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2-Azanorbornane-based amine organocatalyst for enantioselective aldol reaction of isatins with ketones

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ABSTRACT

Optically active 2-azanorbornane-based organocatalysts were designed and synthesized, and the catalytic activity of these catalysts in enantioselective aldol reactions of isatins with ketones was investigated. Among these catalysts, 2-azanorbornylmethanol showed the best catalytic activity to afford the corresponding aldol product in excellent chemical yield (up to 95%) and with moderate stereoselectivity (up to 64% ee, up to *syn*:*anti* = 36:64).

1. Introduction

The development of new optically active organocatalysts for their use in asymmetric synthesis has attracted considerable interest in the scientific community over the past 10 years. Excellent covalent and non-covalent organocatalysts have been developed in a wide range of reactions.[1] In recent years, we have developed various β-amino alcohols, which were utilized effectively as organocatalysts in different enantioselective reactions.[2] 2-Azanorbornane **1** with a cage type structure, could be synthesized from the Diels–Alder reaction of cyclopentadiene with chiral iminodienophiles, which could find use as excellent synthetic intermediates, for deriving various biologically active compounds.[3] 2-Azanorbornane-based cage compound **A**, with a bulky 2-azanorbornane backbone and an amino nitrogen atom in the cage structure for the formation of an enamine moiety as a covalent site, could be synthesized from compound **1** (Scheme 1). Furthermore, compound **A** has the side chain at the 3-position on the 2-azanorbornane backbone, which can show strong electronic and steric effects through the formation of a hydrogen bond with the substrate and through steric control for the stereoselective reaction course. Considering these structural characteristics, it is expected that this cage type compound **A** might show an efficient functionality as an organocatalyst. However, only a few studies of the asymmetric reactions using compound **A** as an organocatalyst have been reported.[3b,c] Furthermore, to the best of our knowledge, the use of an organocatalyst with a cage structure such as 2-azanorbornane has never been reported in aldol reactions except for the use of a cinchonidine–thiourea type catalyst.[3] For these reasons, we decided to explore the catalytic efficiency of 2-azanorbornane-based organocatalysts **B** in the aldol reaction of isatins with acyclic or cyclic ketones.[4] The aldol reaction of isatins with acyclic or cyclic ketones is a versatile reaction for affording chiral 3-hydroxyl-2-oxindoles containing a stereogenic quaternary carbon center at the 3-position, which are useful intermediates for the synthesis of various biologically active compounds and pharmaceuticals.[5] We hypothesized that the designed organocatalyst **B** having steric and electric control elements on both the 2-azabicyclo[2.2.1]octane backbone and at the side chain, could effectively control the stereoselective reaction course in the transition state **X** of this reaction (Scheme 2). Thus, the enamine intermediate, which is formed from the condensation of catalyst **B** with acyclic or cyclic ketones, could be fixed by both the hydrogen bonding of the nitrogen atom in the enamine part with the hydrogen atom of hydroxyl group on the side chain, and the two sterically bulky phenyl groups on the side chain. The enamine moiety might selectively attack the isatins to afford the corresponding aldol product in good chemical yield and stereoselectivity (Scheme 2).

Herein we report that the prepared 2-azanorbornane-based organocatalysts showed asymmetric catalytic activity in the aldol reactions of isatins with acyclic or cyclic ketones to afford the corresponding aldol products in excellent chemical yield (up to 95%) and with moderate stereoselectivity (up to 64% ee, up to *syn*:*anti* = 36:64).

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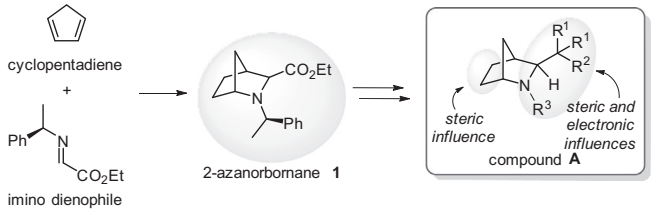
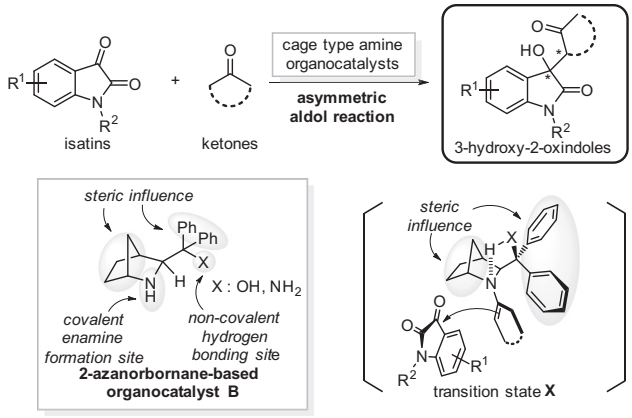


Scheme 1. Functional of 2-azanorbornanes.

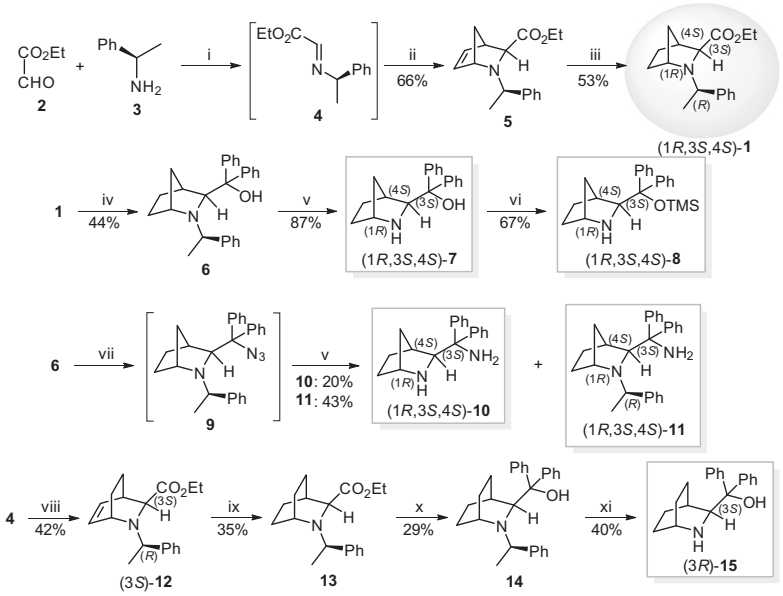


Scheme 2. Concept of catalyst design.

2. Results and discussion

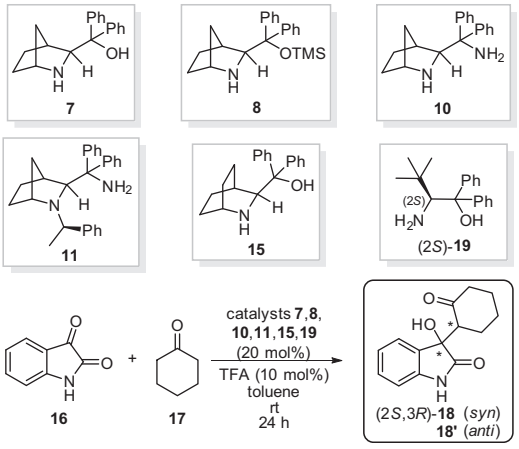
Cage type amine organocatalysts **7**, **8**, **10**, **11** and **15** with 2-azanorbornane or isoquinuclidine backbones were prepared as follows (Scheme 3).[1,6] First, our previously reported 2-azanorbornylmethanol **5** with a diphenyl methanol moiety in the side chain was synthesized by the Diels–Alder reaction of cyclopentadiene with chiral imino dienophile **4**, which was obtained by the condensation of aldehyde **2** with chiral amine **3**. The catalytic hydrogenation of Diels–Alder adduct **5** gave hydrogenated compound **1**. The Grignard reaction of the obtained product **1** with phenyl magnesium bromide, followed by catalytic hydrogenolysis with palladium hydroxide afforded the desired compound **7** in good yield. 2-Azanorbornyltrimethylsilyldiphenylether **8** with a trimethylsilyl (TMS) protected hydroxyl group was obtained by the protection of **7** with TMSOTf in moderate yield. 2-Azanorbornyldiphenylamines **10** and **11** bearing a primary amino group in the side chain were prepared as a separable mixture from the reaction of **6** with NaN_3, followed by catalytic hydrogenolysis of **9** with palladium hydroxide. Isoquinuclidine-based catalyst **15** with a 2-azabicyclo [2.2.2]octane ring system was also synthesized via the same route as **7** using the Diels–Alder reaction of cyclohexadiene with **4**, catalytic hydrogenation of **12**, Grignard reaction of **13** with phenyl magnesium bromide, followed by the catalytic hydrogenolysis of **14** with palladium hydroxide sequence in a moderate yield.

Initially, we examined the aldol reaction of isatin **16** with cyclohexanone **17** using the synthesized cage type amine organocatalysts **7**, **8**, **10**, **11** and **15** (20 mol %) in the presence of trifluoroacetic acid (TFA) (10 mol %) as a co-catalyst at room temperature for 24 h (Table 1). All of the catalysts showed asymmetric catalytic activities (7–38% ee) and the corresponding aldol products, **18** (*syn*) and **18′** (*anti*), were obtained in low to good chemical yields (10–84%) and with low to moderate diastereoselectivities (*syn*:*anti* = 48:52–86:14). The absolute configuration and *syn*:*anti* stereoselectivity of the aldol products, **18** and **18′**, were determined by comparison with the literature data.[4c,4g,4j,4r,4u] The reaction using catalyst **7** with diphenyl hydroxyl group afforded the product **18** in good chemical yield and enantioselectivity (84%, 38% ee, entry 1). On the other hand, the use of catalyst **8**, in which the hydroxyl group was protected by a TMS group, gave the product **18′** in low chemical yield and enantioselectivity (10%, 24% ee, entry 2). These results indicate that the presence of a free hydroxyl group at the side chain in the catalyst might be necessary to realize satisfactory results. Although catalyst **10** with a diphenyl amino group as a hydrogen bonding site gave the corresponding product **18′** in moderate chemical yield and diastereoselectivity (46%, *syn*:*anti* = 62:38), the enantioselectivity was low (18% ee) (entry 3). The use of catalyst **11** with a primary



Scheme 3. Preparations of cage type organocatalysts **7**, **8**, **10**, **11**, **15**. Reagents. (i) MS 4 Å, CH_2Cl_2, 0 °C, 1 h; (ii) cyclopentadiene, CF_3CO_2H, $BF_3{\cdot}Et_2O$, −50 °C to rt, 16 h; (iii) H_2, 10% Pd–C, EtOAc, rt, 24 h; (iv) PhMgBr, THF, 0 °C to rt, 24 h; (v) H_2, 20% $Pd(OH)_2$, EtOAc, 45 °C, 48 h; (vi) TMSOTf, Et_3N, CH_2Cl_2, −30 °C to rt, 24 h; (vii) NaN_3, H_2SO_4, toluene, rt, 2 h; (viii) cyclohexadiene, CF_3CO_2H, $BF_3{\cdot}Et_2O$, −78 °C to rt, 16 h; (ix) H_2, 10% Pd–C, EtOAc, rt, 12 h; (x) PhMgBr, 1,4-dioxane, reflux, 24 h; (xi) H_2, 20% $Pd(OH)_2$, EtOAc, 45 °C, 72 h.

Table 1
Enantioselective aldol reaction of **16** with **17** using organocatalysts **7**, **8**, **10**, **11**, **15** and **19**



Entry	Cat.	Yield (%)[a]	*syn*:*anti*[b]	ee (%)[c]	
				18	**18′**
1	**7**	84	40:60	38	30
2	**8**	10	54:46	10	24
3	**10**	46	62:38	*Racemic*	18
4	**11**	12	86:14	17	20
5	**15**	39	44:56	19	33
6	**19**	17	48:52	7	22

[a] Isolated yield.
[b] Diastereoselectivity was determined by HPLC of the reaction mixture.
[c] The ee of the isomer was determined by HPLC using CHIRALCEL OJ-H column.

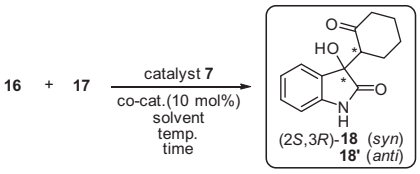
amino group as an enamine formation site at the side chain afforded product **18′** in low chemical yield and enantioselectivity (12%, 20% ee, entry 4). In addition, the catalytic activity of **15** with a 2-azabicyclo[2.2.2]octane ring system was also examined (entry 5). However, the catalyst **15** did not show better catalytic activity than that of catalyst **7** having 2-azabicyclo[2.2.1]heptane ring system. Similarly, the simple β-amino alcohol catalyst **19** was also not effective in this reaction (entry 6). From these results, it was indicated that the use of catalyst **7** bearing diphenyl hydroxyl group as the substituent group on the side chain is effective for this reaction to obtain the aldol product in satisfactory chemical yield and stereoselectivity.

In order to optimize the reaction conditions using superior 2-azanorbornylmethanol organocatalyst **7**, we next examined the effect of the solvent, the molar ratio of catalyst, co-catalyst, the reaction temperature and the reaction time (entries 1–24, Table 2). From the results, it can be seen that the aldol products **18** and **18′** were obtained in good chemical yield (84%) and with moderate diastereoselectivity (*syn*/*anti* = 40:60) and enantioselectivity (38% ee), when the reaction was carried out in toluene by using 20 mol % of catalyst **7** and 10 mol % of TFA as co-catalyst at room temperature for 24 h (Table 2, entry 16).

After optimizing the reaction conditions, we investigated the generality of the reaction of isatins **20a–i** with different substitution patterns and electronic properties with cyclohexanone **17** using catalyst **7** under the best reaction conditions (entries 1–9, Table 3).[4c,j,7] As can be seen from the results, they all afforded the corresponding aldol products **21a–i** (*syn*) and **21′a–i** (*anti*), although the products were obtained as a mixture of *syn*/*anti* diastereomers (*syn*:*anti* = 42:58–43:57). The reaction using synthetically useful *N*-Me-isatin **20a**[5] afforded the aldol product **21a** in good chemical yield and enantioselectivity (86%, 64% ee), although it took a long reaction time (entry 1). The use of *N*-benzyl-**20b** and *N*-allyl-**20c** isatins also gave the aldol products **21′b** and **21c** in moderate chemical yields (**21′b**: 54%, **21c**: 62%) and enantioselectivities (**21′b**: 49% ee, **21c**: 47% ee), respectively, but *syn*:*anti* diastereoselectivity was poor (*syn*:*anti* = 50:50) (entries 2, 3). However, the same reaction using *N*-Boc-isatin **20d** did not proceed, although the reason for this was not clear (entry 4). Isatin **20e** bearing electron donating methyl group on aromatic ring afforded the product **21e** in moderate chemical yield and enantioselectivity (32%, 30% ee, entry 5). Isatins **20f–h** bearing halogen atoms on the aromatic ring also afforded the corresponding products **21′f–h**, respectively, in good chemical yields and enantioselectivities (64–79%, 35–39% ee, entries 6–8). The reaction of isatin **20i** bearing a strong electron withdrawing NO_2 group on the aromatic ring also afforded product **21i** in moderate chemical yield and enantioselectivity (40%, 44% ee, entry 9). These results showed the catalytic activity of **7** to the aldol reaction of different substituted isatins.

Next, we examined the scope of the aldol reaction of isatin **16** with several acyclic or cyclic ketones **22a–f** using catalyst **7** under the same reaction conditions (entries 1–6, Table 4). The reaction with acetone **22a** afforded the corresponding aldol product **23a** with moderate chemical yield and poor enantioselectivity (43%, 13% ee, entry 1).[4c,b,g,k,m,n,r,s,u] The use of cyclopentanone **22b** gave the aldol product **23′b** in good chemical yield (74%) with moderate enantioselectivities (43% ee) and moderate diastereoselectivity (*syn*:*anti* = 36:63) (entry 2).[4c,7] Although bulkier cycloheptanone **22c** provided the product **23′c** with moderate enantioselectivity (46% ee), the reaction hardly proceeded (8%) (entry 3). The use of heterocyclic ketones **22d–f** also afforded the corresponding products, **23′d**,**e** and **23f**, respectively, but the *syn*:*anti* stereoselectivity was poor (entries 4–6). The reaction using tetrahydropyran-4-one **22d** afforded product **23′d** with moderate chemical yield and low enantioselectivity (37%, 14% ee, entry 4).[4c] Although, tetrahydrothipyran-4-one **22e** furnished product **23′e** with good chemical yield (82%), the enantioselectivity was low (23% ee, entry 5).[4c] The reaction with piperidin-4-one **22f** led to an

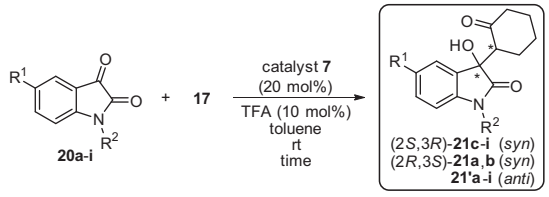
Table 2
Optimization of the reaction conditions of **16** with **17** using organocatalyst **7**



Entry	Solvent	Cat. (mol %)	Temp (°C)	Time (h)	Co-cat.	Yield (%)[a]	*syn*:*anti*[b]	ee (%)[c]	
								18	**18′**
1	DMF	20	rt	24	–	39	49:51	12	1
2	MeCN	20	rt	24	–	51	46:54	15	23
3	CH_2Cl_2	20	rt	24	–	56	35:65	32	25
4	Et^2O	20	rt	24	–	79	39:61	32	32
5	THF	20	rt	24	–	73	40:60	28	26
6	1,4-Dioxane	20	rt	24	–	44	42:58	28	26
7	Toluene	20	rt	24	–	84	37:63	35	32
8	Benzene	20	rt	24	–	83	39:61	30	30
9	MeOH	20	rt	24	–	95	52:48	5	9
10	Water	20	rt	24	–	84	41:59	20	22
11	Sea water	20	rt	24	–	86	42:58	18	30
12	Distilled water	20	rt	24	–	84	42:58	17	17
13	Toluene	15	rt	24	–	84	37:63	33	31
14	Toluene	10	rt	24	–	74	37:63	33	31
15	Toluene	5	rt	24	–	27	37:63	30	30
16	Toluene	20	rt	24	TFA	84	40:60	38	30
17	Toluene	20	rt	24	TCA	36	47:53	35	34
18	Toluene	20	rt	24	TfOH	84	58:42	19	20
19	Toluene	20	rt	24	Formic acid	38	43:57	36	35
20	Toluene	20	rt	24	Benzoic acid	42	39:61	29	32
21	Toluene	20	rt	24	Acetic acid	49	44:56	24	31
22	Toluene	20	rt	24	*p*-TsOH	64	49:51	37	33
23	Toluene	20	0	24	TFA	82	47:53	36	33
24	Toluene	20	rt	12	TFA	29	50:50	36	30

[a] Isolated yield.
[b] Diastereoselectivity was determined by HPLC.
[c] The ee of the isomer was determined by HPLC using CHIRALCEL OJ-H column.

Table 3
Enantioselective aldol reactions of **20a–I** with **17** using organocatalyst **7**



Entry	**20**	R^1	R^2	**21**	Time (h)	Yield (%)[a]	*syn*:*anti*[b]	ee (%)[c]		
								21c–i	**21a,b**	**21′a–i**
1	**20a**	H	Me	**21a**	120	86	43:57		64	32
2	**20b**	H	Bn	**21b**	120	54	50:50		24	49
3	**20c**	H	Allyl	**21c**	120	62	50:50	47		25
4	**20d**	H	Boc	**21d**	120	–	–	–		–
5	**20e**	Me	H	**21e**	24	32	56:44	30		22
6	**20f**	F	H	**21f**	24	79	42:58	32		35
7	**20g**	Cl	H	**21g**	24	64	45:55	31		39
8	**20h**	Br	H	**21h**	24	71	49:51	28		35
9	**20i**	NO_2	H	**21i**	24	40	52:48	44		22

[a] Isolated yield.
[b] Diastereoselectivity was determined by HPLC of the reaction mixture.
[c] The ee of isomer was determined by HPLC using DAICEL CHIRAL column.

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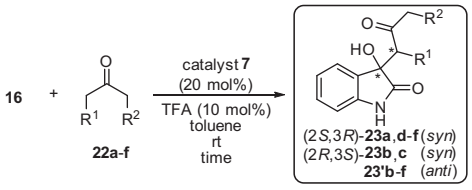
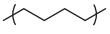
Table 4
Enantioselective aldol reactions of **16** with **22a–f** using organocatalyst **7**



Entry	22	R^1	R^2	23	Time (h)	Yield (%)[a]	*syn*:*anti*[b]	ee (%)[c]		
								23a,d–f	**23b,c**	**23′b–f**
1	**22a**	H	H	**23a**	72	43	—	13		
2	**22b**			**23b**	48	74	36:64		16	43
3	**22c**			**23c**	144	8	38:62		24	46
4	**22d**			**23d**	72	37	55:45	5		14
5	**22e**			**23e**	48	82	57:43	20		23
6	**22f**			**23f**	24	91	55:45	37		5

[a] Isolated yield.
[b] Diastereoselectivity was determined by HPLC of the reaction mixture.
[c] The ee of isomer was determined by HPLC using DAICEL CHIRAL column.

increase in both the chemical yield (91%) and the enantioselectivity (37% ee) (entry 6).[4c]

Unfortunately, although satisfactory enantioselectivities and *syn*:*anti* diastereoselectivities were not observed in this reaction using a cage type organocatalyst, a model of the enantioselective reaction course was proposed based on the observed enantiopurity (38% ee, entry 16, Table 1) of chiral aldol product (2*S*,3*R*)-**18**, which was obtained from the reaction of **16** with **17**, as follows (Scheme 4). The combination of catalyst **7**, cyclohexanone **17** and TFA forms an enamine intermediate **I**. The conformation of intermediate **I** is fixed by the hydrogen bonding interaction between the amine nitrogen atom at the enamine part and the hydroxyl hydrogen atom at the side chain, and it might exist as intermediate **I-1**, which has less steric interaction between the cage structure and the methylene part in the cyclohexene ring at the enamine part than that of **I-2**. The reaction could then proceed through transition state **Ts-1** in **Ts-A**, which has a smaller steric interaction between intermediate **I-1** and isatin **16** than **Ts-2**, which could experience a more severe repulsive interaction between intermediate **I-1** and **16**. Furthermore, the *syn*:*anti* stereochemistry in the reaction might depend on the steric interaction between 2-azanorbornane ring system in **I-1** and **16**. Thus, **Ts-1** (*syn*) has less steric interaction between the 2-azanorbornane ring system and **16**, rather than through **Ts-3** (*anti*), which has greater steric interaction between **I-1** and **16**. Furthermore, considering the results that the use of bulkier *N*-methylisatin **20a** afforded the product **21a** (*syn*) with the best enantioselectivity (64% ee, entry 1, Table 3) in all reactions, the reaction could proceed through the **Ts-4** in **Ts-B**, which has less steric interaction between both the cage structure and the methylene parts in the enamine intermediate and isatin **21a**, rather than that of **Ts-1′**, **Ts-2′** and **Ts-3′**.

3. Conclusion

In conclusion, we have reported on the first example of the enantioselective aldol reaction of isatins with acyclic or cyclic ketones using 2-azanorbornane-based amines **7**, **8**, **10**, **11** and **15** as organocatalysts. Among all of these catalysts, 2-azanorbornanemethanol **7** provided the corresponding aldol products in excellent chemical yields (up to 95%) and with moderate stereoselectivities (up to 64% ee, *syn*:*anti* = 36:64). Further studies, including catalyst design modifications to improve the stereoselectivity and mechanistic investigations are in progress.

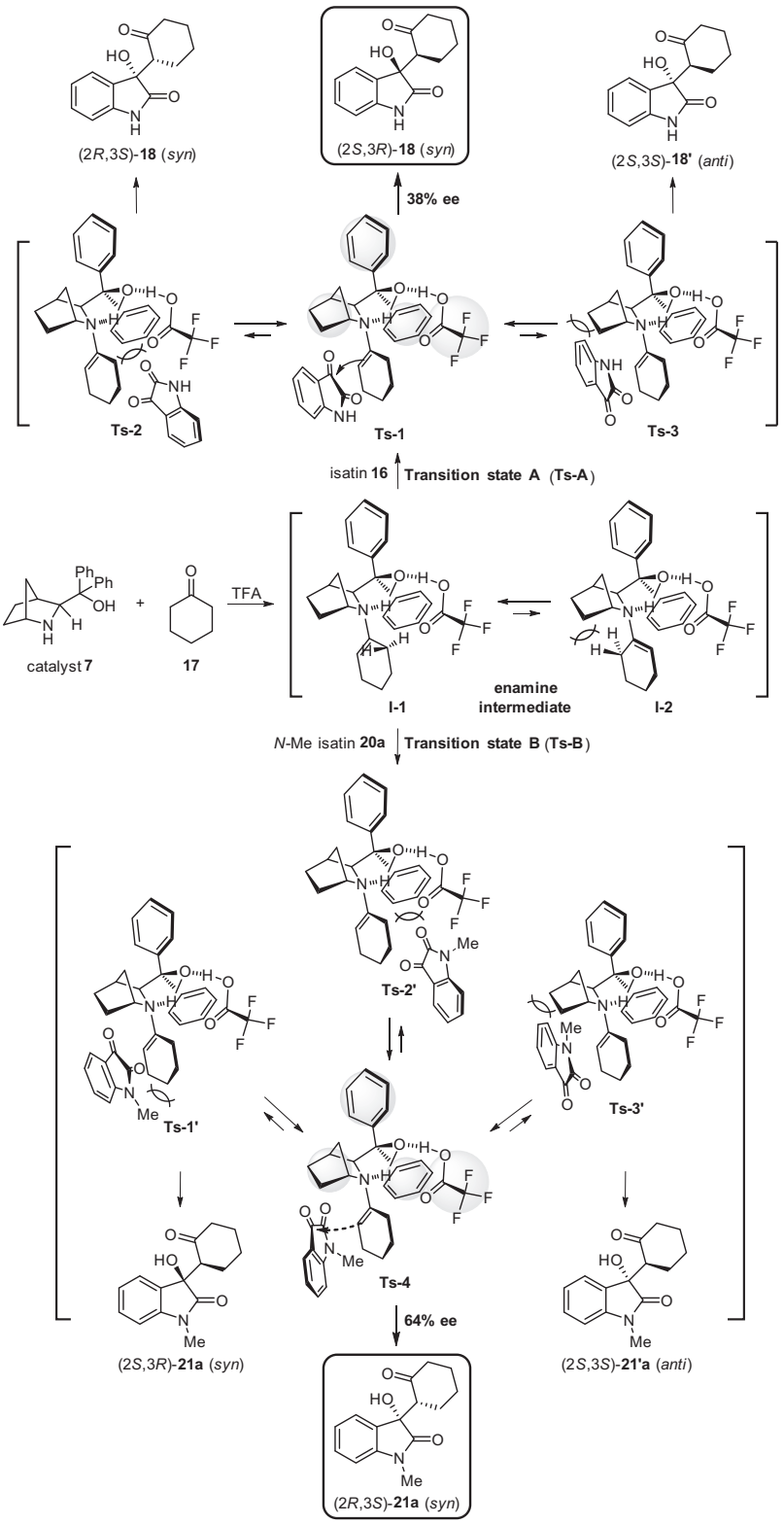
4. Experimental

4.1. General

All commercial reagents were purchased and used without further purification. All reactions were carried out under argon in flame-dried glassware with magnetic stirring. Thin layer chromatography was performed on silica gel 60 F_{254}, and then detected by using UV light (254 nm) and iodine vapor. Column chromatography was carried out on silica gel 60 N (40–100 μm), and preparative TLC was carried out on silica gel 60 F_{254}. Infrared (IR) spectra were measured with a FT/IR spectrophotometer (JASCO FT/IR-400). Melting points were measured using a micro melting point apparatus. NMR spectra were measured using a JEOL JNM-ECA500. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were measured in $CDCl_3$ and DMSO-d_6 as solvent and given in ppm from tetramethylsilane (0.0 ppm) or the residual solvents as a internal standard (DMSO-d_6; 2.50 ppm from ^{1}H NMR, $CDCl_3$; 77.16 ppm from ^{13}C NMR). Multiplicity of chemical shift are reported as s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet and br = broad and coupling constants *J* are given in Hz. Diastereo ratio and enantiomeric excess were determined by high performance liquid chromatography (HPLC) with DAICEL CHIRALPAK AD-H, CHIRALPAK AS-H, CHIRALPAK IC and CHIRALCEL OJ-H.

4.2. (1*R*,3*S*,4*S*)-2-Azabicyclo[2.2.1]heptane-3-*exo*-diphenyl(trimethylsilyoxy)methane 8

To the solution of **7** (0.101 g, 0.4 mmol) in dry CH_2Cl_2 (6 mL) were added trimethylsilyl triflate (0.1 mL, 0.48 mmol) and Et_3N



Scheme 4. Plausible reaction course.

(0.7 mL, 0.48 mmol) simultaneously at −30 °C for 10 min under argon. The solution was stirred at room temperature for 24 h and quenched with H_2O. The resulting mixture was extracted with $CHCl_3$ (3 × 10 mL), and the combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was then removed under reduced pressure and the residue was purified by flash chromatography on silica gel (EtOAc) to give **8** (0.09 g, 67%) as a white solid; mp 180–181 °C (ether/*n*-hexane). $[\alpha]_D^{20}$ = +24.5 (*c* 1.06, $CHCl_3$). IR (neat) cm^{-1}: 3030, 1383, 1226. ^1H NMR ($CDCl_3$, 500 MHz) δ: 7.41–7.32 (m, 8H), 7.27–7.26 (m, 2H), 4.26 (s, 1H), 4.03 (s, 1H), 2.61 (s, 1H), 2.16–2.13 (m, 1H), 1.79–1.72 (m, 3H), 1.21 (d, *J* = 11.7 Hz, 1H), 0.98 (d, *J* = 11.7 Hz, 1H), −0.11 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 141.9, 141.5, 128.8, 128.7, 128.4, 128.3, 81.4, 70.4, 58.5, 39.9, 35.2, 28.7, 25.6, 1.71. Ms *m*/*z*: 351

[M+H]. HRMS (EI) calcd for ($C_{22}H_{29}NOSi$): 351.2018, found: 351.2022.

4.3. General procedure for the synthesis of cage type organocatalysts 10 and 11

To a solution of NaN_3 (0.456 g, 7 mmol) in toluene (14 mL) was added concentrated sulfuric acid (0.38 mL, 7 mmol) dropwise for 10 min, after which the mixture was stirred for 15 min at room temperature. To this mixture, a solution of **7** (0.369 g, 1 mmol) in toluene (15 mL) was added via syringe at ice-cold temperature and the resulting mixture was stirred vigorously for 2 h at room temperature. The reaction mixture was quenched with a saturated $NaHCO_3$ solution, and then organic layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to give **9**. A solution of **9** (0.323 g, 0.8 mmol) and $Pd(OH)_2$ (0.2 g) in EtOAc (25 mL) was stirred under a hydrogen atmosphere at 45 °C for 48 h. After removal of the catalyst by filtration, the filtrate was concentrated in vacuo and residue was purified by flash chromatography on silica gel (MeOH:$CHCl_3$ = 1:7) to give **10** and **11**.

4.3.1. (1*R*,3*S*,4*S*)-2-Azabicyclo[2.2.1]heptane-3-*exo*-diphenylmethylamine 10

White solid; mp 148–149 °C (ether/*n*-hexane). $[\alpha]_D^{20}$ = +39.1 (*c* 0.23, $CHCl_3$); IR (neat) cm^{-1}: 1596, 1473. ^1H NMR ($CDCl_3$, 500 MHz) δ: 7.49–7.42 (m, 4H), 3.97 (s, 1H), 3.45 (s, 1H), 2.40 (s, 1H), 1.68–1.57 (m, 3H), 1.50 (d, *J* = 10.6 Hz, 1H), 1.24 (s, 1H), 1.10 (d, *J* = 10.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 128.6, 128.5, 127.1, 126.9, 126.8, 77.4, 77.1, 68.2, 63.0, 57.1, 38.8, 35.8, 30.8. Ms *m*/*z*: 278 [M+H]. HRMS (EI) calcd for ($C_{19}H_{22}N_2$): 278.1783, found: 278.1788.

4.3.2. (1*R*,3*S*,4*S*)-2-[(*R*)-1-Phenylethyl]-2-azabicyclo[2.2.1]heptane-3-*exo*-diphenylmethyl amine 11

White solid; mp 163–164 °C (ether/*n*-hexane). $[\alpha]_D^{22}$ = +90.9 (*c* 0.11, $CHCl_3$); IR (neat) cm^{-1}: 1596, 1190. ^1H NMR ($CDCl_3$, 500 MHz) δ: 7.61–7.58 (m, 4H), 7.31–7.26 (m, 3H), 7.23–7.14 (m, 7H), 7.04–7.01 (m, 1H), 3.77 (s, 1H), 3.05 (s, 1H), 2.93 (q, *J* = 7.2 Hz, 1H), 2.43 (s, 1H), 1.98–1.92 (m, 1H), 1.68–1.60 (m, 3H), 1.43–1.34 (m, 1H), 1.18 (d, *J* = 7.2 Hz, 3H), 0.85 (d, *J* = 9.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 128.2, 128.1, 128.0, 127.9, 127.8, 126.4, 126.3, 126.2, 126.1, 125.9, 69.9, 63.6, 55.7, 55.2, 42.1, 39.1, 32.4, 30.8, 29.7, 13.8 Ms *m*/*z*: 382 [M+H]. HRMS (EI) calcd for ($C_{27}H_{30}N_2$): 382.2409, found: 382.2413.

4.4. General procedure for the enantioselective aldol reaction of isatins with ketones

To a stirred solution of catalyst **7** (0.02 mmol) in dry toluene (0.2 mL) were added ketone (2 mmol), TFA (0.01 mmol) and isatin (0.1 mmol) simultaneously at room temperature. The reaction mixture was stirred at this temperature for the appropriate time and then quenched with H_2O. Toluene was then removed under reduced pressure, and the residue was extracted with EtOAc (3 × 2 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel (*n*-hexane:EtOAc = 2:3) to give the corresponding aldol products.

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