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Asymmetric aldol reaction using a very simple primary amine catalyst: divergent stereoselectivity by using 2,6-difluorophenyl moiety

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ABSTRACT

Asymmetric aldol reactions of aliphatic ketones or aldehydes with aromatic aldehydes or isatins were catalyzed by a very simple and flexible *N*-(2,6-difluorophenyl)-L-valinamide. Interestingly, stereochemical course of the reaction of hydroxyacetones or α-branched aliphatic aldehydes as aldol donors was different from that of cycloalkanones.

1. Introduction

Asymmetric reaction using organocatalysts has been rapidly developing in recent years because the methodology is metal-free, non-toxic, and environmentally friendly.[1] A great deal of efforts have been devoted to prepare various chiral organocatalysts, however, most strategies for the stereocontrol in the reaction rely on hydrogen bonding interaction and steric repulsion.[2] As a result, large molecules having many chiral centers, or secondary amines having a rigid structure, such as proline derivatives were thought to be necessary in the process of catalyst design. Although recent progress has been shown that primary amine catalysts have also been effective,[3] control of stereoselectivities with simple and flexible catalysts can be a challenge. In the course of our study, we have developed a very simple, small, and flexible *N*-(2,6-difluorophenyl)-L-valinamide **1a** as an organocatalyst, which was easily prepared from Boc-L-valine in two steps (Fig. 1).[4] The asymmetric aldol reaction[5] of aldehydes with cycloalkanones using the catalyst **1a** under environmentally friendly conditions gave the corresponding product in high yields with up to >99% ee. Unlike the organocatalysts reported thus far, the stereoselectivity of the products was controlled by using tilted 2,6-difluorophenylamide group of the catalyst **1a**.[6] As a result, the aldol reaction of aromatic aldehydes with cycloalkanones mainly proceeded by the attack of *Si*-face of the enamine on the *Si*-face of aromatic aldehyde due to the steric hindrance (Fig. 1). The novel approach encouraged us to explore the reaction of other aldol donors and acceptors for a wide variety of application. In this work, unexpectedly, stereochemical preference was different from that in the reaction of aromatic aldehyde with cycloalkanone.[7] Here we report the asymmetric aldol reactions of hydroxyacetones or aliphatic aldehydes with various aromatic aldehydes or isatins as aldol acceptors using our catalyst **1**.

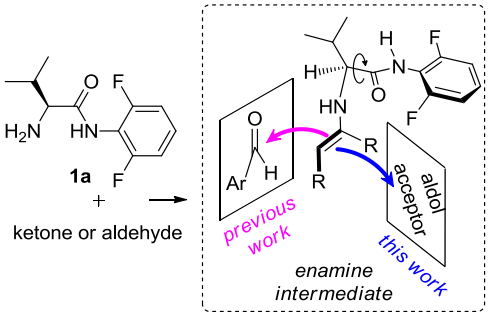

Fig. 1. A model for asymmetric aldol reaction catalyzed by **1a**.

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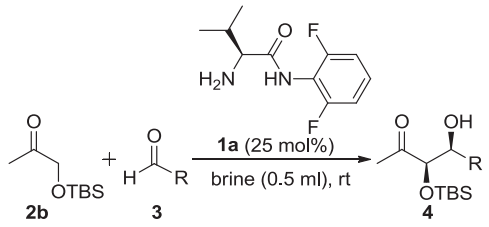
2. Results and discussion

1,2-Diols are found in many natural and biologically active compounds.[8] In spite of many reports on the reaction of hydroxyacetones, most of aldol reactions of hydroxyacetones use toxic additives, co-catalysts, or organic solvents.[9] To the best of our knowledge, only a few papers have been reported on the reaction under environmentally relevant conditions.[7,9e] In addition, stereoselective synthesis of (3*R*, 4*S*) isomers under environmentally benign conditions has not been reported yet. In our initial studies, aldol reaction of hydroxyacetone with 4-nitrobenzaldehyde **3a** using organocatalyst **1a** was examined, however, the reaction consistently resulted in moderate diastereo- and enantio-selectivities under various conditions (*syn*:*anti*=up to 75:25, up to 62% ee (*syn*)). Since the limited selectivity was thought owing to participation of the free hydroxyl group of hydroxyacetone, TBS-protected hydroxyacetone **2b** was used for the reaction (Table 1). After optimizing the reaction conditions, the scope of the reaction was explored. Reaction of various aromatic aldehydes proceeded with 67–94% ee (*syn*:*anti*=up to 85:15). Longer reaction time was necessary without electron-withdrawing group on the aromatic ring (entry 6). It should be noted that the reactions of both cycloalkanones[4] and hydroxyacetones proceeded using the catalyst **1a** with high stereoselectivities,[10] however, the stereochemistry of the products in Table 1 was different from that we expected in the reaction of cycloalkanones.

Table 1
Asymmetric aldol reactions of TBS-protected hydroxyacetone **2b** with various aromatic aldehydes **3**[a]



Entry	R (**3**)	Time (days)[b]	**4**	Yield (%)[c]	*syn*:*anti*[d]	% ee[e]
1	4-$NO_2C_6H_4$ (**3a**)	3	**4a**	94	83:17	85
2	2-$NO_2C_6H_4$ (**3b**)	4	**4b**	92	84:16	94
3	3-$NO_2C_6H_4$ (**3c**)	3	**4c**	94	85:15	80
4	4-$CF_3C_6H_4$ (**3d**)	3	**4d**	89	82:18	84
5	4-ClC_6H_4 (**3e**)	5	**4e**	79	78:22	79
6	C_6H_5 (**3f**)	7	**4f**	76	81:19	67

[a] All reactions were performed with 10 equiv of **2b** and 0.5 mmol of **3** in the presence of **1a** (25 mol %).
[b] Monitored by TLC.
[c] Isolated yield.
[d] Determined by ^{1}H NMR of the crude product.
[e] Determined by chiral HPLC analysis of the *syn*-product.

With these results in hand, DFT calculations were performed for plausible transition state models (Fig. 2). First, enamine structures were fully optimized in the gas phase at the B3LYP/6-31G(d,p) level using Gaussian 09,[11] and the transition states for the reaction including the enamine were optimized at the same theory.[12] It was found that **TS2** giving (3*R*, 4*S*) isomer had the lowest, indicating that the aldol reaction catalyzed by **1a** might pass through **TS2**. Although it is necessary to consider the effect of brine, these models were in good agreement with experimental results. In addition, major isomer was the same even though various solvents were used (66% ee in dry CH_2Cl_2 and 82% ee in water). Unlike the reaction of aromatic aldehydes and cycloalkanones, three hydrogen bonding interactions between oxygen atom of silyloxy group and hydrogen of enamine, oxygen of benzaldehyde and enamine hydrogen, and benzaldehyde oxygen and amide hydrogen of 2,6-difloro phenylamide group would stabilize **TS2**. Additionally, hydrophobic interaction of TBS group of the enamine and phenyl group of benzaldehyde[7] might lead to different course of attack compared to that of cycloalkanones.

To demonstrate the utility of our organocatalyst **1**, the reaction of hydroxyacetone with isatins was investigated (Table 2) because the aldol adducts bearing a chiral 1,2-diol moiety[13] are desirable targets found in drug candidates, such as TMC-95A∼D.[14] Very recently, Hu et al. have reported the diastereoselective three-component reaction of α-diazo esters, water and isatin, and the corresponding products having a 1,2-diol unit were obtained in high diastereoselectivity (up to *syn*:*anti*=9:91),[15] however, the enantioselectivity of the products was not evaluated. Although the asymmetric aldol reactions of ketones with isatins have been described, the reaction of hydroxyacetone has not been reported yet because the reaction proceeded easily with weak bases, such as potassium carbonate. After optimizing the reaction conditions, we found that dry MTBE as a solvent was necessary for higher enantioselectivities. The reaction of **2a** with **5a** was completed within 24 h but with 55% ee (entry 1 in Table 2). The use of the catalyst **1b** derived from phenylalanine gave better ee (entry 3). Addition of

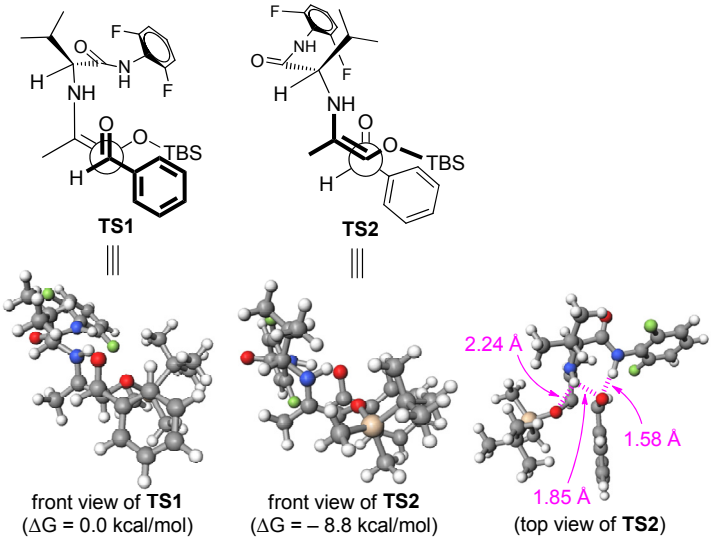
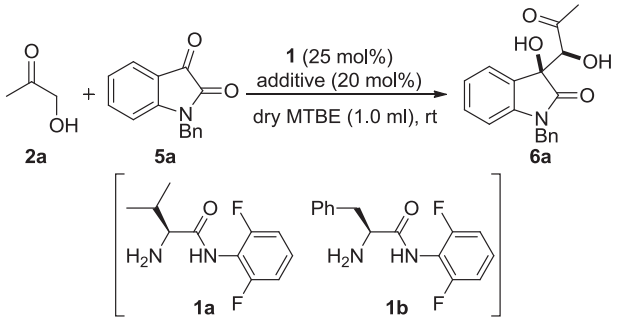


Fig. 2. Calculated 3D structures of **TS1** and **TS2**.

Table 2
Asymmetric aldol reactions of hydroxyacetone **2a** with isatin derivative **5a**[a]



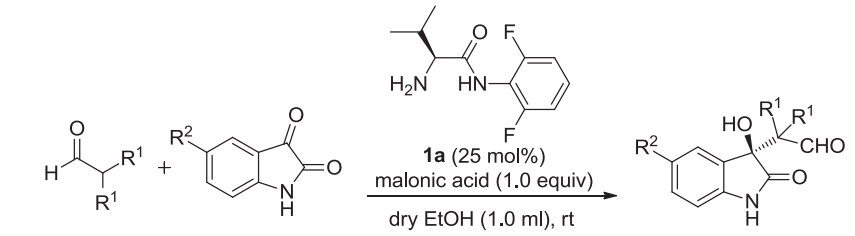
Entry	1	Additive	Time[b] (h)	Yield[c] (%)	*syn*:*anti*[d]	% ee[e]
1	**1a**	—	24	89	85:15	55
2	**1a**	Boc-L-valine	1	90	84:16	59
3	**1b**	—	36	84	85:15	69
4	**1b**	Boc-L-valine	2	89	84:16	70

[a] All reactions were performed with 10 equiv of **2a** and 0.5 mmol of **5a**.
[b] Monitored by TLC.
[c] Isolated yield.
[d] Determined by ^{1}H NMR of the crude product.
[e] Determined by chiral HPLC analysis of the *syn*-product.

found that malonic acid as an additive and dry EtOH as a solvent played an important role for high yields and enantioselectivities (Table 3). Notably, the reactions with other additives, such as succinic acid, acetic acid, or benzoic acid, resulted in low enantioselectivities (up to 32% ee). Changing the equivalent of malonic acid to isatin largely affected the enantioselectivities (33% ee with 0.5 equiv, 47% ee with 1.5 equiv, and 35% ee with 2.0 equiv). Under the optimal reaction conditions, the aldol reactions of α-branched aliphatic aldehydes **7** with isatins **5** proceeded with excellent enantioselectivities (entries 1–3, up to 94% ee (*S*)). The reaction of 5-methylisatin gave low ee but the reason is not clear now (entry 4). The absolute configuration of the product **8a** was unambiguously assigned by single-crystal X-ray analysis.[17] Reaction of non-branched aldehyde, such as acetaldehyde or hexanal was also examined but it did not proceed.

Transition state models of the reaction between isobutyraldehyde **7a** and isatin **5b** were also examined by DFT calculations. After the structures of plausible transition state models *without malonic acid* were fully optimized at the B3LYP/6-31G(d,p) level using PCM model (solvent=ethanol),[11] we found that the energy difference was only 0.9 kcal/mol between calculated transition state models giving (*S*)- and (*R*)-isomers (see Supplementary data), indicating that malonic acid would play a key role for both

Table 3
Enantioselective aldol reactions of aliphatic aldehydes **7** with isatin derivatives **5**[a]



7a: R^1 = Me
7b: R^1 = –$(CH_2)_5$–
5b: R^2 = H
5c: R^2 = methoxy
5d: R^2 = methyl
8a: R^1 = H, R^2 = H
8b: R^1 = –$(CH_2)_5$–, R^2 = H
8c: R^1 = Me, R^2 = methoxy
8d: R^1 = Me, R^2 = methyl

Entry	7	5	8	Time[b](h)	Yield (%)[c]	% ee[d]
1	**7a**	**5b**	**8a**	48	82	94
2	**7b**	**5b**	**8b**	120	81	87
3	**7a**	**5c**	**8c**	90	65	87[e]
4	**7a**	**5d**	**8d**	48	82	33[e]

[a] All reactions were carried out with 10 equiv of **7** and 0.5 mmol of **5**.
[b] Monitored by TLC.
[c] Isolated yields.
[d] Determined by chiral HPLC analysis.
[e] Determined by chiral HPLC analysis after reduction with $NaBH_4$.

commercially available Boc-L-valine accelerated the reaction to afford the product **6a** with 70% ee (89% yield, *syn*:*anti*=84:16 in entry 4), which was quite similar stereoselectivity in entry 3, indicating that Boc-L-valine would not affect the stereoselectivity but its acidity might accelerate the reaction. Other additives, such as *p*-TsOH, malonic acid, and benzoic acid lowered the enantioselectivities (up to 23% ee).

Encouraged by these results, we next focused on the reactions of aliphatic aldehydes with isatin as the same aldol acceptor for further application. To the best of our knowledge, one example has been reported for the aldol reaction between α-branched aliphatic aldehydes and isatins in the presence of organocatalysts (up to 84% ee).[16] The reaction of isobutyraldehyde **7a** with isatin **5b** in the presence of **1a** was examined under various conditions, and we

the acceleration of reactions and high stereoselectivities of the products. Considering from the equivalent effect of malonic acid on enantioselectivities, we proposed that a complex having two hydrogen bonding interactions as in Fig. 3 (optimized at the same level of theory using PCM model) might contribute to highly stereoselective reaction affording (*S*)-isomers.

3. Conclusion

In conclusion, we have developed environmentally friendly asymmetric aldol reactions of TBS-protected hydroxyacetone **2b** with aromatic aldehydes **3** using our organocatalyst **1**, which is small and easily prepared from Boc-L-valine in two steps, to afford the corresponding products in high diastereo- and enantio-

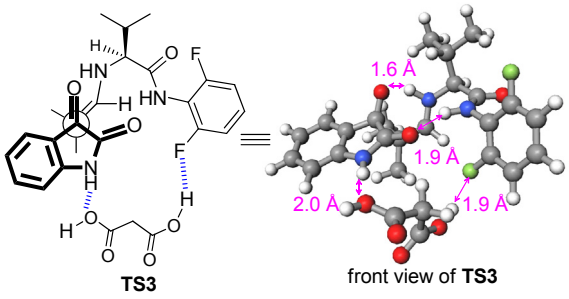


Fig. 3. Plausible transition state model (**TS3**) and calculated 3D structure.

selectivities (*syn*:*anti*=up to 85:15, up to 94% ee (*syn*)). Moreover, we have first succeeded the reaction of hydroxyacetone **2a** with isatin derivative **5a** as a different aldol acceptor to give the aldol product **6a** bearing a pharmaceutically attractive unit with 70% ee (*syn*:*anti*=84:16). The aldol reaction of α-branched aliphatic aldehydes **7** as different aldol donors with isatins **5** using catalyst **1a** also gave the corresponding aldol products **8** in excellent enantioselectivities (up to 94% ee), showing that catalyst **1** was applicable for asymmetric aldol reactions of cycloalkanones, hydroxy acetones, and α-branched aliphatic aldehydes as aldol donors and aromatic aldehydes, isatins as aldol acceptors. Surprisingly, stereochemical course of all reactions reported here was different from that in the reaction of aromatic aldehydes with cycloalkanones, indicating that our catalyst having a 2,6-difluorophenyl moiety has unique properties (Fig. 1).

4. Experimental

4.1. General

All reactions were performed in oven-dried glassware with a magnetic stirrer. Solvents for chromatography and extraction were purchased from commercial suppliers and used without further purification. All organic substrates, such as aldehydes, hydroxyacetone, and isatin were commercially available and were used without any purification. Thin-layer chromatography (TLC) analysis of reaction mixtures was performed using Merck TLC plates (silica gel 60GF-254, 0.25 mm) and visualized by using UV (254 nm). The products were purified by flash column chromatography on silica gel (Merck 1.09386.9025, 230–400 mesh or Kanto Chemical, 40–100 μm). ^{1}H NMR spectrum was measured with JEOL JNM-AL300 BK1 (300 MHz) in $CDCl_3$ or CD_3OD. Multiplicities are reported using the following abbreviations: s=singlet, d=doublet, t=triplet, and q=quartet. The diastereomeric ratios of the aldol products were determined by ^{1}H NMR. Enantiomeric excess values of the products were determined by high performance liquid chromatography (HPLC) with Daicel Chiralpak AD-H, Chiralcel OD-H, Chiralcel OJ-H or Chiralpak IA (4.6 mm×25 cm column). Elemental analyses were performed on Flash EA1112.

4.2. General procedure for the asymmetric aldol reaction of TBS-protected hydroxyacetone with aromatic aldehydes (Table 1)

To a stirred solution of catalyst (0.125 mmol, 25 mol %) in brine (0.5 ml) and TBS-protected hydroxyacetone (5.0 mmol) was added aldehyde (0.5 mmol) at room temperature under an atmosphere of air. The reaction mixture was stirred at room temperature in a closed system for an appropriate time until the reaction was completed by monitoring TLC. Then the mixture was extracted with CH_2Cl_2 (2 ml×3) and the organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flash column chromatography on SiO_2 (*n*-hexane:CH_3CO_2Et=5:1) to afford the corresponding product. The products **4a**,[9a] **4b**–**f**,[9j] were identified by comparing with the spectral data reported in the literature.

*4.2.1. Deprotection of **4a** and determination of the absolute configuration.* To a stirred solution of aldol adduct **4a** (0.39 mmol) in THF (20 ml) was added TBAF (3.5 mmol) and AcOH (0.66 ml) at room temperature. After stirring for 2 h, the reaction mixture was quenched with a small amount of brine. After solution was removed by evaporation, the residue was extracted with CH_2Cl_2. The organic layers were washed with brine and dried over anhydrous sodium sulfate, filtered, and the solvent was concentrated. The residue was purified by flash column chromatography on SiO_2 (hexane:CH_3CO_2Et=1:1) to afford the diol as colorless crystal (69% yield). Compared to the reported chiral HPLC retention time of the diol,[8a] the absolute configuration of **4a** is (3*R*, 4*S*).

4.3. General procedure for the asymmetric aldol reaction of hydroxyacetone with *N*-benzylisatin (Table 2)

To a stirred solution of catalyst (0.125 mmol, 25 mol %), additive (20 mol %), and hydroxyacetone (5.0 mmol) in dry MTBE (1.0 ml) was added *N*-benzylisatin **5a** (0.5 mmol) at room temperature under argon atmosphere. The reaction mixture was stirred at room temperature for an appropriate time until the reaction was completed by monitoring TLC. Then the mixture was purified by flash column chromatography on SiO_2 (CH_3CO_2Et:CH_2Cl_2=3:2) to afford the corresponding product.

*4.3.1. 1-Benzyl-3-hydroxy-3-(1-hydroxy-2-oxopropyl)indolin-2-one (**6a**).* The compound **6a** was obtained as colorless oil. (*syn*-**6a**) $[\alpha]_D^{17}$ +3.85 (*c* 0.1, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45 (d, 1H, *J*=7.5 Hz, Ar), 7.32–7.21 (m, 6H, Ar), 7.07 (t, 1H, *J*=7.5 Hz, Ar), 6.71 (d, 1H, *J*=7.5 Hz, Ar), 4.94 (d, 1H, *J*=15.6 Hz, $-CH_2-$), 4.81 (d, 1H, *J*=15.6 Hz, $-CH_2-$), 4.54 (d, 1H, *J*=3.7 Hz, $-CHOH$), 3.76 (brs, 1H, −OH), 3.72 (d, 1H, *J*=3.7 Hz, −OH), 2.28 (s, 3H, $-COCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 207.8, 175.2, 143.3, 135.0, 130.5, 128.8, 127.8, 127.5, 127.3, 124.4, 123.4, 109.8, 79.4, 44.0, 27.5; IR (KBr): ν 3404, 3061, 3030, 2925, 1711, 1361, 1179, 1081, 754 cm^{-1}; (*anti*-**6a**) $[\alpha]_D^{17}$ +3.80 (*c* 0.1, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31–7.19 (m, 6H, Ar), 7.10 (d, 1H, *J*=7.3 Hz, Ar), 7.02 (t, 1H, *J*=7.3 Hz, Ar), 6.67 (d, 1H, *J*=7.3 Hz, Ar), 5.12 (d, 1H, *J*=16.0 Hz, $-CH_2-$), 4.72 (d, 1H, *J*=7.3 Hz, $-CHOH$), 4.66 (d, 1H, *J*=16.0 Hz, $-CH_2-$), 3.94 (brs, 1H, −OH), 3.57 (d, 1H, *J*=7.3 Hz, −OH), 2.41 (s, 3H, $-COCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 207.3, 143.8, 134.9, 130.6, 128.8, 127.7, 127.1, 125.7, 124.4, 123.1, 109.9, 79.3, 44.0, 28.9; IR (KBr): ν 3404, 3061, 3030, 2925, 1711, 1361, 1179, 1081, 754 cm^{-1}; Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.45; H, 5.50; N, 4.49. Enantiomeric excess was determined by HPLC with CHIRALPAK AD-H column (hexane:2-propanol=90:10), flow rate=1.0 mL/min; λ=254 nm; t_r=23.5 min (*syn*-**6a**), t_r=35.3 min (*syn*-**6a**), t_r=42.0 min (*anti*-**6a**), t_r=46.3 min (*anti*-**6a**). Relative stereochemistry of the aldol product was identified by comparing the spectral data of similar compounds reported in the literature.[15]

*4.3.2. Preparation of **1b** (Table 2).* *N*-Methyl morpholine (2.27 ml, 20.0 mmol) and isobutyl chloroformate (2.67 ml, 20.0 mmol) in 5 ml of dry THF were successively added to a stirred solution of *N*-Boc-L-phenylalanine (5.31 g, 20.0 mmol) in THF (75 ml) at −20 °C. After an activation period of 15 min, 2,6-difluoroaniline (2.82 ml, 25.0 mmol) in THF (15 ml) was added to the above solution over 10 min. The reaction mixture was stirred for 24 h at −5 °C. The resulting solution was allowed to warm to room temperature and quenched with 20 ml of 5% aqueous $NaHCO_3$. The mixture was

extracted with CH_2Cl_2 (50 ml×3), and the organic layers were dried over $MgSO_4$, filtered, and concentrated to give the crude product as colorless oil, which was used for the next reaction without further purification. To a stirred solution of the oil in dry CH_2Cl_2 (30 ml) was slowly added TFA (10 ml) at 0 °C. After the reaction mixture was stirred for 5 h at room temperature, excess reagent and solvent were removed in vacuo. The resulting oil was neutralized by aqueous saturated $NaHCO_3$, extracted with CH_2Cl_2 (50×3 ml), dried over $MgSO_4$, and the solvent was evaporated. The crude product was purified by flash column chromatography on SiO_2 (CH_3CO_2Et:CH_2Cl_2=3:7) to afford the organocatalyst **1b** in 58% yield (3.18 g) as a colorless oil.[4] $[\alpha]_D^{16}$ +4.62 (*c* 0.1, MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.98 (brs, 1H, −N*H*), 7.37–7.26 (m, 5H, Ar), 7.21–7.14 (m, 1H, Ar), 6.88–7.02 (m, 2H, Ar), 3.83 (dd, 1H, *J*=9.2, 4.0 Hz, −C*H*NH_2), 3.36 (dd, 1H, *J*=13.7, 4.0 Hz, −CH_2−), 2.88 (dd, 1H, *J*=13.7, 9.2 Hz, −CH_2−), 1.58 (brs, 2H, −NH_2); ^{13}C NMR ($CDCl_3$, 75 MHz) 172.9, 159.42, 159.35, 156.1, 156.0, 137.4, 129.3, 128.7, 127.3, 126.9, 113.9, 111.8, 111.5, 56.5, 40.6; IR (KBr): ν 3276, 3028, 2922, 1694, 1241, 781, 702 cm^{-1}; Anal. Calcd for $C_{15}H_{14}F_2N_2O$: C, 65.21; H, 5.11; N, 10.14. Found: C, 65.29; H, 5.07; N, 10.11.

4.4. General procedure for the asymmetric aldol reaction of aliphatic aldehydes with isatin (Table 3)

To a stirred solution of catalyst (0.125 mmol, 25 mol %) and aldehyde (10.0 mmol) in dry EtOH (1.0 ml) was added isatin (0.5 mmol) at room temperature under argon atmosphere. The reaction mixture was stirred at room temperature for an appropriate time until the reaction was completed by monitoring TLC. Then the mixture was purified by flash column chromatography on SiO_2 (CH_2Cl_2:CH_3CO_2Et=7:3) to afford the corresponding product **8**. The products **8a** and **8b** were identified by comparing with the spectral data reported in the literature.[15] The products **8c** and **8d** were identified as follows.

4.4.1. (S)-3-Hydroxy-3-(1-hydroxy-2-methylpropan-2-yl)-5-methoxyindolin-2-one. The aldol reaction of aldehyde **7a** with 5-methoxyisatin **5c** was conducted for 90 h to give a corresponding aldol product **8c** (82% yield). To a stirred solution of product **8c** (82.5 mg, 0.33 mmol) in dry EtOH (10.0 ml) was added $NaBH_4$ (0.05 g, 1.3 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred at room temperature for 3 h. After the mixture was quenched by saturated NH_4Cl *aq*, aqueous layer was extracted with CH_2Cl_2. The obtained crude product was purified by flash column chromatography on SiO_2 (CH_2Cl_2:CH_3CO_2Et=7:3) to afford the corresponding product as a pale yellow oil (82.9 mg, >99% yield). $[\alpha]_D^{19}$ +3.80 (*c* 0.1, MeOH); ^{1}H NMR (CD_3OD, 300 MHz) δ 7.00–6.99 (m, 1H, Ar), 6.82 (dd, 1H, *J*=8.5, 2.0 Hz, Ar), 6.76 (d, 1H, *J*=8.5 Hz, Ar), 3.82 (d, 1H, *J*=11.0 Hz, −CH_2−), 3.77 (s, 3H, −OCH_3), 3.64 (d, 1H, *J*=11.0 Hz, −CH_2−), 1.08 (s, 3H, −CH_3), 0.88 (s, 3H, −CH_3); ^{13}C NMR (CD_3OD, 75 MHz) 182.0, 157.0, 136.6, 133.1, 114.9, 114.5, 111.2, 83.5, 69.3, 56.3, 41.4, 20.0, 19.5; IR (KBr): ν 3271, 2971, 1720, 1489, 1390, 1210, 1043, 756 cm^{-1}; Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.10; H, 6.84; N, 5.49. Enantiomeric excess was determined by HPLC with CHIRALPAK AD-H column (hexane:2-propanol=85:15), flow rate=1.0 mL/min; λ=254 nm; t_r=12.4 min (*R*), t_r=22.2 min (*S*).

4.4.2. (S)-3-Hydroxy-3-(1-hydroxy-2-methylpropan-2-yl)-5-methylindolin-2-one. The aldol reaction of aldehyde **7a** with 5-methylisatin **5d** was conducted for 48 h to give the corresponding aldol product **8d** (82% yield). To a stirred solution of **8d** (89.4 mg, 0.38 mmol) in dry EtOH (10.0 ml) was added $NaBH_4$ (0.05 g, 1.3 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred at room temperature for 3 h. After the mixture was quenched by saturated NH_4Cl *aq*, aqueous layer was extracted with CH_2Cl_2. The obtained crude product was purified by flash column chromatography on SiO_2 (CH_2Cl_2:CH_3CO_2Et=7:3) to afford the corresponding product as a colorless oil (89.4 mg, >99% yield). $[\alpha]_D^{18}$ +5.38 (*c* 0.1, MeOH); ^{1}H NMR (CD_3OD, 300 MHz) δ 7.20 (s, 1H, Ar), 7.05 (d, 1H, *J*=7.7 Hz, Ar), 6.72 (d, 1H, *J*=7.7 Hz, Ar), 3.82 (d, 1H, *J*=10.8 Hz, −CH_2−), 3.63 (d, 1H, *J*=10.8 Hz, −CH_2−), 2.31 (s, 3H, −CH_3), 1.07 (s, 3H, −CH_3), 0.86 (s, 3H, −CH_3); ^{13}C NMR (CD_3OD, 75 MHz) 182.2, 140.9, 132.6, 131.9, 130.7, 127.9, 110.6, 83.3, 69.3, 41.3, 21.2, 20.0, 19.5; IR (KBr): ν 3271, 2971, 1720, 1489, 1390, 1210, 1043, 756 cm^{-1}; Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.30; H, 7.41; N, 5.91. Enantiomeric excess was determined by HPLC with CHIRALPAK AD-H column (hexane:2-propanol=85:15), flow rate=1.0 mL/min; λ=254 nm; t_r=8.7 min (*R*), t_r=11.6 min (*S*).

Supplementary data

Copies of ^{1}H and ^{13}C NMR spectra, calculation of plausible transition states, HPLC analysis for the products, and X-ray analysis of **8a** are available. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.02.059.

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