Tetrahedron Letters 53 (2012) 1768–1771

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Primary amine catalyzed aldol reaction of isatins and acetaldehyde

Qunsheng Guo, John Cong-Gui Zhao *

Department of Chemistry, University of Texas at San Antonio, One UTSA Circle, San Antonio, TX 78249-0698, USA

ARTICLE INFO

Article history:
Received 21 November 2011
Accepted 24 January 2012
Available online 2 February 2012

Keywords:
Aldol
Quinine amine
Isatin
Acetaldehyde
Enantioselective

ABSTRACT

Several cinchona alkaloid-derived chiral primary amines were applied as the catalyst for the cross aldol reaction of isatins with acetaldehyde. With the quinine-derived amine catalyst **3**, the desired aldol products were obtained in high yields and good enantioselectivities (up to 93% ee) under the optimized conditions. Although other enolizable aldehydes and ketones may also be applied in this reaction, the ee values obtained are usually low. A mechanism was proposed to account for the formation of the major enantiomer in this reaction.

The 3-alkyl-3-hydroxyindolin-2-one moiety may be found in many natural products that have important biological activities, such as TMC-95 A–D,[1] donaxaridine,[2] convolutamydines,[2] dioxibrassinine,[3] and 3′-hydroxyglucoisatisin.[4] Moreover, organic molecules containing this moiety frequently exhibit different biological activities and, therefore, are important medicinal compounds.[5] Due to its importance as a pharmacophore, many catalytic asymmetric methods,[6–8] especially asymmetric organocatalysis,[7,8] have been developed for the enantioselective synthesis of 3-alkyl-3-hydroxyindolin-2-ones in recent years. Among these reported methods, organocatalyzed cross aldol reaction of isatin and enolizable ketones or aldehydes provides an easy access to these derivatives.[7,8] While many organocatalysts have been developed for the cross aldol reaction of isatin with ketones,[7] only a handful of reports are available on the cross aldol reaction of isatin with acetaldehyde.[8] Nakamura and co-workers reported the first enantioselective aldol reaction of acetaldehyde with an isatin derivative using *N*-(2-thiophenesulfonyl)-prolinamide as the catalyst in 2009.[8a] The reaction was used for the enantioselective synthesis of convolutamydine E.[8a] A recyclable version of this catalyst was also reported recently.[7i] Almost simultaneously, Wang and Hayashi also reported the asymmetric aldol reaction of isatins and acetaldehyde.[8b,c] Wang's group used (*S*)-pyrrolidine tetrazole as the catalyst[8b]; and in this study, products containing two highly hindered contiguous quaternary centers may also be obtained since enolizable aldehydes other than acetaldehyde may also be applied.[8b] Hayashi's group used 4-hydroxydiarylprolinol as the organocatalyst.[8c] A similar catalytic system was also reported later by Yuan's group.[8d] It should be pointed that these reported catalysts are all proline derivatives. Moreover, sometimes the reported reactions were very slow (up to 5 days),[8] which might be due to the low activity of these secondary amine catalysts.

As part of our on-going research[7i,9] on using activated carbonyl compounds in organocatalyzed asymmetric aldol reactions as enamine or enolate acceptors[10] for the synthesis of enantioenriched biologically active molecules, we recently developed a highly enantioselective synthesis of 3-alkyl-3-hydroxyindolin-2-ones using quinidine thiourea as the catalyst, which involves an enolate mechanism.[7i] While this reaction may also be applied to acetaldehyde, the ee value obtained for the product is only mediocre.[7i] On the other hand, we recently found primary amine catalysts derived from cinchona alkaloids catalyze the cross aldol reaction of α-ketophosphonates and acetaldehyde in a highly enantioselective manner.[9g] We reasoned that these primary amines should also be good catalysts for the asymmetric aldol reaction of acetaldehyde with isatins. It should be pointed out that, although primary amines are also frequently used as catalysts in reactions that involve the enamine intermediates,[11] to our knowledge, only recently Cheng and co-workers have reported a primary-tertiary diamine catalyst for the enantioselective reaction of isatins with acetaldehyde to obtain the corresponding aldol products in good ee values.[12] Herein we wish to report our study on the use of primary amines derived from cinchona alkaloids as the catalysts in the asymmetric aldol reaction of isatins with acetaldehyde and related compounds.

Using isatin (**1a**) and acetaldehyde as the model substrates, we first screened a series of chiral primary amine catalysts (**3**–**9**, Fig. 1) for their ability to catalyze the desired aldol reactions. THF was used as the standard solvent, and the reactions were carried out at 5 °C. The results of this screening are summarized in Table 1. As shown by the results in Table 1, when quinine-derived

* Corresponding author. Tel.: +1 210 458 4464; fax: +1 210 458 7428.
E-mail address: cong.zhao@utsa.edu (J.C.-G. Zhao).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2012.01.108

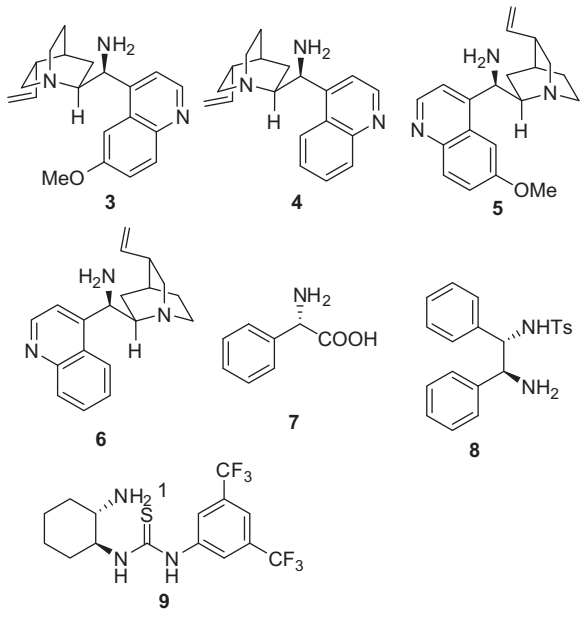
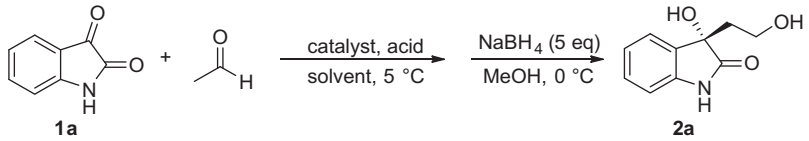


Figure 1. Catalysts screened for the aldol reaction of acetaldehyde and isatin.

amine **3** (10 mol %) was used as the catalyst and benzoic acid as the cocatalyst (30 mol %), the reaction of **1a** and acetaldehyde led to the desired cross aldol product in 48 h. Since the obtained aldol product is not very stable, it was directly reduced by $NaBH_4$ to the diol **2a**. In this way, **2a** was obtained in a 90% yield and 87% ee for the major *S*-enantiomer (entry 1). Similarly, cinchonidine-derived amine catalyst **4** yielded **2a** in a 92% yield and 60% ee (entry 2). In contrast, although the quindine- and cinchonine-derived amine catalysts **5** and **6** are the pseudo-enantiomers of **3** and **4**, respectively, when **5** and **6** were used as the catalysts, the ee values obtained for the opposite *R*-enantiomer were much lower (entries 3 and 4). L-Phenylglycine (**7**) was also found to catalyze the desired aldol reaction; nonetheless, the reactivity is poor (23% yield) and a racemic product was obtained (entry 5). Poor results were also obtained with the primary amine catalysts derived from (*S*,*S*)-1,2-diphenylethane-1,2-diamine (**8**) and (*S*,*S*)-1,2-cyclohexanediamine (**9**) (entries 6 and 7). Thus, this screening identified the quinine-derived amine **3** as the best catalyst for this reaction. The reaction conditions were then further optimized for catalyst **3**. We were intrigued by reports that water may be used as an additive to improve the reactivities and/or enantioselectivities in cross aldol reactions.[13] Thus, water was intentionally added to the reactions catalyzed by **3**. Indeed, big improvements in the reactivity were observed: When 1–3 equiv of water was used, the reaction time was gradually shortened from 48 to 15 h, and the ee value of the product was also slightly improved to 92% (entries 8–10). However, no further improvement in the reactivity was observed when more water was added. Instead, slightly negative effects on the enantioselectivity of the reaction were observed (entries 11 and 12). When a large excess of water (40 equiv) was added, the reaction again became sluggish and a poor ee value of the product

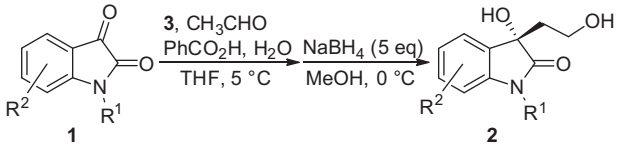
Table 1
Screening of the catalysts and optimization of the reaction conditions[a]



Entry	Catalyst	Acid cocatalyst	H_2O (equiv)	Solvent	Time (h)	Yield[b] (%)	ee[c] (%)
1	**3**	$PhCO_2H$	None	THF	48	90	87
2	**4**	$PhCO_2H$	None	THF	48	92	60
3	**5**	$PhCO_2H$	None	THF	48	93	46[d]
4	**6**	$PhCO_2H$	None	THF	48	89	17[d]
5	**7**	None	None	THF	48	23	0
6	**8**	None	None	THF	48	Not determined	-
7	**9**	None	None	THF	48	89	6[d]
8	**3**	$PhCO_2H$	1	THF	40	83	90
9	**3**	$PhCO_2H$	2	THF	30	88	91
10	**3**	$PhCO_2H$	3	THF	15	90	92
11	**3**	$PhCO_2H$	4	THF	15	88	91
12	**3**	$PhCO_2H$	5	THF	15	88	89
13	**3**	$PhCO_2H$	40	THF	24	88	61
14	**3**	4-$MeOC_6H_4CO_2H$	3	THF	15	81	89
15	**3**	4-(*i*-Pr)$C_6H_4CO_2H$	3	THF	15	82	89
16	**3**	2,4-$(NO_2)_2C_6H_3CO_2H$	3	THF	15	86	69
17	**3**	$MeCO_2H$	3	THF	15	86	78
18	**3**	$PhCO_2H$	3	CH_2Cl_2	15	67	49
19	**3**	$PhCO_2H$	3	Toluene	15	60	64
20	**3**	$PhCO_2H$	3	Et_2O	15	52	55
21	**3**	$PhCO_2H$	3	DME[e]	15	87	88
22	**3**	$PhCO_2H$	3	EtOAc	15	88	79
23	**3**	$PhCO_2H$	3	CH_3CN	15	29	26
24	**3**	$PhCO_2H$	3	1,4-Dioxane/THF (5:1)	15	90	92

[a] Unless otherwise noted, all reactions were conducted with **1a** (0.1 mmol) and acetaldehyde (0.5 mmol) in the presence of the catalyst (0.01 mmol, 10 mol %) and the acid cocatalyst (0.03 mmol, 30 mol %) in the specified solvent (1.0 mL) at 5 °C.
[b] Yield of the isolated product after column chromatography.
[c] Unless otherwise noted, ee values were determined by HPLC analysis on a ChiralCel AD-H column. The major enantiomer obtained was determined to be *S*-configured by comparing the measured optical rotation with the reported data.
[d] The *R*-enantiomer was obtained as the major product.
[e] Dimethoxyethane.

Table 2
Cross-aldol reaction of isatins and acetaldehyde[a]



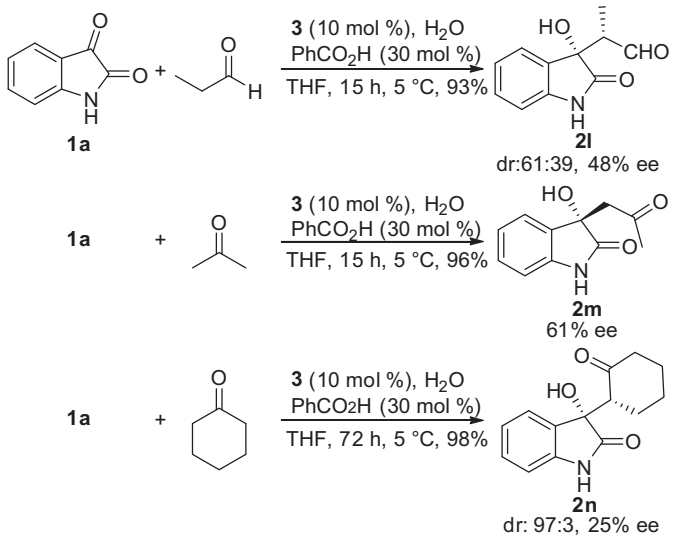
Entry	R^1	R^2	Time (h)	**2**/Yield[b] (%)	ee[c] (%)
1	H	H	15	**2a**/90	92
2	H	5-Me	12	**2b**/90	93
3	H	5-MeO	10	**2c**/95	92
4	H	5,7-Me_2	12	**2d**/87	90
5	H	4-Cl	6	**2e**/95	87
6	H	4-Br	7	**2f**/96	88
7	H	4,7-Cl_2	5	**2g**/95	89
8	H	5-F	16	**2h**/91	82
9	H	5-Br	12	**2i**/93	30
10	H	6-Br	16	**2j**/97	75
11	Bn	H	10	**2k**/96	92

[a] All reactions were conducted with **1** (0.1 mmol) and acetaldehyde (0.5 mmol) in the presence of catalyst **3** (0.01 mmol, 10 mol %) and benzoic acid (0.03 mmol, 30 mol %) in THF (1.0 mL) at 5 °C.
[b] Yield of the isolated product after column chromatography.
[c] Unless otherwise noted, ee values were determined by HPLC analysis on a ChiralPak AD-H or a ChiralCel OJ-H column.

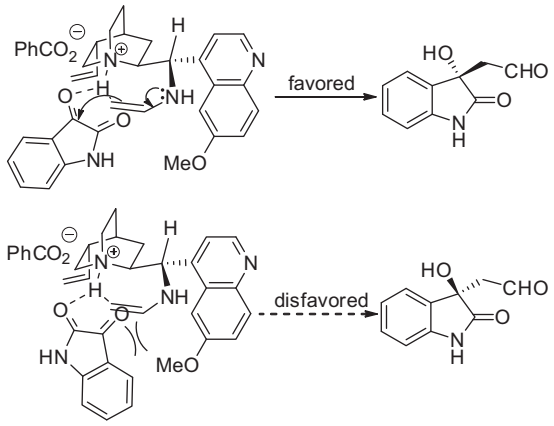
was obtained (61% ee, entry 13). Thus, the best results were obtained when the reaction was conducted in the presence of three equivalents of added water (entry 10). The acid cocatalyst was then optimized under these reaction conditions. As the data showed, benzoic acid is the best cocatalyst (entry 10) since all the other acids screened led to worse results in enantioselectivity (Table 1, entries 14–17). The solvents were also examined. Most of the common organic solvents, such as, CH_2Cl_2, toluene, ether, DME, EtOAc, and CH_3CN all yielded poorer results (entries 18–23). Nonetheless, a 1,4-dioxane-THF (5:1, v/v) mixture was found to be as good as THF in terms of the reactivity and the enantioselectivity obtained (entry 24). Thus, THF was adopted as the solvent in our further studies due to its superior behaviors and simplicity.

The scope of this catalytic system was then evaluated under the optimized reaction conditions with different isatin derivatives as well as other enolizable aldehydes and ketones. The results of this investigation are summarized below in Table 2 and Scheme 1. As shown in Table 2, when acetaldehyde was used, besides the parent isatin (entry 1), isatins with electron-donating substituents at different positions on the phenyl all gave the desired cross aldol products in excellent ee values (90–93% ee, entries 2–4). In contrast, isatins substituted with electron-withdrawing groups lead to slightly lower ee values (entries 5–8). 5-Bromo- and 6-bromoisatins yielded much lower ee values of the corresponding aldol products (entries 9 and 10) as compared to that of 4-bromoisatin (entry 6). This is most likely due to a combination of electronic and steric effects. On the other hand, *N*-benzyl protected isatin yields the corresponding aldol product in a high ee value of 92% (entry 11).

Besides acetaldehyde, propanal, acetone, and cyclohexanone may also be used as substrates in this reaction (Scheme 1). When propanal was reacted under the optimized conditions, the desired aldol product was obtained in a 93% yield. The two diastereomers were obtained in a ratio of 61:39 and the major (*S*,*S*)-diastereomer (**2l**) was obtained in 48% ee.[14] When acetone was applied in this reaction, the corresponding aldol product (**2m**) was obtained in a 96% yield with moderate enantioselectivity (61% ee). In contrast, cyclohexanone yields the expected aldol product in excellent diastereoselectivity (dr 97:3); nevertheless, the ee value of the major *syn* diastereomer is low (25%).[15]



Scheme 1. Cross-aldol reaction of isatins with propanal, acetone, and cyclohexanone.



Scheme 2. Proposed transition states for the quinine amine catalyzed aldol reaction.

Based on the absolute configuration of compounds **2**, a plausible catalytic model for the reaction of acetaldehyde and isatin was proposed (Scheme 2). The primary amine moiety of quinine-derived amine **3** reacts with acetaldehyde to form an enamine intermediate. The acid cocatalyst has multiple roles in this catalysis. It can accelerate the formation of the enamine intermediate through acid catalysis. Simultaneously, it also protonates the nitrogen atom in the quinuclidine backbone of the amine catalyst **3** to form an ammonium salt. The proton in this ammonium salt then forms hydrogen bonds with the isatin carbonyl groups (Scheme 2). Such hydrogen bonds not only activate isatin for the cross aldol reaction, but also direct the approach of isatin. Among the two possible orientations of isatin, the *re* face orientation (Scheme 2, top left) is favored since the unfavorable interaction between the isatin benzene ring and the catalyst is avoided. Attacking of the enamine to the *re* face of the isatin ketone group leads to the observed major *S*-enantiomer.

In summary, we have developed an asymmetric aldol reaction of isatins and acetaldehyde using a quinine-derived primary amine as organocatalysts. The corresponding aldol products were obtained in high enantioselectivities (up to 93% ee). When other aldehydes and ketones were applied in this reaction, the expected

aldol products were obtained in excellent yields, but with only mediocre enantioselectivities.

Acknowledgments

The authors thank the generous financial support of this research from the Welch Foundation (Grant No. AX-1593) and the NSF (Grant No. CHE-0909954).

Supplementary data

Supplementary data (detailed experimental procedures, compound characterization data and HPLC conditions, copy of HPLC chromatograms) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.01.108.

References and notes

1. (a) Koguchi, Y.; Kohno, J.; Nishio, M.; Takahashi, K.; Okuda, T.; Ohnuki, T.; Komatsubara, S. *J. Antibiot.* **2000**, *53*, 105–109; (b) Khono, J.; Koguchi, Y.; Nishio, M.; Nakao, K.; Juroda, M.; Shimizu, R.; Ohnuki, T.; Komatsubara, S. *J. Org. Chem.* **2000**, *65*, 990–995; (c) Lin, S.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 512–515; (d) Albrecht, B. K.; Williams, R. M. *Org. Lett.* **2003**, *5*, 197–200.
2. (a) Kim, S. C.; Gowrisankar, S.; Kim, J. N. *Tetrahedron Lett.* **2006**, *47*, 3463–3466; (b) Takayama, H.; Matsuda, Y.; Masubuchi, K.; Ishida, A.; Kitajima, M.; Aimi, N. *Tetrahedron* **2004**, *60*, 893–900; (c) Khuzhaev, V. U. *Chem. Nat. Compd.* **2004**, *40*, 516–517; (d) Ubaidullaev, K. A.; Shakirov, R.; Yunosov, S. Y. *Khim. Prir. Soedin.* **1976**, *12*, 553–554; (e) Rasmussen, H. B.; MacLeod, J. K. *J. Nat. Prod.* **1997**, *60*, 1152–1154; (f) Kawasaki, T.; Nagaoka, M.; Satoh, T.; Okamoto, A.; Ukon, R.; Ogawa, A. *Tetrahedron* **2004**, *60*, 3493–3503.
3. (a) Monde, K.; Sasaki, K.; Shirata, A.; Takasugi, M. *Phytochemistry* **1991**, *30*, 2915–2917; (b) Suchy, M.; Kutschy, P.; Monde, K.; Goto, H.; Harada, N.; Takasugi, M.; Dzurilla, M.; Balentova, E. *J. Org. Chem.* **2001**, *66*, 3940–3947.
4. Fréchard, A.; Fabre, N.; Péan, C.; Montaut, S.; Fauvel, M.-T.; Rollin, P.; Fourasté, I. *Tetrahedron Lett.* **2001**, *42*, 9015–9017.
5. For examples, see: (a) Goehring, R. R.; Sachdeva, Y. P.; Pisipati, J. S.; Sleevi, M. C.; Wolfe, J. F. *J. Am. Chem. Soc.* **1985**, *107*, 435–443; (b) Labroo, R. B.; Cohen, L. A. *J. Org. Chem.* **1990**, *55*, 4901–4904; (c) Tokunaga, T.; Hume, W. E.; Umezome, T.; Okazaki, K.; Ueki, Y.; Kumagai, K.; Hourai, S.; Nagamine, J.; Seki, H.; Taiji, M.; Noguchi, H.; Nagata, R. *J. Med. Chem.* **2001**, *44*, 4641–4649; (d) Tokunaga, T.; Hume, W. E.; Nagamine, J.; Kawamura, T.; Taiji, M.; Nagata, R. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1789–1792.
6. For examples, see: (a) Zheng, K.; Yin, C.-K.; Liu, X.-H.; Lin, L.-L.; Feng, X.-M. *Angew. Chem., Int. Ed.* **2011**, *50*, 2573–2577; (b) Zhou, F.; Liu, Y.-L.; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381–1407; (c) Shintani, R.; Inoue, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3353–3356; (d) Toullec, P. Y.; Jagt, R. B. C.; Vries, J. G.; Feringa, B. L.; Minnaard, A. *J. Org. Lett.* **2006**, *8*, 2715–2718; (e) Liu, Y.-L.; Wang, B.-L.; Cao, J.-J.; Chen, L.; Zhang, Y.-X.; Wang, C.; Zhou, J. *J. Am. Chem. Soc.* **2010**, *132*, 15176–15178; (f) Nakamura, T.; Shirokawa, S.; Hosokawa, S.; Nakazaki, A.; Kobayashi, S. *Org. Lett.* **2006**, *8*, 677–679; (g) Wang, C.-C.; Wu, X.-Y. *Tetrahedron* **2011**, *67*, 2974–2978; (h) Guan, X.-Y.; Wei, Y.; Shi, M. *Chem. Eur. J.* **2010**, *16*, 13617–13621; (i) Hanhan, N. V.; Sahin, A. H.; Chang, T. W.; Fettinger, J. C.; Franz, A. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 744–747.
7. For reports of the enantioselective aldol reaction of ketones to isatin by using organocatalysts, see: (a) Luppi, G.; Monari, M.; CorrTa, R. J.; Violante, F. A.; Pinto, A. C.; Kaptein, B.; Broxterman, A. B.; Garden, S. J.; Tomasini, C. *Tetrahedron* **2006**, *62*, 12017–12024; (b) Chen, J.-R.; Liu, X.-P.; Zhu, X.-Y.; Li, L.; Qiao, Y.-F.; Zhang, J.-M.; Xiao, W.-J. *Tetrahedron* **2007**, *63*, 10437–10444; (c) Malkov, A. V.; Kabeshov, M. A.; Bella, M.; Kysilka, O.; Malyshev, D. A.; Pluháčková, K.; Kočovsky, P. *Org. Lett.* **2007**, *9*, 5473–5476; (d) Luppi, G.; Cozzi, P. G.; Monari, M.; Kaptein, B.; Broxterman, Q. B.; Tomasini, C. *J. Org. Chem.* **2005**, *70*, 7418–7421; (e) Chen, G.; Wang, Y.; He, H.; Gao, S.; Yang, X.; Hao, X. *Heterocycles* **2006**, *68*, 2327–2333; (f) Nakamura, S.; Hara, N.; Nakashima, H.; Kubo, K.; Shibata, N.; Toru, T. *Chem. Eur. J.* **2008**, *14*, 8079–8081; (g) Angelici, G.; Corrêa, R. J.; Garden, S. J.; Tomasini, C. *Tetrahedron Lett.* **2009**, *50*, 814–817; (h) Hara, N.; Nakamura, S.; Shibata, N.; Toru, T. *Adv. Synth. Catal.* **2010**, *352*, 1621–1624; (i) Guo, Q.-S.; Bhanushali, M.; Zhao, C.-G. *Angew. Chem., Int. Ed.* **2010**, *49*, 9460–9464; (j) Raj, M.; Veerasamy, N.; Singh, V. K. *Tetrahedron Lett.* **2010**, *51*, 2157–2159; (k) Allu, S.; Molleti, N.; Panem, R.; Singh, V. K. *Tetrahedron Lett.* **2011**, *52*, 4080–4083; (l) Kinsella, M.; Duggan, P. G.; Lennon, C. M. *Tetrahedron: Asymmetry* **2011**, *22*, 1423–1433.
8. For reports of the enantioselective addition of acetaldehyde to isatin by using organocatalysts, see: (a) Hara, N.; Nakamura, S.; Shibata, N.; Toru, T. *Chem. Eur. J.* **2009**, *15*, 6790–6793; (b) Xue, F.; Zhang, S.-L.; Liu, L.; Duan, W.-H.; Wang, W. *Chem. Asian J.* **2009**, *4*, 1664–1667; (c) Itoh, T.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2009**, *11*, 3854–3857; (d) Chen, W.-B.; Du, X.-L.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C. *Tetrahedron* **2010**, *66*, 1441–1446.
9. (a) Samanta, S.; Zhao, C.-G. *J. Am. Chem. Soc.* **2006**, *128*, 7442–7443; (b) Dodda, R.; Zhao, C.-G. *Org. Lett.* **2006**, *8*, 4911–4914; (c) Samanta, S.; Perera, S.; Zhao, C.-G. *J. Org. Chem.* **2010**, *75*, 1101–1106; (d) Dodda, R.; Zhao, C.-G. *Synlett* **2007**, 1605–1609; (e) Mandal, T.; Samanta, S.; Zhao, C.-G. *Org. Lett.* **2007**, *9*, 943–945; (f) Ding, D.; Zhao, C.-G.; Guo, Q.-S.; Arman, H. *Tetrahedron* **2010**, *66*, 4423–4427; (g) Perera, S.; Naganaboina, V. K.; Wang, L.; Zhang, B.; Guo, Q.-S.; Rout, L.; Zhao, C.-G. *Adv. Synth. Catal.* **2011**, *353*, 1729–1734; (h) Guang, J.; Zhao, C.-G. *Tetrahedron: Asymmetry* **2011**, *22*, 1205–1211; For a review, see: (i) Bhanushali, M.; Zhao, C.-G. *Synthesis* **2011**, 1815–1830.
10. For examples of using activated carbonyl compounds in organocatalyzed aldol reactions, see: (a) Shen, Z.; Li, B.; Wang, L.; Zhang, Y. *Tetrahedron Lett.* **2005**, *46*, 8785–8788; (b) Tokuda, O.; Kano, T.; Gao, W.-G.; Ikemoto, T.; Maruoka, K. *Org. Lett.* **2005**, *7*, 5103–5105; (c) Samanta, S.; Zhao, C.-G. *Tetrahedron Lett.* **2006**, *47*, 3383–3386; (d) Pousse, G.; Le Cavelier, F.; Humphreys, L.; Rouden, J.; Blanchet, J. *Org. Lett.* **2010**, *12*, 3582–3585; (e) Qiu, L.-H.; Shen, Z.-X.; Shi, C.-Q.; Liu, Y.-H.; Zhang, Y.-W. *Chinese J. Chem.* **2005**, *23*, 584–588; (f) Liu, J.; Yang, Z.; Wang, Z.; Wang, F.; Chen, X.; Liu, X.; Feng, X.; Su, Z.; Hu, C. *J. Am. Chem. Soc.* **2008**, *130*, 5654–5655; (g) Jiang, J.; Chen, X.; Wang, J.; Hui, Y.; Liu, X.; Lin, L.; Feng, X. *Org. Biomol. Chem.* **2009**, *7*, 4355–4357; (h) Urushima, T.; Yasui, Y.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2010**, *12*, 2966–2969; (i) Tang, Z.; Cun, L.-F.; Cui, X.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Org. Lett.* **2006**, *8*, 1263–1266; (j) Hara, N.; Tamura, R.; Funahashi, Y.; Nakamura, S. *Org. Lett.* **2011**, *13*, 1662–1665.
11. For selected examples of primary amine catalyzed enantioselective reactions, see: (a) Reisinger, C. M.; Wang, X.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 8112–8115; (b) Martin, N. J. A.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13368–13369; (c) Lu, X.; Liu, Y.; Sun, B.; Cindric, B.; Deng, L. *J. Am. Chem. Soc.* **2008**, *130*, 8134–8135; (d) Wang, X.; Reisinger, C. M.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 6070–6071; (e) McCooey, S. H.; Connon, S. *J. Org. Lett.* **2007**, *9*, 599–602; (f) Liu, T.-Y.; Cui, H.-L.; Zhang, Y.; Jiang, K.; Du, W.; He, Z.-Q.; Chen, Y.-C. *Org. Lett.* **2007**, *9*, 3671–3674; (g) Zheng, B.-L.; Liu, Q.-Z.; Guo, C.-S.; Wang, X.-L.; He, L. *Org. Biomol. Chem.* **2007**, *5*, 2913–2915; (h) Zhou, J.; Wakchaure, V.; Kraft, P.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 7656–7658; (i) Bartoli, G.; Melchiorre, P. *Synlett* **2008**, 1759–1772; (j) Chen, Y.-C. *Synlett* **2008**, 1919–1930; (k) Gogoi, S.; Zhao, C.-G.; Ding, D. *Org. Lett.* **2009**, *11*, 2249–2252; (l) Mandal, T.; Zhao, C.-G. *Angew. Chem., Int. Ed.* **2008**, *47*, 7714–7717; (m) 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*, 389–392; (n) Huang, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 7170–7171; (o) Ding, D.-R.; Zhao, C.-G. *Eur. J. Org. Chem.* **2010**, 3802–3805; for a review on primary amine catalysis, see: (p) Peng, F.; Shao, Z. J. *Mol. Catal. A* **2008**, *285*, 1–13.
12. During the progress of our research, Cheng and coworkers published a chiral primary–tertiary diamine catalyzed aldol reaction of acetaldehyde and isatins, see: Hu, S.-S.; Zhang, L.; Li, J.-Y.; Luo, S.-Z.; Cheng, J.-P. *Eur. J. Org Chem.* **2011**, 3347–3352.
13. For selected examples, see: (a) Hernandez, J. G.; Juaristi, E. *Tetrahedron* **2011**, *67*, 6953–6959; (b) Bhanushali, M.; Zhao, C.-G. *Tetrahedron Lett.* **2012**, *53*, 359–362; (c) Miura, T.; Ina, M.; Imai, K.; Nakashima, K.; Yasaku, Y.; Koyata, N.; Murakami, Y.; Imai, N.; Tada, N.; Itoh, A. *Tetrahedron: Asymmetry* **2011**, *22*, 1028–1034; (d) Kumar, A.; Singh, S.; Kumar, V.; Chimni, S. S. *Org. Biomol. Chem.* **2011**, *9*, 2731–2742; (e) Hayashi, Y.; Yasui, Y.; Kawamura, T.; Kojima, M.; Ishikawa, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 2804–2807; (f) Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 958–961; (g) Fu, Y.-Q.; An, Y.-J.; Liu, W.-M.; Li, Z.-C.; Zhang, G.; Tao, J. C. *Catal. Lett.* **2008**, *124*, 397–404; (h) Giacalone, F.; Gruttadauria, M.; Meo, P. L.; Riela, S.; Noto, R. *Adv. Synth. Catal.* **2008**, *350*, 2747–2760; (i) Font, D.; Sayalero, S.; Bastero, A.; Jimeno, C.; Pericàs, M. A. *Org. Lett.* **2008**, *10*, 337–340; (j) Liu, Y.-X.; Sun, Y.-N.; Tan, H.-H.; Liu, W.; Tao, J.-C. *Tetrahedron: Asymmetry* **2007**, *18*, 2649–2656; (k) Raj, M.; Maya, V.; Ginotra, S. K.; Singh, V. K. *Org. Lett.* **2006**, *8*, 4097–4099; (l) Peng, F.-Z.; Shao, Z.-H.; Pu, X.-W.; Zhang, H.-B. *Adv. Synth. Catal.* **2008**, *350*, 2199–2204; (m) Fu, Y.-Q.; Li, Z.-C.; Ding, L.-N.; Tao, J.-C.; Zhang, S.-H.; Tang, M.-S. *Tetrahedron: Asymmetry* **2006**, *17*, 3351–3357; (n) Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc.* **2006**, *128*, 734–735; (o) Zu, L.; Xie, H.; Li, H.; Wang, J.; Wang, W. *Org. Lett.* **2008**, *10*, 1211–1214; For a review, see: (p) Gruttadauria, M.; Giacalone, F.; Noto, R. *Adv. Synth. Catal.* **2009**, *351*, 33–57.
14. The relative stereochemistry of the two stereogenic centers in this compound was determined by reducing product 21 to the corresponding diol, for which the stereochemistry is known. For details, please see the Supplementary data and: Higuchi, K.; Saito, K.; Hirayama, T.; Watanabe, Y.; Kobayashi, E.; Kawasaki, T. *Synthesis* **2010**, 3609–3614.
15. The relative stereochemistry of the two stereogenic centers in this compound was determined by comparing the spectroscopic data of this product with those of an authentic sample prepared according to Ref. 7j