ChemPubSoc Europe

DOI: 10.1002/ejoc.201600414

EurJOC European Journal of Organic Chemistry

Full Paper

Organocatalysts

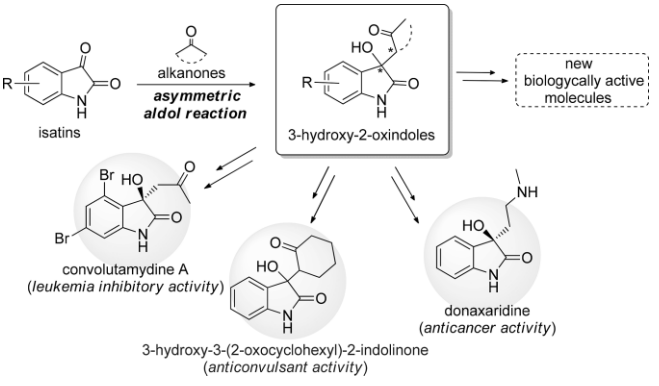
Simple Primary Amino Amide Organocatalyst for Enantioselective Aldol Reactions of Isatins with Ketones

Jo Kimura,[a] Ummareddy Venkata Subba Reddy,[a] Yoshihito Kohari,[a] Chigusa Seki,[a] Yasuteru Mawatari,[a] Koji Uwai,[a] Yuko Okuyama,[b] Eunsang Kwon,[c] Michio Tokiwa,[d] Mitsuhiro Takeshita,[d] Tatsuo Iwasa,[e] and Hiroto Nakano*[a]

Abstract: Enantioselective aldol reactions of various isatins with ketones using newly designed amino amide organocatalysts were found to provide chiral 3-substituted 3-hydroxy-2-oxindoles in good to excellent yields and with excellent stereoselectivities (up to 99 %, up to 98 % *ee*, *syn*/*anti* = 99:1); one catalyst, **3i**, proved particularly successful. One of the resulting oxindoles, 3-hydroxy-3-(2-oxocyclohexyl)-2-indolinone may serve as a synthetic intermediate for pharmaceutically important compounds and, in its own right, shows interesting anticonvulsant activities.

Introduction

The development of new optically active organocatalysts for use in asymmetric synthesis has drawn considerable interest in the scientific community over the past 10 years. Excellent covalent and non-covalent organocatalysts have been developed for use in a wide range of reactions.[1] Most recently, we reported that a primary β-amino alcohol acts as an efficient organocatalyst in some reactions.[2] The enantioselective aldol reaction using organocatalysts is recognized as one of the most powerful carbon–carbon bond-forming reactions.[3] This method provides a useful route to chiral β-hydroxy carbonyl compounds, which are versatile synthetic motifs for many biologically and pharmaceutically important intermediates.[4] In particular, the utilization of isatin as an electrophile has attracted much attention, because this reaction affords chiral 3-hydroxy-2-oxindoles (3-substituted 3-hydroxy-2-oxindoles) containing an asymmetric quaternary carbon atom at the 3-position. Such species are desirable targets, because many related structural motifs are found in natural products and pharmaceutically active compounds such as 3-hydroxy-3-(2-oxocyclohexyl)-2-indolinone (possessing anticonvulsant activity), convolutamydine A (displaying leukemia inhibitory activity) and donaxaridine (displaying anticancer activity) (Scheme 1).[5]

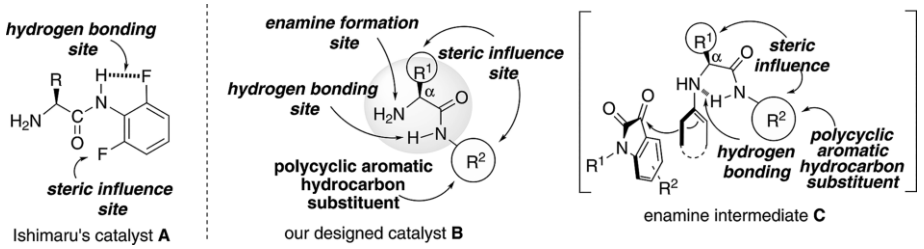


Scheme 1. Utility of 3-hydroxy-2-oxindoles.

Although organocatalyzed asymmetric reactions of isatins with cyclic or acyclic ketones have been described,[6] only a few examples have been reported of highly stereoselective reactions displaying significant enantioselectivity. Therefore, the design and development of highly functionalized organocatalysts for this reaction is a significant, albeit challenging, research goal.

Most recently, Ishimaru et al. have developed a new amino amide organocatalyst **A** containing a (2,6-difluorophenyl)amide group for this reaction (Scheme 2).[6e] A unique feature of this catalyst is that it has an electrostatic repulsion between one fluorine atom on the aromatic ring and the amide oxygen atom. Furthermore, the H-bonding of the other fluorine atom with the amide hydrogen atom fixes the conformation of the catalyst in such a way as to enable shielding of one enantiotopic face of the enamine intermediate formed between the catalyst and substrate ketones.

[a] *Department of Bioengineering, Graduate School of Engineering, Muroran Institute of Technology*
27-1 Mizumoto, Muroran 050-8585, Japan
E-mail: catanaka@mmm.muroran-it.ac.jp
http://www3.muroran-it.ac.jp/hnakano/
[b] *Tohoku Pharmaceutical University,*
4-4-1 Komatsushima, Aoba-ku, Sendai 981-8585, Japan
[c] *Research and Analytical Center for Giant Molecules, Graduate School of Sciences, Tohoku University,*
6-3 Aoba, Aramaki, Aoba-ku, Sendai 980-8578, Japan
[d] *Tokiwakai Group,*
62 Numajiri Tsuduri-chou Uchigo Iwaki 973-8053, Japan
[e] *Division of Engineering for Composite Functions, Graduate School of Engineering, Muroran Institute of Technology,*
27-1 Mizumoto, Muroran 050-8585, Japan
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201600414.



Scheme 2. Concept of catalyst design.

We planned to create a new amino amide organocatalyst based on a new concept, which is different from Ishimaru's catalyst. In designing our catalyst, we envisioned the simpler amino amide **B**, which bears a flexible bulky amide polycyclic aromatic hydrocarbon group. In contrast to the Ishimaru model, this moiety is not fixed by H-bonding, yet the catalyst should shield one enantiotopic enamine face on the basis of steric factors. Our catalyst **B** is easily prepared by condensation of the corresponding amino acid and polycyclic aromatic hydrocarbon substituted amines. Reaction of catalyst **B** with cyclic or acyclic ketones was envisioned to afford enamine intermediate **C**.

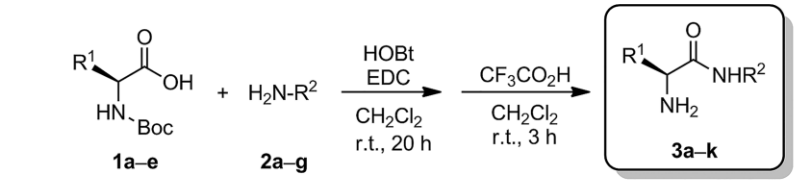
In intermediate **C**, H-bonding of the amino nitrogen atom at the α-position with the amide hydrogen atom might strongly fix the conformation of this intermediate. Thus, the bulkier flexible polycyclic aromatic hydrocarbon group (R^2) on the amide nitrogen atom and substituent (R^1) at the α-position might shield one face of the isatin from the incoming nucleophile. The result was envisioned to be satisfactory stereoselectivity (chemical yield, enantioselectivity and diastereoselectivity) in an aldol reaction using a variety of isatins and ketones (Scheme 2).

We report herein that amino amide organocatalyst **3i** enables excellent yields and a high degree of stereocontrol (enantioselectivities and diastereoselectivities) (up to 99 % yield, up to 98 % *ee*, *syn*/*anti* = 99:1) to be achieved in aldol reactions of isatins with several cyclic and acyclic ketones.

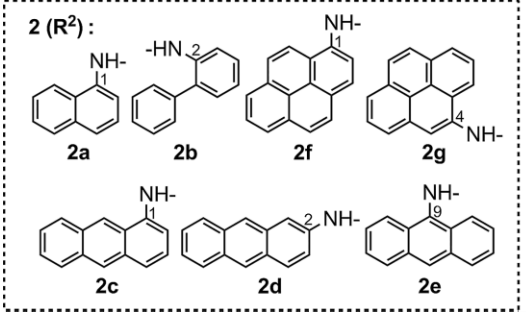
Results and Discussion

Amino amide organocatalysts **3a**–**k** were prepared easily by condensation of the corresponding *N*-protected amino acids **1a**–**e** with amines **2a**–**g**, respectively, in the presence of stoichiometric amounts of 1-hydroxybenzotriazole (HOBt) and 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide (EDC) followed by removal of the Boc group from crude *N*-protected amino amide compounds using CF_3CO_2H. The catalysts were prepared in yields up to 72 % (Scheme 3).[6u,7]

Initially, we examined the aldol reaction of isatin **4** with cyclohexanone **5** using organocatalysts **3a**–**k** (25 mol-%) in the presence of *p*TsOH at room temperature (Table 1) under Ishim-



1a : R^1= *i*Pr **1b** : R^1= Me
1c : R^1= *t*Bu **1d** : R^1= Ph
1e : R^1= Bn

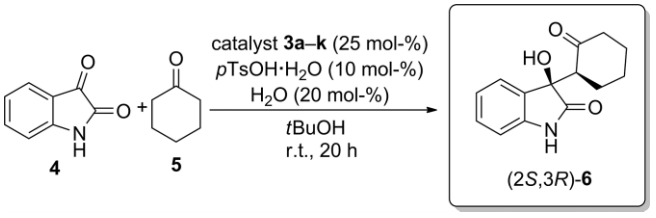


3a	R^1= *i*Pr,	R^2 = 1-naphthyl	66%
3b	R^1= *i*Pr,	R^2 = 2-biphenylyl	59%
3c	R^1= *i*Pr,	R^2 = 1-anthracenyl	72%
3d	R^1= *i*Pr,	R^2 = 2-anthracenyl	62%
3e	R^1= *i*Pr,	R^2 = 9-anthracenyl	50%
3f	R^1= *i*Pr,	R^2 = 1-pyrenyl	65%
3g	R^1= *i*Pr,	R^2 = 4- pyrenyl	46%
3h	R^1= Me,	R^2 = 1-anthracenyl	51%
3i	R^1= *t*Bu,	R^2 = 1-anthracenyl	57%
3j	R^1= Ph,	R^2 = 1-anthracenyl	59%
3k	R^1= Bn,	R^2 = 1-anthracenyl	60%

Scheme 3. Preparation of amino amide organocatalysts **3a**–**k**.

aru conditions.[6u] All catalysts proved effective, and the corresponding aldol product (2*S*,3*R*)-**6** was generated in excellent *syn*/*anti* selectivities (91:9–99:1). The absolute configurations and *syn*/*anti* stereoselectivities of **6** were determined on the basis of comparisons with literature data.[6b,6e,6r,6u] The use of α-isopropyl catalyst **3a** with 1-naphthylamide afforded **6** in good chemical yield (90 %) with 70 % *ee* (Table 1, Entry 1). Similarly, the use of catalyst **3b** with its 2-biphenylylamide also gave good chemical yield and moderate enantioselectivity (89 %, 67 % *ee*) (Table 1, Entry 2). Bulkier catalyst **3c** with the 1-anthracenylamide gave **6** in fairly good chemical yield (89 %) and with good enantioselectivity (76 % *ee*) (Table 1, Entry 3), but the use of catalyst **3d** with its 2-anthracenylamide brought about a decrease in both chemical yield and enantioselectivity (62 %, 38 % *ee*) (Table 1, Entry 4). On the other hand, catalyst **3e** with the 9-anthracenylamide afforded **6** in excellent chemical yield and with moderate enantioselectivity (93 %, 65 % *ee*) (Table 1, Entry 5). The bulkiest catalysts **3f** and **3g** with their pyrene moieties also showed higher catalytic activities than did catalysts **3a**–**e**, and product **6** was obtained in excellent chemical yields with moderate to good enantioselectivities (**3f**: 99 %, 75 % *ee*; **3g**: 96 %, 67 % *ee*) (Table 1, Entries 6 and 7). From these results, it was shown that catalyst **3c** with its 1-anthracenylamide is best for generating **6** in good chemical yield and enantioselectivity (Table 1, Entry 3).

Table 1. Asymmetric aldol reaction of **4** with **5** using organocatalysts **3a**–**k**.



Entry	Cat.	Yield [%][a]	*syn*/*anti*[b]	*ee* [%][c]
1	3a	90	97:3	70
2	3b	89	96:4	67
3	3c	89	98:2	76
4	3d	62	99:1	38
5	3e	93	97:3	65
6	3f	99	97:3	75
7	3g	96	95:5	67
8	3h	80	98:2	62
9	3i	96	97:3	80
10	3j	94	92:8	4
11	3k	91	91:9	48

[a] Isolated yield. [b] Diastereoselectivity was determined on the basis of HPLC analyses of the reaction mixture. [c] The *ee* of **6** was determined on the basis of chiral HPLC analyses using a DAICEL column.

These results indicate that one face of the enamine in intermediate **C** might be shielded effectively by the linear 1-anthracenyl moiety on the catalyst amide nitrogen atom. We also screened the catalytic activity of catalysts **3h**–**k**; these retain the anthracenylamide but contain substituents other than isopropyl at the α-position. The best result was obtained using catalyst **3i**, which contains a *tert*-butyl group at the α-position (96 %, 80 % *ee*, *syn*/*anti* = 97:3) (Table 1, Entry 9); the use of **3h**,**j**,**k** did not afford satisfactory results (Table 1, Entries 8, 10, 11). It was thus realized that both the polycyclic aromatic amide moieties and groups present at the α-position play important roles needed to achieve satisfactory enantioselectivity.

To optimize the reaction conditions using superior catalyst **3i**, we next examined the effects of solvent, the molar ratio of catalyst, co-catalyst, reaction temperature and reaction time (Table 2, Entries 1–19). Aldol product **6** was obtained in 99 % yield with 90 % *ee* when the reaction was carried out in THF

Table 2. Optimization of the reaction conditions of **4** with **5** using organocatalyst **3i**.

Entry	Solvent	Cat. [mol-%]	Co-cat. (10 mol-%)	*T* [°C]	*t* [h]	Yield [%][a]	*syn*/*anti*[b]	*ee* [%][c]
1	DMF	25	–	r.t.	20	79	94:6	77
2	acetone	25	–	r.t.	20	99	97:3	81
3	Et_2O	25	–	r.t.	20	87	97:3	85
4	THF	25	–	r.t.	20	99	99:1	90
5	1,4-dioxane	25	–	r.t.	20	99	97:3	86
6	THF	20	–	r.t.	20	99	99:1	90
7	THF	15	–	r.t.	20	99	99:1	90
8	THF	10	–	r.t.	20	98	99:1	89
9	THF	15	phenol	r.t.	20	99	99:1	87
10	THF	15	*p*TsOH/H_2O	r.t.	20	99	97:3	64
11	THF	15	TFA	r.t.	20	99	90:10	59
12	THF	15	benzoic acid	r.t.	20	99	98:2	78
13	THF	15	–	0	20	99	97:3	86
14	THF	15	–	–15	20	48	90:10	78
15	THF	15	–	–25	20	29	82:18	78
16	THF	15	–	r.t.	15	99	99:1	90
17	THF	15	–	r.t.	10	99	99:1	90
18	THF	15	–	r.t.	5	84	96:4	88
19	THF	15	–	r.t.	2.5	61	94:6	87

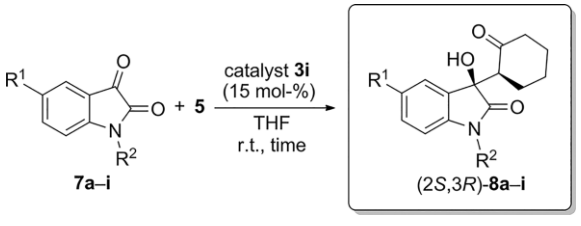
[a] Isolated yield. [b] Diastereoselectivity was determined on the basis of HPLC analyses of the reaction mixture. [c] The *ee* of **6** was determined on the basis of chiral HPLC using a DAICEL column.

using 15 mol-% of **3i** at room temperature for 20 h (Table 2, Entry 7). In contrast to Ishimaru's reaction conditions using an acidic co-catalyst (*p*TsOH), our reaction system using organocatalyst **3i** did not afford satisfactory enantioselectivity (64 % *ee*), although the reasons for this are not yet clear (Table 2, Entry 10).

After optimizing the reaction conditions, we investigated the generality of the reaction of isatins **7a**–**i** with cyclohexanone **5** using catalyst **3i** (Table 3, Entries 1–9). Isatins **7a**–**i** with different substitution patterns and electronic properties were evaluated, and all were readily converted into their corresponding aldol products (2*S*,3*R*)-**8a**–**i** with high stereoselectivities (*syn*/*anti* = 97:3–99:1), high chemical yields (90–99 %), and with moderate to excellent enantioselectivities (65–98 % *ee*; see Table 3, Entries 1–9).[6b,6j,8] In the attempted reactions, *N*-methylisatin (**7a**) afforded aldol product **8a** in fairly good chemical yield and with excellent enantioselectivity (91 %, 98 % *ee*), although a long reaction time was required (Table 3, Entry 1). Aldol reactions of both *N*-benzyl- (**7b**) and *N*-allylisatin (**7c**), afforded products **8b** and **8c** in fairly good chemical yields (**8b**: 93 %; **8c**: 95 %), although the observed enantioselectivities were only moderate (**8b**: 65 % *ee*; **8c**: 66 % *ee*) (Table 3, Entries 2 and 3). On the other hand, the reaction using synthetically useful *N*-Boc-isatin (**7d**), similar to the simplest isatin **4**, afforded product **8d** in excellent yield and with satisfactory enantioselectivity (98 %, 78 % *ee*, Table 3, Entry 4). Isatin **7e**, bearing an electron-donating methyl group on the aromatic ring, also gave rise in fairly good chemical yield and enantioselectivity to product **8e** (93 %, 86 % *ee*, Table 3, Entry 5). Aldol chemistry with isatins **7f**–**h**, bearing halogen atoms on their aromatic rings, also afforded the corresponding indolinones **8f**–**h** with good yields and enantioselectivities (90–93 %, 74–81 % *ee*, Table 3, Entries 6–8). Additionally, fairly good results (99 %, 92 % *ee*) were obtained from the reaction of isatin **7i**, bearing a strong electron-withdrawing NO_2 group on its aromatic ring, with ketone **5** (Table 3, Entry 9). These results indicate that catalyst **3i** is generally applicable to the aldol reaction of differently substituted isatins.

We next examined the aldol reaction of isatin **4** with several acyclic or cyclic ketones **9a**–**f** using the optimal catalyst **3i** under the same reaction conditions used to generate earlier products (Table 4). The reaction of **4** with acetone **9a** proceeded smoothly to give the corresponding aldol product **10a** in good chemical yield (97 %), although the enantioselectivity for this conversion was poor (12 % *ee*) (Table 4, Entry 1).[6c,6e,6i,6k,6m,6p,6r,6t,6u] The use of cyclopentanone **9b** afforded the corresponding product **10b** in 55 % yield with 32 % *ee* (Table 4, Entry 2).[6i,8] Although bulkier cycloheptanone **9c** gave rise to product **10c** in moderate chemical yield (54 %), the enantioselectivity of this conversion increased to 63 % *ee* (Table 4, Entry 3).[8b] The use of heterocyclic ketone tetrahydropyran-4-one (**9d**), afforded the corresponding product **10d** with an increase in yield up to 99 % and with moderate enantioselectivity (58 % *ee*) (Table 4, Entry 4).[6i] The reaction of tetrahydrothiopyran-4-one (**9e**) afforded product **10e** in 92 % yield and an improved enantioselectivity (relative to **10d** formation) of 75 % *ee* (Table 4, Entry 5).[6i] Additionally, piperidin-4-one (**9f**) gave rise to product **10f** in 94 % yield with 53 % *ee* (Table 4, Entry 6).[6i] Notably, aldol products **8a**–**i** and **10a**–**f** were characterized on the basis of full spectroscopic data analyses and were found to be consistent with previously reported data.[6b,6j,8] Absolute configurations of all aldol products were determined by comparing specific optical rotation values obtained herein with literature values.[6b,6j,8]

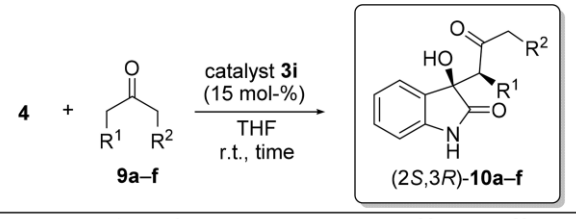
Table 3. Asymmetric aldol reaction of **7a**–**i** with **5** using organocatalyst **3i**.



Entry	7	R^1	R^2	8	*t* [h]	Yield [%][a]	*syn*/*anti*[b]	*ee* [%][c]
1	**7a**	H	Me	**8a**	144	91	98:2	98
2	**7b**	H	Bn	**8b**	144	93	98:2	65
3	**7c**	H	allyl	**8c**	144	95	97:3	66
4	**7d**	H	Boc	**8d**	6	98	95:5	78
5	**7e**	Me	H	**8e**	10	93	97:3	86
6	**7f**	F	H	**8f**	10	91	99:1	74
7	**7g**	Cl	H	**8g**	10	93	97:3	81
8	**7h**	Br	H	**8h**	10	90	99:1	75
9	**7i**	NO_2	H	**8i**	10	99	98:2	92

[a] Isolated yield. [b] Diastereoselectivity was determined on the basis of HPLC analyses of the reaction mixture. [c] The *ee* of **8** was determined on the basis of HPLC analyses using a chiral DAICEL column.

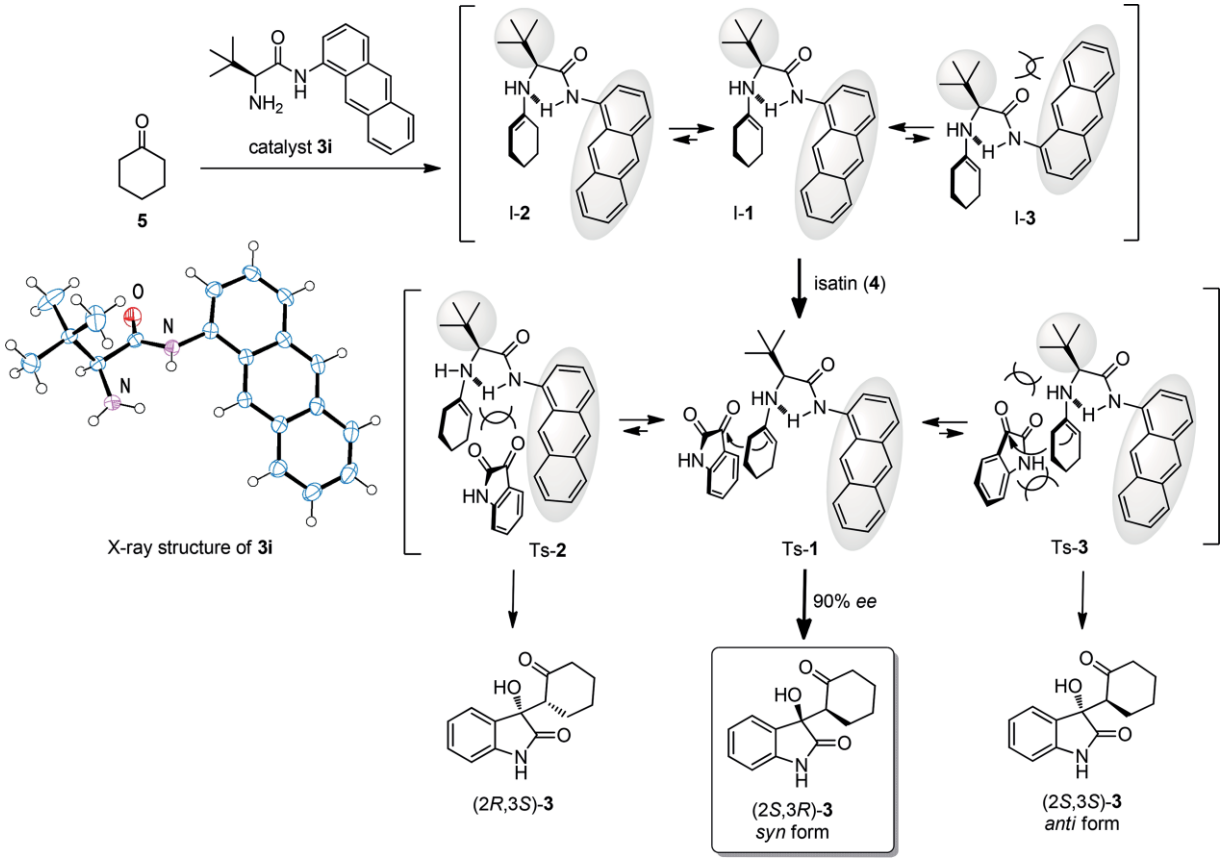
Table 4. Asymmetric aldol reactions of **4** with **9a**–**f** using organocatalyst **3i**.



Entry	9	R^1	R^2	10	Time [h]	Yield [%][a]	*syn*/*anti*[b]	*ee* [%][c]
1	**9a**	H	H	**10a**	72	97	–	12
2	**9b**			**10b**	96	55	83:17	32
3	**9c**			**10c**	144	54	97:3	63
4	**9d**			**10d**	144	99	95:5	58
5	**9e**			**10e**	168	92	98:2	75
6	**9f**			**10f**	144	94	93:7	53

[a] Isolated yield. [b] Diastereoselectivity was determined on the basis of HPLC analyses of the reaction mixture. [c] The *ee* of **10** was determined on the basis of HPLC using a DAICEL CHIRAL OJ-H column.

On the basis of the high enantiopurity (90 % *ee*) of optically active aldol product (2*S*,3*R*)-**6** obtained from the reaction of



Scheme 4. Plausible reaction course for **3i**-catalyzed aldol chemistry.

isatin (**4**) with cyclohexanone (**5**), a model of the enantioselective reaction course is proposed (Scheme 4). The condensation of catalyst **3i** with **5** forms the enamine intermediate, which is conformationally fixed by the H-bonding interaction between the enamine N-atom and the amide H-atom of the catalyst. The enamine intermediate may exist as I-**1** or I-**2**; both suffer from reduced steric interactions involving the α-position *tert*-butyl moiety and the catalyst-bourne 1-anthracenyl substituent than that for I-**3**. Furthermore, the more stable I-**1** has a *trans* configuration between the *tert*-butyl substituent at the α-position and the enamine olefin; I-**2** likely has a predominantly *cis* configuration involving these functional groups. The reaction may then proceed through transition state Ts-**1**, which has reduced steric interactions between intermediate I-**1** and isatin (**4**) than does Ts-**2**, which experiences more severe repulsive interactions between intermediate I-**1** and **4**. Furthermore, the *syn*/*anti* stereochemistry in this reaction may be dictated largely by steric interactions involving both the enamine element of the intermediate and isatin (**4**). Thus, Ts-**1**, which suffers from reduced repulsive steric interactions, is superior to Ts-**3**, which has larger repulsive interactions between I-**1** and **4**.

To better understand the proposed reaction course (Scheme 4), theoretical investigations were performed (Figures 1 and 2).

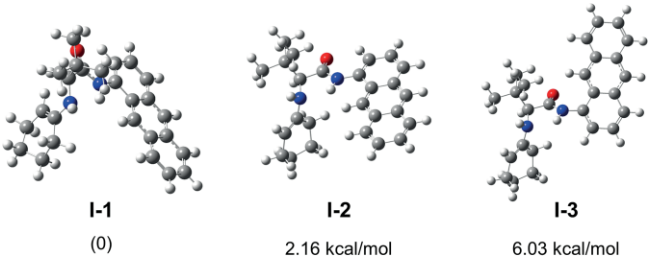


Figure 1. Structures and relative energies of intermediates I-**1**–**3** calculated at the B3LYP/6-311++G(d,2p)//B3LYP/6-31+G(d) levels of theory. Energy values are compared to the lowest-energy isomer I-**1**.

Based on the structure of catalyst **3i**, as determined by X-ray analysis, and conformational analyses for enamine intermediates I-**1**–**3**, I-**1** has been found to be the most stable of the intermediates formed in the reaction of **3i** with **5** (Figure 1).[9] Also, transition state Ts-**1** can be inferred on the basis of frontier molecular orbital energies of isomers I-**1**–**3** and isatin (**4**) (Figure 2). Thus, the success of **3i**-catalyzed stereoselective aldol reaction between **4** and **5** can be rationalized and was, in fact, suggested on the basis of these calculations and their support of the proposed reaction course (Scheme 4).

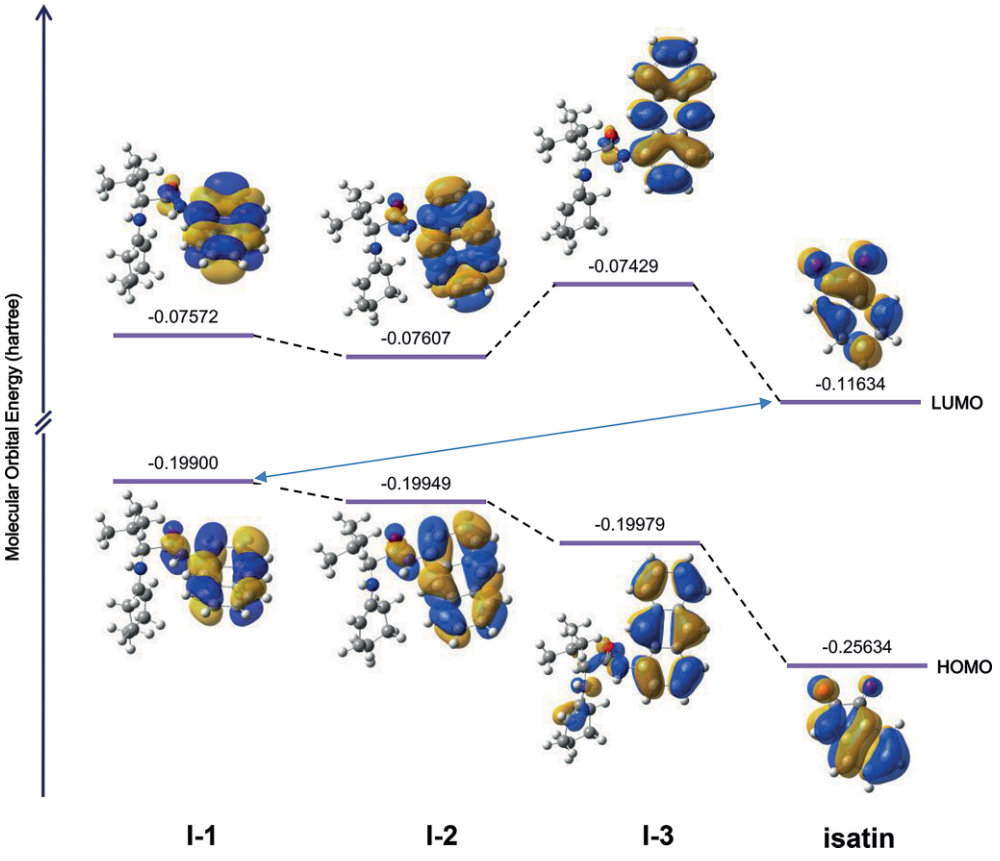


Figure 2. Frontier orbitals as calculated at the B3LYP/6-311++G(d,2p) level on 6-31+G(d)-optimized geometries.

Conclusions

We have developed a simple new amino amide organocatalyst **3i** with a bulky 1-anthracenyl substituent on the amide N-atom based on a new catalyst design concept. This catalyst is stable when exposed to air, and has the two significant features of easy preparation and desirable structural characteristics. Thus, it can be derived easily from the corresponding amino acid ester by two steps, and it contains both an amino group for transient enamine generation and a modifiable amide group that enables non-covalent conformational locking of the enamine intermediate within a single molecule. Furthermore, the bulkier 1-anthracenyl substituent on the amide N-atom in the catalyst makes possible high levels of enantioselectivity during aldol condensations. Thus, when **3i** was used in the asymmetric aldol reaction of several isatins with cyclic and acyclic ketones, one enantiotopic face of the enamine intermediate was effectively shielded by the amide-linked anthracenyl substituent; the corresponding aldol products were consequently generated in excellent chemical yields (up to 99 %) and stereoselectivities (up to 98 % *ee*, *syn*/*anti* = 99:1) under mild and environmentally friendly conditions. Moreover, catalyst **3i** is inexpensive relative to proline derivatives and other organocatalysts that have seen use in this reaction. Further studies, including alterations to the catalyst design and detailed mechanistic investigations using calculation methods, are currently in progress.

Experimental Section

General Methods: All glassware was used after flame drying, and reactions were performed under argon. Reactions were monitored by thin layer chromatography (TLC) and analysed by UV light (254 nm), iodine vapor, ninhydrin staining and anisaldehyde staining. TLC was performed on silica gel 60 F_{254} glass plates from Merck. Purifications of reaction products were carried out by flash chromatography on silica gel 60N (40–50 μm) from Kanto Chemical. Unless mentioned otherwise, all chemical reagents were used without further purification. NMR spectra were measured using a JEOL JNM-ECA500 instrument. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were measured in $CDCl_3$ or [D_6]DMSO as solvent and are given in terms of ppm from tetramethylsilane (δ = 0.00 ppm) or the residual solvents as an internal standard ([D_6]DMSO: δ = 2.50 ppm for ^{1}H NMR; $CDCl_3$: δ = 77.16 ppm for ^{13}C NMR). Multiplicity of chemical shifts are reported as s = singlet, d = doublet, t = triplet, q = quadruplet, dd = doublet of doublets, td = triplet of doublets, m = multiplet and br. = broad, and coupling constants *J* are given in Hz. Infrared (IR) spectra were measured using a JASCO FT/IR-4100 instrument. Optical rotations were measured using a JASCO DIP-360 instrument with EtOH as solvent. Melting points were measured using a Yanaco micro melting point apparatus. HRMS spectra were measured in EI mode using Hitachi RMG-6MG and JEOL-JNM-DX303 spectrometers. Diastereomeric ratios and enantiomeric excesses were determined by HPLC analyses using DAICEL CHIRALPAK AD-H, CHIRALPAK AS-H, CHIRALCEL OJ-H and CHIRALPAK IC columns.

General Procedure for the Synthesis of Amino Amide Organocatalysts 3a–k: To a stirred solution of amine **2a**–**g** (0.36 mmol) in

anhydrous CH_2Cl_2 (3 mL) at 0 °C, was added *N*-Boc acid **1a**–**e** (0.3 mmol), followed by sequential addition of EDC (64 μL, 0.36 mmol) and HOBt (49 mg, 0.36 mmol) at the same temperature and stirred for 1 h. Then, the reaction mixture was allowed to warm to room temperature for 24 h. After the reaction was complete, as determined by TLC, the reaction mixture was diluted with EtOAc and then washed with 0.1 N HCl, saturated $NaHCO_3$ solution and brine. The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. This crude reaction mixture was used for the next reaction without further purification. To the dilute reaction solution in dry CH_2Cl_2 was added TFA (0.4 mL) dropwise at 0 °C and the mixture then stirred at room temperature for 3 h. After removal of the CH_2Cl_2 under reduced pressure, the reaction mixture was neutralized by dropwise addition of a saturated $NaHCO_3$ solution at 0 °C and stirred at room temperature for 1 h. Finally, the reaction mass was extracted with CH_2Cl_2, the resulting organic layer then dried with Na_2SO_4 and the mixture concentrated under reduced pressure. The resulting residue was then purified by flash column chromatography on SiO_2 (CH_2Cl_2 and *n*-hexane/EtOAc = 3:1 to 1:1) to afford amino amide organocatalysts **3a**–**k**.

(*S*)-2-Amino-*N*-(naphthalen-1-yl)-3-methylbutanamide (3a): White crystals (EtOAc), 66 % yield. M.p. 77–78 °C. $[\alpha]_D^{25}$ = –29.99 (*c* = 0.12, EtOH). IR (neat): $\tilde{\nu}$ = 3246, 2958, 1649, 1530, 1499, 795 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 10.34 (br. s, 1 H, NH), 8.28–8.26 (dd, *J* = 7.73, 0.86 Hz, 1 H, ArH), 7.93–7.91 (d, *J* = 8.31 Hz, 1 H, ArH), 7.87–7.86 (m, 1 H, ArH), 7.65–7.64 (d, *J* = 8.31 Hz, 1 H, ArH), 7.55–7.47 (m, 3 H, ArH), 3.54–3.53 (d, *J* = 3.44 Hz, 1 H, CH), 2.59–2.50 (m, 1 H, CH), 1.63 (br. s, 2 H, NH_2), 1.11–1.10 (d, *J* = 6.87 Hz, 3 H, CH_3), 0.95–0.94 (d, *J* = 6.87 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.85, 134.17, 132.61, 128.93, 126.23, 126.20, 126.16, 126.14, 125.94, 124.66, 120.39, 118.14, 60.89, 30.89, 20.03, 16.09 ppm. MS (EI): *m/z* = 242 $[M + H]^+$. HRMS (EI): calcd. for $C_{15}H_{18}N_2O$ $[M + H]^+$ 242.1419, found 242.1410.

(*S*)-2-Amino-*N*-(biphenyl-2-yl)-3-methylbutanamide (3b): Colorless oil, 59 % yield. $[\alpha]_D^{24}$ = –14.59 (*c* = 1.03, EtOH). IR (neat): $\tilde{\nu}$ = 3276, 2959, 1675, 1512, 1447, 750, 700 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 9.58 (br. s, 1 H, NH), 8.44–8.42 (dd, *J* = 8.31, 1.15 Hz, 1 H, ArH), 7.48–7.36 (m, 6 H, ArH), 7.25 (d, *J* = 1.43 Hz, 1 H, ArH), 7.18–7.15 (td, *J* = 7.45, 1.15 Hz, 1 H, ArH), 3.29–3.28 (d, *J* = 3.44 Hz, 1 H, CH), 2.40–2.34 (m, 1 H, CH), 1.50 (br. s, 2 H, NH_2), 0.96–0.95 (d, *J* = 7.16 Hz, 3 H, CH_3), 0.79–0.78 (d, *J* = 6.87 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.72, 138.58, 135.03, 132.51, 130.15, 129.54, 128.84, 128.50, 127.80, 124.05, 120.82, 60.67, 30.86, 19.85, 15.97 ppm. MS(EI): *m/z* = 268 $[M + H]^+$. HRMS (EI): calcd. for $C_{17}H_{20}N_2O$ $[M + H]^+$ 268.1576, found 268.1567.

(*S*)-2-Amino-*N*-(anthracen-1-yl)-3-methylbutanamide (3c): Beige crystals (EtOAc), 72 % yield. M.p. 113–114 °C. $[\alpha]_D^{23}$ = –7.87 (*c* = 0.51, EtOH). IR (neat): $\tilde{\nu}$ = 3293, 2962, 1678, 1508, 869, 729, 705 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 10.51 (br. s, 1 H, NH), 8.42 (s, 2 H, ArH), 8.28–8.26 (d, *J* = 7.16 Hz, 1 H, ArH), 8.03–7.98 (m, 2 H, ArH), 7.80–7.78 (d, *J* = 8.31 Hz, 1 H, ArH), 7.49–7.44 (m, 3 H, ArH), 3.59–3.58 (d, *J* = 3.72 Hz, 1 H, CH), 2.62–2.55 (m, 1 H, CH), 1.75 (br. s, 2 H, NH_2), 1.14–1.13 (d, *J* = 7.16 Hz, 3 H, CH_3), 0.99–0.98 (d, *J* = 6.87 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.94, 132.28, 132.23, 131.57, 128.51, 128.08, 127.31, 125.83, 125.52, 125.44, 124.86, 118.94, 116.82, 60.98, 30.95, 20.05, 16.14 ppm. MS (EI): *m/z* = 292 $[M + H]^+$. HRMS (EI): calcd. for $C_{19}H_{20}N_2O$ $[M + H]^+$ 292.1576, found 292.1583.

(*S*)-2-Amino-*N*-(anthracen-2-yl)-3-methylbutanamide (3d): Beige crystals (EtOAc), 62 % yield. M.p. 202–203 °C. $[\alpha]_D^{24}$ = –75.12 (*c* = 1.03, EtOH). IR (neat): $\tilde{\nu}$ = 3249, 2957, 1650, 1512, 892, 736 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 9.75, (br. H, 1 H, NH), 8.54 (d, *J* = 1.43 Hz, 1 H, ArH), 8.37–8.36 (d, *J* = 6.59 Hz, 2 H, ArH), 7.98–7.96 (m, 3 H, ArH), 7.49–7.41 (m, 3 H, ArH), 3.46 (d, *J* = 3.72 Hz, 1 H, CH), 2.56–2.50 (m, 1 H, CH), 1.55 (br. s, 2 H, NH_2), 1.10–1.08 (d, *J* = 7.16 Hz, 3 H, CH_3), 0.93–0.92 (d, *J* = 7.16 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.06, 134.56, 132.30, 132.18, 131.18, 129.34, 129.30, 128.31, 128.10, 126.17, 125.83, 125.63, 125.07, 120.68, 115.07, 60.63, 30.89, 20.02, 16.11 ppm. MS (EI): *m/z* = 292 $[M + H]^+$. HRMS (EI): calcd. for $C_{19}H_{20}N_2O$ $[M + H]^+$ 292.1576, found 292.1580.

(*S*)-2-Amino-*N*-(anthracen-9-yl)-3-methylbutanamide (3e): Brown crystals (EtOAc), 50 % yield. M.p. 98–99 °C. $[\alpha]_D^{20}$ = +14.85 (*c* = 1.01, EtOH). IR (neat): $\tilde{\nu}$ = 3235, 2958, 1646, 1506, 1357, 877, 731 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 9.85, (br. s, 1 H, NH), 8.42 (s, 1 H, ArH), 8.02–8.00 (m, 4 H, ArH), 7.51–7.45 (m, 4 H, ArH), 3.71–3.70 (d, *J* = 3.44 Hz, 1 H, CH), 2.69–2.63 (m, 1 H, CH), 1.72 (br. s, 2 H, NH_2), 1.19–1.17 (d, *J* = 7.16 Hz, 3 H, CH_3), 1.13–1.12 (d, *J* = 6.87 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.17, 131.83, 128.77, 128.41, 128.07, 126.64, 126.21, 125.38, 123.45, 60.77, 30.78, 20.18, 16.45 ppm. MS (EI): *m/z* = 292 $[M + H]^+$. HRMS (EI): calcd. for $C_{19}H_{20}N_2O$ $[M + H]^+$ 292.1576, found 292.1581.

(*S*)-2-Amino-*N*-(pyren-1-yl)-3-methylbutanamide (3f): White crystals (EtOAc), 65 % yield. M.p. 168–169 °C. $[\alpha]_D^{22}$ = –15.00 (*c* = 2.00, EtOH). IR (neat): $\tilde{\nu}$ = 3251, 2954, 1641, 1515, 841, 711, 504 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 10.57 (br. s, 1 H, NH), 8.75–8.74 (d, *J* = 8.31 Hz, 1 H, ArH), 8.16–8.11 (m, 3 H, ArH), 8.06 (s, 2 H, ArH), 8.01–7.95 (m, 3 H, ArH), 3.60–3.59 (d, *J* = 3.44 Hz, 1 H, CH), 2.65–2.56 (m, 1 H, CH), 1.69 (br. s, 2 H, NH_2), 1.14–1.13 (d, *J* = 6.73 Hz, 3 H, CH_3), 1.00–0.99 (d, *J* = 6.87 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.01, 131.53, 130.95, 130.92, 128.38, 127.79, 127.55, 126.42, 126.17, 125.55, 125.37, 125.25, 124.96, 124.85, 122.02, 120.05, 119.98, 60.93, 30.97, 20.07, 16.18 ppm. MS (EI): *m/z* = 316 $[M + H]^+$. HRMS (EI): calcd. for $C_{21}H_{20}N_2O$ $[M + H]^+$ 316.1576, found 316.1573.

(*S*)-2-Amino-*N*-(pyren-4-yl)-3-methylbutanamide (3g): White crystals (EtOAc), 46 % yield. M.p. 168–169 °C. $[\alpha]_D^{20}$ = –6.66 (*c* = 0.30, EtOH). IR (neat): $\tilde{\nu}$ = 3252, 2957, 1650, 1522, 823, 714 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 10.67 (br. s, 1 H, NH), 9.02 (s, 1 H, ArH), 8.25–8.21 (m, 3 H, ArH), 8.14–7.98 (m, 5 H, ArH), 2.67–2.61 (m, 1 H, CH), 2.67–2.61 (m, 1 H, CH), 1.74 (br. s, 2 H, NH_2), 1.17–1.16 (d, *J* = 6.87 Hz, 3 H, CH_3), 1.02–1.01 (d, *J* = 7.16 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.23, 131.77, 131.30, 131.25, 130.86, 127.93, 127.25, 126.48, 125.80, 125.74, 125.62, 125.52, 125.24, 124.50, 122.37, 117.47, 117.30, 61.08, 30.95, 20.08, 16.17 ppm. MS (EI): *m/z* = 316 $[M + H]^+$. HRMS (EI): calcd. for $C_{21}H_{20}N_2O$ $[M + H]^+$ 316.1576, found 316.1572.

(*S*)-2-Amino-*N*-(anthracen-1-yl)propanamide (3h): Yellow crystals (EtOAc), 51 % yield. M.p. 141–142 °C. $[\alpha]_D^{21}$ = +29.99 (*c* = 0.60, EtOH). IR (neat): $\tilde{\nu}$ = 2961, 2925, 1524, 1261, 1098, 1026, 803, 721 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 10.49 (br. s, 1 H, NH), 8.44 (s, 2 H, ArH), 8.29–8.27 (d, *J* = 7.16 Hz, 1 H, ArH), 8.05–7.99 (m, 2 H, ArH), 7.81–7.79 (d, *J* = 8.59 Hz, 1 H, ArH), 7.50–7.45 (m, 3 H, ArH), 3.85–3.81 (m, 1 H, CH), 1.82 (br. s, 2 H, NH_2), 1.59–1.57 (d, *J* = 7.16 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.11, 132.27, 132.23, 131.58, 128.51, 128.10, 127.37, 125.86, 125.52, 125.38, 124.92, 118.87, 116.79, 51.83, 21.99 ppm. MS (EI): *m/z* = 264 $[M + H]^+$. HRMS (EI): calcd. for $C_{17}H_{16}N_2O$ $[M + H]^+$ 264.1263, found 264.1268.

(*S*)-2-Amino-*N*-(anthracen-1-yl)-3,3-dimethylbutanamide (3i): Beige crystals (EtOAc), 57 % yield. M.p. 145–147 °C. $[\alpha]_D^{20}$ = +80.00 (*c* = 1.00, EtOH). IR (neat): $\tilde{\nu}$ = 1670, 1495, 879, 729 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 10.07 (br. s, 1 H, NH), 8.44–8.41 (d, *J* = 13.46 Hz, 2 H, ArH), 8.25–8.24 (d, *J* = 7.16 Hz, 1 H, ArH), 8.04–7.99 (m, 2 H, ArH), 7.81–7.79 (d, *J* = 8.59 Hz, 1 H, ArH), 7.50–7.45 (m, 3

H, ArH), 3.49 (s, 1 H, CH), 1.77 (br. s, 2 H, NH_2), 1.19 [s, 9 H, $(CH_3)_3$] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.09, 132.23, 131.56, 128.52, 128.07, 127.30, 125.82, 125.81, 125.49, 125.47, 124.85, 118.94, 117.05, 65. 31, 34.66, 27.14 ppm. MS (EI): *m/z* = 306 $[M + H]^+$. HRMS (EI): calcd. for $C_{20}H_{22}N_2O$ $[M + H]^+$ 306.1732, found 306.1728.

(*S*)-2-Amino-*N*-(anthracen-1-yl)-2-phenylethanamide (3j): Brown crystals (EtOAc), 57 % yield. M.p. 52–53 °C. $[\alpha]_D^{22}$ = –11.50 (*c* = 2.00, EtOH). IR (neat): $\tilde{\nu}$ = 1685, 1509, 868, 727, 696 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 10.24 (br. s, 1 H, NH), 8.41 (s, 1 H, ArH), 8.32 (s, 1 H, ArH), 8.19–8.17 (d, *J* = 7.16 Hz, 1 H, ArH), 7.98–7.97 (m, 2 H, ArH), 7.79–7.77 (d, *J* = 8.31 Hz, 1 H, ArH), 7.57–7.34 (m, 8 H, ArH), 4.83 (s, 1 H, CH), 2.12 (br. s, 2 H, CH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.49, 140.90, 132.18, 132.00, 131.61, 131.60, 129.23, 128.50, 128.44, 128.09, 127.38, 127.16, 125.90, 125.48, 125.41, 125.27, 118.83, 117.36, 60.94 ppm. MS (EI): *m/z* = 326 $[M + H]^+$. HRMS (EI): calcd. for $C_{22}H_{18}N_2O$ $[M + H]^+$ 326.1419, found 326.1411.

(*S*)-2-Amino-*N*-(anthracen-1-yl)-3-phenylpropanamide (3k): Brown crystals (EtOAc), 60 % yield. M.p. 43–45 °C. $[\alpha]_D^{20}$ = +19.00 (*c* = 1.00, EtOH). IR (neat): $\tilde{\nu}$ = 3294, 2963, 1673, 1509, 1263, 869, 727, 699 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 10.32 (br. s, 1 H, NH), 8.43 (s, 1 H, ArH), 8.27–8.24 (m, 2 H, ArH), 8.00–7.97 (m, 2 H, ArH), 7.82–7.80 (d, *J* = 8.59 Hz, 1 H, ArH), 7.49–7.46 (m, 3 H, ArH), 7.37–7.27 (m, 5 H, ArH), 3.97–3.95 (m, 1 H, CH), 3.48–3.45 (dd, *J* = 14.03, 4.01 Hz, 1 H, CH_2), 3.02–2.98 (dd, *J* = 13.75, 9.16 Hz, 1 H, CH_2), 2.02 (br. H, 2 H, NH_2) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.78, 172.78, 137.73, 132.24, 132.17, 131.64, 131.58, 129.58, 129.04, 128.53, 128.10, 127.34, 127.19, 125.87, 125.85, 125.48, 125.16, 118.98, 117.24, 57.32, 40.95 ppm. MS (EI): *m/z* = 340 $[M + H]^+$. HRMS (EI): calcd. for $C_{23}H_{20}N_2O$ $[M + H]^+$ 340.1576, found 340.1583.

General Procedure for the Enantioselective Aldol Reaction of Isatins with Ketones: To a stirred solution of catalyst **3i** (0.015 mmol) in dry THF (2 mL) were added ketone (2 mmol) and isatin (0.1 mmol) at room temperature. The reaction mixture was stirred at this temperature and monitored by TLC until the reaction was completed. Then, THF was removed under reduced pressure. The concentrated reaction mixture was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc = 5:1 to 1:1) to give the corresponding product.

Acknowledgments

This research was partially supported by the Adaptable & Seamless Technology Transfer Program through Targetdriven R&D from the Japan Science and Technology Agency, JST (AS231Z01382G and AS221Z01186D), the Northern Advancement Center for Science & Technology and the Muroran Institute of Technology.

Keywords: Amino amide · Organocatalysis · Aldol reactions · Isatin · 3-Hydroxy-2-oxindole · Enantioselectivity

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[9] For details of the calculations, see the Supporting Information. The molecular structure of catalyst **3i** was confirmed by single-crystal X-ray crystallography, which showed the anthracene group in a *cis* orientation with respect to the amino group (NH_2) (shown in the Supporting Information, Figure S1).

Received: April 3, 2016
Published Online: ■

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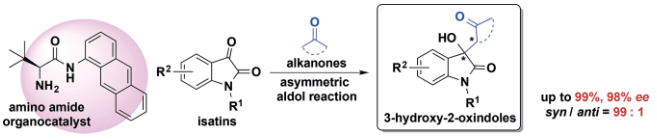

New simple primary amino amide organocatalysts display a high degree of activity in asymmetric aldol reactions between isatins and alkanones to afford optically active 3-hydroxy-2-oxindoles.

DOI: 10.1002/ejoc.201600414