ORGANIC LETTERS

2012
Vol. 14, No. 15
4018–4021

Enantioselective Construction of 3-Hydroxy Oxindoles via Decarboxylative Addition of β-Ketoacids to Isatins

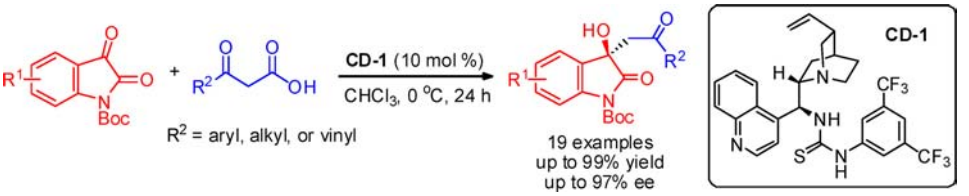
Fangrui Zhong, Weijun Yao, Xiaowei Dou, and Yixin Lu*

Department of Chemistry & Medicinal Chemistry Program, Life Sciences Institute, National University of Singapore, 3 Science Drive 3, Republic of Singapore, 117543

chmlyx@nus.edu.sg

Received July 6, 2012

ABSTRACT



The first highly enantioselective decarboxylative addition of β-ketoacids to isatins mediated by a bifunctional tertiary amine–thiourea catalyst has been developed, allowing facile synthesis of biologically important 3-hydroxy oxindoles in good yields and excellent enantioselectivities. The method reported represents a valuable approach of utilizing β-ketoacids as synthetic equivalents of aryl/alkyl methyl ketone enolates.

Since the seminal work by List, Barbas, and Lerner on the L-proline-catalyzed intermolecular aldol reaction in 2000,[1] asymmetric enamine catalysis has been established as a powerful strategy to access chiral molecules via direct bond-forming reactions.[2] Notably, pyrrolidine-based secondary amines and primary amine catalysts[3] often complement each other in their ability to activate different substrates, and enable applications of a wide range of carbonyl compounds via enamine catalysis. However, methyl ketones, particularly aryl methyl ketones, are difficult substrates in enamine activation.[4] Thus, preactivation of such less reactive ketones is often required. For instance, silyl enol ethers[5] are commonly employed. To develop a straightforward and effective approach for reactions involving methyl ketones as a donor, we reasoned that decarboxylation of β-ketoacids promoted by an amino catalyst may conveniently generate a methyl ketone enolate, which should readily react with suitable substrates in the following reaction step (Scheme 1).

Nature's ability to perform organic reactions is truly astonishing and serves as an inspiration to chemists.[6] Mimicking the biosynthesis of polyketides, the decarboxylative reactions of malonic acid half thioesters (MAHTs) have drawn much attention recently.[7] In the decarboxylative processes of MAHTs, various electrophiles including aldehydes, ketones, imines, activated alkenes, and azodicarboxylates are used as reaction partners under either

(1) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395.

(2) For selected excellent reviews and books, see: (a) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (c) Berkessel, A.; Groger, H. *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim, 2005. (d) Dalko, P. I. *Enantioselective Organocatalysis: Reactions and Experimental Procedures*; Wiley-VCH: Weinheim, 2007. (e) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638. (f) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138.

(3) For reviews on asymmetric catalysis mediated by primary amines/amino acids and synthetic peptides, see: (a) Xu, L.-W.; Luo, J.; Lu, Y. *Chem. Commun.* **2009**, 1807. (b) Xu, L.-W.; Lu, Y. *Org. Biomol. Chem.* **2008**, *6*, 2047. (c) Davie, E. A. C.; Mennen, S. M.; Xu, Y.; Miller, S. J. *Chem. Rev.* **2007**, *107*, 5759. (d) Peng, F.; Shao, Z. *J. Mol. Catal. A* **2008**, *285*, 1. (e) Chen, Y.-C. *Synlett* **2008**, 1919.

(4) (a) Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1983. (b) 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. (c) Carpenter, R. D.; Fettinger, J. C.; Lam, K. S.; Kurth, M. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 6407. (d) Funabiki, K.; Itoh, Y.; Kubota, Y.; Matsui, M. *J. Org. Chem.* **2011**, *76*, 3545.

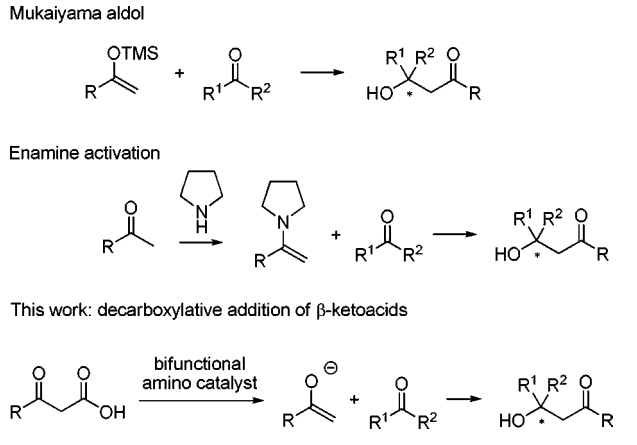
(5) (a) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503. For recent reviews, see: (b) Mukaiyama, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 5590. (c) Palomo, C.; Oiarbide, M.; García, J. M. *Chem. Soc. Rev.* **2004**, *33*, 65. (d) Schetter, B.; Mahrwald, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 7506.

(6) Knowles, R. R.; Jacobsen, E. N. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20678.

(7) For a review, see: Pan., Y.; Tan, C.-H. *Synthesis* **2011**, 2044.

10.1021/ol301855w
Published on Web 07/25/2012

Scheme 1. Activations of Methyl Ketones in Aldol Reaction



metal[8] or organocatalytic conditions.[9] Surprisingly, β-ketoacids were rarely employed in the decarboxylative reactions,[10] which may be due partly to their intrinsic instability. To the best of our knowledge, there were only three asymmetric examples reporting such applications. Evans disclosed a Ni(II) complex-catalyzed Michael addition of β-ketoacids to nitroalkenes.[11] The other two reports from the groups of Mahrwald and Tian described stereoselective decarboxylative aldol and Mannich reactions, respectively, utilizing chiral aldehydes or *N*-sulfinyl α-imino esters as the substrate.[12] At the outset of our research, we questioned the possibility of generating a methyl ketone enolate from β-ketoacids via an amine-initiated decarboxylative process.[13] To test our hypothesis, we chose to study the decarboxylative aldol reaction between β-ketoacids and isatins, since the reaction products, 3-hydroxy-3-substituted oxindoles,[14] are important structural motifs in medicinal chemistry (Figure 1).[15] Recently, a couple of reports based on enamine catalysis for the synthesis of 3-hydroxy oxindoles via a direct aldol reaction between aryl methyl ketones and isatins appeared.[16] However, such direct reactions were very slow, requiring four to seven days to complete. Herein, we document our successful development of enantioselective decarboxylative addition of β-ketoacids to isatins, creating biologically important 3-hydroxy-3-substituted oxindoles in excellent yields and enantiomeric excesses.[17]

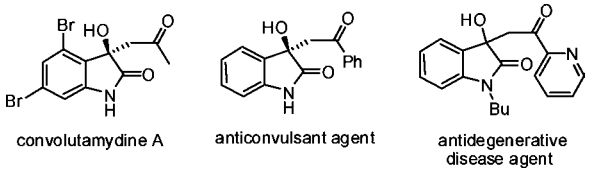


Figure 1. Bioactive 3-hydroxy-3-substituted oxindoles.

We started our investigation by examining the reaction between *N*-Boc isatin **1a** and β-ketoacid **2a** in chloroform (Table 1). The noncatalyzed background reaction was very slow, suggesting the feasibility of a catalytic approach (entry 1). A number of bifunctional amino catalysts were evaluated, and they all displayed good catalytic activities, furnishing the desired decarboxylative products in high yields. While quinidine (**QD-1**) and its sulfonamide-containing derivative **QD-2**,[18] ***β*-ICD**, and threonine-derived thiourea **L-Thr-1**[19] led to disappointing enantioselectivities (entries 2−5), tryptophan-derived tertiary amine−thiourea **Trp-1**[20] was an excellent catalyst and **3a** was isolated with 88% ee (entry 6). Cinchona alkaloid-derived bifunctional thioureas showed remarkable catalytic effects, and excellent enantioselectivities were achieved (entries 7−10). Among them, cinchonidine-based **CD-1** gave the best results (entry 8). Subsequent solvent

(8) (a) Lalic, G.; Aloise, A. D.; Shair, M. D. *J. Am. Chem. Soc.* **2003**, *125*, 2852. (b) Orlandi, S.; Benaglia, M.; Cozzi, F. *Tetrahedron Lett.* **2004**, *45*, 1747. (c) Magdziak, D.; Lalic, G.; Lee, H. M.; Fortner, K. C.; Aloise, A. D.; Shair, M. D. *J. Am. Chem. Soc.* **2005**, *127*, 7284. (d) Fortner, K. C.; Shair, M. D. *J. Am. Chem. Soc.* **2007**, *129*, 1032. (e) Furutachi, M.; Mouri, S.; Matsunaga, S.; Shibasaki, M. *Chem.—Asian J.* **2010**, *5*, 2351.

(9) (a) Brunner, H.; Müller, J.; Spitzer, J. *Monatsh. Chem.* **1996**, *127*, 845. (b) Ryu, Y.; Scott, A. I. *Tetrahedron Lett.* **2003**, *44*, 7499. (c) List, B.; Doehring, A.; Fonseca, M.; Wobser, K.; van Thienen, H.; Torres, R.; Galilea, P. *Adv. Synth. Catal.* **2005**, *347*, 1558. (d) Blanchet, J.; Baudoux, J.; Amere, M.; Lasne, M. C.; Rouden, J. *Eur. J. Org. Chem.* **2008**, 5493. (e) Blaquiere, N.; Shore, D. G.; Rousseaux, S.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 6190. (f) Ricci, A.; Pettersen, D.; Bernardi, L.; Fini, F.; Fochi, M.; Herrera, R. P.; Sgarzani, V. *Adv. Synth. Catal.* **2007**, *349*, 1037. (g) Lubkoll, J.; Wennemers, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 6841. (h) Pan, Y.; Kee, C. W.; Jiang, Z.; Ma, T.; Zhao, Y.; Yang, Y.; Xue, H.; Tan, C.-H. *Chem.—Eur. J.* **2011**, *17*, 8363. (i) Bae, H. Y.; Some, S.; Lee, J. H.; Kim, J.-Y.; Song, M. J.; Lee, S.; Zhang, Y. J.; Song, C. E. *Adv. Synth. Catal.* **2011**, *353*, 3196. (j) Baudoux, J.; Lefebvre, P.; Legay, R.; Lasne, M.-C.; Rouden, J. *Green Chem.* **2010**, *12*, 252. (k) Hara, N.; Nakamura, S.; Funahashi, Y.; Shibata, N. *Adv. Synth. Catal.* **2011**, *353*, 2976.

(10) (a) Stiles, M.; Wolf, D.; Hudson, G. V. *J. Am. Chem. Soc.* **1959**, *81*, 628. (b) Tsuda, T.; Okada, M.; Nishi, S.; Saegusa, T. *J. Org. Chem.* **1986**, *51*, 421. (c) Tsuda, T.; Tokai, M.; Ishida, T.; Saegusa, T. *J. Org. Chem.* **1986**, *51*, 5216. (d) Kourouli, T.; Kefalas, P.; Ragoussis, N.; Ragoussis, V. *J. Org. Chem.* **2002**, *67*, 4615. (e) Yang, C.-Y.; Wang, J.-Y.; Tian, S.-K. *Chem. Commun.* **2011**, *47*, 8343.

(11) Evans, D. A.; Mito, S.; Seidel, D. *J. Am. Chem. Soc.* **2007**, *129*, 11583.

(12) (a) Rohr, K.; Mahrwald, R. *Org. Lett.* **2011**, *13*, 1878. (b) Yang, C.-F.; Shen, C.; Wang, J.-Y.; Tian, S.-K. *Org. Lett.* **2012**, *14*, 3092.

(13) During the preparation of this manuscript, Ma and co-workers described a biscinchona alkaloid-catalyzed decarboxylative addition of β-ketoacids to trifluoromethyl ketones; see: Zheng, Y.; Xiong, H.-Y.; Nie, J.; Hua, M.-Q.; Ma, J.-A. *Chem. Commun.* **2012**, *48*, 4308.

(14) For reviews, see: (a) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209. (b) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748. (c) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945. (d) Zhou, F.; Liu, Y.-L.; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381. (e) Lin, H.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 36. (f) Peddibhotla, S. *Curr. Bioact. Compd.* **2009**, *5*, 20.

(15) (a) Popp, F. D. *J. Heterocycl. Chem* **1982**, *19*, 589. (b) Beeson, C. C.; Rohrer, B.; Perron, N. R. *PCT Int. Appl.* **2011**, WO 2011119869 A1 20110929.

(16) (a) Guo, Q.; Bhanushali, M.; Zhao, C.-G. *Angew. Chem., Int. Ed.* **2010**, *49*, 9460. (b) Allu, S.; Molleti, N.; Panem, R.; Singh, V. K. *Tetrahedron Lett.* **2011**, *52*, 4080.

(17) For our recent examples of enatioselective creation of oxindole cores, see: (a) Zhu, Q.; Lu, Y. *Angew. Chem., Int. Ed.* **2010**, *49*, 7753. (b) Zhong, F.; Chen, G.-Y.; Lu, Y. *Org. Lett.* **2011**, *13*, 82. (c) Zhong, F.; Han, X.; Wang, Y.; Lu, Y. *Angew. Chem., Int. Ed.* **2011**, *50*, 7837. (d) Zhong, F.; Han, X.; Wang, Y.; Lu, Y. *Chem. Sci.* **2012**, *3*, 1231. (e) Dou, X.; Lu, Y. *Chem.—Eur. J.* **2012**, *18*, 8315.

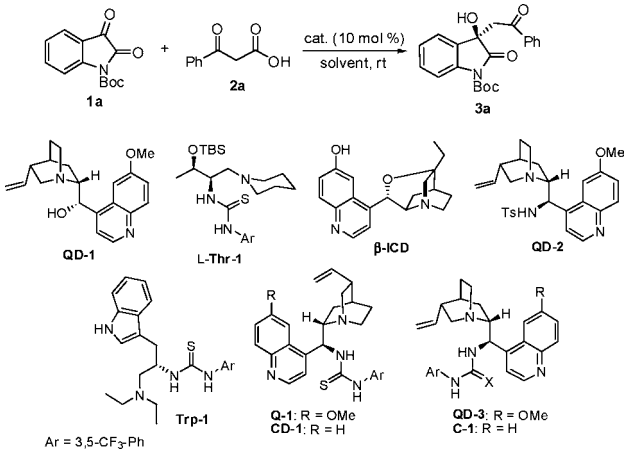
(18) Luo, J.; Xu, L.-W.; Hay, R. A. S.; Lu, Y. *Org. Lett.* **2009**, *11*, 437.

(19) Dou, X.; Han, X.; Lu, Y. *Chem.—Eur. J.* **2012**, *18*, 85.

(20) Han, X.; Kwiakowski, J.; Xue, F.; Huang, K.-W.; Lu, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 7604.

screening did not offer further imporvement, and chloroform remained as the best reaction medium.[21] It is noteworthy that the reaction also proceeded smoothly in protic solvents such as methanol and water, albeit with decreased enantioselectivities (entries 11–12). When the reaction was carried out at 0 °C for 24 h, the desired product was obtained in quantitative yield and with 96% ee (entry 13).

Table 1. Exploration of the Decarboxylative Addition of β-Ketoacids to *N*-Boc Isatins[a]

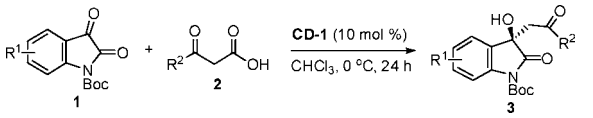


entry	cat.	solvent	time (h)	yield (%)[b]	ee (%)[c]
1	–	$CHCl_3$	24	<10	–
2	**QD-1**	$CHCl_3$	24	96	2
3	**L-Thr-1**	$CHCl_3$	24	85	50
4	***β*-ICD**	$CHCl_3$	2	95	−20
5	**QD-2**	$CHCl_3$	2	98	−64
6	**Trp-1**	$CHCl_3$	3	99	88
7	**Q-1**	$CHCl_3$	6	97	91
8	**CD-1**	$CHCl_3$	6	98	92
9	**QD-3**	$CHCl_3$	6	96	−87
10	**C-1**	$CHCl_3$	6	93	−89
11	**CD-1**	MeOH	10	92	71
12	**CD-1**	H_2O	12	88	65
13[d]	**CD-1**	$CHCl_3$	24	99	96

[a] Reactions were performed with **1a** (0.05 mmol), **2a** (0.075 mmol), and the catalyst (0.005 mmol) in the solvent specified (0.5 mL). [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Reaction was performed at 0 °C.

The current reaction system was applicable to isatins with different substituents on the aromatic ring, including halogens as well as electron-donating and -withdrawing groups, and high chemical yields and excellent enantioselectivities were obtained (entries 2–7, Table 2). When 5,7-dimethyl isatin was used, the enantioselectivity of the reaction dropped slightly (entry 8). Furthermore, aromatic moieties of β-ketoacids could also be varied; high yields and excellent enantioselectivities were achieved regardless of the positions and electronic nature of the substituents on the phenyl rings (entries 9–12). β-Ketoacids with a 2-naphthyl, 2-thiophenyl, and vinylic group were well-tolerated for the reaction as well (entries 13–15). Notably, the reaction proceeded smoothly with aliphatic β-ketoacids, affording the adducts in excellent yields and high enantiomeric excesses (entries 16–19). In particular, 92% ee was attainable when *tert*-butyl β-ketoacid was employed in the reaction (entry 19). To the best of our knowledge, this represents the only protocol to access the chiral aldol product with methyl *tert*-butyl ketone as a donor. The activation of such a highly hindered ketone usually requires very harsh conditions, in sharp contrast to the mild reaction conditions utilized here. The absolute configurations of aldol products were determined by comparison of the optical rotation of a **3a** derivative with the value reported in the literature.[21]

Table 2. Substrate Scope[a]



entry	R^1/R^2	3	yield (%)[b]	ee (%)[c]
1	H/C_6H_5	**3a**	96	96
2	5-Me/C_6H_5	**3b**	94	96
3	5-OMe/C_6H_5	**3c**	90	97
4	5-Cl/C_6H_5	**3d**	91	94
5	5-Br/C_6H_5	**3e**	90	94
6	5-NO_2/C_6H_5	**3f**	96	91
7	7-F/C_6H_5	**3g**	95	93
8	5,7-Me/C_6H_5	**3h**	84	86
9	H/4-Me-C_6H_4	**3i**	93	91
10	H/4−F-C_6H_4	**3j**	97	96
11[d]	H/3-Cl-C_6H_4	**3k**	75	96
12	H/2-OMe-C_6H_4	**3l**	89	92
13	H/2-naphthyl	**3m**	99	95
14	H/2-thiophenyl	**3n**	85	92
15	H/(E)-PhCH=CH	**3o**	82	91
16	H/Me	**3p**	91	82
17	H/*n*-Pr	**3q**	92	86
18	H/*i*-Pr	**3r**	92	87
19	H/*t*-Bu	**3s**	95	92

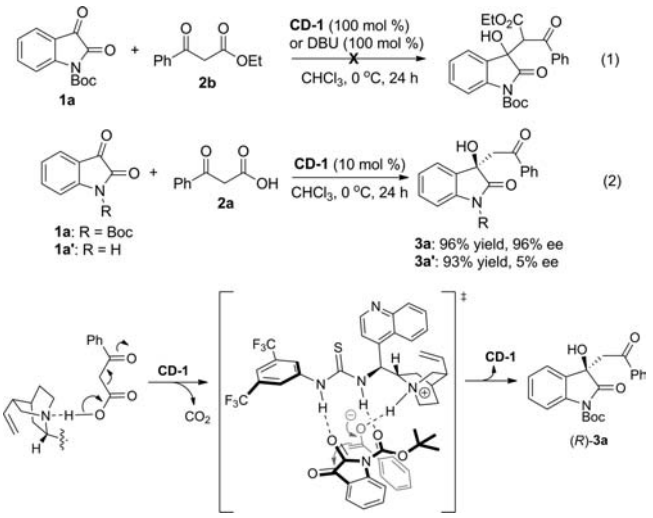
[a] Reactions were performed with **1** (0.05 mmol), **2** (0.075 mmol) and **CD-1** (0.005 mmol) in $CHCl_3$ (0.5 mL). [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Reaction was performed in the presence of **CD-1** (20 mol %) for 48 h.

We next tried to gain some insight into the reaction mechanism. Notably, even though the decarboxylative reaction of related MAHTs has been widely explored, the reaction mechanism remains unclear. While the decarboxylation–nucleophilic addition pathway is widely accepted for enzyme-catalyzed Claisen condensation in polyketide biosynthesis,[22] the alternative addition–decarboxylation reaction sequence was also well supported in a number of catalytic systems.[8d,9e,h] In our current

(21) See the Supporting Information for details.

(22) Austin, M. B.; Izumikawa, M.; Bowman, M. E.; Udwary, D. W.; Ferrer, J.-L.; Moore, B. S.; Noel, J. P. *J. Biol. Chem.* **2004**, *279*, 45162.

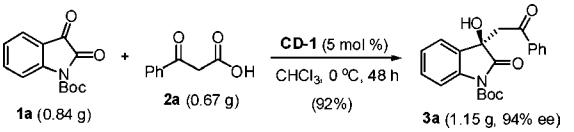
Scheme 2. Plausible Mechanism



system, since the β-ketoacids are highly labile for decarboxylation, we suspect the keto enolate is first formed via decarboxylation, which then adds on to the isatin substrates. To provide some evidence to our proposal, we tested the stability of β-ketoacids under the reaction conditions. When **2a** was exposed to a catalytic amount of **QD-1** or **CD-1**, extensive decomposition of **2a** was observed. Acetonphenone was isolated during the decomposition, supporting the formation of the keto enolate species. On the other hand, had the addition step taken place prior to the decarboxylation, a highly sterically hindered intermediate containing adjacent quaternary and tertiary carbon centers would have to generated, which seems to be a difficult process. An analogous aldol reaction between isatin **1a** and β-ketoester **2b** was carried out in the presence of a stoichiometric amount of **CD-1** or DBU (Scheme 2, eq 1), and no desired aldol product was detected. This experimental result suggested the difficulty of adding ketoesters to isatins. The thiourea moiety of catalyst **CD-1** is believed to be crucial for the observed high enantioselectivity, as evidenced from our initial catalyst screening (Table 1). When we performed the same reaction with isatin bearing a free NH group (**1a′**), the product was obtained with only 5% ee, in stark contrast to the same reaction with the employment of *N*-Boc isatin **1a** as a substrate (Scheme 2, eq 2). Based on the experimental findings we have gathered so far, we propose a plausible mechanism as depicted in Scheme 2. The tertiary amine catalyst deprotonates **2a** to create a keto enolate, with the concurrent release of CO_2. The protonated ammonium then forms an ion pair with the keto enolate. The double hydrogen bonding interactions between the carbonyls of isatin **1a** and the thiourea group of the catalyst play a key role in stereochemical control, giving rise to the observed stereoisomer.

The method described here is operationally simple and efficient and, thus, may be valuable for practical chemical synthesis. As an illustrative example, we carried out a gram-scale synthesis of 3-hydroxy-3-phenacyloxindole (**3a**), an anticonvulsant agent.[15] When isatin **1a** was treated with β-ketoacid **2a** in the presence of 5 mol % of **CD-1** at 0 °C, the decarboxylative aldol product (*R*)-**3a** was obtained in 92% yield and with 94% ee within 48 h (Scheme 3).

Scheme 3. Scaled-up Reaction with 5 mol % **CD-1**



In conclusion, we have successfully developed the first highly enantioselective catalytic decarboxylative addition of β-ketoacids to isatins mediated by bifunctional tertiary amine−thiourea catalysts. The method reported represents an efficient approach of employing β-ketoacids as synthetic equivalents of aryl/alkyl methyl ketone enolates. We have also demonstrated the value of our method in a practical synthesis of biologically important 3-hydroxy-3-phenacyloxindole. Further investigations toward a deeper understanding of the reaction mechanism and extension of the current method to other reactions are being pursued in our laboratory.

Acknowledgment. We wish to thank the National University of Singapore (R-143-000-469-112), GSK-EDB (R-143-000-491-592), and the Ministry of Education (MOE) of Singapore (R-143-000-494-112) for generous financial support.

Supporting Information Available. Representative experimental procedures, determination of absolute configurations of products, HPLC chromatogram, and NMR spectra for all the compounds described. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.