in DMF at 60 °C for 10 h under Ar. [b]Isolated yields. [c]The d.r. value was detected by ^{31}P NMR. [d]Separation from the column chromatography.

Next, several derivatization of our products were carried out, the deprotection of tosyl group of **6aa** was achieved by simply using hydrochloric acid as the reagent (10M aq.)[15] , and α-aminophosphonic acid **7a** was obtained in 58% yield (**A**, Scheme 2). we have also used thieno[2,3-d]pyrimidin-4(3H)-one (**1**) as the starting material to synthesis **8a** in four steps and then underwent Ni-catalyzed allylamine isomerization and hydrophosphonylation with diethyl phosphite, and **9a** which is an allosteric inhibitor of hFPPS was produced in a 43 yield[4] , this result highlight the synthetic utility of our method (**B**, Scheme 2).



Scheme 2. Synthesis of α-aminophosphonic acid 7a and hFPPS (9a)

To gain some insight into the this allylamine isomerization and hydrophosphonylation reaction, some control experiments were carried out. We first excluded the radical process because after we added BHT as a radical scavenger in the reaction, the desired product was obtained in 97% yield. (detail see Supporting Information). Next, different deuterium experiments were preformed under standard reaction condition (Scheme 3). When we used the deuterated diphenylphosphine oxide (**2a**-*d*) and deuterated *N*-phenylallylamine (**1a**-*d*) under reaction system, only a small amount of the both C-1 and C-2 deuterated product was observed (**a**, Scheme 3). However, when 3.0 equivalent D_2O was added into the same reaction system (**b**, Scheme 3), C-2 deuterated product was increased remarkably. It's worth to note that the no deuteration was occur on NH group. These results indicated that only enamine produced in the olefin isomerization process and the deuterated product mainly was generated from D_2O in the reaction system. To further gain direct evidence, we used *N*-deuterated phenylallylamine (**1a-N$_d$**) as substrate under standard reaction condition (**c**, Scheme 3), the correspodding *N*-deuterated product (N$_d$-**3aa**) was obtained in a quantitative yield. This result showed that there was no imine intermediate formed in the reaction. Most notably, the selective deuterium incorporation at the C-1 and C-3 positions in the product was consist with the π-allyl-type mechanism. Moreover, the kinetic isotope effects (KIE) experiment result (k_H/k_D = 1.62) (**d**, Scheme 3) indicated that the Rh-allyl intermediate is generated through C-H addition from the allylic carbon (allylic C–H activation).



Scheme 3. Deuterium Experiments Under Rh(I)-catalyzed Catalytic System

Based on literature reports [14,16] and above results, we proposed a possible mechanism for Rh-catalyzed isomerization-hydrophosphonylation reaction in scheme 4.

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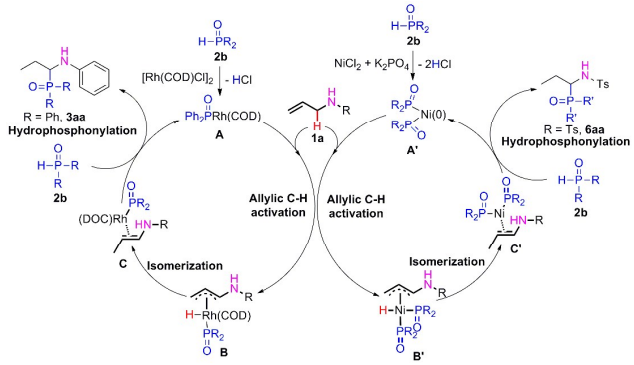
The rhodium first go though ligand exchange with diphenylphosphine oxide to form complex **A**, then the double bond of allylamine was coordinated to the metal complex **A,** followed by C-H addition of allylic carbon to generate the Rh-allyl intermediates **B**. Then, C-H reductive elimination led the formation of enamine intermediates **C**. At the same time, the diphenylphosphine oxide experiences a nucleophilic addition to enamine intermediates **C** to produce the hydrophosphonylated product **3aa** and release the Rh-catalyst to finish the catalytic cycle. Same mechanism is proposed for Ni(II)-catalyzed transformation process.



Scheme 4. Possible Mechanism of Cascade Sequence Transformations of Allylamine

Conclusions

In summary, we have developed a novel and efficient method for the construction of α-aminophosphonates by a cascade sequence of allylamine isomerization and hydrophosphonylation. The reaction process benefits from a broad selection of the comparatively stable and readily available substrates, and potential biological useful products are produced in moderate to excellent yields.

Acknowledgement

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