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In Situ Formed Bifunctional Primary Amine-Imine Catalyst: Application to the Construction of Chiral Tertiary Alcohols through Asymmetric Aldol-Type Reaction

Zhijie Mao,[+a] Xi Zhu,[+a] Aijun Lin,[a] Weipeng Li,[a] Yan Shi,[a] Haibin Mao,[a] Chengjian Zhu,[a,b,*] and Yixiang Cheng[a,*]

[a] State Key Laboratory of Coordination Chemistry, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210093, People's Republic of China
Fax: (+86)-25-8359-4886; e-mail: cjzhu@nju.edu.cn or yxcheng@nju.edu.cn

[b] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, People's Republic of China

[+] Zhijie Mao and Xi Zhu contributed equally to this work.

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Abstract: An *in situ* formation method to obtain chiral bifunctional primary amine-imine catalysts from the C_2-symmetric chiral diimines has been developed. The efficiency of this method in the construction of chiral tertiary alcohols which are valuable pharmaceutical intermediates is proved by its application to the asymmetric aldol-type reaction of cyclic ketones with other activated ketone compounds as the enamine acceptors, i.e., β,γ-unsaturated α-keto esters and isatins. In general, good to excellent diastereoselectivities and enantioselectivities (up to 96/4 *dr*, 96% *ee* for β,γ-unsaturated α-keto esters and up to 91/9 *dr*, 94% *ee* for isatins) were obtained. The active primary amine-imine catalylst and enamine intermediate in the reaction process could be demonstrated by ESI-MS analysis.

Keywords: aldol reaction; chiral diimines; chiral primary amine-imine; chiral tertiary alcohols; *in situ* formation

Introduction

As one class of compounds containing a quaternary stereocenter, tertiary alcohols and especially chiral tertiary alcohols hold an important position in the pharmaceutical industry and biological sciences.[1] For example, tertiary hydroxy esters are highly important intermediates in the asymmetric synthesis of natural products and medicinal agents[2] containing a tertiary hydroxyl moiety, such as oxybutynin (ditropan), which is a widely prescribed medicine for the treatment of urinary incontinence. As another example, 3-alkyl-3-hydroxyindolin-2-ones are particularly important molecules in a number of biologically active natural products and pharmaceuticals[3] among which 3-cycloalkanone-3-hydroxy-2-oxindoles are quite promising in the field of medicinal chemistry because of their anticonvulsant activity. As an efficient method to construct such compounds, organocatalytic asymmetric intermolecular aldol reactions of the ketone-ketone type[4] remain a challenge although significant achievements have been made for the organocatalytic direct aldol reactions of the ketone-aldehyde and aldehyde-aldehyde types.[5]

Chiral primary amines as an organocatalyst play an increasingly important role in organocatalytic asymmetric reactions, and many reactions promoted by chiral primary amine catalysts have been reported, for example, aldol reactions,[6] Michael additions,[7] α-aminations,[8] and cycloaddition reactions.[9] To improve the efficiency and universality of these catalysts, several mutifunctional chiral primary amine catalysts such as chiral primary amine-thiourea,[10] primary-tertiary diamine,[11] and sulfonamide-primary amine[12] organocatalysts have also been successfully developed (Figure 1). Despite these significant advances,[13] the multifunctional chiral primary amine catalysts can only be obtained by complex synthetic procedures, which limits their further applications. Given the importance of these mutifunctional primary amine cata-

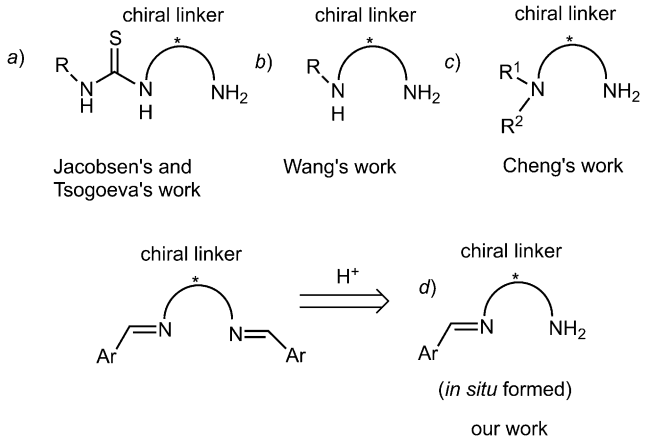


Figure 1. Bifunctional primary amine catalysts.

lysts, it is necessary to develop more easily available chiral primary aminocatalysts to enrich the types of organocatalyst. Just recently, we successfully developed a bifunctional primary-imine catalyst[14] from the stable C_2-symmetric chiral diimines[15] for the first time through a new concept in organocatalysis – the use of an *in situ* formation method, which promotes the direct aldol reaction between different ketones and α-keto esters in high yields and excellent enantioselectivities. To broaden its potential applications, herein, we would like to report the details for the construction of several valuable chiral tertiary alcohols using aldol-type reaction of cyclic ketones with β,γ-unsaturated α-keto esters and isatins based on the enamine process through this protocol.

Results and Discussion

Our preliminary study demonstrated that a chiral diimine could be hydrolyzed efficiently in acid conditions to obtain a chiral primary-imine catalyst, which could further activate unactivated ketones through enamine intermediates.[14] Based on these observations, a series of synthetic easily accessible chiral diimine precatalysts **Ia**–**IIe** was examined for the construction of tertiary alcohols (Figure 2 and Figure 3).

At first, the synthesis of β,γ-unsaturated tertiary hydroxy esters was studied using the reaction of cyclohexanone and β,γ-unsaturated α-keto ester **1a** as a model reaction, and the results are summarized in Table 1. As expected, the aldol-type reaction of the β,γ-unsaturated α-keto ester occurred preferentially under these conditions to give the desired product successfully. The best result was obtained when precatalyst **Id** was employed with up to 96/4 *dr* and 92% *ee* (Table 1, entry 4). Encouraged by this result, further optimization of the reaction conditions was carried out. Subsequent investigation of the reaction parameters gave as the optimal conditions: 0.2 mmol **1a** as

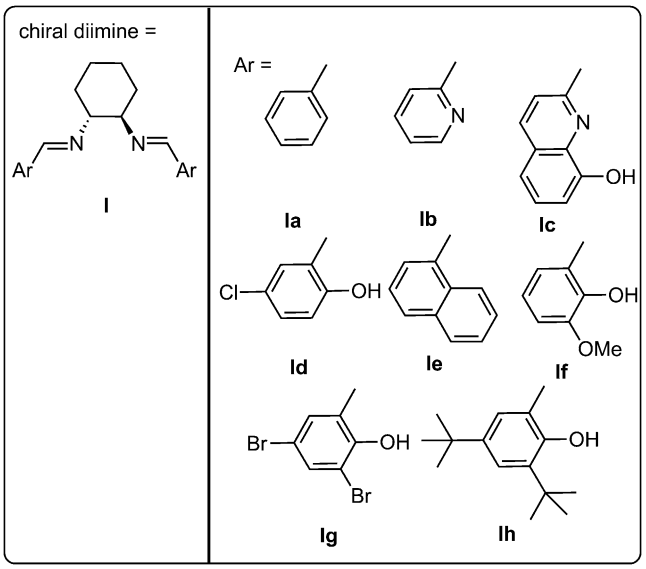


Figure 2. Chiral diimines derived from (1*R*,2*R*)-cyclohexane-1,2-diamine.

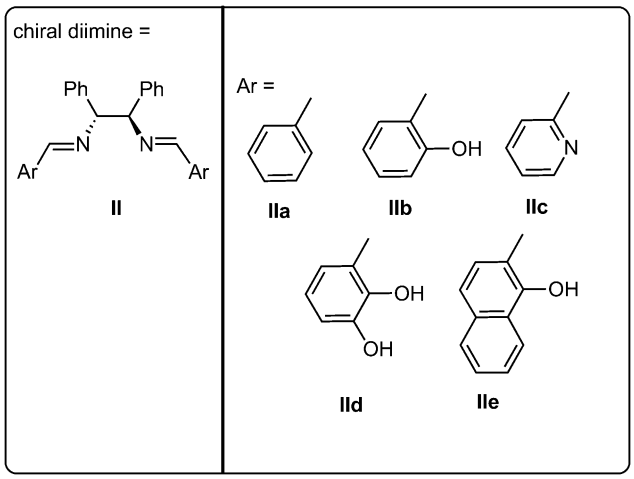
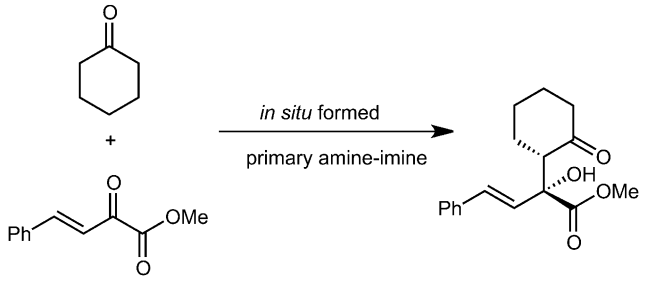


Figure 3. Chiral diimines derived from (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine.

the substrate, 10 mol% **Id** as the precatalyst, at 25 °C in 0.2 mL cyclohexanone under solvent-free conditions with 5 equiv. acetic acid as the additive (Table 1, entry 12). Of all the Brønsted acids screened (formic acid, acetic acid, TFA, TfOH, benzoic acid, *n*-butyric acid, *n*-hexanoic acid, trimethylacetic acid, propanedioic acid), acetic acid was found to be the most effective. As shown in Table 1, the yield and *ee* value of the product increased with increased amount of acetic acid (Table 1, entry 4 and entries 9–11), which underlines that the generation of the primary amine-imine catalyst could be affected by the concentration of acetic acid. Both the *dr* and *ee* value of the product remained almost unchanged when lowering the preca-

Table 1. Screening of the reaction conditions for the synthesis of β,γ-unsaturated tertiary hydroxy esters using *in situ* formed primary-imine catalysts.[a]



Entry	Precat (mol%)	*t* [h]	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	**Ia** (20)	24	74	92/8	86
2	**Ib** (20)	24	80	92/8	83
3	**Ic** (20)	24	57	95/5	89
4	**Id** (20)	24	95	96/4	92
5	**Ie** (20)	24	72	91/9	77
6	**If** (20)	24	73	94/6	93
7	**Ig** (20)	24	61	96/4	90
8	**Ih** (20)	24	35	89/11	80
9[e]	**Id** (20)	24	31	95/5	75
10[f]	**Id** (20)	24	63	96/4	85
11[g]	**Id** (20)	24	94	96/4	92
12	**Id** (10)	30	93	96/4	92
13	**Id** (5)	30	75	94/6	92

[a] The reaction was carried out with **1a** (0.2 mmol), precatalyst, AcOH (5 equiv.) in cyclohexanone (0.2 mL) at 25 °C for the indicated time.
[b] Yield of isolated products containing a mixture of diastereoisomers.
[c] Determined by chiral HPLC.
[d] Determined by chiral HPLC for the major product.
[e] 0.2 equiv. AcOH were added.
[f] 1 equiv. AcOH was added.
[g] 10 equiv. AcOH were added.

talyst loading from 20% to 1% despite the decrease in yields (Table 1, entries 4, 12 and 13).

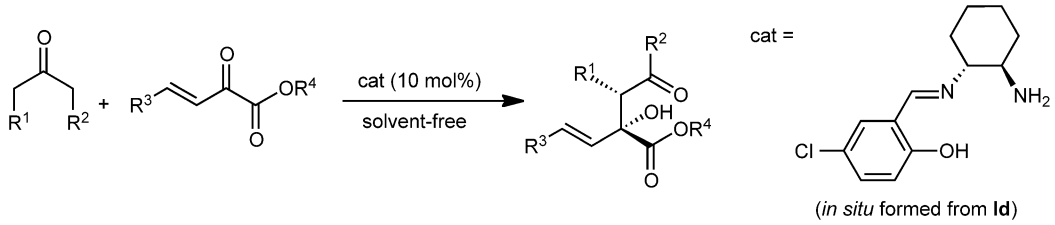
With the optimized conditions in hands, we next studied the scope of the reaction. At first, the reactions of cyclohexanone with different β,γ-unsaturated α-keto esters were tested. The alkoxy group of the ester had little effect on the stereoselectivity of the reaction, and the best result was obtained in the presence of an isopropoxy group (Table 2, entries 1–4). Except for some discrepancies in yields, high diastereoselectivities and enantioselectivities were obtained for a series of β,γ-unsaturated keto esters having differently substituted phenyl groups regardless of the electron-withdrawing or electron-donating properties of the substituents (Table 2, entries 5–14). Moreover, fused ring and heteroaromatic substrates were also investigated, giving the desired products with similar results (Table 2, entries 15–17). As for other cyclic ketones, both yields and selectivities were inferior to cyclohexanone (Table 2, entries 18–22). A mixture of diastereoisomers with only 23% *ee* for major product was obtained for cyclobutanone (Table 2, entry 18). Cycloheptanone was found to react slowly and only 7% yield was achieved even after 96 h (Table 2, entry 20). The 6-membered heterocyclic ketones gave high diastereoselectivities and good *ee* values (Table 2, entries 21 and 22). Unfortunately, no *ee* value was observed under the same conditions for the acyclic ketone such as acetone although the reaction proceeded well to afford the desired product.

An additional scaled-up experiment was performed to show the potential of this method in the practical synthesis of chiral β,γ-unsaturated tertiary hydroxy esters (Scheme 1). By treatment of 4 mmol (0.88 g) of **1c** under the optimal reaction conditions, the desired product **2c** was obtained in 85% yield without obvious loss of diastereoselectivity and enantioselectivity (*dr*: 93/7, *ee*: 95%).

In a further extension of this methodology, we expand the scope of activated ketone compounds, and isatin was introduced to synthesize 3-alkyl-3-hydroxyindolin-2-ones, which are present in many important biologically active natural products and medicinal compounds. The reaction of isatin and cyclohexanone using precatalysts derived from (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine was selected as a model reaction to explore the feasibility of this strategy. The results are summarized in Table 3.

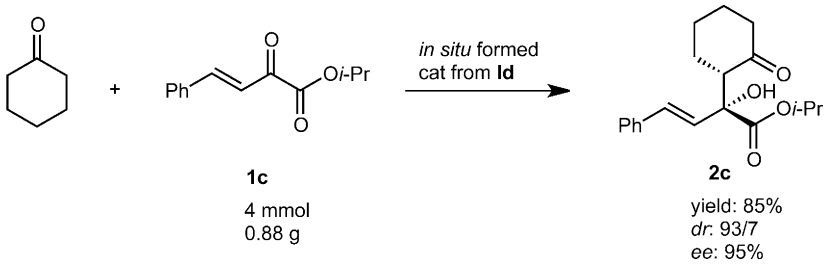
Initially, diimine **IIa** was investigated as the precatalyst. As we anticipated, the desired product was afforded in 92% yield with good enantioselectivity and diastereoselectivity in the presence of 5 equiv. of AcOH and 5 mol% of **IIa (**Table 3, entry 1). (1*R*,2*R*)-1,2-Diphenylethane-1,2-diamine as the catalyst gave the desired adduct in high yield (96%) but with low enantioselectivity and diastereoselectivity (Table 3, entry 2). Subsequent investigation showed that precatalyst **IIb** exhibited the best enantioselectivity and diastereoselectivity (Table 3, entries 3–6). Furthermore, a primary amine-imine hydrochloride similar to the *in situ* formed primary amine-imine catalyst from **IIb** was also tested but unfortunately an unsatisfactory result was obtained, presumably caused by the strong acidity of hydrochloric acid (90/10 *dr*, 30% *ee*, for more details see the Supporting Information). Further optimization of reaction condition revealed that the reaction carried out with 10 mol% loading of **IIb** and 10 equiv. AcOH in 0.2 mL cyclohexanone at 25 °C afforded the best result (95% yield, 93/7 *dr*, 93% *ee*) in 24 h (Table 3, entry 15). AcOH was proven to be the most effective Brønsted acid once again, achieving the highest enantioselectivity (Table 3, entry 3, entries 9–12). Increasing the precatalyst loading of **IIb** to 10 mol% led to an improvement of the enantioselectivity (Table 3, entry 13). Further increasing the amount of **IIb** did no help the reaction (Table 3,

Table 2. Asymmetric aldol reaction of cyclic ketones with β,γ-unsaturated α-keto esters using *in situ* formed primary-imine catalyst.[a]



Entry	1			*t* [h]	Product	Yield [%][b]	*dr* [%][c]	*ee* [%][d]
	R^1, R^2	R^3	R^4					
1	-$(CH_2)_3$-	Ph	Me	30	**2a**	93	96/4	92
2	-$(CH_2)_3$-	Ph	Et	30	**2b**	90	96/4	93
3	-$(CH_2)_3$-	Ph	*i*-Pr	30	**2c**	93	96/4	96
4	-$(CH_2)_3$-	Ph	Bn	30	**2d**	92	96/4	95
5	-$(CH_2)_3$-	2-ClC_6H_4	*i*-Pr	36	**2e**	81	93/7	92
6	-$(CH_2)_3$-	2-BrC_6H_4	*i*-Pr	36	**2f**	86	92/8	93
7	-$(CH_2)_3$-	3-ClC_6H_4	*i*-Pr	36	**2g**	84	94/6	92
8	-$(CH_2)_3$-	3-BrC_6H_4	*i*-Pr	36	**2h**	83	93/7	91
9	-$(CH_2)_3$-	4-FC_6H_4	*i*-Pr	36	**2i**	91	93/7	91
10	-$(CH_2)_3$-	4-ClC_6H_4	*i*-Pr	36	**2j**	93	94/6	92
11	-$(CH_2)_3$-	4-BrC_6H_4	*i*-Pr	36	**2k**	83	92/8	90
12	-$(CH_2)_3$-	4- $CH_3C_6H_4$	*i*-Pr	36	**2l**	94	91/9	95
13	-$(CH_2)_3$-	4- $CF_3C_6H_4$	*i*-Pr	36	**2m**	61	89/11	90
14	-$(CH_2)_3$-	4-$OCH_3C_6H_4$	*i*-Pr	36	**2n**	74	91/9	94
15	-$(CH_2)_3$-	2-naphthyl	*i*Pr	36	**2o**	66	94/6	94
16	-$(CH_2)_3$-	3-pyridinyl	*i*-Pr	36	**2p**	88	89/11	84
17	-$(CH_2)_3$-	2-thiophenyl	*i*-Pr	36	**2q**	87	94/6	92
18	-H, CH_2-	Ph	*i*-Pr	36	**2r**	57	70/30	22/0
19	-CH_2CH_2-	Ph	*i*-Pr	36	**2s**	69	87/13	52
20	-$(CH_2)_4$-	Ph	*i*-Pr	96	**2t**	7	n.d.	n.d.
21	-CH_2OCH_2-	Ph	*i*-Pr	36	**2u**	72	94/6	76
22	-CH_2SCH_2-	Ph	*i*-Pr	36	**2v**	41	94/6	81

[a] The reaction was carried out with **1** (0.2 mmol), precatalyst **Id** (0.02 mmol), AcOH (5 equiv.) in cyclic ketones (0.2 mL) at 25 °C for the indicated time.
[b] Yield of isolated product.
[c] Determined by chiral HPLC.
[d] Determined by chiral HPLC and absolute configurations assigned to be *S*,*R* by comparison with literature data.[16]

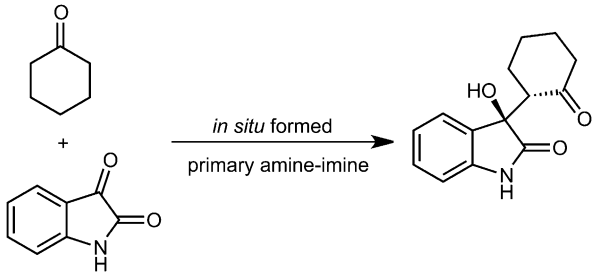


Scheme 1. Scaled-up experiment of cyclohexanone and **1c**.

entry 14). With 10 mol% loading of **IIb**, 10 equiv. AcOH were found to be suitable for the reaction (Table 3, entries 15 and 16).

With the optimized conditions, the substrate generality was investigated. As summarized in Table 4, the reaction proceeded smoothly with a variety of substituted isatins and cyclic ketones to generate the corresponding adducts with high yields and stereoselectivities. The isatins with electron-donating or electron-withdrawing substituents on aromatic rings were introduced and showed good tolerance to these conditions (Table 4, entries 2–7). The 5-methylindolin-3-

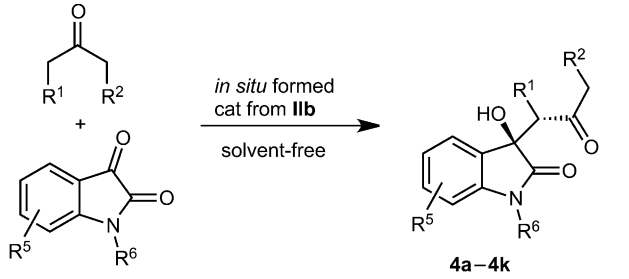
Table 3. Optimization for *in situ* formed primary amine-catalyzed reaction of isatin and cyclohexanone.[a]



Entry	Precat or cat	Acid	Yield [%][b]	*dr anti/syn*[c]	*ee* [%][d]
1	**IIa**	AcOH	92	81/19	70
2	dpen	AcOH	96	65/35	62
3	**IIb**	AcOH	90	83/17	79
4	**IIc**	AcOH	93	75/25	76
5	**IId**	AcOH	94	80/20	76
6	**IIe**	AcOH	90	74/26	72
7[e]	**IIb**	AcOH	88	84/16	77
8[f]	**IIb**	AcOH	99	78/22	79
9	**IIb**	HCOOH	94	86/14	78
10	**IIb**	TFA	93	85/15	73
11	**IIb**	TfOH	81	76/24	65
12[g]	**IIb**	PhCOOH	84	82/18	76
13[h]	**IIb**	AcOH	94	92/8	88
14[i]	**IIb**	AcOH	96	92/8	88
15[j]	**IIb**	AcOH	95	93/7	93
16[k]	**IIb**	AcOH	95	93/7	93

[a] The reaction was carried out with isatin (0.2 mmol), pre-catalyst (5 mol%), Brønsted acid (5 equiv.) in cyclohexanone (0.2 mL) at 25 °C for 24 h.
[b] Isolated yield.
[c] Determined by chiral HPLC.
[d] Determined by chiral HPLC for *anti* product.
[e] Reaction was carried out at 0 °C for 48 h.
[f] Reaction was carried out at 40 °C for 12 h.
[g] Reaction was carried out at 25 °C for 48 h.
[h] With 10 mol% loading of **IIb**.
[i] With 20 mol% loading of **IIb**.
[j] With 10 mol% of **IIb** and 10 equiv. AcOH.
[k] With 10 mol% of **IIb** and 20 equiv. AcOH.

Table 4. *In situ* formed primary amine-catalyzed asymmetric reaction of isatins and cyclic ketones.[a]



Entry	**3**			Yield [%][b]	*dr anti/syn*[c]	*ee* [%][d]
	R^1, R^2	R^5	R^6			
1	-$(CH_2)_3$-	H	H	95	93/7	93
2	-$(CH_2)_3$-	5-Me	H	92	91/9	94
3	-$(CH_2)_3$-	5-F	H	97	87/13	89
4	-$(CH_2)_3$-	5-Cl	H	92	94/6	89
5	-$(CH_2)_3$-	5-Br	H	98	89/11	90
6	-$(CH_2)_3$-	4-Cl	H	94	87/13	94
7	-$(CH_2)_3$-	4-Br	H	95	96/4	92
8	-$(CH_2)_3$-	H	Me	90	89/11	84
9	-$(CH_2)_3$-	H	Bn	87	94/6	89
10[e]	-$(CH_2)_2$-	H	H	40	91/9	89
11[e]	-$(CH_2)_4$-	H	H	32	91/9	93

[a] The reaction was carried out with **3** (0.2 mmol), **IIb** (10 mol%), AcOH (10 equiv.) in the indicated ketone (0.2 mL) at 25 °C for 24 h.
[b] Isolated yield.
[c] Determined by chiral HPLC for *anti* product.
[d] Determined by chiral HPLC for the major product.
[e] The reaction was carried out for 48 h.

one and 4-chloroindoline-2,3-dione gave the best enantioselectivity (94% *ee*) and 4-bromoindoline-2,3-dione gave the best diastereoselectivity (Table 4, entries 2, 6 and 7). The methyl and benzyl 1-substituted isatins were shown to be also good aldol acceptors (Table 4, entries 8 and 9). Other cyclic ketones were also investigated and provided the products with high enantioselectivities despite much losses in yields (Table 2, entries 10 and 11). The absolute configuration of the major *anti* diastereoisomer was determined to be *S,R* by comparing its HPLC profile with reported results[17] and a single-X-ray structural analysis of **4a** (Figure 4).[18] The newly formed carbon center containing the hydroxy group was found to be of the *R* configuration, and the cyclohexanone chiral center was assigned to be of the *S*-configuration.

Similar to our previous studies, the *in situ* formed primary amine-imine catalyst from chiral diimine **Id** and its enamine intermediates formed with cyclohexanone could be detected significantly from the ESI-MS analysis (Figure 5), and similar results could be obtained for chiral diimine **IIb** (see the Supporting Information for more details).

Conclusions

In conclusion, the aldol-type asymmetric reaction of cyclic ketones with other activated ketone compounds, i.e., β,γ-unsaturated α-keto esters and isatins, could be catalyzed by an *in situ* formed primary amine-imine catalyst in high yields and good to excellent enantioselectivities to give biologically valuable chiral tertiary alcohols successfully. Given the easy synthetic accessible of chiral diimines and their stability for storage, this method provides a new alternative

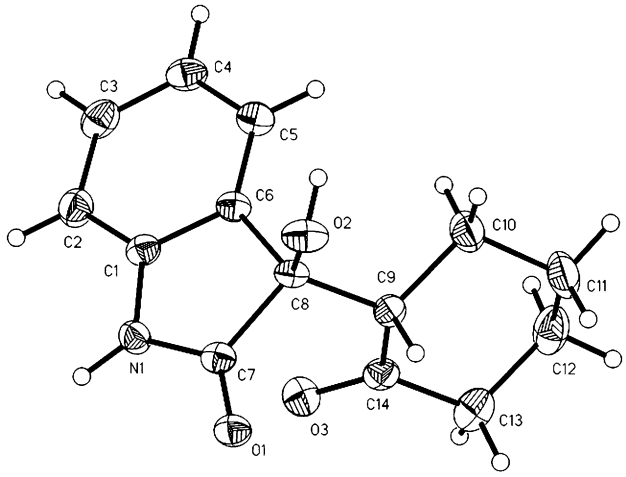


Figure 4. X-ray crystal structure of compound **4a**.

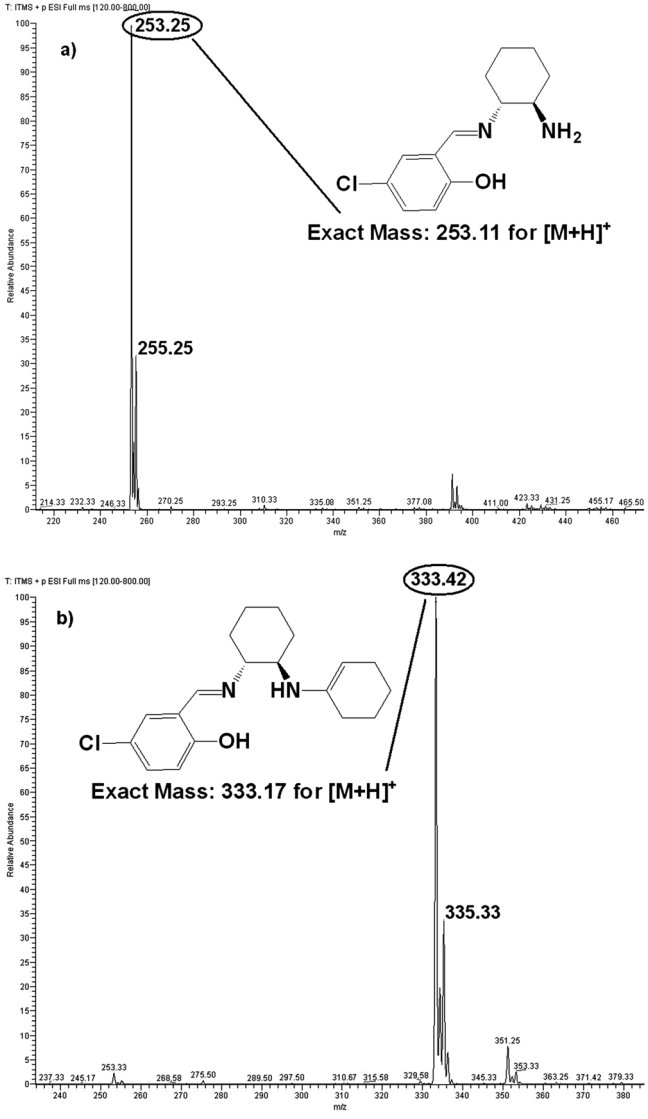


Figure 5. ESI-MS analysis of a mixture of **Id** with AcOH; a) in CH_2Cl_2, b) in cyclohexanone.

for the synthesis of chiral tertiary alcohols through organocatalytic asymmetric reactions. Efforts aimed at further applications of the catalyst system are ongoing in our laboratory.

Experimental Section

Typical Procedure for the Preparation of 2 using Precatalyst Id

To the mixture of diimine **Id** (7.8 mg, 0.02 mmol), β,γ-unsaturated α-keto ester **1a** (38 mg, 0.2 mmol) in cyclohexanone (0.2 mL) was added AcOH (57.0 μL, 1 mmol) at 25 °C. The reaction mixture was stirred at 25 °C for 30 h. After a simple treatment, purification by flash chromatography (ethyl acetate/petroleum ether = 1/8) afforded the desired product **2a** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.39$–7.37 (m, 2H), 7.32–7.29 (m, 2H), 7.26–7.22 (m, 1H), 6.88 (d, $J = 15.6$ Hz, 1H), 6.02 (d, $J = 15.6$ Hz, 1H), 3.77 (s, 3H), 3.63 (s, 1H), 3.13–3.09 (m, 1H), 2.44–2.34 (m, 2H), 2.15–2.08 (m, 2H), 1.95–1.90 (m, 1H), 1.73–1.62 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 211.8$, 174.9, 136.1, 131.6, 128.6, 127.9, 127.6, 126.7, 76.9, 57.1, 53.0, 42.2, 27.3, 27.1, 24.8; HR-MS: $m/z = 311.1253$, calculated for $C_{17}H_{20}O_4Na$: 311.1259 $[M+Na]^+$; HPLC (Chiralpak AS-H, hexane/*i*-PrOH = 90:10, flow rate 1.0 mL min^{-1}, $\lambda = 254$ nm): retention time = 12.32 min (major), 19.47 min (minor); $[\alpha]_D^{23.3}$: −107.3 ($c = 0.80$, $CHCl_3$, 92% *ee*).

Typical Procedure for the Preparation of 4 using Precatalyst IIb

To a stirred solution of precatalyst **IIb** (4.2 mg, 0.01 mmol) in cyclohexanone (0.2 mL) was added isatin (14.7 mg, 0.1 mmol) and then AcOH (10 equiv.) at 25 °C. The resulting mixture was stirred at 25 °C for 24 h, and then was directly purified through flash column chromatography on a silica gel (CH_2Cl_2/CH_3OH = 20/1) to afford the product **4a** as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 10.18$ (s, 1H), 7.22–7.14 (m, 2H), 6.87–6.78 (m, 2H), 5.80 (s, 1H), 3.07 (dd, $J = 13.2$, 4.8 Hz, 1H), 2.61–2.56 (m, 1H), 2.36–2.27 (m, 1H), 1.97–1.64 (m, 5H), 1.49–1.44(m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 209.0$, 178.7, 143.4, 130.8, 128.5, 124.7, 120.7, 109.3, 73.8, 57.3, 41.4, 26.6, 26.5, 24.4; HR-MS: $m/z = 268.0949$, calculated for $C_{14}H_{15}NNaO_3$: 268.0950 $[M+Na]^+$; HPLC (Chiralcel OJ-H, hexane/*i*-PrOH = 80:20, flow rate 1.0 mL min^{-1}, $\lambda = 210$ nm): retention time = 11.2 min (major), 13.8 min (minor). $[\alpha]_D^{25}$: −31.2 ($c = 0.11$, $CHCl_3$, 93% *ee*).

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References

[1] a) K. Narasaka, T. Sakakura, T. Uchimaru, D. Guedin-vuong, *J. Am. Chem. Soc.* **1984**, *106*, 2954; b) A. N. Cuzzupe, R. Di Florio, J. M. White, M. A. Rizzacasa, *Org. Biomol. Chem.* **2003**, *1*, 3572; c) D. A. Nicewicz, A. D. Satterfield, D. C. Schmitt, J. S. Johnson, *J. Am. Chem. Soc.* **2008**, *130*, 17281; d) Y. Hayashi, H. Yamaguchi, M. Toyoshima, K. Okado, T. Toyo, M. Shoji, *Chem. Eur. J.* **2010**, *16*, 10150; e) P. Li, J. Zhao, F. Li, A. S. C. Chan, F. Y. Kwong, *Org. Lett.* **2010**, *12*, 5616; f) C. Liu, X. Dou, Y. Lu, *Org. Lett.* **2011**, *13*, 5248; g) H. Yang, M. Sun, S. Zhao, M. Zhu, Y. Xie, C. Niu, C. Li, *J. Org. Chem.* **2013**, *78*, 339; h) Y.-H. Deng, J.-Q. Chen, L. He, T.-R. Kang, Q.-Z. Liu, S.-W. Luo, W.-C. Yuan, *Chem. Eur. J.* **2013**, DOI: 10.1002/chem.201300478.

[2] a) C. H. Senanayake, K. Fang, P. Grover, R. P. Bakale, C. P. Vandenbossche, S. A. Wald, *Tetrahedron Lett.* **1999**, *40*, 819; b) P. T. Grover, N. N. Bhongle, S. A. Wald, C. H. Senanayake, *J. Org. Chem.* **2000**, *65*, 6283; c) S. Masumoto, M. Suzuki, M. Kanai, M. Shibasaki, *Tetrahedron Lett.* **2002**, *43*, 8647; d) P. Gupta, R. A. Fernandes, P. Kumar, *Tetrahedron Lett.* **2003**, *44*, 4231; e) S. Masumoto, M. Suzuki, M. Kanai, M. Shibasaki, *Tetrahedron* **2004**, *60*, 10497; f) M. Hatano, K. Ishihara, *Synthesis* **2008**, 1647; g) S. Kong, W. Fan, G. Wu, Z. Miao, *Angew. Chem.* **2012**, *124*, 8994; *Angew. Chem. Int. Ed.* **2012**, *51*, 8864.

[3] a) R. R. Goehring, Y. P. Sachdeva, J. S. Pisipati, M. C. Sleevi, J. F. Wolfe, *J. Am. Chem. Soc.* **1985**, *107*, 435; b) R. B. Labroo, L. A. Cohen, *J. Org. Chem.* **1990**, *55*, 4901; c) H. B. Rasmussen, J. K. MacLeod, *J. Nat. Prod.* **1997**, *60*, 1152; d) J. Jimenez, U. Huber, R. Moore, G. Patterson, *J. Nat. Prod.* **1999**, *62*, 569; e) T. Tokunaga, W. E. Hume, T. Umezome, K. Okazaki, Y. Ueki, K. Kumagai, S. Hourai, J. Nagamine, H. Seki, M. Taiji, H. Noguchi, R. Nagata, *J. Med. Chem.* **2001**, *44*, 4641; f) T. Tokunaga, W. E. Hume, J. Nagamine, T. Kawamura, M. Taiji, R. Nagata, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1789; g) A. V. Malkov, M. A. Kabeshov, M. Bella, O. Kysilka, D. A. Malyshev, K. Pluháčková, P. Kocovský, *Org. Lett.* **2007**, *9*, 5473; h) S. Nakamura, N. Hara, H. Nakashima, K. Kubo, N. Shibata, T. Toru, *Chem. Eur. J.* **2008**, *14*, 8079; i) Q. Guo, M. Bhanushali, C.-G. Zhao, *Angew. Chem.* **2010**, *122*, 9650; *Angew. Chem. Int. Ed.* **2010**, *49*, 9460; j) Q. Guo, J. C.-G. Zhao, *Tetrahedron Lett.* **2012**, *53*, 1768.

[4] a) S. E. Denmark, Y. Fan, *J. Am. Chem. Soc.* **2002**, *124*, 4233; b) O. Tokuda, T. Kano, W.-G. Gao, T. Ikemoto, K. Maruoka, *Org. Lett.* **2005**, *7*, 5103; c) S. E. Denmark, Y. Fan, M. D. Eastgate, *J. Org. Chem.* **2005**, *70*, 5235; d) Z. Tang, L.-F. Cun, X. Cui, A.-Q. Mi, Y.-Z. Jiang, L.-Z. Gong, *Org. Lett.* **2006**, *8*, 1263; e) S. Samanta, C.-G. Zhao, *J. Am. Chem. Soc.* **2006**, *128*, 7442; f) T. Wang, G.-W. Zhang, Y. Teng, J. Nie, Y. Zheng, J.-A. Ma, *Adv. Synth. Catal.* **2010**, *352*, 2773; g) J. Luo, H. Wang, X. Han, L.-W. Xu, J. Kwiatkowski, K.-W. Huang, Y. Lu, *Angew. Chem.* **2011**, *123*, 1901; *Angew. Chem. Int. Ed.* **2011**, *50*, 1861; h) F. Zhong, G.-Y. Chen, Y. Lu, *Org. Lett.* **2011**, *13*, 82.

[5] For some selected reviews, see: a) B. List, *Tetrahedron* **2002**, *58*, 5573; b) B. List, *Acc. Chem. Res.* **2004**, *37*, 548; c) W. Notz, F. Tanaka, C. F. Barbas III, *Acc. Chem. Res.* **2004**, *37*, 580; d) H. Pellissier, *Tetrahedron* **2007**, *63*, 9267; e) M. Bhanushali, C.-G. Zhao, *Synthesis* **2011**, 1815; f) M. M. Heravi, S. Asadi, *Tetrahedron: Asymmetry* **2012**, *23*, 1431.

[6] For some selected references, see: a) A. Bassan, W. Zou, E. Reyes, F. Himo, A. Córdova, *Angew. Chem.* **2005**, *117*, 7190; *Angew. Chem. Int. Ed.* **2005**, *44*, 7028; b) A. Córdova, W. Zou, P. Dziedzic, I. Ibrahem, E. Reyes, Y. Xu, *Chem. Eur. J.* **2006**, *12*, 5383; c) X. Wu, Z. Jiang, H.-M. Shen, Y. Lu, *Adv. Synth. Catal.* **2007**, *349*, 812; d) S. S. V. Ramasastry, H. Zhang, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2007**, *129*, 288; e) X.-Y. Xu, Y.-Z. Wang, L.-Z. Gong, *Org. Lett.* **2007**, *9*, 4247; f) L.-W. Xu, Y.-D. Ju, L. Li, H.-Y. Qiu, J.-X. Jiang, G.-Q. Lai, *Tetrahedron Lett.* **2008**, *49*, 7037; g) J. Zhou, V. Wakchaure, P. Kraft, B. List, *Angew. Chem.* **2008**, *120*, 7768; *Angew. Chem. Int. Ed.* **2008**, *47*, 7656.

[7] a) D. A. Yalalov, S. B. Tsogoeva, S. Schmatz, *Adv. Synth. Catal.* **2006**, *348*, 826; b) K. Liu, H.-F. Cui, J. Nie, K.-Y. Dong, X.-J. Li, J.-A. Ma, *Org. Lett.* **2007**, *9*, 923; c) S. H. McCooey, S. J. Connon, *Org. Lett.* **2007**, *9*, 599; d) Z. Yang, J. Liu, X. Liu, Z. Wang, X. Feng, Z. Su, C. Hu, *Adv. Synth. Catal.* **2008**, *350*, 2001.

[8] T.-Y. Liu, H.-L. Cui, Y. Zhang, K. Jiang, W. Du, Z.-Q. He, Y.-C. Chen, *Org. Lett.* **2007**, *9*, 3671.

[9] a) A. Sakakura, K. Suzuki, K. Ishihara, *Adv. Synth. Catal.* **2006**, *348*, 2457; b) W. Chen, W. Du, Y.-Z. Duan, Y. Wu, S.-Y. Yang, Y.-C. Chen, *Angew. Chem.* **2007**, *119*, 7811; *Angew. Chem. Int. Ed.* **2007**, *46*, 7667; c) Y. Wang, H. Li, Y.-Q. Wang, Y. Liu, B. M. Foxman, L. Deng, *J. Am. Chem. Soc.* **2007**, *129*, 6364; d) R. P. Singh, K. Bartelson, Y. Wang, H. Su, X. Lu, L. Deng, *J. Am. Chem. Soc.* **2008**, *130*, 2422.

[10] a) M. P. Lalonde, Y. Chen, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 6514; *Angew. Chem. Int. Ed.* **2006**, *45*, 6366; b) H. Huang, E. N. Jacobsen, *J. Am. Chem. Soc.* **2006**, *128*, 7170; c) S. B. Tsogoeva, S. Wei, *Chem. Commun.* **2006**, 1451; d) P. Li, Y. Wang, X. Liang, J. Ye, *Chem. Commun.* **2008**, 3302; e) P. Li, S. Wen, F. Yu, Q. Liu, W. Li, Y. Wang, X. Liang, J. Ye, *Org. Lett.* **2009**, *11*, 753.

[11] a) S. Luo, H. Xu, J. Li, L. Zhang, J.-P. Cheng, *J. Am. Chem. Soc.* **2007**, *129*, 3074.

[12] F. Xue, S. Zhang, W. Duan, W. Wang, *Adv. Synth. Catal.* **2008**, *350*, 2194.

[13] a) S. B. Tsogoeva, S. W. Wei, *Tetrahedron: Asymmetry* **2005**, *16*, 1947; b) D. A. Yalalov, S. B. Tsogoeva, T. E. Shubina, I. M. Martynova, T. Clark, *Angew. Chem.* **2008**, *120*, 6726; *Angew. Chem. Int. Ed.* **2008**, *47*, 6624; c) F.-Z. Peng, Z.-H. Shao, X.-W. Pu, H.-B. Zhang, *Adv. Synth. Catal.* **2008**, *350*, 2199; d) R.-Q. Mei, X.-Y. Xu, Y.-C. Li, J.-Y. Fu, Q.-C. Huang, L.-X. Wang, *Tetrahedron Lett.* **2011**, *52*, 1566; e) K. Dudziński, A. M. Pakulska, P. Kwiatkowski, *Org. Lett.* **2012**, *14*, 4222.

[14] a) X. Zhu, A. Lin, L. Fang, W. Li, C. Zhu, Y. Cheng, *Chem. Eur. J.* **2011**, *17*, 8281; b) X. Zhu, A. Lin, Y. Shi, J. Guo, C. Zhu, Y. Cheng, *Org. Lett.* **2011**, *13*, 4382.

[15] a) W. Zhang, J. L. Loebach, S. R. Wilson, E. N. Jacobsen, *J. Am. Chem. Soc.* **1990**, *112*, 2801; b) J. Sun, C.

Zhu, Z. Dai, M. Yang, Y. Pan, H. Hu, *J. Org. Chem.* **2004**, *69*, 8500; c) Y. Huang, F. Yang, C. Zhu, *J. Am. Chem. Soc.* **2005**, *127*, 16386; d) M. Yang, C. Zhu, F. Yuan, Y. Huang, Y. Pan, *Org. Lett.* **2005**, *7*, 1927; e) C. Baleizão, H. Garcia, *Chem. Rev.* **2006**, *106*, 3987; f) S. J. Wezenberg, A. W. Kleij, *Angew. Chem.* **2008**, *120*, 2388; *Angew. Chem. Int. Ed.* **2008**, *47*, 2354; g) J. Sun, M. Yang, F. Yuan, X. Jia, X. Yang, Y. Pan, C. J. Zhu, *Adv. Synth. Catal.* **2009**, *351*, 920.

[16] a) C. Zheng, Y. Wu, X. Wang, G. Zhao, *Adv. Synth. Catal.* **2008**, *350*, 2690; b) P. Li, S. H. Chan, A. S. C. Chan, F. Y. Kwonga, *Adv. Synth. Catal.* **2011**, *353*, 1179.

[17] a) A. Ricci, L. Bernardi, C. Gioia, S. Vierucci, M. Robitzerb, F. Quignard, *Chem. Commun.* **2010**, 6288; b) Y. Liu, P. Gao, J. Wang, Q. Sun, Z. Ge, R. Li, *Synlett* **2012**, 1031.

[18] CCDC 877875 [for **4a**, $C_{14}H_{15}NO_3$, unit cell parameters: $a=25.184(4)$, $b=25.184(4)$, $c=10.113(4)$, space group rhombohedra, *R*-3] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

