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# Sulfonyl as a Traceless Activation Group for Enantioselective Mannich Reaction Catalyzed by Thiourea to Access Chiral β-Aminophosphonates

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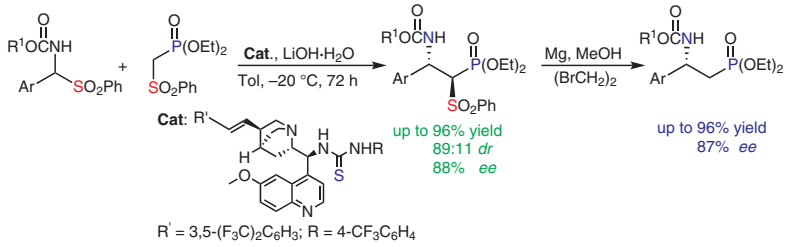


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**Abstract** An efficient enantioselective Mannich reaction of *N*-protected α-sulfones with β-benzenesulfonyl phosphonates was developed by using a chiral cinchona alkaloid-derived thiourea as a catalyst. This method was used to obtain a series of chiral α-sulfonyl-β-aminophosphonates in yields of up to 96% with 89:11 dr and 88% ee. These compounds were further transformed into β-aminophosphonates or chiral azetidines with various functional groups by a Horner–Wadsworth–Emmons/aza-Michael addition reaction sequence.

**Key words** amidosulfones, aminophosphonates, asymmetric synthesis, Mannich Reaction, thioureas, organocatalysis

β-Aminophosphonates are isosteres of carboxylates that have a high resistance to enzymatic hydrolysis and show good bioactivity in biological and pharmaceutical chemistry.[1] β-Aminophosphonates are widely present in natural products,[2] and they have potential applications in the synthesis of inhibitors of human renin and calpain I, and as anti-HIV agents. The development of methods for the synthesis of chiral β-aminophosphonic acid and its derivatives is therefore of interest to synthetic chemists, and many efficient approaches to the construction of these compounds have been established.[3]

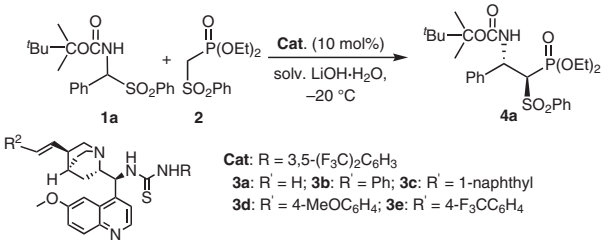
Developed methods include synthesis from natural amino acids, asymmetric Michael addition of phosphites to nitroolefins, and asymmetric hydrogenation of β-amidophosphonates. There are no reports of asymmetric Mannich reactions of methyl phosphonate with imines or their precursors as efficient methods for producing chiral β-aminophosphonic acid derivatives, especially those that cannot be obtained from proteinogenic amino acids. This may be because the low acidity of the α-hydrogen atom of a phosphonate means that a strong base is needed for deprotonation, which can make asymmetric synthesis difficult. Johnston's group[3f] reported that the introduction of an electron-withdrawing group ($NO_2$) at the α-position of a phosphonate enhances the acidity of its α-hydrogen, permitting asymmetric Mannich reactions with imines to give a series of chiral α,β-diaminophosphonic acid derivatives. The sulfone group is an efficient electron-withdrawing group, and we hypothesized that it might be used to activate the α-hydrogen atom of a phosphonate by enhancing its acidity, permitting an asymmetric Mannich reaction to occur under moderate basic conditions.

In continuation of our longstanding research efforts in phosphonate chemistry,[4] we developed a complementary method for the synthesis of chiral β-aminophosphonic acid derivatives. We investigated the asymmetric Mannich reactions of sulfonyl phosphonates with *N*-protected α-sulfones, through formation of imines in situ in the presence of a base and a chiral thiourea catalyst.[5] A series of chiral α-sulfone β-aminophosphonates were obtained, from which the sulfonyl moiety could be removed smoothly by reduction.[6] These compounds were further transformed to furnish chiral azetidines with various functional groups through sequential Horner–Wadsworth–Emmons reaction and aza-Michael addition. Here, we report our alternative strategy in which a sulfonyl group is used as a traceless activation group to obtain chiral β-aminophosphonates with good enantioselectivities and diastereoselectivities.

After conducting initial trials, we examined the reaction of the *N*-protected α-amidosulfone **1a** with the β-benzenesulfonyl phosphate **2** as a model reaction. In the presence of $LiOH·H_2O$ as a base, the chiral thioureas **3a–e** were screened as catalysts at a 10 mol% loading in toluene at –20 °C (Table 1). Catalysis with chiral thiourea **3a** gave the desired product **4a** smoothly in 83% yield with 79:21 dr and 74% ee (Table 1, entry 1). On the basis of this result, we modified the catalyst structure by introducing a phenyl group at the 11-position to give catalyst **3b**, which gave the same stereocon-

trol and maintained the enantioselectivity and diastereoselectivity of the product (entry 2). When the substituent at the 11-position was enlarged to naphthyl (**3c**), the enantioselectivity of the product increased slightly to 80% ee (entry 3). The results obtained by using catalysts **3d** and **3e** showed that the electronic effect of the substituents on the phenyl at the 11-position markedly affected the performance of the catalyst. The presence of an electron-donating methoxy substituent on the phenyl group (**3d**) resulted in a low product yield (27%) and low enantioselectivity (68% ee) (entry 4). An electron-withdrawing $CF_3$ substituent on the phenyl group at the 11-position (**3e**) gave the best results, providing a 93% yield and 83% ee (entry 5). Catalyst **3e** was therefore used to further optimize the solvent (entries 5–10) and the reaction temperature (entries 11 and 12). The results showed that toluene was the best solvent and –20 °C was the optimal temperature.

**Table 1** Catalytic Enantioselective Mannich Reaction under Various Conditions[a]

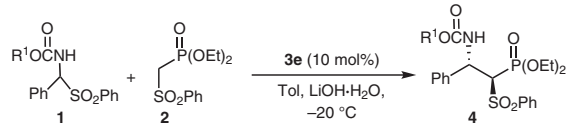



| Entry | Catalyst | Solvent | Yield[b] (%) | dr[c] | ee[d] (%) |
|---|---|---|---|---|---|
| 1 | **3a** | toluene | 83 | 79:21 | 74 |
| 2 | **3b** | toluene | 74 | 78:22 | 74 |
| 3 | **3c** | toluene | 78 | 79:21 | 80 |
| 4 | **3d** | toluene | 27 | 79:21 | 68 |
| 5 | **3e** | toluene | 93 | 80:20 | 83 |
| 6 | **3e** | PhEt | 91 | 79:21 | 83 |
| 7 | **3e** | PhCl | 76 | 78:22 | 67 |
| 8 | **3e** | THF | 35 | 78:22 | 4 |
| 9 | **3e** | $CH_2Cl_2$ | 37 | 79:21 | 16 |
| 10 | **3e** | MeCN | 67 | 79:21 | 0 |
| 11[e] | **3e** | toluene | 98 | 79:21 | 79 |
| 12[f] | **3e** | toluene | 28 | 79:21 | 86 |

[a] Reaction conditions: **1** (0.12 mmol), **2** (0.1 mmol), catalyst (10 mol%), $LiOH·H_2O$ (0.14 mmol), solvent (1.0 mL), –20 °C, 48 h.
[b] Isolated yield.
[c] Determined by $^1H$ NMR spectroscopy.
[d] Determined by chiral HPLC.
[e] Reaction at –10 °C.
[f] Reaction at –30 °C.

The effect of substituent $R^1$ as part of the N-protecting group of the α-sulfone was then explored. Boc ($R^1$ = *t*-Bu, **1d**) and Cbz ($R^1$ = Bn, **1f**), which are typical and widely used N-protecting groups, gave only moderate enantioselectivities of 63% and 45% ee, respectively (Table 2, entries 4 and 6). When the size of $R^1$ was decreased from *t*-Bu in Boc to *i*-Pr (**1e**), the enantioselectivity of the product decreased from 63% to 46% ee (entry 5). In contrast, when the steric hindrance of $R^1$ was increased by changing $R^1$ from *t*-Bu to $C(Me)_2Et$ (**1c**), the product enantioselectivity increased significantly to 78% ee (entry 3). The best result was achieved when $R^1$ was further increased in size by changing it to $C(Me)_2$-*i*-Pr (**1b**; entry 2). The novel $CO_2C(Me)_2$-*i*-Pr group was therefore the best N-protecting group and this was used for further substrate development.

**Table 2** Effect of Various N-Protecting Groups on the Enantioselective Mannich Reaction Catalyzed by **3e**[a]

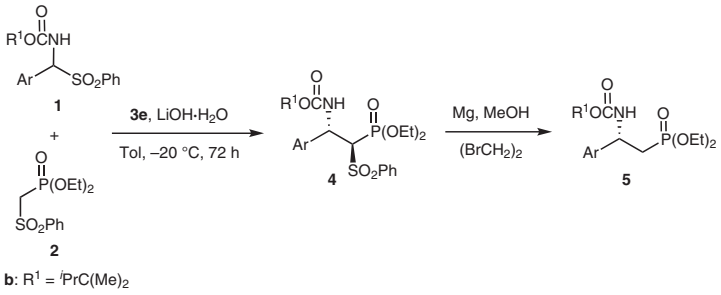



| Entry | Substrate | $R^1$ | Product | Yield[b] (%) | dr[c] | ee[d] (%) |
|---|---|---|---|---|---|---|
| 1 | **1a** | $C(Me)_2$-*t*-Bu | **4a** | 93 | 80:20 | 83 |
| 2 | **1b** | $C(Me)_2$-$^i$Pr | **4b** | 91 | 85:15 | 85 |
| 3 | **1c** | $C(Me)_2Et$ | **4c** | 98 | 88:12 | 78 |
| 4 | **1d** | *t*-Bu | **4d** | 93 | 90:10 | 63 |
| 5 | **1e** | *i*-Pr | **4e** | 95 | 92:8 | 46 |
| 6 | **1f** | Bn | **4f** | 98 | 87:13 | 45 |

[a] Reaction conditions: **1** (0.12 mmol), **2** (0.1 mmol), **3e** (10 mol%), $LiOH·H_2O$ (0.14 mmol), toluene (1.0 mL), –20 °C, 48 h.
[b] Isolated yield.
[c] Determined by $^1H$ NMR spectroscopy.
[d] Determined by chiral HPLC.

Once we had optimized the reaction conditions, we investigated the substrate scope. Various α-amidosulfones **1** were used in the catalytic asymmetric Mannich reaction (Table 3).[7] The reaction proceeded smoothly irrespective of whether there was an electron-withdrawing or an electron-donating group on the phenyl ring of the α-amidosulfone (Table 3, entries 1–11), and it gave the corresponding chiral α-sulfonyl-β-aminophosphonates in good to excellent yields with moderate to good stereoselectivities. The effect of the substituent pattern on the phenyl ring was then examined. A substituent at the *meta*-position decreased the enantioselectivity (entries 3, 5, and 10). Disubstituted α-amidosulfones with two substituents on the phenyl ring were suitable for this reaction (entries 12–14). α-Amidosulfones derived from 2-naphthyl and piperonyl aldehydes also gave good yields and high enantioselectivities (entries 15 and 16). It was difficult to separate the diastereomers of **4** by silica gel chromatography; consequently, therefore the diastereomeric ratios of **4** were determined by means of $^1H$ NMR spectroscopy. Because we intended to use the sulfonyl group as a traceless activation group, the mixtures of

**Table 3** Asymmetric Mannich Reactions of Various α-Amidosulfones Catalyzed by **3e**[a] and Subsequent Desulfonylation Reactions[b]



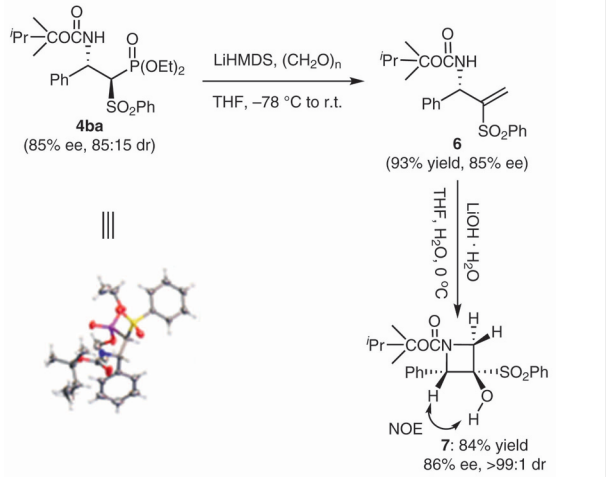

**b**: $R^1$ = $^i$PrC(Me)$_2$

| Entry | Ar | Product | Yield[c] (%) | dr[d] (%) | ee[e] (%) | Product | Yield[c] (%) | ee[e] (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | Ph | **4ba** | 91 | 85:15 | 85 | **5ba** | 81 | 84 |
| 2 | 2-$FC_6H_4$ | **4bb** | 94 | 82:18 | 83 | **5bb** | 96 | 83 |
| 3 | 3-$FC_6H_4$ | **4bc** | 96 | 85:15 | 64 | **5bc** | 84 | 65 |
| 4 | 4-$FC_6H_4$ | **4bd** | 92 | 83:17 | 83 | **5bd** | 80 | 82 |
| 5 | 3-$ClC_6H_4$ | **4be** | 86 | 84:16 | 59 | **5be** | 57 | 61 |
| 6 | 4-$ClC_6H_4$ | **4bf** | 93 | 76:24 | 77 | **5bf** | 60 | 76 |
| 7 | 2-$F_3CC_6H_4$ | **4bg** | 83 | 78:22 | 76 | **5bg** | 96 | 75 |
| 8 | 3-$MeC_6H_4$ | **4bh** | 93 | 83:17 | 86 | **5bh** | 87 | 85 |
| 9 | 4-$MeC_6H_4$ | **4bi** | 94 | 88:12 | 87 | **5bi** | 69 | 86 |
| 10 | 3-$MeOC_6H_4$ | **4bj** | 94 | 85:15 | 81 | **5bj** | 67 | 81 |
| 11 | 4-$MeOC_6H_4$ | **4bk** | 95 | 86:14 | 87 | **5bk** | 94 | 86 |
| 12 | 3,4-$(Cl)_2C_6H_3$ | **4bl** | 82 | 68:32 | 48 | **5bl** | 77 | 49 |
| 13 | 3,4-$(Me)_2C_6H_3$ | **4bm** | 88 | 89:11 | 88 | **5bm** | 87 | 87 |
| 14 | 2-Cl-4-$MeC_6H_3$ | **4bn** | 87 | 79:21 | 73 | **5bn** | 83 | 72 |
| 15 | 2-naphthyl | **4bo** | 92 | 85:15 | 80 | **5bo** | 93 | 80 |
| 16 | piperonyl | **4bp** | 88 | 84:16 | 87 | **5bp** | 82 | 86 |

[a] Reaction conditions: **1** (0.12 mmol), **2** (0.1 mmol), **3e** (10 mol%), LiOH·$H_2O$ (0.14 mmol), toluene (1.0 mL), –20 °C, 72 h.
[b] Reaction conditions: Mg turnings (30 equiv), 1,2-dibromoethane (50 μL), anhyd MeOH (0.1 mmol/mL).
[c] Isolated yield.
[d] Determined by $^1$H NMR spectroscopy.
[e] Determined by chiral HPLC.

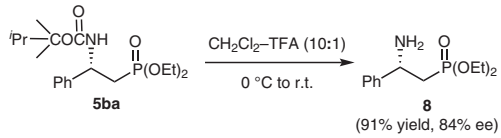
products **4** were treated with magnesium filings and 1,2-dibromoethane in anhydrous methanol to achieve smooth reductive desulfonylation[7] and transformation into the corresponding β-aminophosphonates **5** with retention of the optical purity.

To further demonstrate the potential use of the β-aminophosphonate products **4** (Scheme 1), **4ba** was treated sequentially with LiHMDS and $(CH_2O)_n$. The Horner–Wadsworth–Emmons reaction proceeded smoothly to give the asymmetric aza-Morita–Baylis–Hillman (aza-MBH)-equivalent product **6** of the α,β-unsaturated sulfone. Compound **6** was further transformed into the chiral azetidine **7** by an aza-Michael reaction in the presence of LiOH·$H_2O$ (Scheme 1).[8]




**Scheme 1** Derivatization of chiral α-sulfone β-aminophosphonates

The sulfonyl moiety can be used as a potential functional group in the production of various azetidines containing fluorine, allyl, or olefin substituents.[9] In addition, the N-protecting group $CO_2C(Me)_2$-*i*-Pr in **5** was removed smoothly in a similar manner to that used for removing Boc, to give **8** in good yield without racemization (Scheme 2).




**Scheme 2** Removal of the novel N-protecting group

The absolute configuration of **4ba** was unambiguously determined to be *S*,*S* by means of X-ray crystal analysis,[10] and the configurations of the other products were deduced accordingly. Based on the stereochemical outcome, we propose the possible transition-state model shown in Figure 1. The thiourea activates the imine by two hydrogen-bonding interactions with the nitrogen atom and the oxygen atom of the carbonate, respectively. The deprotonated anion of the β-benzenesulfonyl phosphate is directed by coordination with the tertiary nitrogen atom through its counterion, i.e., lithium. Nucleophilic addition from the *Si* face of the imine then leads to the observed favored product. The definite reason why substituents at the 11-position of the catalysts affect the catalytic performance is unclear. The absolute configuration of the new stereogenic center in **7** was confirmed by using NOESY, which showed a correlation between the benzyl proton and the hydroxy proton.

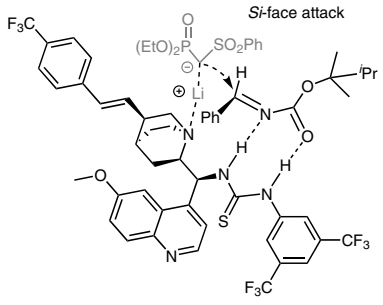



**Figure 1** Proposed transition-state model

In conclusion, we have developed a highly efficient method for synthesizing β-aminophosphonates by an enantioselective Mannich reaction catalyzed by a chiral thiourea, combined with the use of a sulfonyl as a traceless group for activating the α-hydrogen atom of a phosphonate.[11] An alternative method for obtaining aza-MBH products of α,β-unsaturated sulfones and azetidines through a Horner–Wadsworth–Emmons reaction and sequential aza-Michael addition was also established. A novel N-protecting group was also developed. Further exploration of the use of azetidines in organic synthesis is currently ongoing in our laboratory.

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## Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1589156.

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(10) CCDC 1548198 contains the supplementary crystallographic data for compound **4ba**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
(11) **Mannich Products 4 and Aminophosphonates 5; General Procedure**

The N-protected α-amido sulfone **1** (0.12 mmol, 1.2 equiv), **3e** (10 mol%), and LiOH·$H_2O$ (0.14 mmol, 1.4 equiv) were dissolved in toluene (1.0 mL) at –20 °C, and the mixture was stirred for 5 min. β-Benzenesulfonyl phosphate **2** (0.1 mmol, 1.0 equiv) was added at –20 °C, and the mixture was stirred for 72 h. The reaction was quenched with sat. aq $NH_4Cl$, and the aqueous layer was extracted with EtOAc (3 × 30 mL). The organic phases were combined, dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The crude product **4** was purified by chromatography [silica gel, EtOAc–PE].

1,2-Dibromoethane (50 µL) was added to a mixture of product **4** and Mg turnings (30 equiv) in anhyd MeOH (0.1 mmol/mL) at 0 °C, and the mixture was stirred at r.t. for 11 h. The reaction was then quenched with sat. aq $NH_4Cl$ and the mixture was filtered. The aqueous layer was extracted with EtOAc. The organic phases were combined, dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The crude product was then purified by chromatography [silica gel, EtOAc–PE].

**Diethyl ((2*S*)-2-Phenyl-2-{[(1,1,2-trimethylpropoxy)carbonyl]amino}ethyl)phosphonate (5ba)**

Prepared from **4ba** (32 mg, 0.060 mmol), Mg turnings (44 mg, 1.80 mmol), and 1,2-dibromoethane (50 µL), as described above, as a colorless oil; yield: 19 mg (81%), $[\alpha]_D^{25}$ + 13.7 (*c* = 0.38, $CH_2Cl_2$). HPLC: Chiralpak ID column [hexane–*i*-PrOH (80:20), flow rate: 0.5 mL/min, λ = 254 nm]: $t_{minor}$ = 25.6 min, $t_{major}$ = 29.8 min. $^1$H NMR (600 MHz, $CDCl_3$): δ = 7.31 (s, 4 H), 7.24 (s, 1 H), 5.81 (s, 1 H), 5.03 (s, 1 H), 4.03 (s, 2 H), 3.85 (d, *J* = 54.0 Hz, 2 H), 2.42–2.13 (m, 3 H), 1.35 (s, 6 H), 1.28 (t, *J* = 6.0 Hz, 3 H), 1.14 (s, 3 H), 0.93–0.73 (m, 6 H). $^{13}$C NMR (151 MHz, $CDCl_3$): δ = 154.9, 142.3, 128.5, 127.3, 126.0, 84.8, 61.8 (d, *J* = 7.5 Hz), 61.6 (d, *J* = 6.0 Hz), 50.3, 36.2, 33.2 (d, *J* = 140.4 Hz), 23.1, 23.0, 17.3, 16.3 (d, *J* = 6.0 Hz), 16.2 (d, *J* = 6.0 Hz). HRMS (ESI): *m/z* [M + Na]$^+$ Calcd for $C_{19}H_{32}NNaO_5P$: 408.1916; found: 408.1918.