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Organocatalytic Enantioselective Sulfenylation of β-Keto Phosphonates: A Convenient Approach to Construct Hetero-Quaternary Stereocenters

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Abstract: The highly effective and enantioselective sulfenylation of β-keto phosphonates catalyzed by α,α-diaryl-L-prolinols has been developed. The optically active α-sulfenylated β-keto phosphonates could be obtained under mild reaction conditions in good yields (up to 92%) and with excellent enantioselectivities (up to 92% *ee*).

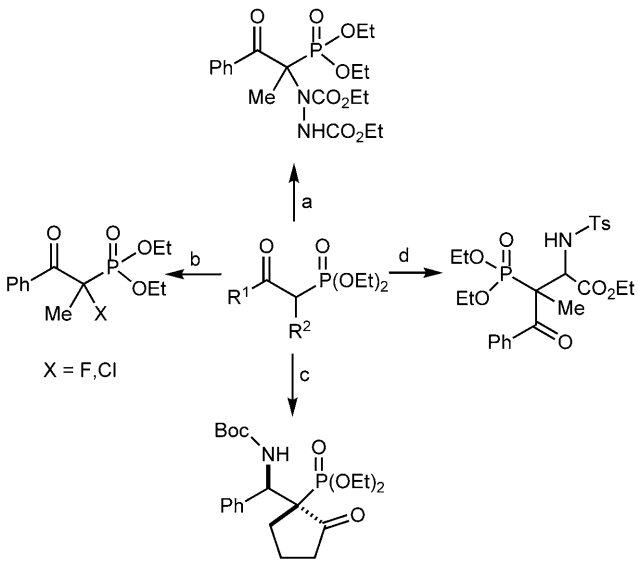
Keywords: hetero-quaternary stereocenters; β-keto phosphonates; organocatalysis; sulfenylation

A quaternary stereocenter is an essential structural motif in numerous biologically active natural molecules and pharmaceuticals, and the construction of such a framework in an asymmetric catalytic manner is one of the most challenging tasks for organic chemists. In the past few years, a lot of effort has been made on it and many powerful catalysts were developed.[1] The introduction of an electrophilic hetero atom to β-dicarbonyl compounds, such as β-keto esters has been successfully established as a simple and powerful method to construct hetero-quaternary stereocenters[2–5] due to the activated C–H bond in β-keto esters.

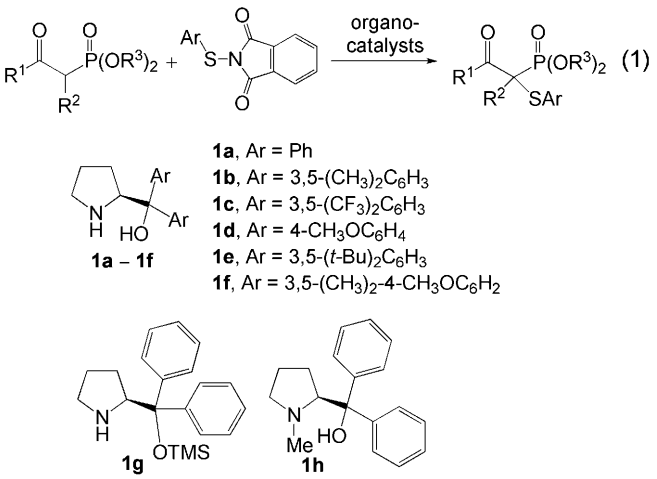
Optically active sulfur-containing compounds constitute an important class of chiral ligands, auxiliaries and synthetic intermediates in organic chemistry.[6] Benzenethiol and thioacetic acid as nucleophiles used in the direct asymmetric sulfenylation reaction have been reported in the literature.[7] Recently, as a complementary procedure, several groups have successfully reported the asymmetric sulfenylation of aldehydes,[8] ketones,[9] and substituted piperazine-2,5-diones[10] with different electrophilic sulfur reagents. Jørgensen[4a] described the first enantioselective α-sulfenylation of β-keto esters using the *Cinchona* alkaloid derivatives as the catalysts, which gave the products in up to 91% *ee*. Moreover, Togni also successfully reported the analogous transformation with chiral Ti complexes.[4b–d]

As a result of the increasing applications of chiral phosphonic acids and derivatives in peptide, pharmaceutical and medicinal chemistry, the development of efficient methods for the synthesis of these compounds is of particular significance.[11] On the basis of the feature of bond-forming reactions, a few reports on enantioselective α-amination (C–N bond formation, path a),[12,13b] α-halogenation (C–Cl or C–F bond formation, path b),[13] and Mannich-type reaction (C–C bond formation, paths c and d)[14] of β-keto phosphonates catalyzed by chiral metal complexes have been reported (Scheme 1).

Due to their inexpensive nature and ready availability, α,α-diarylprolinols as organocatalysts have attracted considerable interest and proved to be effective in many asymmetric reactions.[15] Recently, our group successfully reported the sulfenylation of β-keto esters under the catalysis of α,α-diaryl-L-prolinols with excellent enantioselectivities and satisfactory yields (92–97% *ee* with 70–82% yield).[4e] In this paper, we present the asymmetric α-sulfenylation of β-keto phosphonates based on α,α-diaryl-L-prolinols catalysis [Eq. (1)].

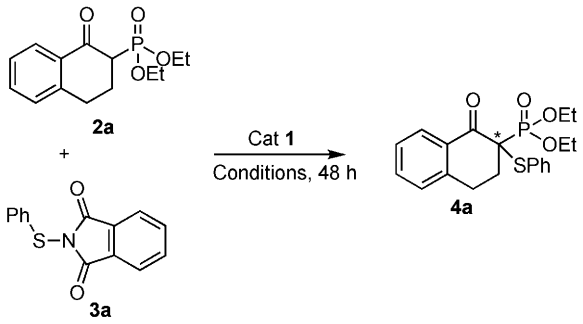


Scheme 1. The system of α-functionalization of β-keto phosphonates.



Initially, the air-stable and non-stinking N-(phenylthio)phthalimide **3a** was chosen as the sulfur source and the β-keto phosphonate **2a** as the model substrate for the optimization of the catalysts and the reaction conditions. Based on entries 1–6 of Table 1, the results indicated that the electronic properties and the substituents of the aromatic ring of the chosen catalysts (**1a–1f**) had an important impact on its performance. The sulfenylated product **4a** could be isolated in 78% yield with 75% *ee* in the presence of catalyst **1a** (Table 1, entry 1). And an increase in enantioselectivity (82% *ee*) was observed with 84% yield (Table 1, entry 2) when the catalyst **1b** was used. A slight decrease in enantioselectivity (74% *ee*) was observed when **1d** bearing an electron-donating group on the aromatic ring was tested (Table 1, entry 4). Lower yield and enantioselectivity were obtained when **1g** or **1h** was chosen as the catalyst (Table 1, entries 7 and 8), which suggested that the free OH and NH groups of the catalyst are necessary in the procedure.

Table 1. Screening of the reaction conditions for the sulfenylation of β-keto phosphonate **2a**.[a]

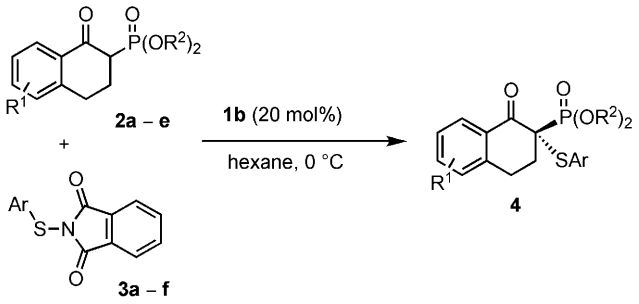


Entry	Cat.	Solvent	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	**1a**	hexane	r.t.	78	75
2	**1b**	hexane	r.t.	84	82
3	**1c**	hexane	r.t.	50	35
4	**1d**	hexane	r.t.	76	74
5	**1e**	hexane	r.t.	73	81
6	**1f**	hexane	r.t.	77	78
7	**1g**	hexane	r.t.	38	5
8	**1h**	hexane	r.t.	37	32
9	**1b**	hexane	0	78	90
10	**1b**	hexane	−20	60	89
11	**1b**	CH_2Cl_2	0	80	72
12	**1b**	DCE	0	79	76
13	**1b**	CH_3CN	0	58	60
14	**1b**	THF	0	74	70
15	**1b**	Et_2O	0	70	83
16	**1b**	toluene	0	73	84
17	**1b**	cyclohexane	0	75	86
18[d]	**1b**	hexane	0	67	88
19[e]	**1b**	hexane	0	58	85

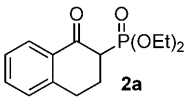
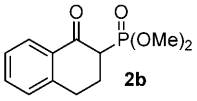
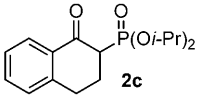
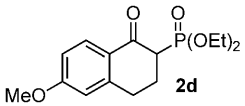
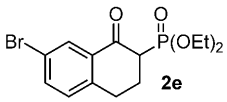
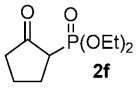
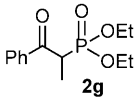
[a] *Reaction conditions:* 0.12 mmol of **3a** was added to the solution of β-keto phosphonate **2a** (0.1 mmol) and catalyst (0.02 mmol, 20 mol%) in solvent (1 mL), and the mixture was stirred for 48 h.
[b] Yield of isolated product.
[c] The *ee* values were determined by chiral HPLC analysis.
[d] 10 mol% of catalyst **1b** was used.
[e] 5 mol% of catalyst **1b** was used.

The enantioselectivity was also found to be influenced by the temperature. A lower temperature (0 °C) can lead to an increase in the *ee* value (from 82% to 90%), but an even lower temperature (−20 °C) can cause an obvious loss of yield from 84% to 60% (Table 1, entries 2, 9 and 10). A survey of solvents demonstrated that hexane is the best reaction medium for this reaction (Table 1, entries 2 and 11–17). Decreasing the catalyst loading to 0.1 or 0.05 mol% had a negative impact on the yield and slightly decreased the enantioselectivity (Table 1, entries 9, 18 and 19).

Table 2. Catalytic enantioselective sulfenylation of β-keto phosphonates.[a]



3a: Ar = Ph **3b**: Ar = *p*-Cl-C_6H_4
3c: Ar = *p*-F-C_6H_4 **3d**: Ar = *p*-Br-C_6H_4
3e: Ar = *p*-Me-C_6H_4 **3f**: Ar = *p*-MeO-C_6H_4

Entry	β-Keto phosphonates **2**	**3**	Yield [%][b]	*ee* [%][c]
1		**3a**	78 (**4a**)	90 (*R*)
2		**3b**	84 (**4b**)	92 (*R*)
3		**3c**	76 (**4c**)	86 (*R*)
4		**3d**	92 (**4d**)	75 (*R*)
5		**3e**	70 (**4e**)	80 (*R*)
6		**3f**	72 (**4f**)	80 (*R*)
7		**3a**	85 (**4g**)	90 (*R*)
8		**3b**	88 (**4h**)	90 (*R*)
9		**3b**	79 (**4i**)	84 (*R*)
10		**3a**	68 (**4j**)	85 (*R*)
11		**3b**	79 (**4k**)	83 (*R*)
12		**3f**	65 (**4l**)	82 (*R*)
13		**3a**	84 (**4m**)	87 (*R*)
14		**3b**	85 (**4n**)	88 (*R*)
15		**3f**	67 (**4o**)	84 (*R*)
16		**3b**	83 (**4p**)	59
17		**3b**	<5%	ND

[a] *Reaction conditions:* 0.12 mmol of compound **3** was added to the solution of β-keto phosphonate 2 (0.1 mmol) and catalyst **1b** (0.02 mmol, 20 mol%) in hexane (1 mL), the mixture was stirred for 48–60 h.

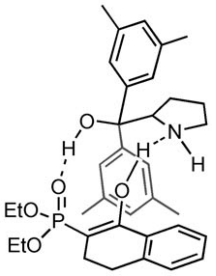
[b] Yield of isolated product.

[c] The *ee* values were determined by chiral HPLC analysis and the determination of absolute configuration was assigned on the comparison of CD spectroscopy of the product with that of sulfenylated β-keto esters with established absolute configuration.[4e]

After having established the optimal protocol for the asymmetric sulfenylation reaction, we further extended the reaction with a series of β-keto phosphonates **(2a–2g)** and different sulfur reagents (**3a–3f**) in hexane (1 mL) at 0 °C in the presence of the catalyst **1b** (20 mol%). The results are summarized in Table 2. When β-keto phosphonate **2a** was chosen as the substrate, sulfur reagents (**3a–3f**) with an electron-rich or an electron-deficient group on the aromatic ring can afford the optically active α-sulfenylated β-keto phosphonates (**4a–4f)** with excellent enantioselectivities in up to 92% *ee* (Table 2, entries 1–6). As is evident from entries 7–9 of Table 2, the enantioselectivity is slightly dependent on the substituted ester groups of the given phosphonic acid ester (**2b** and **2c**). Moreover, the β-keto phosphonate **2d** containing an electron-donating group on the aromatic ring could afford **4j** with 85% *ee* (Table 2, entry 10), and **2e** with an electron-withdrawing group could give **4n** with 88% *ee* and satisfactory yield (Table 2, entry 14). When the aliphatic five-membered ring β-keto phosphonate **2f** was chosen as the substrate, the asymmetric sulfenylation reaction could be completed in 83% yield with moderate enantioselectivity (Table 2, entry 16), which revealed that the sterically demanding β-keto phosphonates can play a key role in enantioselectivity under the catalysis of diarylprolinols. We have also tested the acyclic β-keto phosphonate **2g** with sulfur reagent **3b** under the optimal protocol, however, the result was not as positive as presented above (Table 2, entry 17).

On the basis of the results described above, the activation mode of the sulfenylation of β-keto phosphonates may be attributed to a molecular interaction rather than a covalent bond[4e,15e–k,16] (Scheme 2).The catalysts, α,α-diarylprolinols could activate the β-keto phosphonates (probably in the enol form) *via* the H-bonds, which can increase the nucleophilic ability of the reacting carbon center, and the electrophilic sulfur reagents could attack the *Re*-face of the substrate-catalyst complex to give the (*R*)-configured product **4**.

In summary, we have successfully developed the enantioselective sulfenylation of β-keto phosphonates and constructed the chiral C–S quaternary stereocenter under the catalysis of α,α-diaryl-L-prolinols. The reaction proceeds in good yields and with excellent



Scheme 2. The proposed activation mode between β-keto phosphonates and α,α-diarylprolinols.

enantioselectivities (up to 92%) for various β-keto phosphonates with *N*-(arylthio)-phthalimides as sufur reagents. Further exploration of other α-functionalizations of β-keto phosphonates using chiral organocatalyst is now in progress in our laboratory.

Experimental Section

Typical Procedure for the Organocatalytic Enantioselective Sulfenylation of β-Keto Phosphonates

A solution of catalyst **1b** (6.2 mg, 0.02 mmol) and β-keto phosphonate **2a** (28.2 mg, 0.1 mmol) in hexane (1 mL) was stirred for 10 min at 0 °C before the sulfur reagent **3a** (30.6 mg, 0.12 mmol) was added, and then the resulting mixture was stirred for 48 h. The crude reaction mixture was diluted with ethyl acetate and then directly purified by flash chromatography on silica gel to afford the corresponding product **4a**, the *ee* value was determined by chiral HPLC analysis, ^{1}H and ^{13}C NMR spectroscopy, respectively see Supporting Information for details.

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