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Asymmetric Hydrophosphonylation of α-Ketoesters Catalyzed by Cinchona-Derived Thiourea Organocatalysts

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The asymmetric reaction between a carbonyl compound and a phosphite is a powerful synthetic tool for the construction of C–P bonds in organic chemistry,[1] providing efficient access to chiral α-hydroxy phosphonates and phosphonic acids, which show biological activity and have applications in the pharmaceutical industry.[2] In recent years, several efficient, catalytic, and enantioselective methods to perform this reaction have been described. Typically, an aldehyde is treated with a phosphite in the presense of a chiral metal complex to obtain α-hydroxy phosphonates and phosphonic acids with good to excellent optical purities.[3–7] Shibasaki et al. reported the first highly enantioselective hydrophosphonylation by using heterobimetallic complexes,[3] Kee et al. studied the catalytic performance of chiral [Al(salcyen)] (salcyen= 2,2′-(1*E*,1′*E*)-[cyclohexane-1,2-diylbis(azan-1-yl-1-ylidene)]bis(methan-1-yl-1-ylidine)diphenol) and [Al(salcyan)] (salcyan=2,2′[cyclohexane-1,2-diylbis-(azanediyl)]bis(methylene)diphenol) complexes,[4] and Katsuki et al. reported highly efficient C_1-symmetric [Al(salalen)] (salalen=(*E*)-2-({2-[(2-hydroxybenzyl)(methyl)-amino]cyclohexylimino}methyl)phenol) complexes.[5] Subsequently, our group has found that both the tridentate Schiff base and 1,1′-bi-2-naphthol (BINOL)-derivative Al^{III} complexes effectively catalyze the hydrophosphonylation of aldehydes.[6] Despite these successes, there have been few reports of the hydrophosphonylation of α-ketoesters to give α-hydroxy phosphonates and phosphonic acids, therefore research into this area remains significant. Herein, we wish to describe the asymmetric hydrophosphonylation of α-ketoesters catalyzed by cinchona-derived thiourea organocatalysts.

Chiral cinchona-alkaloid-derived thioureas[7–9] are a type of bifunctional organocatalyst that combine a basic bridgehead nitrogen with a readily tunable hydrogen-bonding group, which originates from the 9-amino functionality, and have emerged as powerful tools for the asymmetric construction of chiral molecules. Accordingly, our initial investigation began by screening thiourea organocatalysts **1a–h** derived from cinchona alkaloids to evaluate their ability to promote the addition of methyl phenylglyxoylate (**2a**) with dimethyl phosphite (**3**) at 0°C in toluene. As shown in

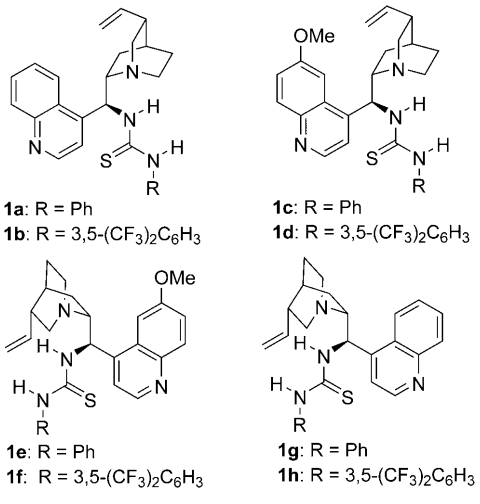

Table 1, the cinchonidine- and quinine-derived thioureas **1a–d** preferentially gave the dextrogyrous *S* compounds, whereas the quinidine- and cinchonine-derived thioureas **1e–h** gave the levorotatory *R* compounds (for discussion of the absolute configuration, see below; Table 1, entries 1–4

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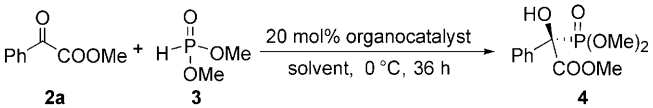
Table 1. Asymmetric hydrophosphonylation of methyl phenylglyxoylate with dimethyl phosphite.



2a 3 4

Entry[a]	Catalyst	Solvent	Yield [%][b]	*ee* [%][c]
1	**1a**	toluene	94	85
2	**1b**	toluene	93	75
3	**1c**	toluene	90	80
4	**1d**	toluene	92	72
5	**1e**	toluene	95	−76
6	**1f**	toluene	95	−66
7	**1g**	toluene	94	−82
8	**1h**	toluene	92	−73
9	**1a**	THF	94	87
10	**1g**	THF	93	−84
11[d]	**1a**	THF	92	90
12[e]	**1g**	THF	94	−88

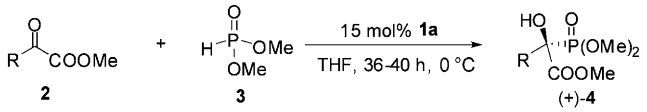
[a] Reactions were carried out with methyl phenylglyxoylate (0.1 mmol) and dimethyl phosphite (0.2 mmol) in solvent (0.4 mL). [b] Isolated yield. [c] Determined by HPLC analysis (Chiralpak AD-H). The minus means that the product is a levorotatory compound according to the optical rotation. [d] Reaction was carried out by using 15 mol% of **1a**. [e] Reaction was carried out by using THF (0.6 mL) as the solvent.

vs. 5–8). The presence of a methoxyl group on the aromatic ring has a detrimental effect on enantioselectivities (Table 1, entries 1 and 2 vs. entries 3 and 4; entries 5 and 6 vs. entries 7 and 8). With regards to the thiourea moiety, compounds **1a** and **1g**, which have a phenyl group attached, gave promising *ee* values of 85 and 82%, respectively (Table 1, entries 1 and 7). However, when **1b** and **1h**, which possess a bulky 3,5-bis(trifluoromethyl)phenyl group, were used, the *ee* values decreased appreciably (Table 1, entries 2 and 8).

To obtain the optimal conditions, a variety of variables including the choice of solvent, catalyst loading, reaction concentration, and the ester group of the phosphite and phenylglyoxylate were systematically explored (see the Supporting Information for details). A survey of various solvents revealed that THF gave the product with better reactivities and enantioselectivities (Table 1, entries 9 and 10). The change of the ester group of the phosphite and phenylglyoxylate was not beneficial to the *ee* value of the product. Subsequently, we examined the effects of catalyst loading and the reaction concentration. The reaction in the presence of the cinchonidine-derived thiourea **1a** (15 mol%) and **2a** (0.25 M) in THF gave (+)-**4a** in 92% yield with 90% *ee* (Table 1, entry 11), and the enantiomer of the hydrophosphonylation product (−)-**4a** could also be obtained in 94% yield with 88% *ee* in a reaction catalyzed by the cinchonine-derived thiourea **1g** (20 mol%) and **2a** (0.167 M) in THF (Table 1, entry 12).

Under the optimized conditions, a diverse array of aromatic α-ketoesters was examined, and the corresponding products were formed in high yields with good to excellent enantioselectivities. As shown in Table 2, methyl phenylglyoxylates with electron-donating (-CH_3, -OCH_3) substituents

Table 2. Catalyst **1a**-promoted asymmetric hydrophosphonylation of α-ketoesters with dimethyl phosphite under optimum conditions.



2 3 (+)-4

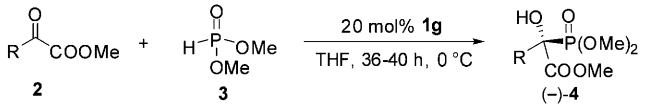
Entry[a]	R	Product	Yield [%][b]	*ee* [%][c]
1	Ph	(+)-**4a**	92	90
2	3-$CH_3C_6H_4$	(+)-**4b**	92	90
3	4-$CH_3C_6H_4$	(+)-**4c**	90	90
4	4-$CH_3OC_6H_4$	(+)-**4d**	90	91
5	3-FC_6H_4	(+)-**4e**	94	90
6	4-FC_6H_4	(+)-**4f**	90	90
7	4-ClC_6H_4	(+)-**4g**	85	90
8	4-BrC_6H_4	(+)-**4h**	87	90
9	2-thiophenyl	(+)-**4i**	91	91
10	2-naphthyl	(+)-**4j**	86	88

[a] Reactions were carried out with α-ketoester (0.1 mmol) and dimethyl phosphite (0.2 mmol) in THF (0.4 mL). [b] Isolated yield. [c] Determined by HPLC analysis (Chiralpak AD-H).

gave the corresponding products with 90–91% *ee* (Table 2, entries 2–4). The electron-withdrawing (-F, -Cl, -Br) substituted methyl phenylglyoxylates were also suitable substrates, and good isolated yields with excellent enantioselectivities (up to 90% *ee*) were obtained (Table 2, entries 5–8). Furthermore, even the heteroaromatic and fused-ring α-ketoesters could be smoothly converted to the desired products with 91 and 88% *ee*, respectively (Table 2, entries 9 and 10).

It is well known that levorotatory and dextrogyrous compounds have different biological activities. To our delight, the treatment of methyl phenylglyoxylate and **3** gave the adduct (−)-**4a** with the opposite configuration, promoted by catalyst **1g**, as shown in Table 3. Compound **3** reacted with the electron-donating (-CH_3, -OCH_3) substituted methyl phenylglyoxylates to provide the corresponding products with 81–90% *ee* (Table 3, entries 2–4). However, 80–90% *ee* were obtained when electron-withdrawing (-F, -Cl) substituted methyl phenylglyoxylates were used (Table 3, entries 5–

Table 3. Catalyst **1g**-promoted asymmetric hydrophosphonylation of α-ketoesters with dimethyl phosphite under optimum conditions.



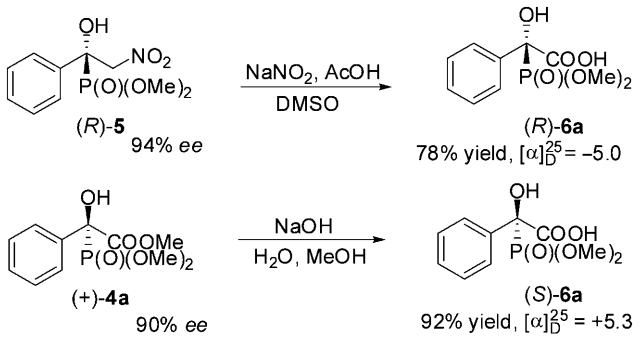
2 3 (−)-4

Entry[a]	R	Product	Yield [%][b]	*ee* [%][c]
1	Ph	(−)-**4a**	94	88
2	3-$CH_3C_6H_4$	(−)-**4b**	91	90
3	4-$CH_3C_6H_4$	(−)-**4c**	91	87
4	4-$CH_3OC_6H_4$	(−)-**4d**	84	81
5	3-FC_6H_4	(−)-**4e**	95	90
6	4-FC_6H_4	(−)-**4f**	92	86
7	4-ClC_6H_4	(−)-**4g**	85	80
8	2-thiophenyl	(−)-**4i**	90	84
9	2-naphthyl	(−)-**4j**	86	84

[a] Reactions were carried out with α-ketoester (0.1 mmol) and dimethyl phosphite (0.2 mmol) in THF (0.6 mL). [b] Isolated yield. [c] Determined by HPLC analysis (Chiralpak AD-H).

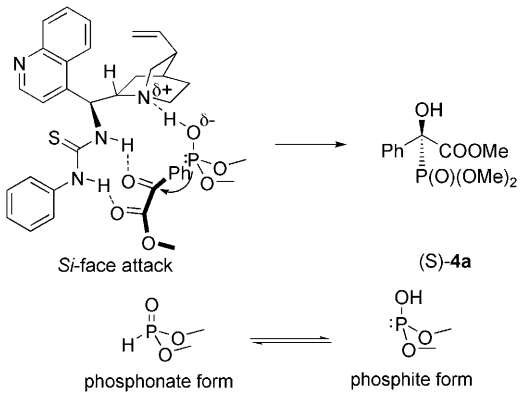
7). Moreover, *ee* values of 84% were also attained in the case of heteroaromatic and fused-ring substrates (Table 3, entries 8 and 9).

With the (*R*)-nitroaldol product **5** in hand,[10] we found it could be further elaborated into the chiral α-hydroxy acid (***R***)-**6a** ($[\alpha]_D^{25} = -5.0$) through treatment with sodium nitrite in acetic acid and DMSO.[11] However, the adduct (+)-**4a** from the reaction between **2a** and **3** could also be easily converted into the chiral α-hydroxy acid (*S*)-**6a** ($[\alpha]_D^{25} = +5.3$). The absolute configuration of (+)-**4a** as the *S* enantiomer was assigned from the optical rotation value correlation results (Scheme 1).



Scheme 1. Determination of the absolute configuration of (+)-**4a**.

Based on the absolute configuration of (+)-**4a**, a plausible catalytic model for the reaction of **2a** and **3** has been proposed (Scheme 2). The α-ketoester is activated by the



Scheme 2. Proposed asymmetric catalytic reaction model of **1a** through concerted activation.

thiourea moiety through double hydrogen bonding, which would be formed from the interaction between the NH group of **1a** and the carbonyl group of **2a**,[12–14] while the basic bridgehead nitrogen in the catalyst may shift the phosphite–phosphonate equilibrium toward the phosphite form.[1a,14c] The dimethyl phosphonate would be activated by hydrogen bonding through the interaction between the quinuclidine nitrogen atom and the hydrogen on the phosphite. Then the desired *S* product could be produced by the *Si*-face attack of the activated α-ketoester.

In conclusion, we have developed the first cinchona-derived thiourea organocatalyst that catalyzes the hydrophosphonylation of α-ketoesters. Aromatic and heteroaromatic α-ketoesters were converted in high yields (up to 95%) with high enantioselectivies (up to 91% *ee*). The *S* and *R* products were attained with the readily available cinchonidine- and cinchonine-derived catalysts **1a** and **1g**, respectively. This contribution provides a simple and practical synthetic strategy for the direct formation of α-hydroxy phosphonates and phosphonic acids from α-ketoesters. Current studies are underway to investigate the synthetic utility of the hydrophosphonylation products.

Experimental Section

Typical experimental procedures: Methyl phenylglyoxylate (15 μL, 0.1 mmol) was added to a stirred solution of catalyst **1a** (6.5 mg, 0.015 mmol) in anhydrous THF (0.4 mL) at 0°C, then dimethyl phosphite (19 μL, 0.2 mmol) was added. The resulting mixture was stirred at 0°C for 36–40 h. The mixture was purified by flash chromatography by using EtOAc/petroleum ether (1:1) as the eluent to afford (+)-**4a** as a pale-yellow liquid (25.2 mg, 92% yield, 90% *ee*).

Methyl phenylglyoxylate (15 μL, 0.1 mmol) was added to a stirred solution of catalyst **1g** (8.6 mg, 0.020 mmol) in anhydrous THF (0.6 mL) at 0°C, then dimethyl phosphite (19 μL, 0.2 mmol) was added. The resulting mixture was stirred at 0°C for 36–40 h. The mixture was purified by flash chromatography by using EtOAc/petroleum ether (1:1) as the eluent to afford (−)-**4a** as a pale-yellow liquid (25.7 mg, 94% yield, 88% *ee*).

Acknowledgements

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Keywords: asymmetric catalysis · enantioselectivity · hydrophosphonylation · ketoesters · thiourea

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