MVK to proceed in 62–91% *ee*. More recently, Sodeoka and co-workers reported a Pd–binap complex (binap = 2,2'-bis-(diphenylphosphanyl)-1,1'-binaphthyl) that afforded 86–93% *ee* for the conjugate addition of α -substituted β -ketoesters to methyl and ethyl vinyl ketones.^[5] These chiral metal-complex-mediated reactions, which demonstrated substantial scope with respect to ketoester donors, gave greater than 90% *ee* only with MVK as the Michael acceptor. While representing remarkable progress, these results also underscore the importance as well as the challenge of the development of an operationally simple and efficient enantioselective catalytic conjugate addition of broad substrate scope for both α -substituted β -ketoesters and α , β -unsaturated ketones.

Herein, we report the first efficient and general conjugate addition of α -substituted β -ketoesters to α , β -unsaturated ketones catalyzed by a chiral organic catalyst. The reaction affords excellent enantioselectivity, diastereoselectivity, and yield, not only for a wide variety of α -substituted β -ketoesters but also, importantly, for a wide range of α , β -unsaturated ketones. Furthermore, the high stereoselectivity is often achieved at or near room temperature in air with as little as 1.0 mol% of the chiral organic catalyst.

Although 6'-hydroxy cinchona alkaloids 1 (Scheme 1) were shown to be efficient bifunctional chiral organic



Scheme 1. Structures of the 6'-hydroxy cinchona alkaloid catalysts **1** used.

catalysts for the conjugate addition of various carbon nucleophiles to nitroalkenes and vinyl sulfones,^[10] our initial attempts to apply 1 to promote the enantioselective addition of α -substituted β -ketoesters 2 to vinyl ketones 3 were unsuccessful. The reaction of ketoester 2A and MVK (3a) with catalysts 1a-c in toluene went to completion at room temperature after 0.5–2 h, but the 1,4-adduct 4Aa was formed in only moderate enantioselectivity (Table 1, entries 1–3). The enantioselectivity could be improved by performing the reaction in either dichloromethane or diethyl ether^[11] and by decreasing the reaction temperature. However, even at –78 °C, the enantioselectivity did not reach a synthetically useful level (Table 1, entry 6).

We then investigated the effect of modifying the ester group^[12] of ketoesters **2** on the enantioselectivity. The conjugate addition of *tert*-butyl ketoester **2B** to **3a** with QD-**1b** and Q-**1b** proceeded to completion in 30 min and 1 h, respectively. Significantly, these reactions occurred in a highly enantioselective fashion even at room temperature (Table 1, entries 7 and 8). The enantioselectivity could be further increased with catalyst **1c**, generating the 1,4-adduct **4Ba** in up to 97% *ee* (Table 1, entry 10). A rapid, complete, and highly enantioselective conjugate addition could even be

Conjugate Addition

DOI: 10.1002/anie.200502658

Construction of Quaternary Stereocenters by Efficient and Practical Conjugate Additions to α , β -Unsaturated Ketones with a Chiral Organic Catalyst**

Fanghui Wu, Hongming Li, Ran Hong, and Li Deng*

The conjugate addition of α -substituted β -ketoesters to α,β unsaturated ketones represents a highly versatile strategy for the creation of all-carbon quaternary stereocenters, because of the accessibility of a wide range of these Michael donors and acceptors and the proven wide utility of the 1,4-adducts. The successful coupling of the strategic power of this C-C bond formation process with an operationally simple protocol for efficient and reliable enantioselective/diastereoselective control will lead to a direct and exceptionally versatile approach for the stereocontrolled construction of all-carbon quaternary stereocenters.^[1] Consequently, this task has captured the attention of synthetic chemists since Wynberg's seminal report on the cinchona alkaloid-catalyzed addition of cvclic β -ketoesters to methyl vinyl ketone (MVK), which is the first documented catalytic enantioselective conjugate addition.^[2–8] In spite of the numerous great strides made since then in catalytic asymmetric synthesis,^[9] this task remains a formidable challenge of undiminished synthetic significance.

A breakthrough in the development of a highly enantioselective catalytic conjugate addition of α -substituted β ketoesters to vinyl ketones was reported by Shibasaki and co-workers in 1994.^[4a] A bifunctional chiral La–Na–binol complex (binol = 2,2'-dihydroxy-1,1'-binaphthyl) allowed the addition of cyclic and acyclic α -substituted β -ketoesters to

[*]	F. Wu, H. Li, Dr. R. Hong, Prof. L. Deng
	Department of Chemistry
	Brandeis University
	Waltham, MA 02454-9110 (USA)
	Fax: (+1) 781-736-2516
	E-mail: deng@brandeis.edu

^[**] This work was financially supported by the National Institutes of Health (GM-61591).



Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

Communications

Table 1: Conjugate addition of ketoesters 2A and 2B to MVK (3a).^[a,b]

	$ \begin{array}{c} 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \\$	+ Me 3a	Catalyst Solvent	→ 4Aa F 4Ba F	R = Me R = tBu	
Entry	Ketoester	Catalyst	Solvent	7 [°C]	<i>t</i> [h]	ee [%] [[]
1	2A	QD-1a	toluene	23	1	40
2	2A	QD-16	toluene	23	0.5	59
3	2 A	QD- 1 c	toluene	23	2	58
4	2A	QD-16	Et_2O	23	0.5	64
5	2A	QD-16	CH_2Cl_2	23	0.5	66
6	2 A	QD-16	CH_2Cl_2	-78	12	80
7	2 B	QD-16	CH_2Cl_2	23	0.5	91
8	2 B	Q-1 b	CH_2Cl_2	23	1	92
9	2 B	QD- 1 c	CH_2Cl_2	23	1	94
10	2 B	Q-1 c	CH_2Cl_2	23	1	97
11	2 B	Q-1c ^[d]	CH_2Cl_2	23	3	96

[a] Unless otherwise specified, the reaction was run with 2 (0.5 м in the indicated solvent) and 3 (2.5 equiv) in the presence of 1 (10 mol%). [b] All the reactions went to completion at the indicated time. [c] Determined by HPLC analysis. [d] 1.0 mol% of the catalyst was used.

1

3

4

7

8

9

10

2 G

2H

secured with a catalyst loading of only 1.0 mol% (Table 1, entry 11). As shown by a preparative-scale reaction that employed 24 mg of catalyst QD-1c (see Experimental Section), gram quantities of the chiral 1,4-adduct 4Ba could be produced within 3 h in high optical purity. Furthermore, QD-1c could be easily recovered in high yield. Thus, this gram-scale reaction consumed only 1.0 mg of the 6'-hydroxy cinchona alkaloid.

We subsequently investigated the scope of the reaction. The addition of cyclic aromatic βketoesters **2B–D** to methyl, ethyl, and aryl vinyl ketones (3a-d) proceeded rapidly to completion in excellent enantioselectivity and 93-100% yield (Table 2, entries 1-5). Similarly, high enantioselectivity and yield could also be obtained with 2E, an aliphatic ketoester (Table 2, entry 6). However, relative to the addition of 2B to 3a, the reaction rate decreased noticeably for the addition of 2E to 3a (Table 2, entry 6 versus entry 1). Guided by the hypothesis that the significantly decreased acidity of the α proton of **2E** relative to that of 2B could be the cause of the dramatically reduced rate, we attempted the addition of 2F, an

aliphatic ketoester bearing a strong electron-withdrawing hexafluoroisopropyl ester group, to 3a. Gratifyingly, the reaction with 10 mol% of Q-1c and QD-1c proceeded to completion in 30 min to afford the 1,4-adduct 4Fa with 96 and 95% ee, respectively, and excellent yields (Table 2, entry 7). Again, both the enantioselectivity and yield remained high when the catalyst loading was reduced to 1.0 mol% (Table 2, entry 8). The addition reactions of the six-membered cyclic ketoester 2G and the acyclic ketoester 2H to 3a with 1c as catalyst were also found to be highly enantioselective (Table 2, entries 9 and 10).

Our study establishes a rapid, clean, and highly enantioselective conjugated addition of a wide range of substrates that include cyclic and acyclic β-ketoesters as donors and vinyl ketones bearing alkyl and aryl substituents of varying steric and electronic properties as acceptors. The ability of 1c to afford consistently excellent enantioselectivity for various vinyl ketones is particularly noteworthy, as excellent enantioselectivity (>90% ee), to our knowledge, had not been achieved for catalytic conjugate additions of a-substituted ketoesters to vinyl ketones other than 3a.

We next explored the possibility of using 1 to promote a conjugate addition of ketoesters 2 to β -substituted enones. The achievement of high enantioselectivity and diastereose-

23

-24

24

20

89(86) 82(85^[h])

Table 2: Asymmetric conjugate addition of α -substituted β -ketoesters to vinyl ketones with bifunctional cinchona alkaloid catalyst **1 c**.^[a]



[a] Unless otherwise specified, the reaction was performed by treatment of 2 (0.3 mmol) with 3 (0.75 mmol, 2.5 equiv) and the catalyst in CH_2Cl_2 (0.6 mL). The data in parentheses are for the enantiomer obtained with QD-1c instead of Q-1c. [b] Yield of isolated product. [c] Determined by HPLC analysis. [d] The absolute configuration was determined to be R; see Supporting Information for details. [e] The reaction was performed based on gram scale of 2B (1.16 g, 5.0 mmol); see Experimental Section and Supporting Information for details. [f] The reaction was started with a solution of 2 (0.2 mmol) and 1c (0.02 mmol, 10 mol%) in CH_2Cl_2 (0.4 mL), then a solution of 3 (0.5 mmol, 2.5 equiv) in CH_2Cl_2 (0.4 mL) was added at 0.07 mL $h^{-1}.$ [g] The absolute configuration was determined to be S; see Supporting Information for details. [h] The reaction was run for 40 h.

10

10

3 a

3 a

98 (96)

90(90)

lectivity for such a conjugate addition, which involves a sterically highly hindered Michael donor and a sterically hindered and electronically relatively weak Michael acceptor, has proven to be a significant challenge. In spite of its synthetic potential for the direct enantioselective creation of adjacent all-carbon quaternary and tertiary stereocenters, to our knowledge there were only three examples of conjugate additions of trisubstituted carbon nucleophiles to β -substituted enones in synthetically useful stereoselectivity. All three literature examples, reported by Sodeoka^[5] and Jacobsen,^[7] used a trans-acyclic enone as the Michael acceptor and were promoted by chiral metal complexes.

Table 3 summarizes the results obtained for the conjugate addition of ketoesters 2 to β -substituted enones 5a-c catalyzed by cinchona alkaloids 1b and 1c. High enantioselectivity and diastereoselectivity as well as excellent yields could be attained for conjugate additions with both five- and six-membered cyclic enones (Table 3, entries 1-3). To the best

Table 3: Construction of adjacent quaternary-tertiary stereocenters by enantioselective and diastereoselective conjugate addition of β -ketoester to β -substituted $\alpha,\beta\text{-unsaturated ketones.}^{[a]}$

		0 ↓ OR ² + 2	Catal CH ₂ Cl ₂ , R ⁵ , 5		lyst 23 °C	$\rightarrow R^{1} \xrightarrow{R^{3}} R^{5}$		
			0 (5a	2) 5b	Et	О ^Д Ме 5с	6	
Entry	Ketoester	Enone	Catalyst (m	ol %)	t [h]	Yield $[\%]^{[b]}$	d.r. ^[c]	ee [%] ^[d]
1 ^[e]	2 B	5 a	QD- 1b (10)		12	99	96:4 ^[f]	98
2	2 F	5 a	Q-1c (20)		2	95	93:7	95
3 ^[g]	2 B	5 b	QD-1b (20)		120	87	93:7	85
4	2 F	5c	O-1c (20)		20	83	86:14	99 (94 ^[h])

[a] Unless otherwise specified, the reaction was performed by treatment of 2 (0.3 mmol) with 5 (0.75 mmol, 2.5 equiv) and catalyst (20 mol%) in CH_2Cl_2 (0.3 mL). [b] Yield of isolated product. [c] Unless otherwise specified, d.r. values were determined by HPLC. [d] For the major diastereomer of 6. [e] The reaction was performed with 2B (0.3 mmol) and 5a (0.7 mmol, 2.5 equiv). [f] Determined by ¹H NMR analysis of crude products. [g] The reaction was performed with **2B** (0.3 mmol) and 5b (0.7 mmol, 2.5 equiv). [h] For the minor diastereomer of 6.

of our knowledge, these represent the first examples of a highly enantioselective and diastereoselective catalytic conjugate addition of a trisubstituted carbon nucleophile to a cyclic enone. Remarkably, excellent enantioselectivity and useful diastereoselectivity could also be attained with the trans-acyclic enone 5c. Relative to the conjugate additions with vinyl ketones 3, these reactions require a longer reaction time and higher catalyst loading (Table 3, entry 4). Importantly, the reaction can be conveniently performed at room temperature and the catalysts are easily recyclable in greater than 95% yield.^[13]

In conclusion, we have demonstrated the feasibility of using a chiral organic catalyst to mediate a highly efficient and general conjugate addition of α -substituted β -ketoesters to α , β -unsaturated ketones. By giving high stereoselectivity with easily accessible catalysts under operationally simple conditions for a wide range of α -substituted β -ketoesters as well as an unprecedented wide range of enones, the current reaction represents an advance of both conceptual and synthetic significance for the development of catalytic asymmetric conjugate additions. Investigations are currently under way to fully define the scope and understand the mechanism of the reaction.

Experimental Section

Preparative-scale synthesis of tert-butyl 1-oxo-2-(3-oxobutyl)-2indancarboxylate **4Ba**: α , β -Unsaturated ketone **3a** (1.02 mL, 12.5 mmol) was added dropwise to a solution of QD-1c (24.0 mg, 0.05 mmol) and β -ketoester **2B** (1.16 g, 5.0 mmol) in CH₂Cl₂ (10.0 mL) at room temperature. The resulting clear solution was stirred at room temperature for 3 h, when 2B was completely consumed as indicated by TLC analysis. The reaction mixture was concentrated under vacuum and subjected to chromatography (SiO₂, hexanes/EtOAc 10:1) to give the desired 1,4-adduct 4Ba as a colorless

oil (1.51 g, >99% yield, 97% ee). The enantiomeric excess was determined by HPLC (Daicel Chiralcel OJ, hexanes/isopropyl alcohol (90:10), 1.00 mL min⁻¹, $\lambda =$ 220 nm, $t_r(major) = 27.9 min$, $t_r(minor) = 33.8 min$). ¹H NMR (400 MHz, CDCl₃): $\delta = 7.76$ (d, J = 8.0 Hz, 1 H), 7.62 (td, J = 7.2 Hz, 1.2 Hz, 1 H), 7.47 (d, J =8.0 Hz, 1 H), 7.40 (t, J = 7.2 Hz, 1 H), 3.61 (d, J =17.2 Hz, 1 H), 3.01 (d, J = 17.2 Hz, 1 H), 2.68–2.47 (m, 2H), 2.21–2.16 (m, 2H), 2.13 (s, 3H), 1.39 ppm (s, 9H); ¹³C NMR (100 MHz, CDCl₃): $\delta = 207.6$, 202.7, 170.1, 152.6, 135.2, 127.7, 126.3, 124.6, 81.9, 59.8, 38.8, 37.9, 29.8, 28.3, 27.2 ppm; IR (CHCl₃): $\tilde{\nu} = 2978$, 2932, 1733, 1715, 1607, 1368, 1153 cm⁻¹.

After the 1,4-adduct was collected, the column was washed with methanol to allow the recovery of QD-1c in NMR spectroscopically pure form (23 mg, 96%).

Received: July 28, 2005 Published online: December 30, 2005

Keywords: alkaloids · conjugate addition · diastereoselectivity · enantioselectivity · enones

[1] For reviews covering catalytic enantioselective conjugate additions of β -ketoesters to enones, see: a) M. Yamaguchi in Comprehensive Asymmetric Catalysis (Eds.: E. N. Jacobsen, A. Pfaltz, H.

Yamamoto), Springer, Heidelberg, 2003, Suppl. 1 to Chap. 31.2, p. 151; b) M. Shibasaki, N. Yoshikawa, Chem. Rev. 2002, 102, 2187-2209; c) N. Krause, A. Hoffmann-Röder, Synthesis 2001, 171-196; d) M. P. Sibi, S. Manyem, Tetrahedron 2000, 56, 8033-8061; for reviews on an enantioselective construction of allcarbon quaternary stereocenters, see: e) C. J. Douglas, L. E. Overman, Proc. Natl. Acad. Sci. USA 2004, 101, 5363-5367; f) J. Christoffers, A. Baro, Angew. Chem. 2003, 115, 1726-1728; Angew. Chem. Int. Ed. 2003, 42, 1688-1690; g) J. Christoffers, Chem. Eur. J. 2003, 9, 4862-4867; h) J. Christoffers, A. Mann, Angew. Chem. 2001, 113, 4725-4732; Angew. Chem. Int. Ed. 2001, 40, 4591-4597; i) E. J. Corey, A. Guzman-Perez, Angew. Chem. 1998, 110, 402-415; Angew. Chem. Int. Ed. 1998, 37, 388-401

[3] For an example of enantioselective conjugate addition of α methyl a-cyanoacetate to vinyl ketones or acrolein, see: M.

^[2] H. Wynberg, R. Helder, Tetrahedron Lett. 1975, 4057-4060.

Communications

Sawamura, H. Hamashima, Y. Ito, J. Am. Chem. Soc. 1992, 114, 8295-8296.

- [4] a) H. Sasai, T. Arai, M. Shibasaki, J. Am. Chem. Soc. 1994, 116, 1571–1572; b) H. Sasai, E. Emori, T. Arai, M. Shibasaki, *Tetrahedron Lett.* 1996, 37, 5561–5564.
- [5] Y. Hamashima, D. Hotta, M. Sodeoka, J. Am. Chem. Soc. 2002, 124, 11240–11241.
- [6] For a recent report of enantioselective addition of cyclic α substituted β -diketones to alkynones catalyzed by a cinchona alkaloid-based catalyst, see: M. Bella, K. A. Jørgensen, *J. Am. Chem. Soc.* **2004**, *126*, 5672–5673.
- [7] For chiral Al-salen complex-catalyzed conjugate addition of αphenyl α-cyanoacetate to acyclic α,β-unsaturated ketones, see:
 M. S. Taylor, D. N. Zalatan, A. M. Lerchner, E. N. Jacobsen, J. Am. Chem. Soc. 2005, 127, 1313–1317.
- [8] For an example of highly enantioselective Michael addition of cyclic β-ketoesters to MVK catalyzed by a phase-transfer catalyst, see: T. Ooi, T. Miki, M. Taniguchi, M. Shiraishi, M. Takeuchi, K. Maruoka, *Angew. Chem.* **2003**, *115*, 3926–3928; *Angew. Chem. Int. Ed.* **2003**, *42*, 3796–3798.
- [9] For a special issue focusing on asymmetric catalysis, see: a) *Proc. Natl. Acad. Sci. USA* 2004, 101, 5347-5850; for a thematic issue on enantioselective catalysis, see: b) *Chem. Rev.* 2003, 103, 2761-3400; c) *Comprehensive Asymmetric Catalysis, Vol. 1-3* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, 1999.
- [10] a) H. Li, Y. Wang, L. Tang, L. Deng, J. Am. Chem. Soc. 2004, 126, 9906–9907; b) H. Li, Y. Wang, L. Tang, F. Wu, X. Liu, C. Guo, B. M. Foxman, L. Deng, Angew. Chem. 2005, 117, 107–110; Angew. Chem. Int. Ed. 2005, 44, 105–108; c) H. Li, J. Song, X. Liu, L. Deng, J. Am. Chem. Soc. 2005, 127, 8948–8949.
- [11] Ethyl acetate, tetrahydrofuran, dimethylformamide, chloroform, tert-butyl methyl ether, diethyl ether, methanol, and toluene were screened, and reactions in these solvents proceeded in 16– 63 % ee.
- [12] Sodeoka and co-workers also observed a dramatic effect of changing the ester group of the ketoester donor on the enantioselectivity of the Pd-binap complex-catalyzed conjugate addition; for details see reference [5].
- [13] See the Supporting Information for details.