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Chiral Bifunctional Thiourea-Catalyzed Enantioselective Michael Addition of Ketones to Nitrodienes

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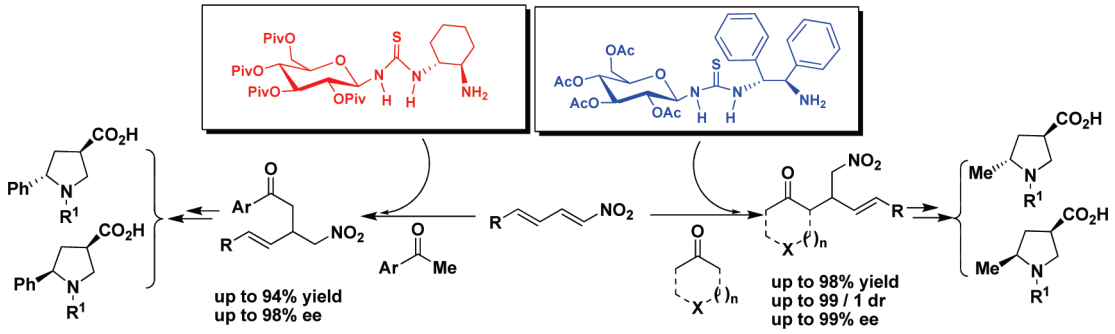
Received October 13, 2009



Simple bifunctional thioureas, derived from the commercially available saccharides and chiral diamines, have been shown tunably to promote Michael-type addition of ketones to α,β−γ, δ-nitrodienes. The Michael adducts were obtained in good yields albeit with high enantioselectivites (84−99% ee). Furthermore, these products can be readily transformed into more useful molecules.

Introduction

Michael addition is one of the most important carbon−carbon bond-forming reactions in organic synthesis.[1] Over the past decades, considerable efforts have been made to achieve asymmetric catalytic versions of the process.[2] More recently, the need for environmentally friendly and metal-free reactions has led to great progress in the organocatalyst-mediated Michael addition.[3,4] Of the developed organocatalysts, chiral bifunctional amine−thioureas have been proven to be powerful and have been applied successfully in asymmetric catalytic Michael addition reactions.[5] For example, the asymmetric Michael addition of various carbon nucleophiles to nitrolefins is proving a particularly attractive target, due largely to (a) the ready availability and high reactivity of nitroalkenes, (b) the ability

(1) (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: Oxford, 1992. (b) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005**, *105*, 933.

(2) For reviews of asymmetric Michael addition reactions, see: (a) Tomioka, K.; Nagaoka, Y.; Yamaguchi, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. III, Chapters 31.1 and 31.2, pp 1105−1139. (b) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171. (c) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877. (d) Christoffers, J.; Baro, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1688. (e) Guo, H.-C.; Ma, J.-A. *Angew. Chem., Int. Ed.* **2006**, *45*, 354.

(3) For selected reviews of organocatalysis, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726. (b) List, B. *Synlett* **2001**, 1675. (c) List, B. *Tetrahedron* **2002**, *58*, 5573. (d) Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481. (e) List, B. *Acc. Chem. Res.* **2004**, *37*, 548. (f) Notz, W.; Tanaka, F.; Barbas, C. F. III. *Acc. Chem. Res.* **2004**, *37*, 580.

(4) For reviews of organocatalytic Michael addition reaction, see: (a) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701. (b) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570.

(5) For reviews on chiral thiourea promoted organocatalytic reactions: (a) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299. (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) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (e) Chen, Y.-C. *Synlett* **2008**, 1919. (f) Xu, L.-W.; Luo, J.; Lu, Y. *Chem. Commun.* **2009**, 1807.

(6) Results of organocatalytic Michael addition reactions reported by Jacobsen's group, see: (a) Huang, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 7170. (b) Lalonde, M. P.; Chen, Y.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 6366.

(7) Results of organocatalytic Michael addition reactions reported by Takemoto's group, see: (a) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672. (b) Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625. (c) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119. (d) Hoashi, Y.; Okino, T.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 4032. (e) Xu, X.; Yabuta, T.; Yuan, P.; Takemoto, Y. *Synlett* **2006**, 137. (f) Hoashi, Y.; Yabuta, T.; Yuan, P.; Miyabe, H.; Takemoto, Y. *Tetrahedron* **2006**, *62*, 365.

(8) For the results of organocatalytic Michael addition reactions reported by the Tsogoeva's group, see: (a) Tsogoeva, S. B.; Yalalov, D. A.; Hateley, M. J.; Weckbecker, C.; Huthmacher, K. *Eur. J. Org. Chem.* **2005**, 4995. (b) Tsogoeva, S. B.; Hateley, M. J.; Yalalov, D. A.; Meindl, K.; Weckbecker, C.; Huthmacher, K. *Bioorg. Med. Chem.* **2005**, *13*, 5680. (c) Tsogoeva, S. B.; Wei, S.-W. *Tetrahedron: Asymmetry* **2005**, *16*, 1947. (d) Tsogoeva, S. B.; Wei, S.-W. *Chem. Commun.* **2006**, 1451. (e) Yalalov, D. A.; Tsogoeva, S. B.; Schamtz, S. *Adv. Synth. Catal.* **2006**, *348*, 826. (f) Wei, S.; Yalalov, D. A.; Tsogoeva, S. B.; Schmatz, S. *Catal. Today* **2007**, *121*, 151.

Published on Web 02/05/2010 DOI: 10.1021/jo901991v

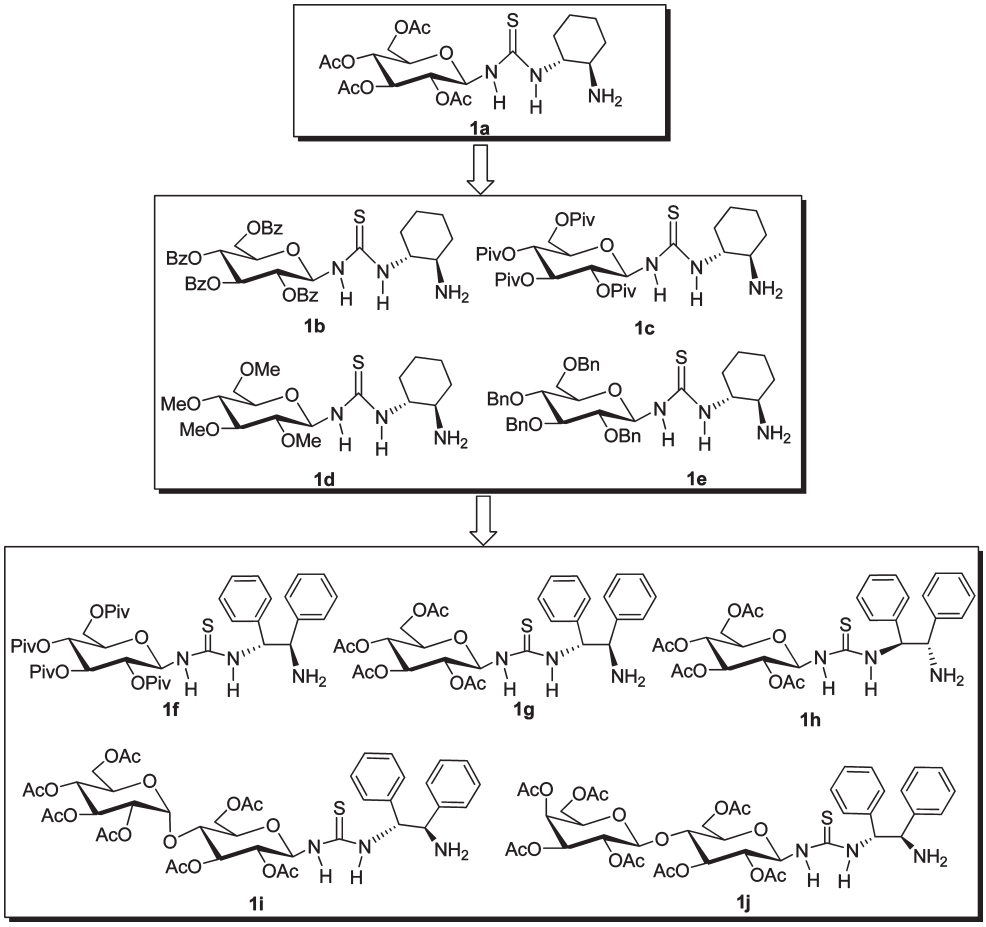


FIGURE 1. Saccharide-derived bifunctional thiourea catalysts.

of the nitro functionality to accept hydrogen bonds from suitably designed catalyst systems, and (c) the high synthetic utility of the nitroalkane adducts.[6−9] In contrast, little progress has been made in the development of nitrodienes as Michael acceptors.[10,12h−12j]

Efforts from our laboratory have focused on the design and synthesis of a new class of bifunctional amine−thiourea catalysts based on saccharides.[11] These simple organic molecules have been shown to be excellently enantioselective for direct Michael addition of ketones and malonates to nitroolefins. Furthermore, the saccharide-derived thiourea seemed to be an interesting backbone for the design of new organocatalysts for asymmetric synthesis. Herein, we report that saccharide-derived bifunctional thioureas tunably promote catalytic asymmetric addition reactions of ketones to nitrodienes, providing very useful adducts in high yields and stereoselectivities. Such studies would be of immense benefit for expanding the scope of application of these conjugate reactions in organic synthesis.

Results and Discussion

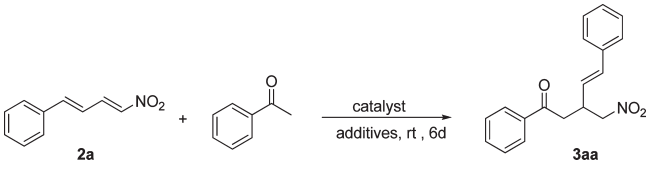
At the beginning of this work, we have started our investigation with the addition of acetophenone to phenylnitrodiene **2a** in the presence of the simplest thiourea **1a** (Figure 1). The results were listed in Table 1. Interestingly, no trace of 1,6-addition adduct has ever been observed during the preliminary optimization study. Only 1,4-addition occurred with perfect control of the regioselectivity for the

(9) Other chiral thiourea-catalyzed Michael addition reactions; selected examples: (a) McCooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367. (b) Wang, J.; Li, H.; Duan, W.; Zu, L.; Wang, W. *Org. Lett.* **2005**, *7*, 4713. (c) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481. (d) McCooey, S. H.; McCabe, T.; Connon, S. J. *J. Org. Chem.* **2006**, *71*, 7494. (e) Cao, C.-L.; Ye, M.-C.; Sun, X.-L.; Tang, Y. *Org. Lett.* **2006**, *8*, 2901. (f) Cao, Y.-Y.; Lu, H.-H.; Lai, Y.-Y.; Lu, L.-Q.; Xiao, W.-J. *Synthesis* **2006**, 3795. (g) Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 6048. (h) Wang, J.; Li, H.; Zu, L. S.; Jiang, W.; Xie, H. X.; Duan, W. H.; Wang, W. *J. Am. Chem. Soc.* **2006**, *128*, 12652. (i) Jiang, L.; Zheng, H.-T.; Liu, T.-Y.; Yue, L.; Chen, Y.-C. *Tetrahedron* **2007**, *63*, 5123. (j) Cao, Y.-J.; Lai, Y.-Y.; Wang, X.; Li, Y.-J.; Xiao, W.-J. *Tetrahedron Lett.* **2007**, *48*, 21. (k) Wang, Y.; Li, H. M.; Wang, Y. Q.; Liu, Y.; Foxman, B. M.; Deng, L. *J. Am. Chem. Soc.* **2007**, *129*, 6364. (l) Zu, L. S.; Wang, J.; Li, H.; Xie, H. X.; Jiang, W.; Wang, W. *J. Am. Chem. Soc.* **2007**, *129*, 1036. (m) McCooey, S. H.; Conon, S. J. *Org. Lett.* **2007**, *9*, 599. (n) Wang, C.-J.; Zhang, Z.-H.; Dong, X.-Q.; Wu, X.-J. *Chem. Commun.* **2008**, 1431. (o) Han, B.; Liu, Q. P.; Li, R.; Tian, X.; Xiong, X. F.; Deng, J.-G.; Chen, Y.-C. *Chem.—Eur. J.* **2008**, *14*, 8094. (p) Jiang, X.; Zhang, Y.; Chan, A. S. C.; Wang, R. *Org. Lett.* **2009**, *11*, 153. (q) Kokotos, C. G.; Kokotos, G. *Adv. Synth. Catal.* **2009**, *351*, 1355. (r) Bui, T.; Syed, S.; Barbas, C. F. III. *J. Am. Chem. Chem.* **2009**, *131*, 8758. (s) Nodes, W. J.; Nutt, D. R.; Chippindale, A. M.; Cobb, A. J. A. *J. Am. Chem. Soc.* **2009**, *131*, 16016. (t) Guo, L.; Chi, Y.; Almeida, A. M.; Guzei, I. A.; Parker, B. K.; Gellman, S. H. *J. Am. Chem. Soc.* **2009**, *131*, 16018.

(10) Recently, Alexakis and co-workers provided an excellent example of the diphenylprolinol-catalyzed additions of aldehydes to nitrodienes: Belot, S.; Massaro, A.; Tenti, A.; Mordini, A.; Alexakis, A. *Org. Lett.* **2008**, *10*, 4557.

(11) (a) Liu, K.; Cui, H.-F.; Nie, J.; Dong, K.-Y.; Li, X.-J.; Ma, J.-A. *Org. Lett.* **2007**, *9*, 923. (b) Li, X.-J.; Liu, K.; Ma, H.; Nie, J.; Ma, J.-A. *Synlett* **2008**, 3242.

TABLE 1. Enantioselective Addition of Acetophenone to Phenylnitrodiene 2a[a]



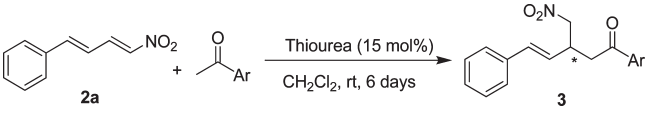
2a **3aa**

entry	solvent	catalyst (mol %)	additive (mol %)	yield[b] (%)	ee[c] (%)
1	CH_2Cl_2	**1a** (15)		23	97
2	CH_2Cl_2	**1a** (15)	AcOH (15)	33	98
3	CH_2Cl_2	**1a** (15)	H_2O (20)	41	97
4	CH_2Cl_2	**1a** (15)	$PhCO_2H$ (15)	40	98
5	CH_2Cl_2	**1a** (15)	TsOH (15)	20	98
6	CH_2Cl_2	**1a** (15)	4-NO_2PhCO_2H (15)	28	98
7	CH_2Cl_2	**1a** (15)	CF_3CO_2H (15)		
8	CH_2Cl_2	**1a** (15)	$PhCO_2H$ (10)	50	98
9	CH_2Cl_2	**1a** (15)	$PhCO_2H$ (5)	55	98
10	toluene	**1a** (15)	$PhCO_2H$ (5)	36	97
11	THF	**1a** (15)	$PhCO_2H$ (5)	10	94
12	Et_2O	**1a** (15)	$PhCO_2H$ (5)	30	96
13	$CHCl_3$	**1a** (15)	$PhCO_2H$ (5)	41	88
14[d]	CH_2Cl_2	**1a** (15)	$PhCO_2H$ (5)	24	99
15[e]	CH_2Cl_2	**1a** (15)	$PhCO_2H$ (5)	15	99
16	CH_2Cl_2	**1a** (20)	$PhCO_2H$ (5)	60	92
17	CH_2Cl_2	**1b** (15)	$PhCO_2H$ (5)	70	97
18	CH_2Cl_2	**1c** (15)	$PhCO_2H$ (5)	78	98
19	CH_2Cl_2	**1d** (15)	$PhCO_2H$ (5)	60	95
20	CH_2Cl_2	**1e** (15)	$PhCO_2H$ (5)	60	64

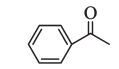
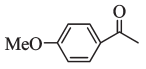
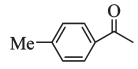
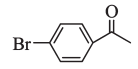
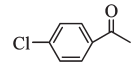
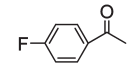
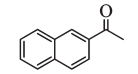
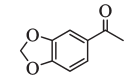
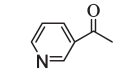
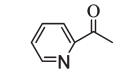
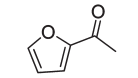
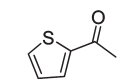
[a]The reaction was conducted with phenylnitrodiene (0.2 mmol), ketone (2.0 mmol), catalyst (0.03 mmol), additives, and solvent. [b]Isolated yield (average of two runs). [c]The ee values were determined by HPLC. [d]The reaction was conducted at 0 °C. [e]The reaction was conducted at −20 °C.

adduct **3aa** with excellent enantioselectivity (97% ee). However, the product yield was low (23%), despite the cleanness of the reaction (entry 1). Subsequently, a screen of weak Brønsted acid additives was undertaken.[4a,9e−9q,12] In most cases an increase of yields was observed by using these additivies, while the enantioselectivity was basically maintained (entries 2−6). However, no product was obtained in the presence of CF_3CO_2H (entry 7). The basis for this intriguing difference in reactivity is not well understood at this stage. With decreasing the loading of the additive of $PhCO_2H$, the catalyst **1a** provided the adduct in modest yields (entries 8 and 9). Variation of other standard reaction parameters (solvent, temperature, and catalyst loading) failed to increase the reaction rate and enantioselectivity. Subsequently, several new thiourea catalysts (**1b**−**e**) were prepared by a simple modification of substituents on the saccharide backbone. The catalysts **1b** and **1c** with bulky substituents at the saccharide scaffold appeared to be more

TABLE 2. Enantioselective Addition of Aromatic Ketones to Nitrodiene 2a



2a **3**

entry	ketone	Thiourea / Additives (mol%)	yield (%)[a]	ee (%)[b]
1		**1c** / $PhCO_2H$ (5)	78 (**3aa**)	97
2		**1c** / $PhCO_2H$ (5)	77 (**3ab**)	97
3		**1c** / $PhCO_2H$ (5)	90 (**3ac**)	96
4		**1c** / $PhCO_2H$ (5)	80 (**3ad**)	96
5		**1c** / $PhCO_2H$ (5)	72 (**3ae**)	94
6		**1c** / $PhCO_2H$ (5)	83 (**3af**)	96
7		**1c** / $PhCO_2H$ (5)	70 (**3ag**)	97
8		**1c** / $PhCO_2H$ (5)	89 (**3ah**)	98
9		**1c** / $PhCO_2H$ (5)	79 (**3ai**)	94
10		**1c** / $PhCO_2H$ (5)	90 (**3aj**)	84
11		**1c** / $PhCO_2H$ (5)	58 (**3ak**)	95
12		**1c** / $PhCO_2H$ (5)	56 (**3al**)	85

[a]Isolated yield (average of two runs). [b]Determined by chiral HPLC.

active than the simple compounds **1a** (entries 17 and 18). When replacing of ester moiety with ether protecting groups, a decrease of both yields and the ee values of the product was observed (entries 19 and 20). Among them, catalyst **1c** with four pivaloyl groups gave the highest yield (78%), while the enantioselectivity was maintained (98% ee).

A series of aromatic ketone substrates was probed next. It was found that the **1c**-catalyzed conjugate addition processes were also applicable to various aromatic ketones in good to high yields (70−90%) with excellent enantioselectivities (up to 97% ee) (Table 2, entries 1−7). Good to excellent stereoselection was also observed with heteroaromatic ketones (84−98% ee) (Table 2, entries 8−12). The major enantiomer

(12) Weak Brønsted acids as additives in asymmetric organocatalytic Michael Addition; see a recent review (ref [4a]). Selected recent examples: (a) Alexakis, A.; Andrey, O. *Org. Lett.* **2002**, *4*, 3611. (b) Andrey, O.; Alexakis, A.; Bernardinelli, G. *Org. Lett.* **2003**, *5*, 2559. (c) Andrey, O.; Alexakis, A.; Tomassini, A.; Bernardinelli, G. *Adv. Synth. Catal.* **2004**, *346*, 1147. (d) Marigo, M.; Schulte, T.; Franzén, J.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 15710. (e) Wang, W.; Li, H.; Wang, J.; Zu, L. *J. Am. Chem. Soc.* **2006**, *128*, 10354. (f) Luo, S.; Mi, X.; Zhang, L.; Liu, S.; Xu, H.; Cheng, J.-P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3093. (g) Luo, S.; Zhang, L.; Mi, X.; Qiao, Y.; Cheng, J.-P. *J. Org. Chem.* **2007**, *72*, 9350. (h) Lu, A.; Gao, P.; Wu, Y.; Wang, Y.; Zhou, Z.; Tang, C. *Org. Biomol. Chem.* **2009**, *7*, 3141. (i) Chua, P. J.; Tan, B.; Zeng, X.; Zhong, G. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3915. (j) Zeng, X.; Zhong, G. *Synthesis* **2009**, 1545.

(13) CCDC 733670 contains the supplementary crystallographic data for the product **3ad**. These data can also be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

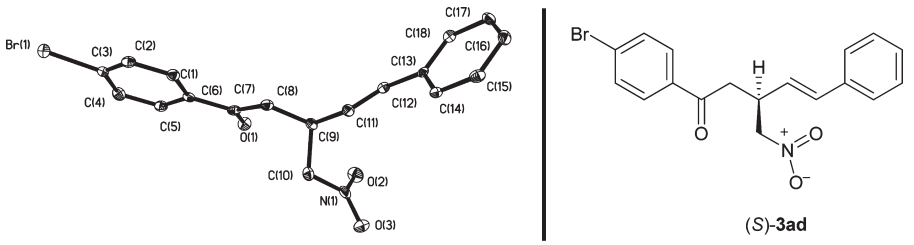


FIGURE 2. Crystal structure of the adduct **3ad**.

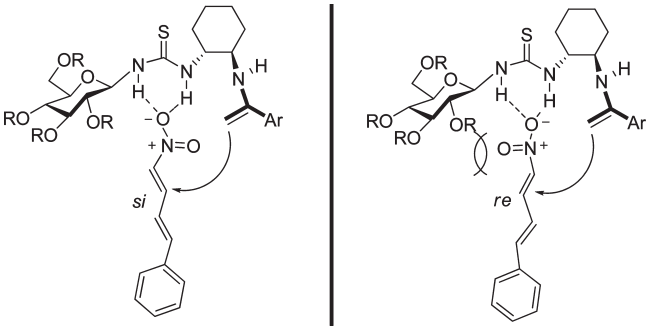


FIGURE 3. TS structures for the formation of the *R* and *S* enantiomers.

for the adduct **3ad** was recrystallized in the enantiomerically pure form (ee > 99.9%) by using dichloromethane/hexane mixture. The absolute configuration was determined to be *S* by X-ray measurement and Röntgen diffraction studies (Figure 2).[13] The results show that the *si*-face of the β-carbon at the nitrodiene was predominantly approached by the enamine intermediate generated from ketone and the primary amine group of the bifunctional catalyst. The attack of the enamine to the *re*-face of the nitrodiene was restricted by the thiourea scaffold of the catalyst (Figure 3).

It is noteworthy that the thioureas **1a**−**e** did not catalyze the conjugate addition of cyclohexanone to phenylnitrodiene **2a** at all. Accordingly, further modifications of modular organocatalyst **1c** have been made by simple replacement of cyclohexane-1,2-diamine moiety with chiral 1,2-diphenylethane-1,2-diamine to give a series of new thiourea−amine catalysts **1f**−**j** (Figure 1). The experimental results showed that the addition reaction of cyclohexanone to phenylnitrodiene **2a** took place in the presence of these new thioureas and additives ($PhCO_2H$) in toluene (Table 3, entries 1−5). The bifunctional thiourea **1g** as a highly enantioselective catalyst afforded the *syn*-Michael adduct in 93% ee. The yields were further improved when H_2O was used as the coadditive (Table 3, entries 6 and 7). The water might accelerate the reaction by facilitating the interconversion of the different intermediates of the catalytic cycle. Having this new organocatalyst system at hand, we examined other cyclic ketone substrates. The corresponding products **3am**−**ar** were obtained in excellent yields (92−98%) with high enantioselectivities (88−99% ee) (Table 3, entries 8−10). In addition, the addition reaction of acetone to phenylnitrodiene **2a** also afforded the desired product in good yield (75%) and high enantioselectivity (95% ee), while the more sterically demanding methyl isopropyl ketone gave completely linear product in 44% yield and 93% ee (Table 3, entries 11 and 12).

The three-dimensional molecular structures of both modular organocatalysts **1a** and **1g** were determined by single-crystal X-ray diffraction analysis (see the Supporting Information).[14] Probably, the flexibility of catalyst **1g** allows the thiourea group and the primary amine moiety to be involved in the catalytic addition process of aliphatic ketones to nitroalkenes with both activation of the nucleophile and the electrophile, while the rigidity of catalyst **1a** or **1c** appears to be suitable to aromatic ketones. A bifunctional catalytic mechanism was suggested in which a thiourea moiety interacts through hydrogen bonding with a nitro group of the nitrodienes and enhances their electrophilicity while the neighboring primary amine activates ketones involving an iminium ion **A** and an enamine intermediate **B** promoted by acid additive. Subsequently, the C-nucleophile attacks the *si*-face of the β-carbon at the nitrodiene to give the imine intermediate **C**. Finally, the regeneration of the catalyst through hydrolysis of the imine **C** is facilitated by water (Scheme 1).[8e]

As noted above, both thioureas **1c** and **1g** proved to be efficient catalysts in the conjugate addition to phenylnitrodienes with aromatic ketones and (a)cyclic aliphatic ketones, respectively. Nitrodienes substituted with electron-poor and -rich arenes (**2b** and **2c**) were also tested (Table 4). The desired 1,4-adducts were obtained in 48−98% yields with good to excellent enantioselectivities (84−99% ee) (Table 4, entries 1−6). When we attempted the enantioselective conjugate addition of ketones to aliphatic nitrodiene (1-nitrohexa-1,3-diene), no desired product was formed, but some insoluble polymeric material was observed. Notably, it was also found that the 1,4-conjugate addition of ketones to phenylnitroeneyne **2d** gave the adducts in high yields and enantioselectivities (Table 4, entries 7−9).

These 1,4-conjugate addition products **3** are versatile building blocks for further modifications. For example, the adducts **3aa** and **3aq** could easily undergo a simple one-pot reduction/intramolecular cyclization, followed by protection, separation of diastereoisomers, oxidation, and recrystallization to give *trans*- and *cis*-(3*R*)-5-substituted 3-pyrrolidinecarboxylic acids (Scheme 2). (3*R*,5*R*)-5-Methyl-3-pyrrolidinecarboxylic acid proved to be an efficient organocatalyst for *anti*-Mannich-type reactions.[15]

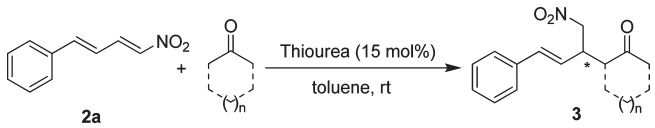
Conclusion

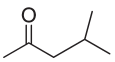
We have developed enantioselective organocatalytic conjugate addition of a series of ketones to $\alpha,\beta-\gamma,\delta$-unsaturated

(14) CCDC 698374 and CCDC 695685 contain the supplementary crystallographic data for the products **1a** and **1g**. These data can also be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_ request/cif.

(15) Mitsumori, S.; Zhang, H.; Cheong, P. Y.-Y.; Houk, K. N.; Tanaka, F.; Barbas, C. F. III. *J. Am. Chem. Soc.* **2006**, *128*, 1040.

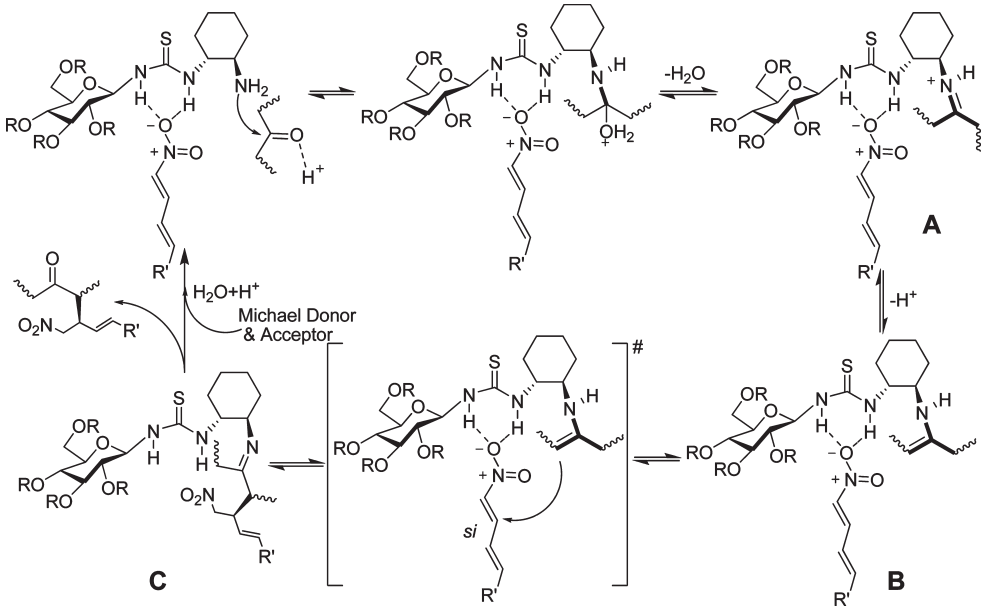
TABLE 3. Enantioselective Addition of Aliphatic Ketones to Nitrodiene 2a



entry	ketone	Thiourea / Additives (mol%)	yield (%) [a]	*syn* / *anti* [b]	ee (%) [c]
1		**1f** / $PhCO_2H$ (5)	40 (**3am**)	74 / 26	93
2		**1g** / $PhCO_2H$ (5)	62 (**3am**)	57 / 43	93
3		**1h** / $PhCO_2H$ (5)	25 (**3am**)	85 / 15	-94
4		**1i** / $PhCO_2H$ (5)	71 (**3am**)	66 / 34	85
5		**1j** / $PhCO_2H$ (5)	15 (**3am**)	66 / 34	85
6		**1g** / $PhCO_2H$ (5) / H_2O (100)	84 (**3am**)	68 / 32	93
7		**1g** / $PhCO_2H$ (5) / H_2O (200)	94 (**3am**)	70 / 30	95
8		**1g** / $PhCO_2H$ (5) / H_2O (200)	97 (**3an**)	63 / 37	97
9		**1g** / $PhCO_2H$ (5) / H_2O (200)	98 (**3ao**)	50 / 50	99
10		**1g** / $PhCO_2H$ (5) / H_2O (200)	92 (**3ap**)	55 / 45	88
11		**1g** / $PhCO_2H$ (5) / H_2O (200)	75 (**3aq**)	-	95
12		**1g** / $PhCO_2H$ (5) / H_2O (200)	44 (**3ar**)	-	93

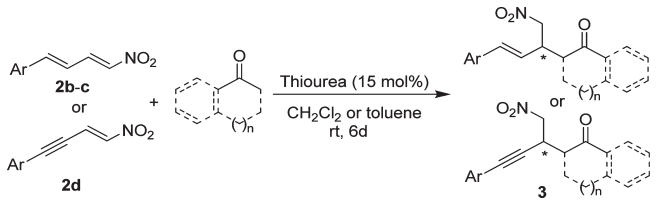
[a]Isolated yield (average of two runs). [b]Determined by ^1H NMR or HPLC of crude product. [c]Determined by chiral HPLC on the *syn* adduct.

SCHEME 1. Plausible Mechanism for Bifunctional Thiourea−Amine Catalysis



nitro compounds using bifunctional amine−thiourea catalysts easily prepared from saccharides and chiral diamines. In all cases, only 1,4-addition occurred without any trace of the 1,6-adduct. The reaction proceeds well for a great

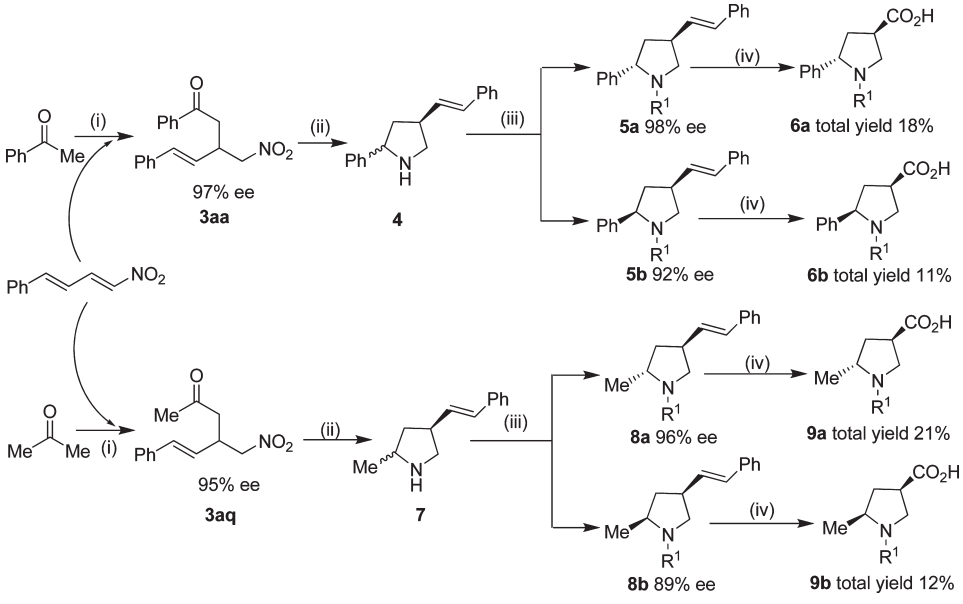
TABLE 4. Enantioselective Addition of Ketones to Nitrodienes and Nitroeneyne[a]



entry	Ar	Ketone	yield (%) [b]	*syn* / *anti* [c]	ee (%) [d]
1	2-NO_2Ph (**2b**)		94 (**3ba**)	-	96
2	2-NO_2Ph (**2b**)		85 (**3bb**)	99 / 1	96
3	2-NO_2Ph (**2b**)		78 (**3bc**)	-	84
4	4-MeOPh (**2c**)		48 (**3ca**)	-	99
5	4-MeOPh (**2c**)		98 (**3cb**)	66 / 34	91
6	4-MeOPh (**2c**)		70 (**3cc**)	-	91
7	Ph (**2d**)		85 (**3da**)	-	96
8	Ph (**2d**)		89 (**3db**)	71 / 29	91
9	Ph (**2d**)		85 (**3dc**)	-	94

[a]For aromatic ketones: **1c** (15 mol %) and $PhCO_2H$ (5 mol %). For alphatic ketones: **1g** (15 mol %), $PhCO_2H$ (5 mol %), and H_2O (200 mol %). [b]Isolated yield (average of two runs). [c]Determined by ^1H NMR or HPLC of crude product. [d]Determined by chiral HPLC on the *syn* adduct.

SCHEME 2. Synthetic Transformations of Adducts 3aa and 3aq



diversity of nucleophilic carbonyl compounds and nitrodienes with high enantioselectivties (84−99% ee). Furthermore, this process provides some synthetically useful intermediates which can easily be transformed into

trans- and *cis*-(3*R*)-5-substituted 3-pyrrolidinecarboxylic acids.

Experimental Section

General Procedure for the Synthesis of Catalysts. To a solution of 1,2-cyclohexyldiamine (3.6 mmol) in dichloromethane (20 mL) was added the corresponding saccharide-derived isothiocyanates (3 mmol). The mixture was stirred at room temperature for 3−24 h (TLC) and concentrated. The resulting residue was purified by flash chromatography with the eluent ($AcOEt/Et_3N$ 100/1) to give the crude solid. The crude solid was dissolved in a minimal amount of dichloromethane and slowly precipitated from solution by the addition of petroleum at 0 °C. Filtration afforded the desired thiourea products **1b**. The catalysts of **1c**−**j** were prepared by this similar procedure.[16,17]

1b: yield 56%; $[\alpha]^{20}_D$ +46.8 (*c* 0.5, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.18−1.28 (m, 6H, cyclohexyl-*H*), 1.62 (br, 1H, N*H*), 1.89 (br, 1H, N*H*), 2.05−2.16 (m, 2H, cyclohexyl-*H*), 3.31 (br, 2H N*H*C(S)N*H*), 3.70−3.74 (m, 1H, cyclohexyl-*H*), 4.10−4.15 (m, 1H, cyclohexyl-*H*), 4.31−4.33 (m, 1H, CH_2), 4.46−4.49 (m, 1H, pyranosyl-*H*), 4.59−4.61 (m, 1H, CH_2), 5.57−5.59 (m, 1H, pyranosyl-*H*), 5.71−5.75 (m, 1H, pyranosyl-*H*), 6.00−6.03 (m, 1H, pyranosyl-*H*), 6.21−6.23 (m, 1H, pyranosyl-*H*), 7.25−8.07 (m, 20H, Ph-*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.7, 166.2, 133.5, 133.2, 130.1, 129.9, 129.7, 129.5, 128.8, 128.7, 128.4, 128.2, 83.4, 73.9, 71.4, 69.5, 63.0, 58.7, 58.2, 53.5, 34.5, 33.4, 31.6, 29.7, 28.1, 24.5, 24.4, 22.9, 18.4, 14.2; IR (KBr) ν 2930, 2855, 1731,1558, 1532, 1470, 1441, 1268, 1093, 1069, 708 cm^{-1}; MS (ESI) *m*/*z* 752.20 $[M + 1]^+$; HRMS (EI) found *m*/*z* 752.2633 $[M + 1]^+$, calcd for $C_{41}H_{41}N_3O_9S$ + H 752.2636.

Procedure for the Thiourea-Promoted Michael Addition of Ketones to Nitrodienes. Procedure A. The nitrodiene (0.2 mmol), aryl ketone (2.0 mmol), $PhCO_2H$ (0.01 mmol), and catalyst **1c** (0.03 mmol) were placed in a 5 mL vial equipped with a Teflon-coated stir bar. The solvent (1 mL) was added under air. The vial was capped with a white polyethylene stopper, and the resulting mixture was stirred at room temperature for the stated time. Then the reaction solution was concentrated in vacuo, and the crude was purified by flash chromatography to afford the product. The compounds **3aa**−**al**, **3ba**, **3ca**, and **3da** were prepared according to this procedure.

3-(Nitromethyl)-1,5-diphenylpent-4-en-1-one (3aa): yield 78%; mp 105−107 °C; $[\alpha]^{20}_D$ +1.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.30−3.31 (d, *J* = 6.5 Hz, 2H, COCH_2), 3.72−3.80 (m, 1H, C*H*), 4.60−4.64 (dd, *J* = 12.0 Hz, 7.5 Hz, 1H, C*H*NO_2), 4.71−4.74 (dd, *J* = 12.0 Hz, 6.0 Hz, 1H, C*H*NO_2), 6.15−6.20 (dd, *J* = 16.0 Hz, 9.0 Hz, 1H, =C*H*), 6.56−6.60 (d, *J* = 16.0 Hz, 1H, =C*H*), 7.23−7.27 (m, 1H, Ph-*H*), 7.29−7.34 (m, 4H, Ph-*H*), 7.48−7.51 (m, 2H, Ph-*H*), 7.59−7.62 (m, 1H, Ph-*H*), 7.96−7.97 (d, *J* = 7.5 Hz, 2H, Ph-*H*); ^{13}C NMR (500 MHz, $CDCl_3$) δ 197.3, 136.7, 136.4, 133.9, 133.7, 129.0, 128.9, 128.3, 128.2, 126.8, 126.7, 79.0, 40.6, 37.5; IR (KBr) ν 3031, 2907, 1680, 1542, 1450, 1218, 969 907, 758, 691 cm^{-1}; MS (ESI) *m*/*z* 296.48 $[M + 1]^+$; HRMS (EI) found *m*/*z* 318.1098 $[M + Na]^+$, calcd for $C_{18}H_{17}NO_3$ + Na 318.1101; 98% ee, determined by HPLC analysis Daicel Chirapak AD-H, *i*-PrOH/hexane (10/90), 254 nm, 1.0 mL/min, t_R = 16.8 min (minor), 14.7 min (major).

Procedure B. The nitrodiene (0.2 mmol), ketone (2.0 mmol), catalyst **1g** (0.03 mmol), $PhCO_2H$ (0.01 mmol), and H_2O (0.4 mmol) were placed in a 5 mL vial equipped with a Teflon-coated stir bar. The solvent (1 mL) was added under air. The vial was capped with a white polyethylene stopper, and the resulting mixture was stirred at room temperature for the stated time. Then the reaction solution was concentrated in vacuo, and the crude was purified by flash chromatography to afford the product. The compounds **3am**−**as**, **3bb**, **3bc**, **3cb**, **3cc**, **3db**, and **3dc** were prepared according to this procedure.

2-(1-Nitro-4-phenylbut-3-en-2-yl)cyclohexanone (3am): yield 94%; mp 111−112 °C; $[\alpha]^{20}_D$ −1.1 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40−1.52 (m, 1H, cyclohexanone-*H*), 1.60−1.71 (m, 4H, cyclohexanone-*H*), 2.05−2.12 (m, 2H, cyclohexanone-*H*), 2.44−2.47 (m, 1H, cyclohexanone-*H*), 2.53−2.58 (m, 1H, cyclohexanone-*H*), 3.33−3.39 (m, 1H, C*H*), 4.56−4.60 (dd, *J* = 12.0 Hz, 8.5 Hz, 1H, C*H*NO_2), 4.66−4.71 (m, 1H, C*H*NO_2), 6.00−6.05 (dd, *J* = 16.0 Hz, 10.5 Hz, 1H, =C*H*), 6.46−6.51 (m, 1H, =CH), 7.23−7.36 (m, 5H, Ph-*H*); ^{13}C NMR (500 MHz, $CDCl_3$) δ 211.5, 136.5, 135.1, 134.6, 128.8, 128.2, 126.7, 125.9, 78.3, 51.9, 42.9, 32.8, 28.3, 25.3; IR (KBr) ν 3080, 2952, 2871, 1699, 1552, 1494, 1384, 966, 743, 691 cm^{-1}; MS (ESI) *m*/*z* 274.62 $(M + 1)^+$; HRMS (EI) found *m*/*z* 296.1259 $[M + Na]^+$, calcd for $C_{16}H_{19}NO_3$+Na 296.1257; 95% ee, 70/30 dr, determined by HPLC analysis Daicel Chirapak AS-H, *i*-PrOH/hexane (20/80), 254 nm, 0.8 mL/min, t_R = 21.5 min (minor), 13.5 min (major).

Procedure for the Transformation of Compounds 3aa and 3aq. (i) To a solution of (*S*)-**3aa** 500 mg (2.1 mmol) in 20 mL of AcOH was added zinc powder (4.2 g, 30 equiv) in portions at 55 °C. The resultant mixture was stirred for 4 h at 65 °C (monitored by TLC). After zinc powder was filtered off, the filtrate was cooled to 0 °C. The filtrate was diluted with ethyl acetate and neutralized by the addition of sodium hydrogen carbonate (70% saturated aqueous). The mixture was extracted with dichloromethane (30 mL × 4), washed with brine, and dried with magnesium sulfate. The solvent was removed under reduced pressure to afford **4** (418 mg, 99%) as a colorless oil, and the residue was directly used to next step without purified.

4: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.81−1.89 (m, 1H, pyrrolidine-*H*), 2.15−2.20 (m, 1H, pyrrolidine-*H*), 2.91−2.96 (m, 1H, pyrrolidine-*H*), 3.11−3.19 (m, 1H, pyrrolidine-*H*), 3.45−3.50 (m, 1H, pyrrolidine-*H*), 4.39−4.46 (m, 1H, pyrrolidine-*H*, pyrrolidine-*H*), 5.57 (s, 1H, N*H*), 6.20−6.27 (m, 1H, =C*H*), 6.46−6.51 (m, 1H, =C*H*), 7.22−7.34 (m, 10H, Ph-*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 132.1, 131.5, 130.2, 129.6, 127.4, 127.3, 127.0, 126.3, 126.1, 61.8, 52.6, 42.3, 40.5; IR (KBr) ν 3414, 3138, 2933, 2836, 2112, 1651, 1494, 1443, 1387, 1320, 1198, 970, 750, 702 cm^{-1}.

(ii) To a solution of 4-nitrobenzoyl chloride (0.47 g, 2.6 mmol) and Et_3N (0.82 mL, 6.0 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise a solution of **4** (418 mg, 1.7 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C. After the mixture was stirred for 24 h (monitored by TLC), solvent was removed under reduced pressure. After column chromatography on silica gel (eluent, ethyl acetate/hexane 1/4), the product **5a** (*trans*) (98% ee) and **5b** (*cis*) (92% ee) as a white solid was isolated in 37% yield and 23% yield.

(iii) Ozone was passed through a solution of **5a** (142 mg, 0.36 mmol) in dry CH_2Cl_2 (1.5 mL) at −78 °C for 2 h. Argon gas was passed through the mixture. The mixture was concentrated at 0 °C and was added to a mixture of formic acid (90%, 1.5 mL) and hydrogen peroxide (30%, 0.75 mL). The mixture was stirred at 40 °C for 1 h and at 70 °C for 1 h and then concentrated. To the solution of the residue in acetone (12 mL) was added a solution of $KMnO_4$ (150 mg) in water (6 mL) at room temperature. After the mixture was stirred for 1 day, concentrated HCl was added to the mixture until a clear solution was obtained. The mixture was extracted with $CHCl_3$ (30 mL × 3). The organic layer was washed with water and then dried over $MgSO_4$. Concentration,

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(17) (a) Ishikawa, T.; Fletcher, H. G. *J. Org. Chem.* **1969**, *34*, 563. (b) Muskat, I. E. *J. Am. Chem. Soc.* **1934**, *56*, 693. (c) Jensen, H. H.; Nordstrm, L. U.; Bols, M. *J. Am. Chem. Soc.* **2004**, *126*, 9205. (d) Bihovsky, R.; Selick, C.; Giusti, I. *J. Org. Chem.* **1988**, *53*, 4026.

flash chromatography (eluent, ethyl acetate/hexane 1/6 to MeOH/ethyl acetate 1/4), and recrystallization (dichloromethane/hexane) afforded **6a** as white solid with an overall yield of 18%. In the same manner, **6b** was obtained in yield of 11%. Starting from (*S*)-**3aq**, **9a** (*trans*) and **9b** (*cis*) were attained with an overall yield of 21% and 12%.

6a: yield 18%; mp 139−140 °C; $[\alpha]^{20}_{D}$ −52.6 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.00−2.04 (m, 1H, pyrrolidine-*H*), 2.58−2.62 (m, 1H, pyrrolidine-*H*), 3.06−3.11 (m, 1H, pyrrolidine-*H*), 3.61−3.64 (dd, J = 10.5 Hz, 4.5 Hz, 1H, pyrrolidine-*H*), 3.92−3.96 (dd, J = 10.5 Hz, 7.0 Hz, 1H, pyrrolidine-*H*), 5.20−5.23 (t, J = 7.0 Hz, 1H, pyrrolidine-*H*), 6.99−7.00 (d, J = 7.0 Hz, 1H, Ph-*H*), 7.23−7.26 (m, 1H, Ph-*H*), 7.36−7.38 (m, 3H, Ph-*H*), 7.84−7.85 (d, J = 8.5 Hz, 2H, Ph-*H*), 8.30−8.31 (d, J = 8.5 Hz, 2H, Ph-*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.0, 169.2, 148.4, 142.3, 142.1, 129.3, 128.2, 127.9, 125.6, 123.5, 63.5, 53.7, 39.3, 18.5; IR (KBr) ν 3427, 3054, 2908, 2350, 1724, 1587, 1514, 1428, 1338, 871, 729 cm^{-1}; MS (ESI) m/z 339.12 $[M - 1]^-$; HRMS (EI) found m/z 363.0953 $[M + Na]^+$, calcd for $C_{18}H_{16}N_2O_5$ + Na 363.0951.

6b: yield 11%; mp 136−138 °C; $[\alpha]^{20}_{D}$ −40.0 (*c* 0.5, CH_2Cl_2); ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.87−1.94 (m, 1H, pyrrolidine-*H*), 2.68−2.74 (m, 1H, pyrrolidine-*H*), 3.11−3.18 (m, 1H, pyrrolidine-*H*), 3.63−3.67 (m, 1H, pyrrolidine-*H*), 3.96−4.00 (t, J = 10.5 Hz, 1H, pyrrolidine-*H*), 5.11−5.14 (t, J = 8.0 Hz, 1H, pyrrolidine-*H*), 7.05−7.07 (d, J = 6.5 Hz, 1H, Ph-*H*), 7.20−7.23 (t, J = 7.0 Hz, 1H, Ph-*H*), 7.31−7.34 (t, J = 7.5 Hz, 3H, Ph-*H*), 7.38−7.40 (d, J = 7.5 Hz, 2H, Ph-*H*), 7.88−7.89 (d, J = 7.5 Hz, 2H, Ph-*H*); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.4, 167.2, 148.7, 143.6, 142.9, 129.4, 128.8, 127.2, 126.1, 124.1, 61.4, 55.4, 52.9, 43.2; IR (KBr) ν 3433, 3012, 2897, 2344, 1699, 1577, 1505, 1433, 1320, 855, 693 cm^{-1}; MS (ESI) m/z 339.14 $(M - H)^-$; HRMS (EI) found m/z 363.0954 $[M + Na]^+$, calcd for $C_{18}H_{16}N_2O_5$ + Na 363.0951.

Acknowledgment. We gratefully appreciate the National Natural Science Foundation of China (No. 20772091 and 20972110) and Tianjin Municipal Science & Technology Commission (No. 07JCDJC04700) for financial support.

Supporting Information Available: Experimental details for the preparation of organocatalysts **1c**−**j**, the adducts **3ab**−**al**, **3ba**, **3ca**, **3da**, **3an**−**as**, **3bb**, **3bc**, **3cb**, **3cc**, **3db**, and **3dc**, the intermediate **7**, and the products **9a** and **9b**; ^{1}H and ^{13}C NMR spectra for all of the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.