JOC Article
pubs.acs.org/joc

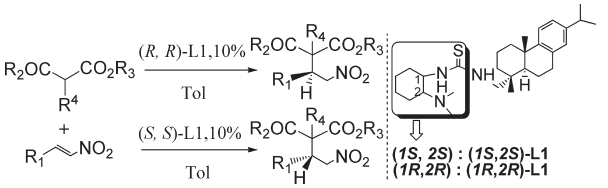
Enantio- and Diastereoselective Asymmetric Addition of 1,3-Dicarbonyl Compounds to Nitroalkenes in a Doubly Stereocontrolled Manner Catalyzed by Bifunctional Rosin-Derived Amine Thiourea Catalysts

Xianxing Jiang,[†,‡] Yifu Zhang,[†] Xing Liu,[†] Gen Zhang,[†] Luhao Lai,[†,‡] Lipeng Wu,[†] Jiannan Zhang,[†] and Rui Wang*[,†,‡]

[†]*State Key Laboratory of Applied Organic Chemistry, Institute of Biochemistry and Molecular Biology, Lanzhou University, Lanzhou 730000, China, and* [‡]*Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Kowloon, Hong Kong*

wangrui@lzu.edu.cn; bcrwang@polyu.edu.hk

Received May 4, 2009



Starting from commercially available natural rosin derivatives, a class of bifunctional rosin-derived amine thiourea catalysts were designed and synthesized. The doubly stereocontrolled asymmetric addition of a variety of 1,3-dicarbonyl compounds to nitroalkenes was investigated. These rosin-derived chiral thioureas have been shown to serve as effective catalysts for this double-sterecontrolled organocatalytic process by the investigation of the efficacy of the thiourea catalysts in comparison with other thiourea catalysts reported. In addition, these chiral thiourea ligands are easily available. Furthermore, the rosin-derived tertiary amine−thiourea was also revealed to be highly efficient for construction of contiguous stereogenetic centers containing an asymmetric quaternary carbon by the Michael reaction of α-substituted β-ketoesters to nitroalkenes.

Introduction

A key goal of the synthesis of chiral catalysts is to both maximize the efficiency of using readily available materials and minimize the generation of waste. Thus, the current synthetic strategy often relies on the derivatization of the available chiral pool of the natural organic products, which limits the number of accessible derivatives, and the natural compounds and their easily available derivatives as chiral scaffolds for the design and synthesis of catalysts have received great attention so far. Although the natural rosin with excellent structural backbone and well-defined stereocenters is abundant in nature, its easily available derivatives have rarely been developed in the synthesis of efficient catalysts for asymmetric catalytic reactions to date.[1] We recently reported[2] a class of primary amine−thiourea bifunctional catalysts based on rosin, which have successfully been applied to the highly enantioselective and doubly stereocontrolled synthesis of γ-nitro heteroaromatic ketones. While previous studies on doubly stereocontrolled catalytic conjugate addition of ketones gained limited success, in view of the doubly stereocontrolled synthesis of chiral organic molecules remains as an elusive goal, the investigation of potential application of thiourea catalysts based on rosin in other doubly stereocontrolled asymmetric reactions is urgently needed. Encouraged by the good results from previous experiments, we consider if other Michael donors such as 1,3-dicarbonyl compounds could also be suitable for this doubly stereocontrolled catalytic process catalyzed by rosin-derived chiral thiourea.

In the past few years, a series of thiourea-based catalysts were designed and synthesized because of their strong hydrogen-bonding activity[3] and effectively catalyzed various

(1) For the use of rosin derivatives as organocatalysts, see: Tayana, B. K.; Nikalai, N. K.; Olga, V. T.; Alexander, G. T. *Chirality* **2004**, *16*, 40.
(2) Jiang, X. X.; Zhang, Y. F.; Chan, A. S. C.; Wang, R. *Org. Lett.* **2009**, *11*, 153.
(3) (a) Linton, B. R.; Goodman, M. S.; Hamilton, A. D. *Chem.—Eur. J.* **2000**, *6*, 2449. (b) Wilcox, C. S.; Kim, E.; Romano, D.; Kuo, L. H.; Burt, A. L.; Curran, D. P. *Tetrahedron* **1995**, *51*, 621. (c) Kelly, T. R.; Kim, M. H. *J. Am. Chem. Soc.* **1994**, *116*, 7072. (d) Etter, M. C.; Urbañczyk-Lipkowska, Z.; Zia-Ebrahimi, M.; Panunto, T. W. *J. Am. Chem. Soc.* **1990**, *112*, 8415.

Published on Web 06/24/2009 DOI: 10.1021/jo9009276

types of asymmetric reactions.[4,5] The most remarkable advances in this field were achieved by Jacobsen's group.[6] Takemoto and co-workers[7,8] reported the first bifunctional thiourea catalyst bearing a dimethyl amino group, which was capable of the efficient promotion of the addition of malonate esters and ketoesters to nitroalkenes. Herein, we first report a class of bifunctional rosin-derived amine thiourea catalysts and their application in the doubly stereocontrolled catalytic conjugate addition of a variety of 1,3-dicarbonyl compounds to nitroalkenes under mild conditions.

Results and Discussion

Synthesis and Activity of Bifunctional Thiourea Catalysts. Bifunctional rosin-derived tertiary amine−thiourea bifunctional catalysts (1*R*,2*R*)-**L1** and (1*S*,2*S*)-**L1** were synthesized as shown in Scheme 1. Using the same procedure, thiourea catalysts **L2**[8f] and **L3** were also synthesized from 3,5-bis (trifluoromethyl)aniline and α-phenylethanamine, respectively (Figure 1). The efficacy of thiourea catalysts was initially evaluated by the reaction of 2,4-pentanedione to *trans*-*β*-nitrostyrene in the presence of 10 mol % of thiourea ligands under different conditions (Table 1).

In the initial experiment, a range of solvents were screened for the process (entries 1−7, Table 1). An investigation of different reaction media revealed that solvent had a significant effect on the efficiency of this process. Reactions in solvents (THF, Et_2O, and $CHCl_3$) afforded the desired Michael adduct (*R*)-**3a** with low yields (15−58%) and enantioselectivities (8−40%, entries 1−7, Table 1), whereas those in dichloromethane proceeded in higher yields and enantioselectivities (entries 4 and 5, Table 1). The best results were attained when toluene was used as solvent of the reactions (entries 6 and 7, Table 1). From the results of recent studies,[2] we have disclosed that the stereochemical control of the reaction is mainly provided by the 1,2-diaminocyclohexane moiety of thiourea and the mutual relationship between the catalytic activity and two chiral moieties of thiourea. These results indicated that the replacement of thiourea catalysts bearing a dehydroabietic amine scaffold with a 3,5-bis(trifluoromethyl)aniline scaffold did not impact the stereoselection, and bifunctional thiourea catalysts **L1** and **L2** provided almost the same high enantioselectivities ((*R*)-adducts, 82%; (*S*)-adducts, 80−84%; entries 6−9, Table 1). However, catalysts **L2** showed relatively low catalytic activity, resulting in lower yields ((*R*)-adducts,

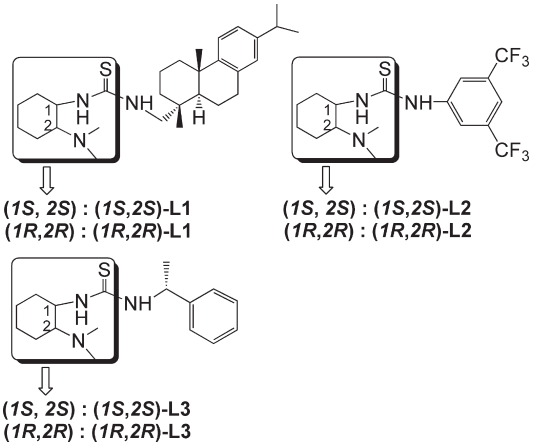
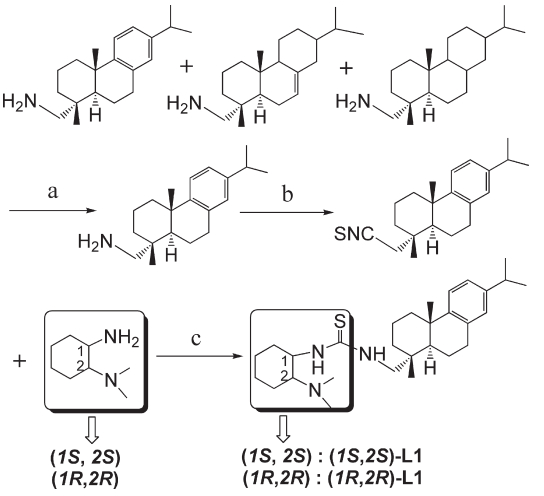


FIGURE 1. Structure of thiourea catalysts.

SCHEME 1. Preparation of Rosin-Derived Amine Thiourea Catalysts[a]



[a]Reagents and conditions: (a) AcOH, 10% NaOH, Tol and Et_2O, 45%; (b) CS_2, DCC, dry Et_2O, 15 h, 92%; (c) CH_2Cl_2, 12 h, 83%.

(4) For reviews concerning bifunctional thiourea organocatalysis, see: (a) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (b) Connon, S. J. *Chem.—Eur. J.* **2006**, *12*, 5418. (c) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520. (d) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299.

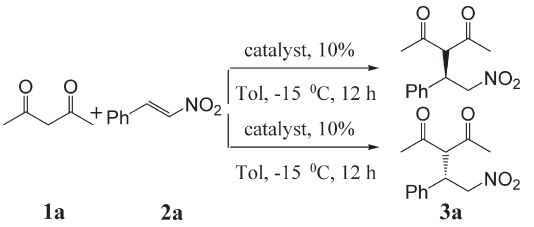
(5) Selected for bifunctional chiral thiourea catalyzed reactions: (a) Wang, Y.; Li, H. M.; Wang, Y. Q.; Liu, Y.; Foxman, B. M.; Deng, L. *J. Am. Chem. Soc.* **2007**, *129*, 6364. (b) Wang, B. M.; Wu, F. H.; Wang, Y.; Liu, X. F.; Deng, L. *J. Am. Chem. Soc.* **2007**, *129*, 768. (c) Sibi, M. P.; Itoh, K. *J. Am. Chem. Soc.* **2007**, *129*, 8064. (d) Pan, S. C.; Zhou, J.; List, B. *Angew. Chem., Int. Ed.* **2007**, *46*, 612. (e) Zu, L. S.; Wang, J.; Li, H.; Xie, H. X.; Jiang, W.; Wang, W. *J. Am. Chem. Soc.* **2007**, *129*, 1036. (f) Zu, L. S.; Xie, H. X.; Li, H.; Wang, H.; Jiang, W.; Wang, W. *Adv. Synth. Catal.* **2007**, *349*, 1882. (g) McCooey, S. H.; Conon, S. J. *Org. Lett.* **2007**, *9*, 599. (h) Liu, K.; Cui, H.-F.; Nie, J.; Dong, K.-Y.; Li, X.-J.; Ma, J.-A. *Org. Lett.* **2007**, *9*, 923. (i) Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 6048. (j) Wang, J.; Li, H.; Zu, L. S.; Jiang, W.; Xie, H. X.; Duan, W. H.; Wang, W. *J. Am. Chem. Soc.* **2006**, *128*, 12652. (k) McCooey, S. H.; McCabe, T.; Connon, S. J. *J. Org. Chem.* **2006**, *71*, 7494. (l) Tillman, A. L.; Ye, J. X.; Dixon, D. J. *Chem. Commun.* **2006**, 1191. (m) Dixon, D. J.; Richardson, R. D. *Synlett* **2006**, 81. (n) Yalalov, D. A.; Tsogoeva, S. B.; Schmatz, S. *Adv. Synth. Catal.* **2006**, *348*, 826. (o) Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Ricci, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 6576. (p) Tsogoeva, S. B.; Yalalov, D. A.; Hateley, M. J. *Eur. J. Org. Chem.* **2005**, 4995. (q) Sohtome, Y.; Hashimoto, Y.; Nagasawa, K. *Adv. Synth. Catal.* **2005**, *347*, 1643. (r) Wang, J.; Li, H.; Yu, X. H.; Zu, L. S.; Wang, W. *Org. Lett.* **2005**, *7*, 4293.

(6) For selected recent examples, see: (a) Zuend, S. J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 15872. (b) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404. (c) Tan, K. L.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2007**, *46*, 1315. (d) Lalonde, M. P.; Chen, Y.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 6366. (e) Huang, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 7170. (f) Fuerst, D. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 8964. (g) Yoon, T. P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 466. (h) Taylor, M. S.; Tokunaga, N.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 6700.

(7) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X. N.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119.

(8) For selected recent examples, see: (a) Yamaoka, Y.; Miyabe, H.; Takemoto, Y. *J. Am. Chem. Soc.* **2007**, *129*, 6686. (b) Inokuma, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2006**, *128*, 9413. (c) Hoashi, Y.; Okino, T.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 4032. (d) Xu, X. N.; Furukawa, T.; Okino, T.; Miyabe, H.; Takemoto, Y. *Chem.—Eur. J.* **2005**, *12*, 466. (e) Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625. (f) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672.

TABLE 1. Enantioselective Michael Addition Reactions of 2,4-Pentanedione (1a) to *trans*-β-Nitrostyrene[a]



1a 2a 3a

entry	catalyst	solvent	yield[b] (%)	ee[c] (%)
1	(1*R*,2*R*)-**L1**	THF	15	8 (*R*)
2	(1*R*,2*R*)-**L1**	Et_2O	50	35 (R)
3	(1*R*,2*R*)-**L1**	$CHCl_3$	58	40 (*R*)
4	(1*R*,2*R*)-**L1**	CH_2Cl_2	78	66 (*R*)
5	(1*S*,2*S*)-**L1**	CH_2Cl_2	75	62 (*S*)
6	(1*R*,2*R*)-**L1**	Tol	95	82 (*R*)
7	(1*S*,2*S*)-**L1**	Tol	93	80 (*S*)
8	(1*R*,2*R*)-**L2**	Tol	73	82 (*R*)
9	(1*S*,2*S*)-**L2**	Tol	70	84 (*S*)
10	(1*R*,2*R*)-**L3**	Tol	52	63 (*R*)
11	(1*S*,2*S*)-**L3**	Tol	48	50 (*S*)
12[d]	(1*R*,2*R*)-**L1**	Tol	91	90 (*R*)
13[d]	(1*S*,2*S*)-**L1**	Tol	89	91 (*S*)

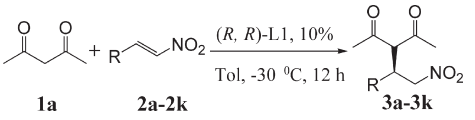
[a]The reaction was conducted with *trans*-β-nitrostyrene (0.1 mmol) and 2,4-pentanedione (0.5 mmol). [b]Isolated yield. [c]The ee values were determined by HPLC, and the configuration was assigned by comparison of the retention time and specific rotation with literature data.[9b,9c] [d]The reaction was stirred at −30 °C.

73%; (*S*)-adducts, 70%; entries 8 and 9, Table 1). In contrast, thiourea catalysts **L3** also gave the desired adduct, but lower yields and enantioselectivities were observed (entries 10 and 11, Table 1). It was realized that the tertiary amine−thiourea **L1** is found to be the best choice for this doubly stereocontrolled organocatalytic process. Gratifyingly, we further lowered the temperature to −30 °C, and better enantioselectivities could be obtained ((*R*)-adducts, 90%; (*S*)-adducts, 91%; entries 12 and 13, Table 1) without a significant decrease in yields ((*R*)-adducts, 91%; (*S*)-adducts, 89%).

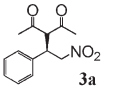
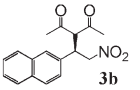
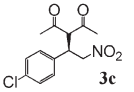
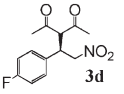
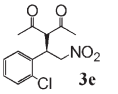
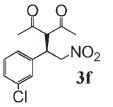
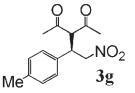
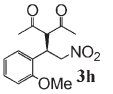
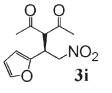
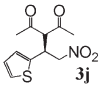
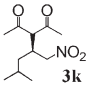
Enantioselective Asymmetric Addition of 2,4-Pentanedione to Nitroalkenes in a Doubly Stereocontrolled Manner Catalyzed by Bifunctional Thiourea Catalysts Based on Rosin ((1*R*,2*R*)-L1 and (1*S*,2*S*)-L1). Results of experiments under the optimized conditions that probe the scope of the reaction are summarized in Tables 2 and 3. The doubly stereocontrolled asymmetric addition of 2,4-pentanedione to a variety of nitroalkenes was examined considering the usefulness and versatility of adducts in organic synthesis[9] (entries 1−11, Table 2, and entries 1−11, Table 3). It is seen that all reactions of aromatic nitroalkenes proceed smoothly affording the desired products of the (*S*) or (*R*) configuration with high to excellent enantioselectivities ((*R*)-adducts, 82−99%, entries 1−10, Table 2, and (*S*)-adducts, 82−99%, entries 1−10, Table 3) and yields. As expected, the reaction proceeded with aliphatic nitroalkenes also to give (*S*)- or (*R*)-adducts

(9) For organocatalytic asymmetric Michael addition of 2,4-pentanedione to nitroalkenes, see: (a) Wang, C. J.; Zhang, Z. H.; Dong, X. Q.; Wu, X. J. *Chem. Commun.* **2008**, 1431. (b) Peng, F. Z.; Shao, Z. H.; Fan, B. M.; Song, H.; Li, G. P.; Zhang, H. B. *J. Org. Chem.* **2008**, *73*, 5202. (c) Wang, J.; Li, H.; Duan, W.-H.; Zu, L. S.; Wang, W. *Org. Lett.* **2005**, *7*, 4713.

TABLE 2. Enantioselective Michael Addition Reactions of 2,4-Pentanedione (1a) to Nitroalkenes by (*R*,*R*)-L1[a]

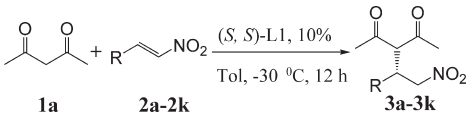


1a 2a-2k 3a-3k

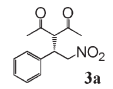
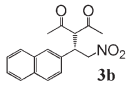
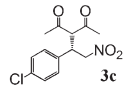
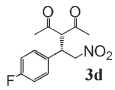
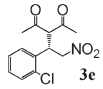
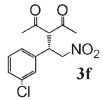
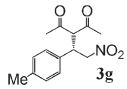
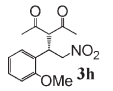
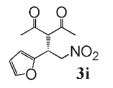
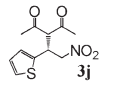
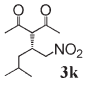
Entry	Product	Yield (%)[b]	ee (%)[c]
1	 **3a**	91	90
2	 **3b**	92	91
3	 **3c**	88	96
4	 **3d**	97	91
5	 **3e**	90	94
6	 **3f**	96	90
7	 **3g**	95	96
8	 **3h**	98	82
9	 **3i**	83	92 (99)[d]
10	 **3j**	90	90 (99)[d]
11	 **3k**	85	59

[a]The reaction was conducted with nitroalkenes (0.1 mmol) and 2,4-pentanedione (0.5 mmol). [b]Isolated yield. [c]The ee values were determined by HPLC, and the configuration was assigned by comparison of the retention time and specific rotation with literature data.[9] [d]Values in parentheses are those after a single recrystallization.

TABLE 3. Enantioselective Michael Addition Reactions of 2,4-Pentanedione (1a) to Nitroalkenes by (*S*, *S*)-L1[a]



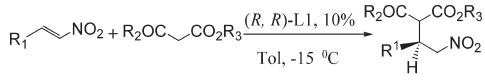
1a **2a-2k** **3a-3k**

Entry	Product	Yield (%) [b]	ee (%) [c]
1	 **3a**	89	91
2	 **3b**	90	91
3	 **3c**	89	93
4	 **3d**	95	90
5	 **3e**	91	92
6	 **3f**	95	81
7	 **3g**	92	95
8	 **3h**	98	80
9	 **3i**	86	90 (99) [d]
10	 **3j**	91	91
11	 **3k**	81	79

[a]The reaction was conducted with nitroalkenes (0.1 mmol) and 2,4-pentanedione (0.5 mmol). [b]Isolated yield. [c]The ee values were determined by HPLC, and the configuration was assigned by comparison of the retention time and specific rotation with literature data.[9] [d]Values in parentheses are those after a single recrystallization.

with high yields ((*R*)-adducts, 85%, entry 11, Table 2, and (*S*)-adducts, 81%, entry 11, Table 3) and moderate to good enantioselectivities.

TABLE 4. Enantio- and Diastereoselective Michael Addition Reactions of 1,3-Dicarbonyl Compounds to Nitroalkenes by (*R*,*R*)-L1[a]

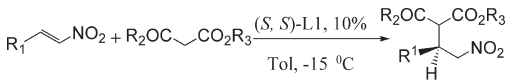


4a-4d **5a-5f**

entry	R_1	R_2	R_3	time (h)	yield[b] (%)	dr[c]	ee[d] (%)
1	2-ClPh	MeO	Me	48	**5a**: 80		57
2	2-ClPh	EtO	Et	48	**5b**: 83		64
3	2-ClPh	BnO	Bn	48	**5c**: 85		59
4 [e,f]	Ph	Ph	Et	12	**5d**: 86	7:3 (99:1)	71 (99)
5 [e,f]	4-ClPh	Ph	Et	12	**5e**: 90	7:3 (99:1)	82 (99)
6 [e,f]	4-MePh	Ph	Et	12	**5f**: 83	6:4 (99:1)	87 (99)

[a]The reaction was conducted with nitroalkenes (0.2 mmol) and 1,3-dicarbonyl compounds (0.6 mmol). [b]Isolated yield. [c]Determined by ^{1}H NMR spectroscopy. [d]The ee values were determined by HPLC, and the configuration was assigned by comparison of the retention time and specific rotation with literatures data (see the Supporting Information).[10e,10h, 11] [e]Values in parentheses are those after a single recrystallization. [f]The reaction was stirred at −60 °C.

TABLE 5. Enantio- and Diastereoselective Michael Addition Reactions of 1,3-Dicarbonyl Compounds to Nitroalkenes by (*S*,*S*)-L1[a]



4a-4d **5a-5f**

entry	R_1	R_2	R_3	time (h)	yield[b] (%)	dr[c]	ee[d] (%)
1	2-ClPh	MeO	Me	48	**5a**: 81		75
2	2-ClPh	EtO	Et	48	**5b**: 81		62
3	2-ClPh	BnO	Bn	48	**5c**: 80		67
4 [e,f]	Ph	Ph	Et	12	**5d**: 82	7.8:2.2 (99:1)	90 (99)
5 [e,f]	4-ClPh	Ph	Et	12	**5e**: 99	5.4:4.6 (99:1)	70 (99)
6 [e,f]	4-MePh	Ph	Et	12	**5f**: 86	6.4:3.6 (99:1)	79 (99)

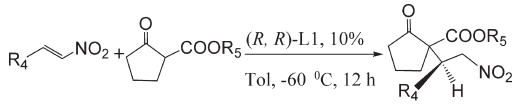
[a]The reaction was conducted with nitroalkenes (0.2 mmol) and 1,3-dicarbonyl compounds (0.6 mmol). [b]Isolated yield. [c]Determined by ^{1}H NMR spectroscopy. [d]The ee values were determined by HPLC, and the configuration was assigned by comparison of the retention time and specific rotation with literatures data (see the Supporting Information).[10e,10h,11] [e]Values in parentheses are those after a single recrystallization. [f]The reaction was stirred at −60 °C.

Enantio- and Diastereoselective Asymmetric Addition of 1,3-Dicarbonyl Compounds to Nitroalkenes[10,11] in a Doubly Stereocontrolled Manner Catalyzed by Bifunctional Thiourea Catalysts Based on Rosin ((1*R*,2*R*)-L1 and (1*S*,2*S*)-L1). Bifunctional thioureas (1*R*,2*R*)-**L1** and (1*S*,2*S*)-**L1** have been proven to be very efficient catalysts for the doubly stereocontrolled asymmetric addition of 2,4-pentanedione. Following that encouraging result, subsequent studies were

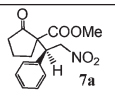
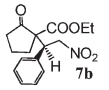
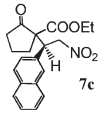
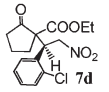
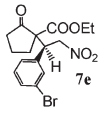
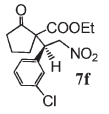
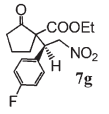
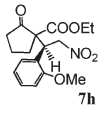
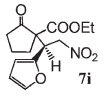
(10) Selected for asymmetric conjugate addition of 1,3-dicarbonyl compounds, see: (a) Evans, D. A.; Mito, S.; Seidel, D. *J. Am. Chem. Soc.* **2007**, *129*, 11583. (b) Terada, M.; Ube, H.; Yaguchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1454. (c) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481. (d) McCooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367. (e) Evans, D. A.; Seidel, D. *J. Am. Chem. Soc.* **2005**, *127*, 9958. (f) Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906. (g) Watanabe, M.; Ikagawa, A.; Wang, H.; Murata, K.; Ikariya, T. *J. Am. Chem. Soc.* **2004**, *126*, 11148. (h) Barnes, D. M.; Ji, J. G.; Fickes, M. G.; Fitzgerald, M. A.; King, S. A.; Morton, H. E.; Plagge, F. A.; Preskill, M.; Wagaw, S. H.; Wittenberger, S. J.; Zhang, J. *J. Am. Chem. Soc.* **2002**, *124*, 13097. (i) Ji, J.; Barnes, D. M.; Zhang, J.; King, S. A.; Wittenberger, S. J.; Morton, H. E. *J. Am. Chem. Soc.* **1999**, *121*, 10215.

(11) Chen, F.-X.; Shao, C.; Wang, Q.; Gong, P.; Zhang, D.-Y.; Zhang, B.-Z.; Wang, R. *Tetrahedron Lett.* **2007**, *48*, 8456.

TABLE 6. Enantio- and Diastereoselective Michael Addition Reactions of Ketoesters to Nitroalkenes by (*R*,*R*)-L1[a]



6a-6b **7a-7i**

Entry	Product	Yield (%) [b]	dr [c]	ee (%) [d]
1	 **7a**	98	97:3	92
2	 **7b**	99	99:1	90
3	 **7c**	99	99:1	>99
4	 **7d**	99	94:6	85
5	 **7e**	99	98:2	81
6	 **7f**	99	97:3	84
7	 **7g**	99	99:1	88
8	 **7h**	99	97:3	>99
9	 **7i**	98	99:1	83

[a]The reaction was conducted with nitroalkenes (0.2 mmol) and ketoesters (0.6 mmol). [b]Isolated yield. [c]Determined by ^{1}H NMR spectroscopy. [d]The ee values were determined by HPLC, and the configuration was assigned by comparison of the retention time and specific rotation with literature data.[11]

focused on other 1,3-dicarbonyl compounds such as various malonates and α-unsubstituted β-ketoesters (Tables 4 and 5). We first investigated the addition of three malonates to nitroalkenes. When malonates (3 equiv) and nitroalkenes were conducted in toluene in the presence of 10 mol % of bifunctional thiourea catalysts **L1** at −15 °C, in general, the reactions were completed within 48 h, giving the desired products of (*S*) or (*R*) configuration in high yields ((*R*)-adducts, 80−85%, entries 1−3, Table 4, and and (*S*)-adducts, 80−81%, entries 1−3, Table 5) and moderate to good enantioselectivities. β-Ketoester **4d** was next employed as a substrate for this process. Unexpectedly, this substrate reacted much more rapidly than the malonates, which may result in low stereoselectivity. The reaction temperature was further lowered to −60 °C for the adducts with a high level of stereoselectivity. Studies revealed that the reaction proceeded not only in the presence of (1*R*,2*R*)-**L1** but also in the presence of (1*S*,2*S*)-**L1** to give the desired adducts with high to excellent yields (83−90%, entries 4−6, Table 4, and 82−99%, entries 4−6, Table 5). Although the diastereoselectivies of products were low (up to 7.8/2.2), the enantioselectivities were still satisfactory (71−87%, entries 4−6, Table 4, and 70−90%, entries 4−6, Table 5). Gratifyingly, the nearly optically pure products could be obtained after a simple single recrystallization for all adducts in diethyl ether.

Application to the Construction of Quaternary Carbon Centers. Conjugate addition of carbon nucleophiles to activated C−C double bonds is one of the most important and versatile reactions for the construction of quaternary or tertiary carbon centers. Several catalytic systems for the enantioselective construction of quaternary carbon centers through Michael addition have been developed in recent years.[12] Nevertheless, to the best of our knowledge, the construction of quaternary carbon centers is still a difficult task in organic synthesis, and there are only two reports of organocatalytic Michael addition of α-substituted β-ketoesters to nitroalkenes constructing a stereogenic quaternary carbon center with high enantio- and diastereoselectivity.[7,13] Having succeeded in the Michael reaction of nitroalkenes with 1,3-dicarbonyl compounds such as 2,4-pentanedione, malonates and α-unsubstituted β-ketoesters catalyzed by our tertiary amine−thiourea **L1**, the Michael reaction of a variety of nitroalkenes with α-substituted β-ketoesters **6a**,**b**, which generates a configurationally stable quaternary stereocenter, was performed in the presence of 10 mol % of (1*R*,2*R*)-**L1** at −60 °C (Table 6). To our delight, all reactions underwent clean reactions affording the desired adducts that contain quaternary carbon centers with quantitive chemical yields (98−99%, entries 1−9), excellent diastereoselectivies (96/4−99/1, entries 1−9), and high to excellent enantioselectivities (81−99%, entries 1−9). These observations suggest that tertiary amine−thiourea **L1** can serve as a very efficient promoter for this process.

Conclusion

In conclusion, we have developed a class of bifunctional rosin-derived amine−thiourea catalysts that have been successfully applied to the doubly stereocontrolled asymmetric addition of 1,3-dicarbonyl compounds to nitroalkenes. Furthermore, this tertiary amine−thiourea under mild conditions could be used for construction of contiguous stereogenetic centers containing an asymmetric quaternary

(12) (a) Forbeck, E. M.; Evans, C. D.; Gilleran, J. A.; Li, P.; Joullie, M. M. *J. Am. Chem. Soc.* **2007**, *129*, 14463. (b) Denmark, S. E.; Wilson, T. W.; Burk, M. T.; Heemstra, J. R. Jr. *J. Am. Chem. Soc.* **2007**, *129*, 14864. (c) Liu, T. Y.; Long, J.; Li, B. J.; Jiang, L.; Li, R.; Wu, Y.; Ding, L. S.; Chen, Y. C. *Org. Biomol. Chem.* **2006**, *4*, 2097. (d) Zu, L.; Wang, J.; Li, H.; Wang, W. *Org. Lett.* **2006**, *8*, 307. (e) Christoffers, J.; Baro, A. *Quaternary stereocenters: challenges and solutions for organic synthesis*. Wiley-VCH: Weinheim, 2005. (f) Wu, J.; Mampreian, D. M.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 4584. (g) Christoffers, J.; Baro, A. *Angew Chem Int Ed.* **2003**, *42*, 1688. (h) Mase, N.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F. III. *Org. Lett.* **2004**, *6*, 2527. (i) Hamashima, Y.; Hotta, D.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 11240. (j) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171. (k) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033. (l) Leonard, J.; DMez-Barra, E.; Merino, S. *Eur. J. Org. Chem.* **1998**, 2051. (m) Sasai, H.; Emori, E.; Arai, T.; Shibasaki, M. *Tetrahedron Lett.* **1996**, *37*, 5561.

(13) Li, H.; Wang, Y.; Tang, L.; Wu, F.; Liu, X.; Guo, C.; Foxman, B. M.; Deng, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 105.

carbon by the Michael reaction of α-substituted β-ketoesters to nitroalkenes. In this process, the adducts that contain quaternary carbon centers were obtained with quantitive chemical yields, excellent diastereoselectivies, and high to excellent enantioselectivities.

Experimental Section

Synthesis of Rosin-Derived Amine−Thiourea Catalysts. Using the reported procedures,[14] the pure dehydroabietic amine as a white solid was obtained in 45% yield. Carbon bisulfide (4.0 mL) and *N*,*N*′-dicyclohexylcarbodiimide (10 mmol) were added to a solution of dehydroabietic amine (10 mmol) in dry ether (35 mL) at 0 °C. The reaction mixture was allowed to warm slowly to room temperature over a period of 3 h and then was stirred for a further 12 h at room temperature. After separation of the precipitated thiourea by filtration, the solvent was removed under reduced pressure. After column chromatography on silica gel eluted with 25% ethyl acetate in hexanes, the corresponding isothiocyanate as a white solid was isolated in 92% yield. Under argon atmosphere, to a solution of the above isothiocyanate (9.17 mmol) in dry dichloromethane (80 mL) was added *N*,*N*-dimethyl-*trans*-diaminocyclohexane (10 mmol). The reaction mixture was stirred for 12 h at room temperature and was concentrated in vacuo. After column chromatography on silica gel (ethyl acetate/hexane = 2/1 as eluent), the thiourea **L1** as a white solid was isolated in 83% yield.

1-((1*R*,2*R*)-2-(Dimethylamino)cyclohexyl)-3-(((1*R*,4a*S*,10a*R*)-7-isopropyl-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-yl)methyl)thiourea ((1*R*,2*R*)-L1):. $[\alpha]^{20}_D = +2$ (c = 2.0, $CHCl_3$); mp 82 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14−7.17 (d, J = 8.1 Hz, 1 H), 6.97−6.99 (m, 1 H), 6.88 (s, 1H), 6.45 (br, 1 H), 3.68−3.70 (m, 1 H), 3.35 (m, 1 H), 2.79−2.91 (m, 3 H), 2.39−2.45 (m, 1 H), 2.20−2.34 (m, 7 H), 1.67−1.88 (m, 8 H), 1.43−1.50 (m, 2 H), 1.21−1.38 (m, 16 H), 0.85−1.64 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.1, 145.7, 134.7, 126.8, 124.1, 123.8, 67.1, 56.3, 55.4, 45.6, 40.3, 38.3, 37.8, 37.4, 36.6, 33.4, 33.1, 30.0, 25.2, 25.1, 24.5, 24.0, 23.9, 22.1, 19.1, 18.6, 18.5; IR 3437, 3259, 3066, 2928, 2248, 2122, 1550, 1452, 1380, 1058, 1029, 913, 822, 759, 624 cm^{-1}; ESI-MS m/z 470 [M$^+$]; HRMS-ESI (m/z) calcd for $C_{29}H_{47}N_3S$ [M + H]$^+$ 470.3563, found 470.3573, 2.1 ppm.

Representative Procedure for the Asymmetric Addition of 2,4-Pentanedione to Nitroalkenes. To a stirred solution of (1*R*,2*R*)-**L** or (1*S*,2*S*)-**L** (0.01 mmol, 10 mol %) and nitroalkene (0.1 mmol) in dry toluene (1.0 mL) under Ar was added 2,4-pentanedione (0.5 mmol) over a period of 30 min. The solution was stirred at −30 °C for 12 h. After the reaction was completed (monitored by TLC), the resulting mixture was concentrated under reduced pressure, and the residue was purified through column chromatography on silica gel (eluent, ethyl acetate/hexane 1:8) to give the optical pure product. The enantiomeric purity of the product was determined by using HPLC (see the Supporting Information).

(*R*)-3-(2-Nitro-1-phenylethyl)pentane-2,4-dione (3a):. colorless needles; $[\alpha]^{20}_D = -13.3$ (c = 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29−7.37 (m, 3 H), 7.18−7.20 (t, J = 1.5 Hz, 2 H), 4.58−4.67 (m, 2 H), 4.36−4.40 (d, J = 10.8 Hz, 1 H), 4.21−4.28 (m, 1 H), 2.30 (s, 3 H), 1.94 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.8, 201.0, 136.0, 129.3, 128.6, 128.0, 78.2, 70.7, 42.8, 30.4, 29.5; IR 3155, 2924, 2254, 1794, 1702, 1558, 1469, 1381, 1095, 908, 734, 651 cm^{-1}; ESI-MS m/z 272 [M + Na]$^+$. ee was determined by HPLC analysis (Chiralcel AS-H, i-PrOH/hexane = 15/85, 1.0 mL/min, 210 nm): retention time t_{minor} = 14.78 min, t_{major} = 21.63 min, ee = 90%. (*S*)-**3a**: colorless needles; $[\alpha]^{20}_D = +5.4$ (c = 0.5, $CHCl_3$). ee was determined by HPLC analysis (Chiralcel AS-H, i-PrOH/hexane = 15/85, 1.0 mL/min, 210 nm): retention time t_{major} = 14.46 min, t_{minor} = 21.28 min, ee = 91%.

Representative Procedure for the Asymmetric Addition of Malonates and α-Unsubstituted β-Ketoesters to Nitroalkenes. To a stirred solution of (1*R*,2*R*)-**L1** or (1*S*,2*S*)-**L1** (0.02 mmol, 10 mol %) and nitroalkene (0.2 mmol) in dry toluene (1.0 mL) under Ar was added 1,3-dicarbonyl compound (0.6 mmol) over a period of 15 min. After the reaction was completed (monitored by TLC), the resulting mixture was concentrated under reduced pressure and the residue was purified through column chromatography on silica gel (eluent, ethyl acetate/hexane 1:6) to give the optical pure product. The enantiomeric purity of the product was determined by using HPLC and the dr values determined by 400 MHz ^{1}H NMR (see the Supporting Information).

(*R*)-Dimethyl 2-(1-(2-chlorophenyl)-2-nitroethyl)malonate (5a):. colorless oil; $[\alpha]^{20}_D = -10.0$ (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (m, 1H), 7.23 (m, 3H), 5.11 (dd, J = 8.7 Hz, 13.5 Hz, 1H), 4.96 (dd, J = 4.5 Hz, 13.5 Hz 1H), 4.73 (dt, J = 4.5 Hz, 8.4 Hz 1H), 4.11 (d, J = 8.4 Hz, 1H), 3.74 (s, 3H), 3.64 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 167.2, 134.0, 133.6, 130.5 129.5, 128.5, 127.3, 75.4, 52.9, 52.8, 52.9, 39.3; IR 3008, 2955, 1734, 1594, 1554, 1435, 1379, 1255, 1074 cm^{-1}; MS (CI) m/z 315 [M]$^+$. ee was determined by HPLC analysis (Chiralcel AD-H, i-PrOH/hexane = 15/85, 1.0 mL/min, 215 nm): retention time t_{minor} = 11.32 min, t_{major} = 34.87 min, ee = 57%. Configuration assignment: The absolute stereochemistry was assigned as *R* by comparison of the optical rotation with the following literature value: Lit.[11] (*S*)-**5a**: colorless oil; $[\alpha]^{20}_D = +7.0$ (c = 1.0, $CHCl_3$). ee was determined by HPLC analysis (Chiralcel AD-H, i-PrOH/hexane = 15/85, 1.0 mL/min, 215 nm): retention time t_{major} = 10.44 min, t_{minor} = 34.19 min, ee = 75%.

Representative Procedure for the Asymmetric Addition of α-Substituted β-Ketoesters to Nitroalkenes. To a stirred solution of (1*R*,2*R*)-**L1** or (1*S*,2*S*)-**L1** (0.02 mmol, 10 mol %) and nitroalkene (0.2 mmol) in dry toluene (1.0 mL) under Ar was added α-substituted β-ketoester (0.6 mmol). The solution was stirred at −60 °C for 12 h. After the reaction was completed (monitored by TLC), the resulting mixture was concentrated under reduced pressure and the residue purified through column chromatography on silica gel (eluent, ethyl acetate/hexane 1:6) to give the optical pure product. The enantiomeric purity of the product was determined by using HPLC, and the dr values were determined by 400 MHz ^{1}H NMR (see the Supporting Information).

Methyl 1-(2-nitro-1-phenylethyl)-2-oxocyclopentanecarboxylate (7a):. colorless oil; $[\alpha]^{20}_D = -33.0$ (c = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23−7.33 (m, 5 H), 5.14−5.20 (dd, J = 4.2 Hz, 13.8 Hz, 1 H), 4.98−5.09 (dd, J = 10.8 Hz, 13.5 Hz, 1 H), 4.06−4.11 (dd, J = 3.9 Hz, 10.8 Hz, 1 H), 3.76 (m, 3 H), 2.34−2.41 (m, 2 H), 1.79−2.09 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.3, 169.8, 135.2, 129.3, 128.8, 128.3, 76.4, 62.4, 53.1, 46.1, 37.9, 31.1, 19.3; IR 3020, 2959, 2872, 2400, 1729, 1556, 1435, 1377, 1215, 1161, 1045, 758, 669 cm^{-1}; ESI-MS m/z 314 [M + Na]$^+$. Major diastereomer: ee was determined by HPLC analysis (Chiralcel OD-H, *i*-PrOH/hexane = 10/90, 1.0 mL/min, 213 nm): retention time t_{minor} = 18.49 min, t_{major} = 29.65 min, ee = 92%.

Acknowledgment. We are grateful for the grants from the National Natural Science Foundation of China (nos. 20525206, 20772052, 90813012, and 20621091) and the Chang Jiang Program of the Ministry of Education of China for financial support.

Supporting Information Available: Experimental details and characterization data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

(14) Gottstein, W. J.; Cheney, L. C. *J. Org. Chem.* **1965**, *30*, 2072.