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Asymmetric Synthesis of α-Amino Phosphonic Acids Using Stable Imino Phosphonate as a Universal Precursor

Tsubasa Inokuma,* Takuya Sakakibara, Takatoshi Someno, Kana Masui, Akira Shigenaga, Akira Otaka, and Ken-ichi Yamada*[a]

Abstract: A practical method for synthesizing chiral α-amino phosphonic acid derivatives was developed. Readily available and stable *N*-*o*-nitrophenylsulfenyl (Nps) imino phosphonate was utilized as a substrate for a highly enantioselective Friedel–Crafts-type addition of indole or pyrrole nucleophiles catalyzed by chiral phosphoric acid. The resulting adduct was easily converted to *N*-9-fluorenylmethyloxycarbonyl (Fmoc) amino phosphonic acid, which is useful for synthesizing peptides containing an amino phosphonic acid.

Introduction

α-Amino phosphonate derivatives often serve as protease inhibitory agents acting as amino acid mimics or transition state (TS) analogues of protease substrates (Figure 1).[1] For example, α-indolyl and pyrrolyl amino phosphonates **1**[2a] and **2**[2b] possess antibacterial and anticancer activity, respectively. Peptides **3**[2c] and **4**[2d] containing a phosphonamide linkage exhibit inhibitory activity against angiotensin-converting enzyme and HIV protease, respectively. Therefore, this type of new compounds is a promising novel drug candidate. Numerous methods exist for synthesizing this structural motif in an asymmetric manner, including asymmetric hydrogenation of α-imino phosphonate[3] or enantioselective addition of phosphite to imine.[4] In these protocols, the preparation of imines having different substituents is necessary for the synthesis of amino phosphonate variants bearing different side chains. On the other hand, the addition of nucleophiles to α-imino phosphonate produces diverse derivatives from the same imine as a universal precursor by changing only the nucleophiles.[5] Kobayashi reported an enantioselective catalytic Mannich reaction of *N*-trichloroethoxycarbonyl (Troc) imino phosphonate and silyl enol ether, allylsilane, or enamide nucleophiles.[5a-c] Recently, Vicario's group applied a similar *N*-acyl imino phosphonate to the asymmetric installation of indole.[5d] Zhao reported enantioselective alkynylation of *N*-4-methoxyphenyl (PMP) imino phosphonate.[5e] The preparation of these imines, however, requires laborious manipulations. To prepare *N*-alkoxycarbonyl and *N*-acyl imines, unstable imines were generated from unstable precursors, α-halo amino acids, by an elimination reaction with a resin-supported base and used immediately before they hydrolyzed. Although the *N*-PMP imine is more stable, it also hydrolyzes on silica gel. The precursor of the imine is formylphosphonate hydrate, which is synthesized from diethyl diazomethylphosphonate by oxidation using dimethyldioxirane.[6] Furthermore, removal of the PMP protection after constructing the amino phosphonate unit has not been reported and is likely difficult due to the harsh conditions required for the deprotection. These issues hamper the synthesis of α-amino phosphonic acid derivatives by these established methods on a preparative scale, and the development of a novel imine substrate that overcomes these obstacles is in high demand.

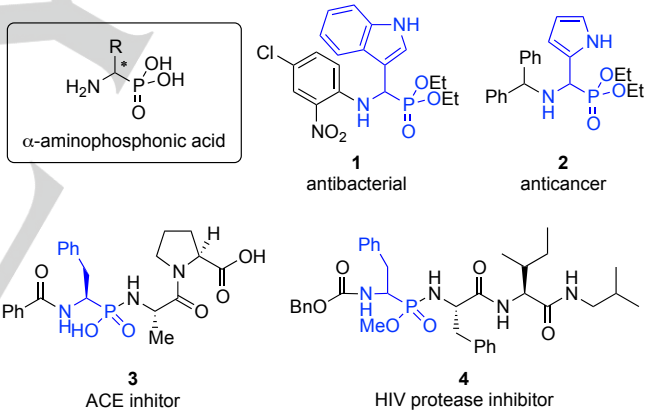

Figure 1. Examples of the biologically active α-amino phosphonate derivatives.

The *o*-nitrophenylsulfenyl (Nps) group[7] has attracted attention as a protective group of the nitrogen atom of imine for the synthesis of α-amino acid derivatives. Hiemstra and we independently reported an asymmetric Friedel–Crafts-type addition of indole to *N*-Nps imino ester[8] or amide.[9] We also reported that the *N*-Nps imino amide could be prepared by MnO_2-mediated oxidation of readily available *N*-Nps-glycine amide. The imine was so stable that it was easily purified by silica gel column chromatography and could be stored on the bench for more than 6 months. Furthermore, the Nps group could be removed under mild conditions in high chemical yield.[10] We envisioned that *N*-Nps imino phosphonate would be a suitable substrate for the efficient synthesis of α-amino phosphonic acids. Here we report the preparation of *N*-Nps imino phosphonate as a novel substrate for asymmetric

[a] Dr. T. Inokuma, T. Sakakibara, K. Masui, Dr. A. Shigenaga, Prof. Dr. A. Otaka, Prof. Dr. K. Yamada
Institute of Biomedical Sciences and Graduate School of Pharmaceutical Sciences, Tokushima University; Tokushima 770-8505, Japan
E-mail: tinokuma@tokushima-u.ac.jp (T.I.)
yamak@tokushima-u.ac.jp (K.Y.)

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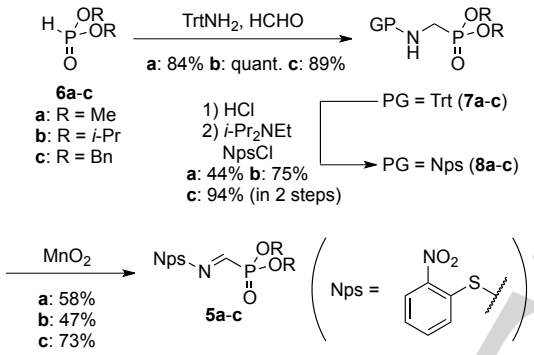
Mannich-type reactions and its application to the practical synthesis of α-amino phosphonic acids.

Results and Discussion

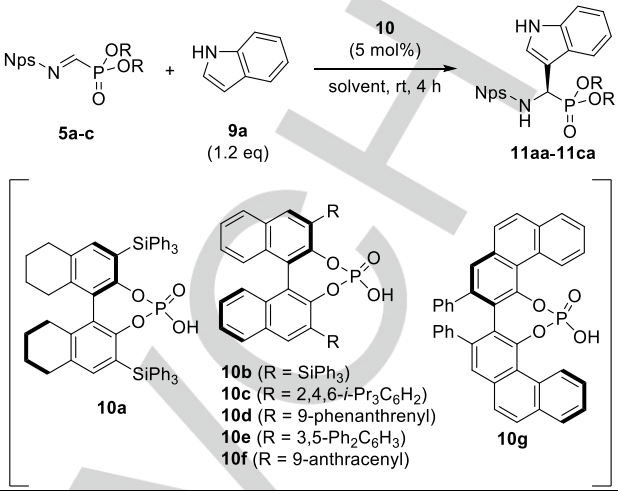
We first established a synthetic route for *N*-Nps imino phosphates **5a**–**c**, bearing different alkyl substituents at phosphonate ester moieties (Scheme 1). The three-component reaction using dialkyl phosphite **6a**–**c**, tritylamine, and formaldehyde smoothly produced **7a**–**c** in good yield.[11] Then, the trityl groups of **7a**–**c** were exchanged with an Nps group by removing the trityl group under acidic conditions followed by treatment with NpsCl. Thus-obtained **8a**–**c** were oxidized by MnO_2[12] to give the desired imino phosphonates **5a**–**c**. As expected, **5a**–**c**, as well as the corresponding imino amide, were sufficiently stable to be purified by silica gel column chromatography.[9,13]



Scheme 1. Synthesis of *N*-Nps imino phosphates **5a**–**c**.

After successfully preparing substrates **5a**–**c**, we examined the conditions for asymmetric addition. We used indole as a nucleophile to synthesize α-indolyl amino phosphonate, which is often found in biologically important α-amino phosphonate derivatives (Table 1).[2] First, imino phosphonates **5a**–**c** were subjected to an asymmetric Friedel–Crafts-type reaction with indole **9a** using BINOL-derived chiral phosphoric acid[14] as the asymmetric catalyst.[15,16] In the presence of BINOL-derived phosphoric acid catalyst **10a** in toluene,[9] **5a** gave adduct **11aa** in good yield with moderate selectivity (63% ee, entry 1). The use of more bulky substrates **5b** or **5c** improved the stereoselectivity (entries 2 and 3). On the basis of both the high selectivity and the ease of removing the benzyl groups, we selected **5c** as the substrate for further study. We next tested other BINOL-derived phosphoric acids **10b**–**g**; however, only moderate to good enantioselectivity was provided (entries 4–9), and **10a** induced the best stereoselectivity (entry 3). Solvent screening was also performed and toluene was the optimal reaction media (see SI). The absolute configuration of **11** was determined by converting **11ba** to a known compound (see SI).[5d]

Table 1. Screening of the alkyl groups of **5** and catalyst.[a]

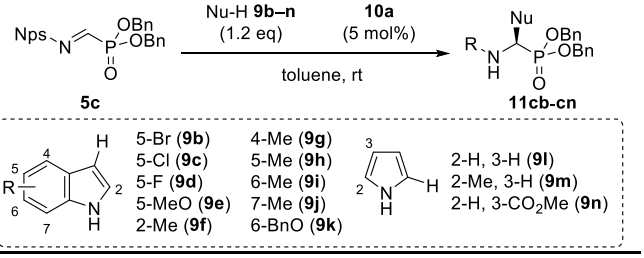


entry	R	10	11	yield (%)[b]	ee (%)[c]
1	Me (**5a**)	**10a**	**11aa**	65	63
2	*i*-Pr (**5b**)	**10a**	**11ba**	55	87
3	Bn (**5c**)	**10a**	**11ca**	73	86
4	Bn (**5c**)	**10b**	**11ca**	67	82
5	Bn (**5c**)	**10c**	**11ca**	92	1
6	Bn (**5c**)	**10d**	**11ca**	93	58
7[d]	Bn (**5c**)	**10e**	**11ca**	86	66
8	Bn (**5c**)	**10f**	**11ca**	75	73
9	Bn (**5c**)	**10g**	**11ca**	85	59

[a] The reaction was carried out using **5** (0.10 mmol), **9a** (0.12 mmol), and phosphoric acid **10** (5 μmol) in the indicated solvent for 4 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] The reaction time was 2 h.

Having established the optimal conditions, we next examined the scope of nucleophiles (Table 2). Indoles **9b**–**e**, which possess an electron-withdrawing or an electron-donating group at the 5-position, gave desired adducts **11cb**–**ce** in high enantioselectivities (entries 1–4). We examined the effect of the substituent position and found that methyl-substitution at the 5-, 6-, or 7-position was tolerated, but the reaction involving 2- or 4-substituted indoles **9f** and **9g** resulted in decreased selectivity (entries 5–9). The use of 6-benzyloxyindole **9k** successfully produced adduct **11ck**, which could be regarded as a conformationally-fixed analogue of phosphotyrosine (entry 10). The reaction was also applicable to the synthesis of α-pyrrole substituted derivatives, which have structures similar to anticancer compound **2** (entries 11). Although the yields of the reactions using substituted pyrroles **9m** or **9n** were very low, the enantioselectivities were still satisfactory (entries 12 and 13).

Table 2. Scope of nucleophiles.[a]



entry	9	time (h)	11	yield (%)[b]	ee (%)[c]
1	**9b**	24	**11cb**	67	85
2	**9c**	24	**11cc**	58	86
3	**9d**	24	**11cd**	70	85
4	**9e**	3	**11ce**	87	87
5	**9f**	6	**11cf**	95	40
6	**9g**	4	**11cg**	52	59
7	**9h**	4	**11ch**	73	86
8	**9i**	4	**11ci**	75	77
9	**9j**	6	**11cj**	72	78
10	**9k**	4	**11ck**	79	85
11	**9l**	3	**11cl**	83	75
12	**9m**	24	**11cm**	23	83
13	**9n**	24	**11cn**	8	76

[a] The reaction was carried out using **5c** (0.10 mmol), **9** (0.12 mmol) and catalyst **10a** (5 μmol). [b] Isolated yield. [c] Determined by chiral HPLC analysis.

The TS geometries were calculated at the B3LYP/6-31G** level of theory for a simplified substrate and catalyst, providing geometries TS_{major} and TS_{minor} that give (*R*)- and (*S*)-products, respectively (Figure 2). The C=N bond as well as indole N–H is likely activated by the hydrogen-bond network involving a phosphoric acid catalyst. When *N*-methyl substituted indole **9o** was used, the reaction was sluggish and the resulting stereoselectivity was poor (Scheme 2), suggesting that the hydrogen bond, $C_8H_6NH\cdots O{=}P$ (1.65 and 1.66Å, respectively) is important for stabilizing the TSs.[17] Analysis of the TS_{minor} geometry revealed that the steric repulsion between one of the bulky substituents of the catalyst and the dibenzyl phosphonate moiety of the substrate are key factors that destabilize TS_{minor}, consistent with the experimental results that substrates bearing the more bulky phosphonate had better enantioselectivity (Table 1, entries 1–3). The $\Delta\Delta G^{\ddagger}$ between TS_{major} and TS_{minor} was 0.98 kcal/mol at the wB97x-D/6-311+G**//B3LYP/6-31G** level of theory, corresponding to 67% ee at 27 °C; this is in good agreement with the experimental results (Table 1, entry 8).

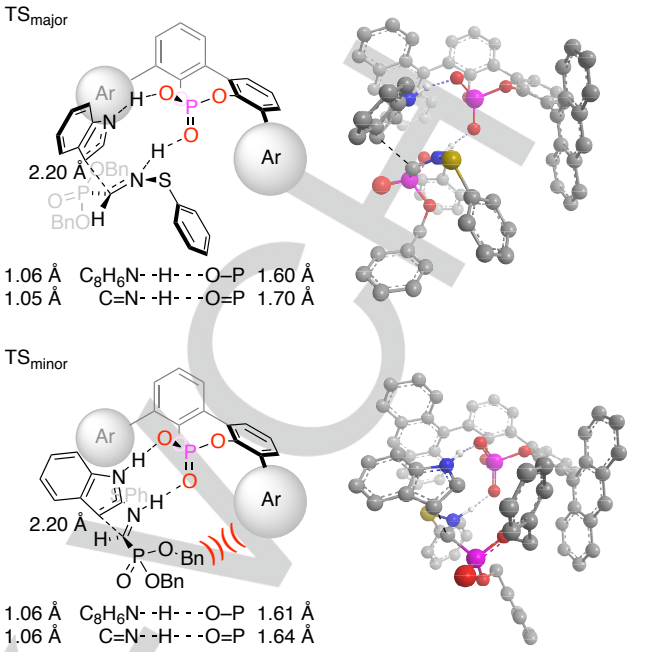
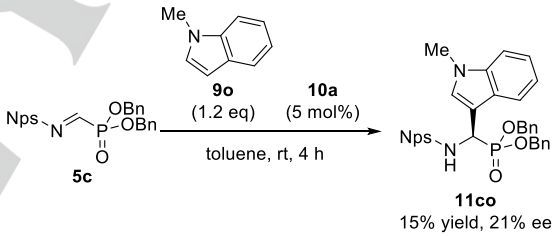
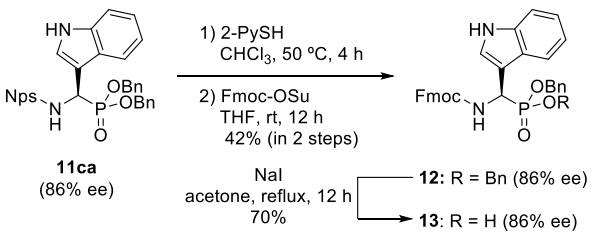


Figure 2. ChemDraw presentation and Chem3D perspective view of transition state structures TS_{major} and TS_{minor} to give (*R*)- and (*S*)-product, respectively, at the B3LYP/6-31G** level of theory.



Scheme 2. Effect of indole NH proton.

We then converted adduct **11ca** into an Fmoc-amino phosphonate (Scheme 3). The Nps group of **11ca** was removed using 2-PySH[10] and an Fmoc group was installed without racemization. Removal of one of the Bn groups of **12** was accomplished without any racemization using NaI in acetone[18] to successfully yield Fmoc amino phosphonate monobenzyl ester **13**, which is useful for the synthesis of the various amino phosphonic acid derivatives and the peptides containing phosphonamide linkage.



Scheme 3. Conversion of **11ca** into Fmoc amino phosphonate **13**.

Conclusions

We developed a novel method for the enantioselective synthesis of α-amino phosphonic acid derivatives using readily available and stable *N*-Nps imino phosphonate substrate **5c** as a universal precursor. We also successfully converted adduct **11ca** into a synthetically important derivative **13**. Development of novel biologically active compounds based on amino phosphonic acid is ongoing and will be discussed in due course.

Acknowledgements

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Keywords: amino phosphonic acid • asymmetric catalysis • Friedel–Crafts–type reaction • imino phosphonate • organocatalysis

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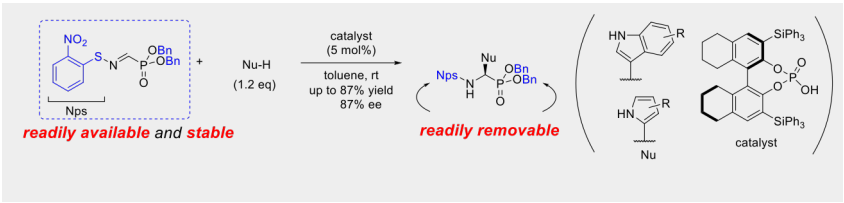

Stable imino phosphonate: Enantioselective Friedel–Crafts–type reaction of imino phosphonate and indoles or pyrroles is achieved. The readily available and stable *N*-2-Nitrophenylsulfenyl (Nps) imino phosphonate can be used as a universal substrate. The protective groups of the adducts (Nps and Bn) could be readily removed to generate the biologically important α-amino phosphonic acid derivatives.

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