

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 presence 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-ylidene)diphenol) and [Al(salcyan)] (salcyan = 2,2' [cyclohexane-1,2-diylbis(azanediy)]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 bridge-head 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 phenylglyoxylate (**2a**) with dimethyl phosphite (**3**) at 0°C in toluene. As shown in

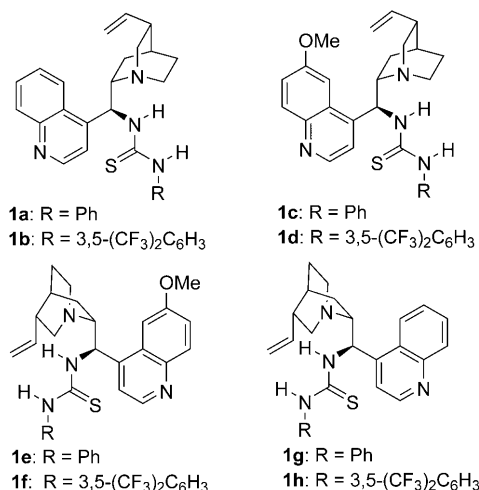


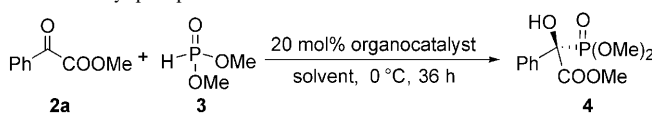
Table 1, the cinchonidine- and quinine-derived thioureas **1a–d** preferentially gave the dextrogyrous *S* compounds, whereas the quinidine- and cinchonine-derived thioureas **1e–h** gave the levorotatory *R* compounds (for discussion of the absolute configuration, see below; Table 1, entries 1–4

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



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

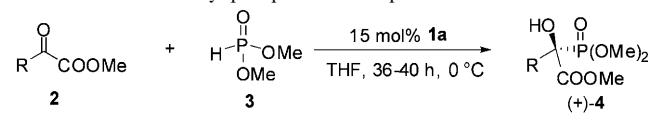
[a] Reactions were carried out with methyl phenylglyoxylate (0.1 mmol) and dimethyl phosphite (0.2 mmol) in solvent (0.4 mL). [b] Isolated yield. [c] Determined by HPLC analysis (Chiralpak AD-H). The minus means that the product is a levorotatory compound according to the optical rotation. [d] Reaction 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 (−CH₃, −OCH₃) substituents

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



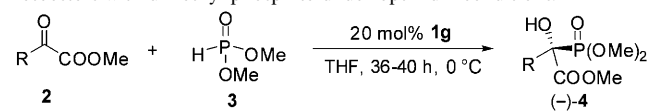
Entry ^[a]	R	Product	Yield [%] ^[b]	ee [%] ^[c]
1	Ph	(+)- 4a	92	90
2	3-CH ₃ C ₆ H ₄	(+)- 4b	92	90
3	4-CH ₃ C ₆ H ₄	(+)- 4c	90	90
4	4-CH ₃ OC ₆ H ₄	(+)- 4d	90	91
5	3-FC ₆ H ₄	(+)- 4e	94	90
6	4-FC ₆ H ₄	(+)- 4f	90	90
7	4-ClC ₆ H ₄	(+)- 4g	85	90
8	4-BrC ₆ H ₄	(+)- 4h	87	90
9	2-thiophenyl	(+)- 4i	91	91
10	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 (−CH₃, −OCH₃) 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.

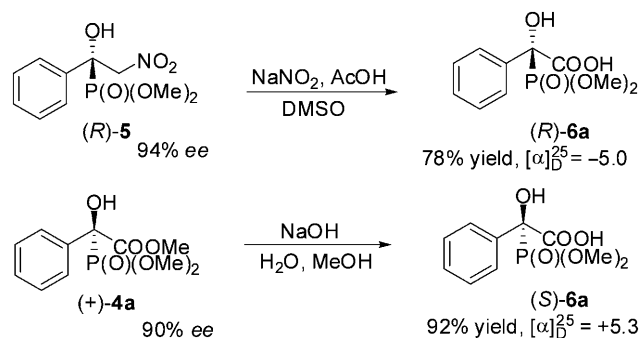


Entry ^[a]	R	Product	Yield [%] ^[b]	ee [%] ^[c]
1	Ph	(−)- 4a	94	88
2	3-CH ₃ C ₆ H ₄	(−)- 4b	91	90
3	4-CH ₃ C ₆ H ₄	(−)- 4c	91	87
4	4-CH ₃ OC ₆ H ₄	(−)- 4d	84	81
5	3-FC ₆ H ₄	(−)- 4e	95	90
6	4-FC ₆ H ₄	(−)- 4f	92	86
7	4-ClC ₆ H ₄	(−)- 4g	85	80
8	2-thiophenyl	(−)- 4i	90	84
9	2-naphthyl	(−)- 4j	86	84

[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).

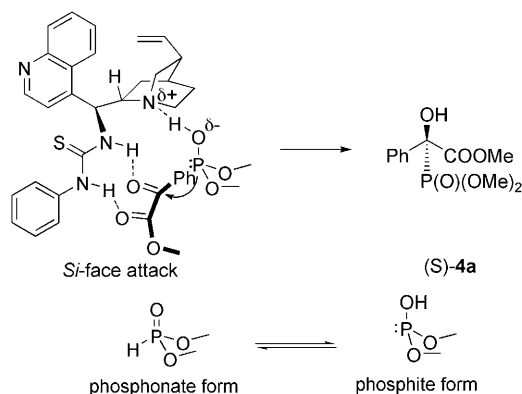
7). Moreover, *ee* values of 84% were also attained in the case of heteroaromatic and fused-ring substrates (Table 3, entries 8 and 9).

With the (*R*)-nitroaldol product **5** in hand,^[10] we found it could be further elaborated into the chiral α -hydroxy acid (**R**)-**6a** ($[\alpha]_{\text{D}}^{25} = -5.0$) 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** ($[\alpha]_{\text{D}}^{25} = +5.3$). 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.^[11a,14c] The dimethyl phosphonate would be activated by hydrogen bonding through the interaction between the qui-

nuclidine 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 enantioselectivities (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*).

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

- [1] a) D. F. Wiemer, *Tetrahedron* **1997**, 53, 16609–16644; b) H. Gröger, B. Hammer, *Chem. Eur. J.* **2000**, 6, 943–948, and references therein; c) N. P. Rath, C. D. Spilling, *Tetrahedron Lett.* **1994**, 35, 227–230; d) C. Qian, T. Huang, C. Zhu, J. Sun, *J. Chem. Soc. Perkin Trans. 1* **1998**, 2097–2104; e) T. Yokomatsu, T. Yamagishi, S. Shibuya, *Tetrahedron: Asymmetry* **1993**, 4, 1779–1782; f) T. Yamagishi, T. Yokomatsu, K. Suemune, S. Shibuya, *Tetrahedron* **1999**, 55, 12125–12136; g) D. M. Cermak, Y. Du, D. F. Wiemer, *J. Org. Chem.* **1999**, 64, 388–393; h) D. Skropeta, R. R. Schmidt, *Tetrahedron: Asymmetry* **2003**, 14, 265–273.
- [2] a) D. V. Patel, K. Rielly-Gauvin, D. E. Ryono, *Tetrahedron Lett.* **1990**, 31, 5587–5590; b) D. V. Patel, K. Rielly-Gauvin, D. E. Ryono, *Tetrahedron Lett.* **1990**, 31, 5591–5594; c) J. A. Sikorski, M. J. Miller, D. S. Braccolino, D. J. Cleary, S. G. Corey, J. L. Font, K. J. Gruys, C. Y. Han, K. C. Lin, P. D. Pansegrau, J. E. Ream, D. Schnur, A. Shah, M. C. Walker, *Phosphorus, Sulfur Silicon Relat. Elem.* **1993**, 76, 375; d) B. Stowasser, K. H. Budt, J. Li, A. Peyman, D. Ruppert, *Tetrahedron Lett.* **1992**, 33, 6625–6628.

- [3] a) T. Arai, M. Bougauchi, H. Sasai, M. Shibasaki, *J. Org. Chem.* **1996**, *61*, 2926–2927; b) H. Sasai, M. Bougauchi, T. Arai, M. Shibasaki, *Tetrahedron Lett.* **1997**, *38*, 2717–2720.
- [4] a) J. P. Duxbury, A. Cawley, M. Thornton-Pett, L. Wantz, J. N. D. Warne, R. Greatrex, D. Brown, T. P. Kee, *Tetrahedron Lett.* **1999**, *40*, 4403–4406; b) C. V. Ward, M. Jiang, T. P. Kee, *Tetrahedron Lett.* **2000**, *41*, 6181–6184; c) J. P. Duxbury, J. N. D. Warne, R. Mushtaq, C. V. Ward, M. Thornton-Pett, M. Jiang, R. Greatrex, T. P. Kee, *Organometallics* **2000**, *19*, 4445–4457.
- [5] a) B. Saito, T. Katsuki, *Angew. Chem.* **2005**, *117*, 4676–4678; *Angew. Chem. Int. Ed.* **2005**, *44*, 4600–4602; b) B. Saito, H. Egami, T. Katsuki, *J. Am. Chem. Soc.* **2007**, *129*, 1978–1986.
- [6] a) X. Zhou, X. H. Liu, X. Yang, D. J. Shang, J. G. Xin, X. M. Feng, *Angew. Chem.* **2008**, *120*, 398–400; *Angew. Chem. Int. Ed.* **2008**, *47*, 392–394; b) S. H. Gou, X. Zhou, J. Wang, X. H. Liu, X. M. Feng, *Tetrahedron* **2008**, *64*, 2864–2870.
- [7] For cinchona-derivative-catalyzed addition of phosphites to aldehydes, see: a) H. Wynberg, A. A. Smaardijk, *Tetrahedron Lett.* **1983**, *24*, 5899–5990; b) A. A. Smaardijk, S. Noorda, F. V. Bolhuis, H. Wynberg, *Tetrahedron Lett.* **1985**, *26*, 493–496; c) F. Yang, D. B. Zhao, J. B. Lan, P. H. Xi, L. Yang, S. H. Xiang, J. S. You, *Angew. Chem.* **2008**, *120*, 5728–5731; *Angew. Chem. Int. Ed.* **2008**, *47*, 5646–5649; for quinine- or thiourea-catalyzed addition of phosphites to imines, see: d) G. N. Joly, E. N. Jacobsen, *J. Am. Chem. Soc.* **2004**, *126*, 4102–4103; e) D. Pettersen, M. Marcolini, L. Bernardi, F. Fini, R. P. Herrera, V. Sgarzani, A. Ricci, *J. Org. Chem.* **2006**, *71*, 6269–6272.
- [8] For asymmetric C–C bond forming reactions with 9-thiourea cinchona alkaloids as bifunctional catalysts, see: a) B. Vakulya, S. Varga, A. Csámpai, T. Soós, *Org. Lett.* **2005**, *7*, 1967–1969; b) S. H. McCooey, S. J. Connon, *Angew. Chem.* **2005**, *117*, 6525–6528; *Angew. Chem. Int. Ed.* **2005**, *44*, 6367–6370; c) J. X. Ye, P. S. Hynes, D. J. Dixon, *Chem. Commun.* **2005**, 4481–4483; d) A. L. Tillman, J. Ye, D. J. Dixon, *Chem. Commun.* **2006**, 1191–1193; e) J. Song, Y. Wang, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 6048–6049; f) Y. Q. Wang, J. Song, R. Hong, H. M. Li, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 8156–8157; g) J. Song, H. Wang, L. Deng, *Org. Lett.* **2007**, *9*, 603–606; h) Y. Wang, H. Li, Y. Wang, Y. Liu, B. M. Foxman, L. Deng, *J. Am. Chem. Soc.* **2007**, *129*, 6364–6365; i) J. Wang, H. Li, L. Zu, W. Jiang, H. Xie, W. Duan, W. Wang, *J. Am. Chem. Soc.* **2006**, *128*, 12652–12653; j) L. S. Zu, J. Wang, H. Li, H. Xie, W. Jiang, W. Wang, *J. Am. Chem. Soc.* **2007**, *129*, 1036–1037; k) M. Amere, M. C. Lasne, J. Rouden, *Org. Lett.* **2007**, *9*, 2621–2624; l) B. Li, L. Jiang, M. Liu, Y. Chen, L. Ding, Y. Wu, *Synlett* **2005**, *4*, 603–606; m) T. Liu, J. Long, B. Li, L. Jiang, R. Li, Y. Wu, L. Ding, Y. C. Chen, *Org. Biomol. Chem.* **2006**, *4*, 2097–2099; n) H. Wennemers, J. Lubkoll, *Angew. Chem.* **2007**, *119*, 6965–6968; *Angew. Chem. Int. Ed.* **2007**, *46*, 6841–6844; o) G. Bartoli, M. Bosco, A. Carlone, M. Locatelli, A. Mazzanti, L. Sambri, P. Melchiorre, *Chem. Commun.* **2007**, 722–724.
- [9] T. Marcelli, R. N. S. van der Haas, J. H. van Maarseveen, H. Hiemstra, *Angew. Chem.* **2006**, *118*, 943–945; *Angew. Chem. Int. Ed.* **2006**, *45*, 929–931.
- [10] X. H. Chen, J. Wang, Y. Zhu, D. J. Shang, B. Gao, X. H. Liu, X. M. Feng, Z. S. Su, C. W. Hu, *Chem. Eur. J.* **2008**, DOI: chem.200801958; CCDC-698885 contains 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.
- [11] C. Matt, A. Wagner, C. Mioskowski, *J. Org. Chem.* **1997**, *62*, 234–235.
- [12] For a review of chiral hydrogen-bonding catalysis, see: a) P. R. Schreiner, *Chem. Soc. Rev.* **2003**, *32*, 289–296; b) M. S. Taylor, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 1550–1573; *Angew. Chem. Int. Ed.* **2006**, *45*, 1520–1543; c) P. M. Pihko, *Angew. Chem.* **2004**, *116*, 2110–2113; *Angew. Chem. Int. Ed.* **2004**, *43*, 2062–2064.
- [13] For the first demonstration of a chiral thiourea as an efficient chiral organic catalyst, see: M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 4901–4902.
- [14] For a mechanistic elucidation of chiral thioureas as highly efficient hydrogen-bond donors, see: a) P. Vachal, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 10012–10014; b) H. Sasai, S. Arai, Y. Tahara, M. Shibasaki, *J. Org. Chem.* **1995**, *60*, 6656–6657; c) B. Springs, P. Haake, *J. Org. Chem.* **1977**, *42*, 472–474.

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