ORGANIC LETTERS

2009
Vol. 11, No. 13
2864−2867

Simple Cyclohexanediamine-Derived Primary Amine Thiourea Catalyzed Highly Enantioselective Conjugate Addition of Nitroalkanes to Enones

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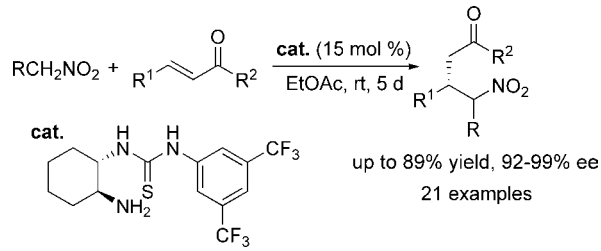
Received March 13, 2009

ABSTRACT



A highly enantioselective conjugate addition of nitroalkanes to enones has been developed. The process is efficiently catalyzed by a simple chiral cyclohexanediamine-derived primary amine thiourea with a broad substrate scope.

Conjugate additions of carbon-centered nucleophiles to electron-deficient alkenes are unrivaled in their power for the formation of fundamental carbon−carbon bonds, whereby a wide variety of substances that can serve as electrophiles and nucleophiles and, consequently, a diverse array of products can be generated.[1−5] In the recent past, significant and impressive progress has been made in the area of organocatalysis.[2−5] However, the use of nitroalkanes for asymmetric conjugate addition to enones remains an unsolved problem despite the fact that chiral versatile nitro carbonyl adducts can be conveniently transformed into a variety of valuable structures such as pyrrolidines,[6] lactones,[7] carbocycles,[8] and amino acids[9] in organic synthesis. To date,

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(1) For reviews of conjugate addition reactions, see: (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: Oxford, 1992. (b) Sibi, M.; Manyem, S. *Tetrahedron* **2001**, *56*, 8033. (c) Christoffers, J.; Baro, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1688. (d) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2007**, *107*, 933.

(2) For recent reviews of organocatalyzed conjugate addition reactions, see: (a) Almaşi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299. (b) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701.

(3) For recent reviews of nitro-Michael reactions, see: (a) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, *12*, 1877. (b) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005**, *105*, 933.

(4) For recent reviews of asymmetric organocatalysis, see: (a) Berkessel, A.; Groger, H. *Asymmetric Organocatalysis-From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2005. (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (c) Special Issue on Asymmetric Organocatalysis . *Acc. Chem. Res.* 2004, *37*, 487.

10.1021/ol9010322 CCC: $40.75
Published on Web 06/01/2009

among the reported methods, it is realized that generally good enantioselectivity of the organocatalytic conjugate addition processes are limited only to cyclic enones.[10] Jørgensen[11a] and Ley[11b] independently reported chiral pyrrolidine tetrazole promoted the addition of 2-nitropropane to acyclic enone with moderate to good enantioselectivity (70−89% ee). Soós and co-workers described a cinchona alkaloid-derived thiourea catalyzed addition of nitromethane with high enantioselectivity.[12] Nevertheless, the method only applied for chalcones as Michael acceptors. More recently, Liang, Ye and co-workers disclosed an improved protocol and 73−86% ee were obtained.[13]

Clearly, improving the enantioselectivity to a useful level (≥90% ee) of the conjugate addition of nitromethane to acyclic enones is an important, but currently unmet goal. Recently, we have initiated an effort on tackling the challenging issue. Herein, we wish to report the results of the investigation, which has led to a new simple primary amine thiourea catalyzed highly enantioselective conjugate addition of nitromethane to acyclic enones. Notably, high to excellent (92−99%) enantioselectivities are achieved and a wide array of α,β-unsaturated ketones can be exploited for the process.

trans-Cyclohexane diamine derived bifunctional catalysts have proved to be valuable promoters in Michel addition reactions.[14] However, their reactivity and selectivity toward a reaction are strongly substrate-dependent. In some cases, the subtle changes in the structure of a catalyst can sometimes significantly improve catalytic activity and stereocontrol. Accordingly, our attempts to identify an effective catalyst for conjugate addition of nitromethane (**1**) to 4-phenylbut-3-en-2-one (**2a**) were carried out in the presence of an organocatalyst (15 mol %) in chloroform at rt (Figure 1).

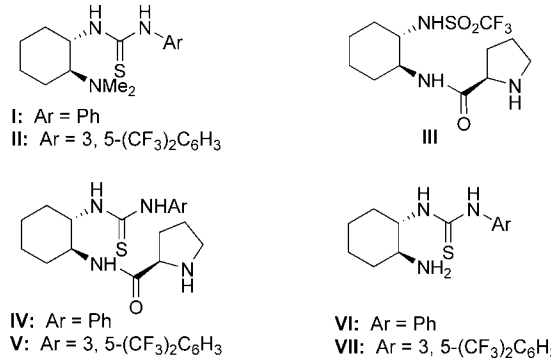
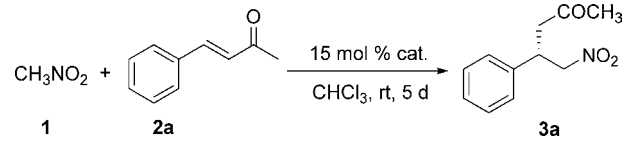


Figure 1. Structures of screened organocatalysts.

Widely used Takemoto's catalysts **I** and **II** failed to promote the process (Table 1, entries 1 and 2).[15] Pyrrolidinesulfonamide (**III**), first developed in our laboratory, displayed an encouraging result (entry 3).[16] It is well established that thioureas with capability of affording two H-bonds generally

Table 1. Asymmetric Michael Addition of Nitromethane (**1**) to 4-Phenylbut-3-en-2-one (**2a**)[a]



1 2a 3a

entry	cat.	% yield[b]	% ee[c]
1	**I**	0	ND[d]
2	**II**	0	ND[d]
3	**III**	60	58
4	**IV**	76	59
5	**V**	52	37
6	**VI**	36	93
7	**VII**	57	97

[a] Teaction was carried out with 0.1 mmol **2a** and nitromethane (0.1 mL) in the presence of 15 mol % an organocatalyst in 0.2 mL of $CHCl_3$ at rt for 5 d. [b] Isolated yields. [c] Determined by HPLC analysis (Chirapak AS-H column). [d] Not determined.

(5) For selected examples of organocatalytic asymmetric Michael additions of stabilized carbanions, see: Nitroalkanes: (a) Li, H.; Wang, Y.; Tang, T.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906. (b) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119. (c) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481. Ketoesters: (d) Berkessel, A.; Cleemann, F.; Mukherjee, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 947. Diketones: (e) Zu, L.; Wang, W.; Wang, J.; Li, H.; Duan, W.-H. *Org. Lett.* **2005**, *7*, 4713. (f) Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2008**, *130*, 14416. Nitroesters: (g) Raheem, I. T.; Goodman, S. N.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 706. Dinitriles: (h) Hoashi, Y.; Okino, T.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 4032. Malonates: (i) Li, P.; Wen, S.; Yu, F.; Liu, Q.; Li, W.; Wang, Y.; Liang, S.; Ye, J. *Org. Lett.* **2009**, *11*, 753.

(6) (a) Cheruku, S. R.; Padmanilayam, M. P.; Vennerstrom, J. L. *Tetrahedron Lett.* **2003**, *44*, 3701. (b) Halland, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 8331. (c) List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423.

(7) Sil, D.; Sharon, A.; Maulikb, P. R.; Rama, V. J. *Tetrahedron Lett.* **2004**, *45*, 6273.

(8) (a) Ballini, R.; Barboni, L.; Bosica, G.; Fiorini, D. *Synthesis* **2002**, 2725. (b) Ballini, R. *Synthesis* **1993**, 687.

(9) (a) Jiang, X.; Zhang, Y.; Chan, A. S. C.; Wang, R. *Org. Lett.* **2008**, *11*, 153. (b) Zhu, S. L.; Yu, S. Y.; Ma, D. W. *Angew. Chem., Int. Ed.* **2008**, *47*, 545. (c) Foresti, E.; Palmieri, G.; Petrini, M.; Profeta, R. *Org. Biomol. Chem.* **2003**, *1*, 4275.

(10) (a) Hanessian, S.; Pham, V. *Org. Lett.* **2000**, *2*, 2975. (b) Tsogoeva, S. B.; Jagtap, S. B.; Ardemasova, Z. A.; Kalikhevich, V. N. *Eur. J. Org. Chem.* **2004**, 4041. (c) Ooi, T.; Takada, S.; Fujioka, S.; Maruoka, K. *Org. Lett.* **2005**, *7*, 5143. (d) Tsogoeva, S. B.; Jagtap, S. B.; Ardemasova, Z. A. *Tetrahedron: Asymmetry* **2006**, *17*, 989. (e) Hanessian, S.; Shao, Z.; Warrier, J. S. *Org. Lett.* **2006**, *8*, 4787. (f) Malmgren, M.; Granander, J.; Amedjkouh, M. *Tetrahedron: Asymmetry* **2008**, *19*, 1934. (g) Szanto, G.; Bombicz, P.; Grun, A.; Kadas, I. *Chirality* **2008**, *20*, 1120. (h) Suresh, P.; Pitchumani, K. *Tetrahedron: Asymmetry* **2008**, *19*, 2037. For related selected examples of organocatalytic addition of nitromethane to enals, see: (i) Palomo, C.; Landa, A.; Mielgo, A.; Oiarbide, M.; Puente, A.; Vera, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 8431. (j) Gotoh, H.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2007**, *9*, 5307. (k) Zu, L.-S.; Xie, H.-X.; Li, H.; Wang, J.; Wang, W. *Adv. Synth. Catal.* **2007**, *349*, 2660.

(11) (a) Prieto, A.; Halland, N.; Jørgensen, K. A. *Org. Lett.* **2005**, *7*, 3897, and ref 5b(b) Mitchell, C. E. T.; Brenner, S. E.; Ley, S. V. *Chem. Commun.* **2005**, 5346. (c) Mitchell, C. E. T.; Brenner, S. E.; García-Fortanet, J.; Ley, S. V. *Org. Biomol. Chem.* **2006**, *4*, 2039.

(12) Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967.

(13) Liang, X.; Ye, J.; Li, P.; Wang, Y. *Chem. Commun.* **2008**, 3302.

(14) For a review, see: Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520. and cited references therein.

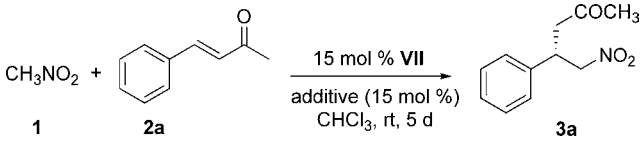
(15) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672.

(16) Wang, W.; Wang, J.; Li, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 1369.

give better catalytic efficiency.[17] Therefore, catalysts **IV** and **V** containing a thiourea moiety were explored (entries 4 and 5).[18] Disappointingly, only marginal improvement in terms of reaction yield and enantioselectivity was observed with **IV** (entry 4). We then turned our attention to the primary amine thioureas **VI** and **VII** although such catalysts had never shown to be effective promoters for asymmetric conjugate addition reactions.[19,20] To our delight, a promising result (93% ee) was achieved when **VI** was employed in spite of low yield (entry 6). It is noted that the acidity of the hydrogen bond donor motifs has a dramatic impact on their catalytic activity. The activity of the catalyst improves as the acidity of the hydrogen bond donor increases. This observation was confirmed with catalyst **VII** (entry 7). Notably, an excellent level of enantioselectivity (97% ee) and an enhanced yield (57%) were obtained. Subsequently, catalyst **VII** was selected for further reaction condition optimization mainly aimed at improving yield of the conjugate addition process without compromising the enantioselectivity.

We first investigated the solvent effect on the Michael addition. As shown in Table 2, the reaction yields were

Table 2. Effect of Solvents and Additives on the Asymmetric Michael Addition of Nitromethane (**1**) to 4-Phenylbut-3-en-2-one (**2a**) catalyzed by **VII**[a]



1 2a 3a

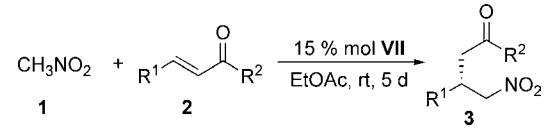
entry	solvent	additive	% yield[b]	% ee[c]
1	CH_2Cl_2	none	39	97
2	THF	none	71	94
3	*i*-PrOH	none	32	92
4	DMSO	none	29	89
5	DMF	none	36	95
6	$CHCl_3$	none	57	98
7	1,4-dioxane	none	36	99
8	EtOAc	none	68	98
9	EtOAc	$PhCO_2H$	48	93
10	EtOAc	AcOH	74	89
11	EtOAc	*n*-$PrCO_2H$	77	93
12	EtOAc	CF_3CO_2H	<5	ND[d]

[a] Reaction conditions: unless specified, see footnote *a* in Table 1. [b] Isolated yields. [c] Determined by HPLC analysis (Chirapak AS-H column). [d] Not determined.

solvent dependent whereas they had a limited impact on the enantioselectivities. Among the solvents probed, it appeared that ethyl acetate was the best one (entry 8). The effect of acid additives was then surveyed. Acid additives such as AcOH and *n*-$C_3H_7CO_2H$ improved the yield but with a decrease in enantioselectivity (entries 10 and 11); $PhCO_2H$ retarded this process and both yield and enantioselectivity dropped (entry 9). It was found that stronger acid such as CF_3CO_2H deteriorated this process significantly and no product was obtained (entry 12).

We are delighted to demonstrate the generality of this highly enantioselective Michael reaction with a broad range of acyclic enones **2** in significant structural variation. As summarized in Table 3, the **VII** promoted conjugate addition

Table 3. Asymmetric Michael Addition of Nitromethane to 4-arylbut-3-en-2-one catalyzed by **VII**[a]



1 2 3

entry	R^1, R^2, **3**	% yield[b]	% ee[c]
1	Ph, Me, **3a**	68	98
2[d]	*p*-$CH_3OC_6H_4$, Me, **3b**	68	98
3	*p*-$N(CH_3)_2C_6H_4$, Me, **3c**	74	97
4	3,4-$(OCH_2O)C_6H_3$, Me, **3d**	61	97
5	*p*-$NO_2C_6H_4$, Me, **3e**	88	92
6	*m*-$NO_2C_6H_4$, Me, **3f**	82	95
7	*o*-$NO_2C_6H_4$, Me, **3g**	70	95
8	*p*-FC_6H_4, Me, **3h**	87	99
9	*p*-BrC_6H_4, Me, **3i**	89	99
10	*o*-IC_6H_4, Me, **3j**	76	96
11	2-furanyl, Me, **3k**	71	94
12	$PhCH_2$, Me, **3 L**	76	95
13	$Ph(CH_2)_2$, Me, **3m**	82	93
14[d]	*n*-$Me(CH_2)_4$, Me, **3n**	83	95
15	*trans*-PhCH=CH, Me, **3o**	64	97
16	Ph, Et, **3p**	61	97
17[d]	Ph, *i*-Pr, **3q**	38	96
18	Ph, $AcOCH_2$, **3r**	58	94
19	Ph, $PhCO_2CH_2$, **3s**	73	98
20[e]	$(CH_2)_4$, **3t**	69	97
21[f]	Ph, Me, **3u**	82[g]	94[h]

[a] Reaction conditions: unless specified, see footnote *a* in Table 1. [b] Isolated yields. [c] Determined by chiral HPLC analysis (Chiralpak AS-H or AD-H). [d] When reactions are carried out for 10 d, the yields are 68% for **3b**, 83% for **3n** and 38% for **3q**, respectively. [e] Reaction time: 4 d. [f] Nitroethane as nucleophile with reaction time of 10 d. [g] Total yield for both diastereomers. [h] 1:1.2 dr and 94% ee for both diastereoisomers, ee determined by converting to corresponding acetal.

reaction with aryl enones bearing electron-neutral (entry 1), -donating (entries 2−4), or -withdrawing (entries 5−10) substituents consistently proceeded in excellent enantioselectivity (92−99% ee). Steric effect of substrates on the conjugate addition was limited as well (entries 7 and 10). Moreover, heteroaromatic furanyl derived enone effectively engaged in the process (entry 11).

The **VII** catalyzed conjugate addition reactions not only work out with aryl methyl enones, but also less reactive alkyl systems at both ends with high efficiency (Table 3, entries 12−15). Moreover, the structural variation in switching of the methyl group to other functionalities in the phenyl enones can be tolerated (entries 16−19). High enantioselectivities are obtained (94−98% ee). It is noted that in cases of **3b** (entry 2), **3n** (entry 14), and **3q** (entry 19), the low reaction yields are due to slow conversion. Prolonging reaction times improve their yields. In addition to acyclic enones, cyclic enones such as cyclichexenone can effectively engage in the

reaction smoothly (69% yield and 97% ee, entry 20). Finally, we probe the other nitroalkanes for the conjugate reaction. It is realized that high yield (82%) and enantioselectivity (94% ee for both diastereomers with 1:1.2 dr) are achieved when nitroethane is used (entry 21).

The absolute configuration of the Michael adducts **3a**[11c] was determined to be *S* by comparison of HPLC traces and optical rotation value with those of the literatures reported (see Supporting Information for detail).

The **VII** promoted highly enantioselective conjugate addition of nitromethane to enones could be rationalized by a proposed model **A** (Figure 2). The primary amine effectively depronates the nitromethane and its small size allows for accomdating R^1 moeitey of the enone,[21] while the thiourea moiety interacts with the carbonyl moiety via two H-bonds. Moreover, the enhanced acidity of the hydrogen bond donor motifs of the thiourea affords stronger activity. Accordingly, such orientation directs nitronate for *Si* face attack (assuming R^2 = Ar) and it is expected that such synergistic activation delivers high enantioselectivity, as demonstrated experimentally.

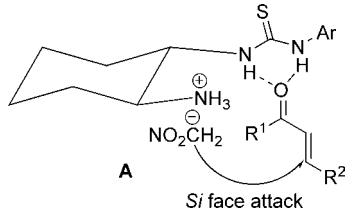


Figure 2. Proposed transition state for **VII** catalyzed conjugate addition of nitromethane to enones.

In summary, we have developed a simple primary amine thiourea catalyzed enantioselective conjugate addition of nitroalkanes to enones. The reaction allows employment of a wide range of enones with a considerable degree of structural variations. Significantly, high to excellent enantioselectivities (92−99%) are achieved. Therefore, the protocol provides a useful catalytic approach to the preparation of synthetic important highly enantiomertic enriched γ-nitro ketones that are otherwise difficult to make by asymmetric catalysis. Furthermore, the current study reveals that, slight structural modification of an organocatalyst can create a more efficient catalytic system for improving reaction efficiency that cannot be achieved with existing promoters.

Acknowledgment. We are grateful for the financial support from School of Pharmacy, East China University of Science, the China 111 Project (Grant No. B07023), the National Science Foundation of China (Nos. 03772648 and 30721005), and the Chinese National Programs for High Technology Research and Development (Nos. 2006AA020602 and 2007AA02Z147).

Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C NMR and HRMS data for Experimental procedures and characterization of the products **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) For recent reviews of thiourea mediated catalysis, see: (a) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289. (b) Tian, S.-K.; Chen, Y.-G.; Hang, J.-F.; Tang, L.; McDaid, P.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 621. (c) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299. (d) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999. (e) Connon, S. J. *Chem.—Eur. J.* **2006**, *12*, 5419. (f) Marcelli, T.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7496. (g) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (h) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (i) Yu, X.-H.; Wang, W. *Chem. Asian J.* **2008**, *3*, 1701.

(18) See their preparation, see: Mei, K.; Zhang, S.; He, S.; Li, P.; Jin, M.; Xue, F.; Luo, G.; Zhang, H.; Song, L.; Duan, W.; Wang, W. *Tetrahedron Lett.* **2008**, *49*, 2681.

(19) Only two examples using catalysts **VI** and/or **VII** for reactions: aldol reaction (ref 18): 6 and 5% ee, respectively; **VII** catalyzed nitro-Mannich reaction, see: Han, B.; Liu, Q.-P.; Li, R.; Tian, X.; Xiong, X.-F.; Deng, J.-G.; Chen, Y.-C. *Chem.—Eur. J.* **2008**, *14*, 8094: 32% ee.

(20) (1*S*,2*S*)-2-Diaminocyclohexane is used for the preparation of catalyst **VII**: $[\alpha]_D^{25} = +38.9$ 1, $c = 1.13$, MeOH), [lit. $[\alpha]_D^{30} = +41.2$ ($c = 1.0$, MeOH) Zhang, G.; Liao, Y.; Wang, Z.; Hiroyuki, N.; Takuji, H. *Tetrahedron: Asymmetry* **2003**, *14*, 3297.].

(21) For recent reviews of primary amine catalyzed reactions, see: (a) Xu, L.-W.; Lu, Y.-X. *Org. Biomol. Chem.* **2008**, *6*, 2047. (b) Chen, Y.-C. *Synlett* **2008**, 1919. For examples, see: (c) Huang, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 7170. (d) Lalonde, M. P.; Chen, Y.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 6366. (e) Liu, K.; Cui, H.-F.; Nie, J.; Dong, K.-Y.; Li, X.-J.; Ma, J.-A. *Org. Lett.* **2007**, *9*, 923. (f) Tsogoeva, S. B.; Wei, S. *Chem. Commun.* **2006**, 1451. (g) Xie, J.-W.; Yue, L.; Chen, W.; Du, W.; Zhu, J.; Deng, J.-G.; Chen, Y.-C. *Org. Lett.* **2007**, *9*, 413. (h) Xie, J.-W.; Chen, W.; Li, R.; Zeng, M.; Du, W.; Yue, L.; Chen, Y.-C.; Wu, Y.; Zhu, J.; Deng, J.-G. *Angew. Chem., Int. Ed.* **2007**, *46*, 389. (i) McCooey, S. H.; Connon, S. J. *Org. Lett.* **2007**, *9*, 599. (j) Ramasastry, S. S. V.; Zhang, H.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc.* **2007**, *129*, 288. (k) Ricci, P.; Carlone, A.; Bartoli, G.; Bosco, M.; Sambri, L.; Melchiorre, P. *Adv. Synth. Catal.* **2008**, *350*, 49. (l) Singh, R. P.; Bartelson, K.; Wang, Y.; Su, H.; Lu, X.; Deng, L. *J. Am. Chem. Soc.* **2008**, *130*, 2422. (m) Wang, X.; Reisinger, C. M.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 6070. (n) Zhu, Q.; Cheng, L.; Lu, Y. *Chem. Commun.* **2008**, 6315.