Asymmetric Synthesis

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Catalytic Asymmetric 1,2-Addition of α-Isothiocyanato Phosphonates: Synthesis of Chiral β-Hydroxy- or β-Amino-Substituted α-Amino Phosphonic Acid Derivatives**

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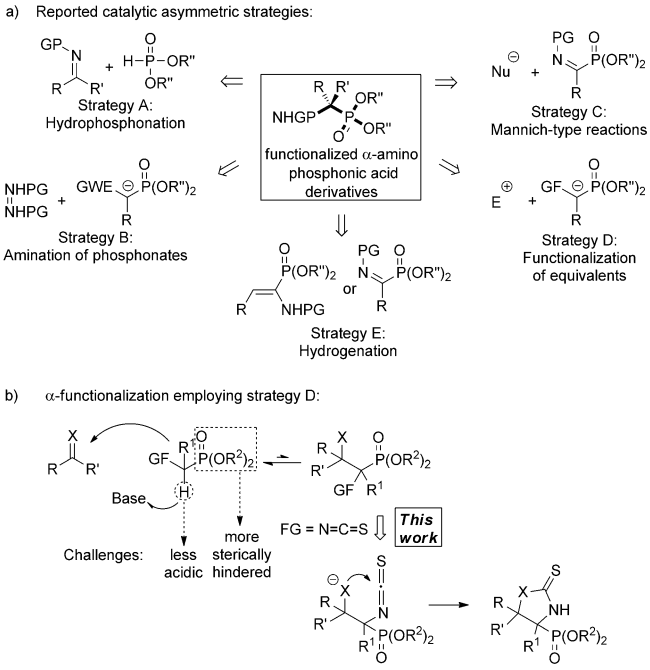
Abstract: *α-Amino phosphonic acid derivatives are considered to be the most important structural analogues of α-amino acids and have a very wide range of applications. However, approaches for the catalytic asymmetric synthesis of such useful compounds are very limited. In this work, simple, efficient, and versatile organocatalytic asymmetric 1,2-addition reactions of α-isothiocyanato phosphonate were developed. Through these processes, derivatives of β-hydroxy-α-amino phosphonic acid and α,β-diamino phosphonic acid, as well as highly functionalized phosphonate-substituted spirooxindole, can be efficiently constructed (up to 99% yield, d.r. > 20:1, and > 99% ee). This novel method provides a new route for the enantioselective functionalization of α-phosphonic acid derivatives.*

Derivatives of α-amino phosphonic acid are considered to be the most important structural analogues of α-amino acids and they also mimic the tetrahedral intermediates of peptide hydrolysis. Naturally occurring[1] and synthetic compounds incorporating such units are widely used in the fields of medicinal chemistry,[2] agriculture,[2c] metallurgy[3] and asymmetric catalysis.[4] Because of their practical importance, such organophophoric molecules have drawn tremendous interest from synthetic and medicinal chemists.[5] Since it is well known that the chirality of the α-carbon center is critical for the properties of the α-amino phosphonic acid derivatives, enantiomerically controlled synthesis is essential, and a number of elegant catalytic asymmetric syntheses have reported.[6] Several approaches were developed in these reports, and these can be divided into five main strategies (Scheme 1 a: strategies A,[7] B,[8] C,[9] D,[10] and E[11]).

Among the above-mentioned routes, nucleophilic addition of the anionic α-amino phosphonic acid equivalents (strategy D) seems to be a very convenient and versatile method because by employing different kinds of electrophiles, a variety of functionalized chiral α-amino phosphonic acid derivatives can be synthesized through several simple and atom-economic catalytic asymmetric C–C bond formation processes (such as Aldol, Mannich, and Michael additions). However, such an approach is in fact very challenging, mostly because of 1) the poor stability of a carbon anion α to the phosphonates and 2) the large steric hindrance caused by the bulky tetrahedral phosphonate group (Scheme 1 b). To date, there have only been a few reports of the application of this strategy and all of them use either relatively strong base (such as LDA and KO*t*Bu) for the deprotonation[10e–i] or incorporation of a strong electron-withdrawing group ($-NO_2$)[10a–d] to activate the α-carbon. In this context, a simple and efficient method for the synthesis of α-amino phosphonic acid derivatives is still very much needed.

Catalytic asymmetric transformations employing α-isothiocyanato compounds have recently been found to be very useful processes for the enantioselective construction of a variety of useful chiral compounds.[12] As part of our ongoing interest in transformations involving α-isothiocyanato compounds[12i,j,n,o,q,r] and the asymmetric synthesis of amino phosphonic acid derivatives,[13] we focused our atten-



Scheme 1. Reported strategies (a) and the strategy presented in this work (b) for the catalytic asymmetric synthesis of α-Amino phosphonic acid derivatives. EWG = electron-withdrawing group, PG = protecting group, FG = precursor of the amino group.

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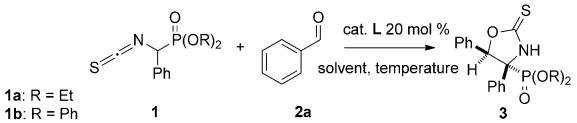
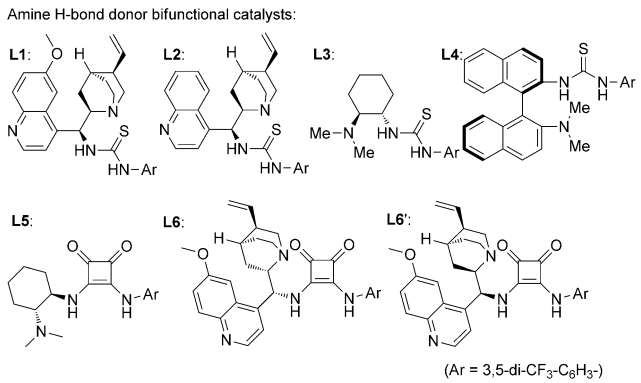
tion on the development of a novel synthetic method involving the use of isothiocyanato compounds for the construction of functionalized chiral α-amino phosphonic acid derivatives. The poor nucleophilicity of anionic α-amino phosphonic acid equivalents results in a small equilibrium constant for their addition to electrophiles. We envisaged that the α-isothiocyanato phosphonates[14] would be perfect reactants because the anion generated in the addition step can subsequently be quenched by the isothiocyanate moiety, thus pushing the reaction forward (Scheme 1b). Through the catalytic asymmetric Aldol and Mannich-type addition of α-phosphonates, optically active β-hydroxy-α-amino (phosphoserine and phosphothreonine analogues) and α,β-diamino phosphonic acid derivatives can be obtained in an efficient manner. These important phosphonic acid derivatives possess biologically significant properties but methods for their catalytic chiral synthesis are very limited.[10d,e,15]

On the basis of our recent studies on organocatalytic enantioselective reactions involving α-isothiocyanato compounds, we surmised that a bifunctional thiourea catalyst[16] would be suitable for catalyzing the 1,2-addition of α-isothiocyanato phosphonates in a double-activation mode. The initial investigation began with the reaction of the diethyl α-isothiocyanato phosphonate **1a** with benzaldehyde (**2a**) in toluene in the presence of the quinidine-derived thiourea **L1** at a 20 mol% loading (Table 1). After 48 h at 50 °C, the expected product **3** was obtained in 58% yield, with d.r. 9:1 and 68% *ee* (Table 1, entry 1). To enhance the reactivity of the isothiocyanates, the diphenyl phosphonate **1b** was then tested, and to our delight, it gave the adduct in an increased yield at 30 °C (83%; Table 1, entry 2). Next, several tertiary amine–thioureas with different types of structural scaffold, namely cinchonine, cyclohexanediamine, and binaphthylamine, were screened (Table 1, entries 3–5). However, the enatioselectivity of the reaction was still moderate. To address the need for enhanced enantioselectivity, we then screened squaramide-based H-bond-donor catalysts[17] with an increased distance between the donor hydrogens, which might be able to constrain the substrates in a well-defined orientation for the asymmetric induction. To our delight, the quinine-derived squaramide-based H-bonding catalyst **L6** gave the product with excellent stereocontrol (96% *ee*, d.r. > 20:1; Table 1, entry 7). Moreover, the reactivity was further enhanced since the adduct was obtained in 92% yield in only half of the time used before. Screening of solvents revealed that Et_2O was the most suitable for this process (95% yield, d.r. > 20:1 and 98% *ee*; Table 1, entry 11). Notably, the *ent* product could also be accessed with the same excellent results when **L6'** was used (Table 1, entry 12).

With the optimal reaction conditions established, the substrate scope of the catalytic asymmetric Aldol-type reaction was investigated by using a series of aldehydes (Table 2). Various benzaldehyde derivatives with either electron-withdrawing or electron-donating groups at the *para* or *meta* positions on the aromatic ring reacted smoothly, and the corresponding products were obtained with excellent chemical yield, diastereoselectivity, and enantioselectivity (Table 2, entries 2–4, 6, 8–12, 14, 15). The sterically hindered *ortho*-chloro/bromo-substituted substrates were also tolerated and gave the corresponding adducts with excellent yield and steroecontrol (Table 2, entry 5 and entry 7). The *ortho*-methyl-substituted substrate, however, resulted in only a moderate yield (66% yield, Table 2, entry 13). Sterically hindered 1-naphthaldehyde was also applicable in the process and gave the product with 86% yield, d.r. > 20:1, and 93% *ee* (Table 2, entry 16). Various aldehydes containing heteroaromatic rings, as well as cinnamaldehyde, were also suitable and afforded the desired compounds with excellent results in terms of yield and stereocontrol (Table 2, entries 17–19). Encouraged by the successful development of this Aldol reaction with diphenyl α-isothiocyanato phosphonate, we then attempted to extend the 1,2-addition to Mannich-type reactions for the enantioselective synthesis of α,β-diamino phosphonic acid derivatives. The model reaction was performed between **1b** and the N-Ts protected imines **4** (Table 3). To our delight, the same conditions were suitable for the new process and no further optimization was needed (Table 3, entry 1). Imines with both electron-donating and electron-withdrawing substituents at different positions on

Table 1: Optimization of the reaction.[a]

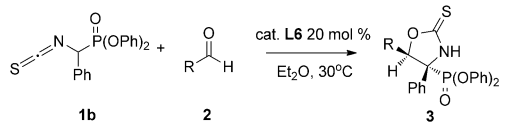


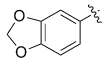


Entry	Cat.	R	Solvent	*T* [°C]	*t* [h]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**L1**	Et	Tol	50	48	58	9:1	68
2	**L1**	Ph	Tol	30	48	83	9:1	56
3	**L2**	Ph	Tol	30	48	79	13:1	60
4	**L3**	Ph	Tol	30	48	78	9:1	69
5	**L4**	Ph	Tol	30	48	trace	–	–
6	**L5**	Ph	Tol	30	48	85	>20:1	73
7	**L6**	Ph	Tol	30	24	92	>20:1	96
8	**L6**	Ph	CH_2Cl_2	30	36	96	>20:1	98
9	**L6**	Ph	MeCN	30	96	89	16:1	97
10	**L6**	Ph	THF	30	72	92	>20:1	97
11	**L6**	Ph	Et_2O	30	16	95	>20:1	98
12	**L6'**	Ph	Et_2O	30	16	94	>20:1	95

[a] Unless otherwise specified, the reaction was performed on a 0.1 mmol scale with **1** (1.0 equiv), **2a** (2.0 equiv), and catalyst **L** (20 mol%) in 1 mL solvent. [b] Yield of isolated product as a mixture of diastereoisomers. [c] Determined by ^1H and ^{31}P NMR analysis. [d] Determined by HPLC analysis on a chiral stationary phase.

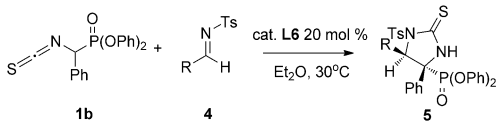
Table 2: Scope of the catalytic asymmetric synthesis of β-hydroxy-α-amino phosphonic acid derivatives.[a]



Entry	R	Product, yield [%][b]	d.r.[c]	*ee* [%][d]
1	Ph	**3ba**, 95	>20:1	98
2	4-F-C_6H_4	**3bb**, 99	>20:1	97
3	4-Cl-C_6H_4	**3bc**, 87	>20:1	95
4	3-Cl-C_6H_4	**3bd**, 81	>20:1	95
5	2-Cl-C_6H_4	**3be**, 95	16:1	90
6	3-Br-C_6H_4	**3bf**, 99	19:1	95
7	2-Br-C_6H_4	**3bg**, 93	20:1	91
8	4-NO_2-C_6H_4	**3bh**, 89	17:1	96
9	3-NO_2-C_6H_4	**3bi**, 96	20:1	>99
10	4-CF_3-C_6H_4	**3bj**, 85	20:1	92
11	4-Me-C_6H_4	**3bk**, 94	>20:1	98
12	3-Me-C_6H_4	**3bl**, 97	>20:1	96
13	2-Me-C_6H_4	**3bm**, 66	>20:1	95
14	4-MeO-C_6H_4	**3bn**, 97	>20:1	98
15		**3bo**, 91	>20:1	98
16	1-naphthyl	**3bp**, 86	>20:1	93
17	2-thienyl	**3bq**, 91	>20:1	96
18	2-furyl	**3br**, 96	>20:1	87
19	cinnamyl	**3bs**, 97	>20:1	96

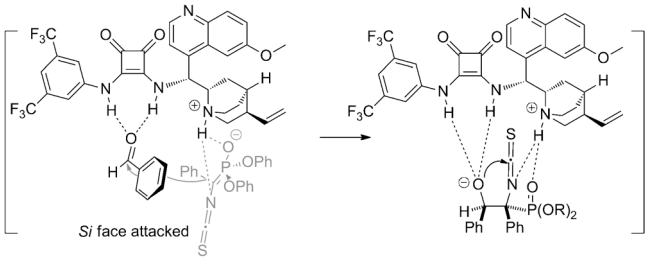
[a] Unless otherwise specified, the reaction was performed on a 0.1 mmol scale with **1b** (1.0 equiv), **2** (2.0 equiv), and catalyst **L6** (20 mol%) in 1 mL Et_2O at 30°C for 48 h. [b] Yield of isolated product as a mixture of diastereoisomers. [c] Determined by ^1H and ^{31}P NMR analysis. [d] Determined by HPLC analysis on a chiral stationary phase.

Table 3: Scope of the catalytic asymmetric synthesis of α,β-diamino phosphonic acid derivatives.[a]

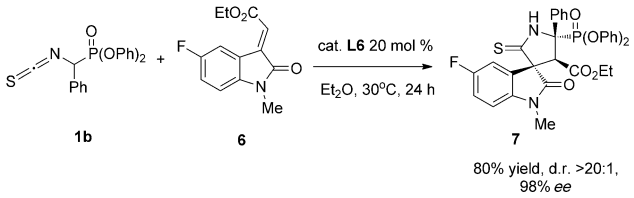


E ntry	R	yield [%][b]	d.r.[c]	*ee* [%][d]
1	Ph	**5ba**, 95	12:1	>99
2	4-F-C_6H_4	**5bb**, 99	10:1	>99
3	4-Cl-C_6H_4	**5bc**, 94	9:1	97
4	2-Cl-C_6H_4	**5bd**, 98	11:1	96
5	4-Me-C_6H_4	**5be**, 96	8:1	>99
6	3-Me-C_6H_4	**5bf**, 92	10:1	>99
7	2-Me-C_6H_4	**5bg**, 92	10:1	92
8[e]	4-MeO-C_6H_4	**5bh**, 80	6:1	>99
9	2-thienyl	**5bi**, 91	10:1	97

[a] Unless otherwise specified, the reaction was performed on a 0.1 mmol scale with **1b** (1.0 equiv), **4** (1.2 equiv), and catalyst **L6** (20 mol%) in 1 mL Et_2O at 30°C for 48 h. [b] Yield of isolated product as a mixture of diastereoisomers. [c] Determined by ^1H and ^{31}P NMR analysis. [d] Determined by HPLC analysis on a chiral stationary phase. [e] The reaction time is 72 h. Ts = toluene-4-sulfonyl.



Scheme 2. Proposed transition states.



Scheme 3. Synthesis of chiral phosphonate-substituted spirooxindole through Michael-cyclization of α-isothiocyanato phosphonate with an activated olefin.

the phenyl ring gave the corresponding products with good results in terms of yield and stereocontrol (Table 3, entries 1–8). A substrate containing a heteroaromatic ring was also tolerated (Table 3, entry 9). Generally, the diastereoselectivity of the Mannich reaction was lower than that of the Aldol reaction, while the *ee* values for the Mannich adducts were slightly higher. The absolute configuration of product **3bb** was unambiguously determined by X-ray crystallography.[18] On the basis of the experimental results, we have proposed a model to explain the stereochemistry of the Aldol/cyclization reaction sequence (Scheme 2). Attack at the *Si* face of the aldehyde leads to the formation of the major (4*R*,5*R*) product.

To further expand the scope of our method, we also investigated the performance of α-isothiocyanato phosphonate in the catalytic asymmetric 1,4-addition process. The methyleneindolinone **6** was employed as the Michael acceptor. The reaction proceeded smoothly under the described conditions and afforded the phosphonate-substituted spirooxindole with 80% yield, d.r. >20:1, and 98% *ee* (Scheme 3).[18]

In summary, an organocatalyzed enantioselective 1,2-addition reaction of α-isothiocyanato phosphonate has been successfully developed. This simple and efficient process provides a novel approach for the asymmetric synthesis of both the β-hydroxy-α-amino (up to 99% yield, d.r >20:1. and >99% *ee*) and α,β-diamino (up to 99% yield, d.r. 12:1 and >99% *ee*) phosphonic acid derivatives. Moreover, Michael addition of the α-isothiocyanato phosphonate was also viable under the established conditions. The versatile method presented herein offers an excellent starting point for the synthesis of diverse functionalized α-amino phosphonic acid derivatives. Further studies on expanding the application of this strategy and modifying peptides by using the obtained compounds are in progress.

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[18] CCDC 936073 and CCDC 963539 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

