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Inherently chiral calix[4]arene-based bifunctional organocatalysts for enantioselective aldol reactions

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ABSTRACT

Two optical pure *m*-dimethylamino substituted inherently chiral calix[4]arene derivatives **8a** and **8b** bearing an L-prolinamido group have been synthesized by two routes, and structurally studied by the usual spectroscopic methods and X-ray crystallographic analysis. It was found that both of **8a** and **8b** could be utilized as bifunctional organocatalysts to efficiently promote the aldol reactions between aromatic aldehydes and ketones in the presence of acetic acid. Especially, with **8a** as the catalyst, the reaction between 4-nitrobenzaldehyde and cyclopentanone at −20 °C gave the *anti*-aldol product up to 94% ee, while the *anti*-aldol product in up to 94:6 dr and 79% ee was obtained when 4-cyanobenzaldehyde was used as the aldol donor. Moreover, it was also demonstrated that the inherently chiral calixarene skeleton with (*cS*)-conformation in **8a** was identified as the matched configuration of the stereogenic elements, and the inherently chiral moiety might play an important role in helping to stereocontrol the reaction.

1. Introduction

Inherently chiral calixarenes[1] are a class of representative chiral macrocyclic compounds whose chiralities originate from the asymmetric array of achiral subunits on the calixarene skeleton. Since, Gutsche and No[2] reported the first example of inherently chiral calix[4]arene in 1982, there has been increasing interest in the synthesis of inherently chiral calixarenes for their unique structures and potential applications in chiral recognition and asymmetric catalysis. Consequently, some approaches to synthesis of inherently chiral calix[4]arenes have been developed during the past two decades.[1] However, there still has been short of effective optical resolution approaches to optical pure inherently chiral calixarenes, which thus impeded their practical applications.[3] As a result, only two reports on asymmetric catalysis of inherently chiral calixarenes with low efficiencies have been hitherto reported.[4]

In recent years, we[5] and other groups[6] have developed an effective approach to enantiopure inherently chiral calixarene derivatives by introduction of a chiral auxiliary and then separation of subsequent diastereomers via column chromatography on silica gel, preparative TLC, or even simple crystallization. More recently, we reported a more convenient approach[7] to the enantiopure *meta*-substituted inherently chiral calix[4]arenes based on the dual functions of Boc-L-proline auxiliary, and also found[8] that Boc-L-proline could be used as the chiral acylating reagent for kinetic resolution of the racemic *meta*-substituted aminocalix[4]arenes. These approaches allow the convenient gram-scale synthesis of the optical pure inherently chiral calixarenes, which provides the basis for the further research on the practical applications of inherently chiral calixarenes in such as asymmetric catalysis.

In the past decade, a great deal of attention has been devoted to the possibility of developing enantioselective catalytic processes with high levels of chemical efficiency and stereocontrol promoted not by organometallic species but by wholly organic molecules,[9] which have shown their synthetic usefulness in enantioselective C–C as well as heteroatom–C bond formation. In both types of transformations, proline[10] has shown its versatility as catalyst, its use being especially successful in the enantioselective direct aldol reaction since the pioneering work by List and co-workers.[11] Since then, its several derivatives,[12] especially L-prolinamides,[13] derived from L-proline and different building block amines appearing promising for catalyst design, have been synthesized and applied for highly enantioselective direct aldol reactions. Promoted by Najera's[13a,b] work that axially chiral 2,2′-diamino-1,1′-binaphthalene-based bifunctional catalysts were recently developed for the promotion of the enantioselective aldol reaction, we herein report the synthesis of two enantiopure *meta*-substituted inherently chiral calixarenes bearing proline moiety, and their applications as novel bifunctional organocatalysts in the enantioselective direct aldol reaction.

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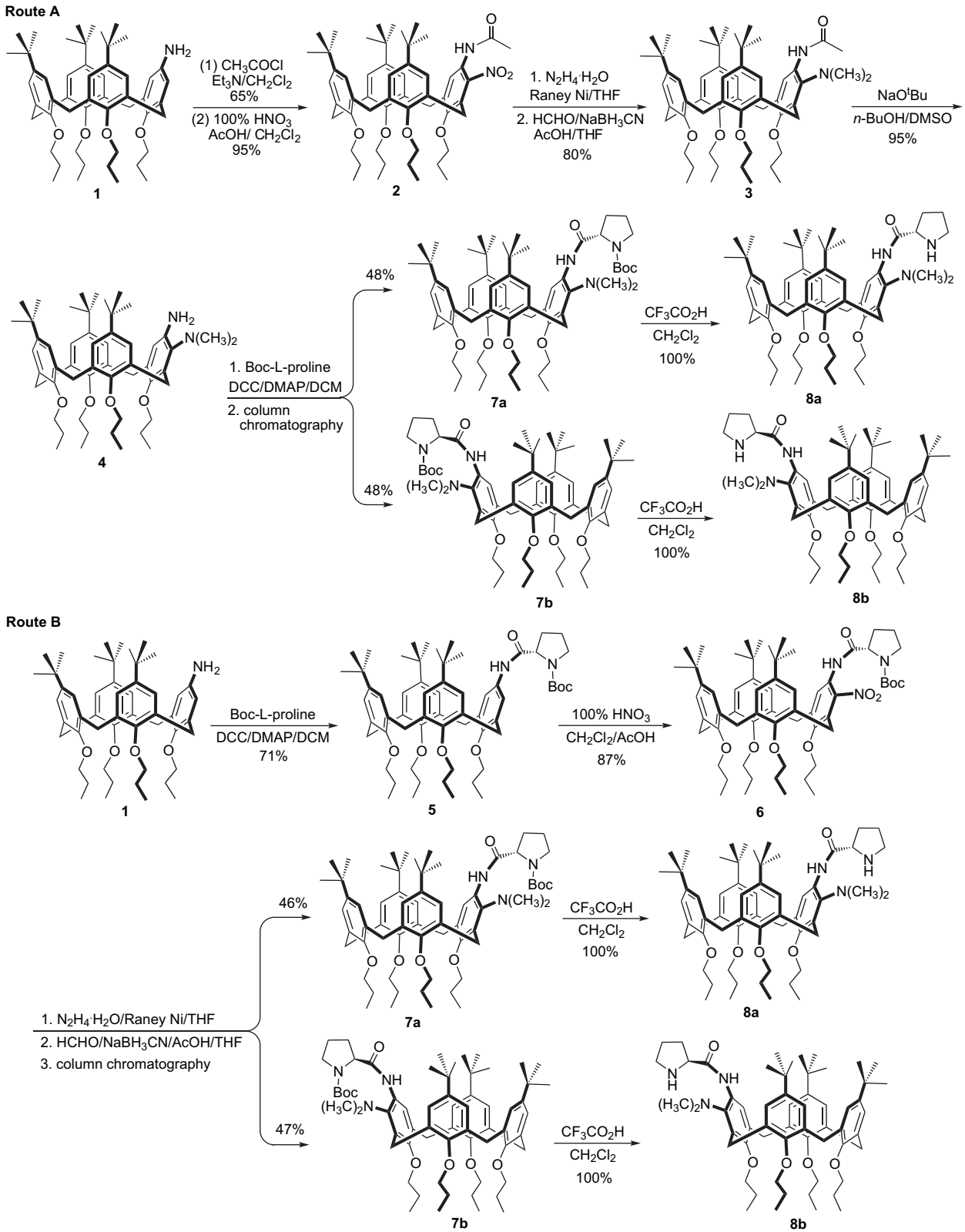
2. Results and discussion

2.1. Synthesis and structure of organocatalysts

The optical pure inherently chiral calix[4]arene-based organocatalysts **8a** and **8b** have been prepared by two routes, which are depicted in Scheme 1. As shown in route A, starting from the aminocalix[4]arene **1**,[14] the racemic inherently chiral calix[4]arene **2** was easily synthesized by two steps according to the procedure we reported before.[8] Reduction of **2** with Raney Ni and hydrazine hydrate in THF, and then direct methylation[15] of the reduction product by HCHO and acetic acid in the presence



Scheme 1. Synthesis of organocatalysts **8a** and **8b**.

of $NaBH_3CN$ gave compound **3** in 80% total yield. Hydrolysis of compound **3** with NaO*t*-Bu in *n*-butanol and DMSO provided the racemic compound **4** in 95% yield. Condensation of **4** with Boc-L-proline in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) gave a pair of diastereomers **7a** and **7b**, which could be resolved by common silica column chromatography. Diastereomeric pure organocatalyst **8a** or **8b** was finally obtained in a quantitative yield by hydrolysis of the diastereomers **7a** and **7b** in dried CH_2Cl_2 in the presence of CF_3CO_2H, respectively. In route B, the optical pure organocatalysts **8a** and **8b** were synthesized by introducing Boc-L-proline as the dual functions of auxiliary according to our published procedure,[7] which showed to be a more convenient and efficient method than the former one. The structures of **8a** and **8b** were characterized by the usual spectroscopic methods (^1H NMR, ^{13}C NMR, and HRMS) and elemental analysis.

Furthermore, we obtained the single crystals of compound **8a** by diffusion of *n*-pentane into the solution of **8a** in acetone and methanol (v/v, 1:1). Based on the X-ray crystallographic analysis, we designated the absolute configuration of inherently chiral calixarene moiety in **8a** to be *cS*, in which the dimethylamino group is located at the C-6 position of the calixarene skeleton (Fig. 1). Thus, the absolute configuration of **8a** was designated to be *cS-S*. Correspondingly, the absolute configuration of **8b** could be designated to be *cR-S*, in which the dimethylamino group is located at the C-4 position of its calixarene skeleton.

As comparison, the L-prolinamide derivative **11** was synthesized by the same procedure as described in route B (Scheme 2). Starting from 4-nitrophenol, compound **10** was synthesized in three steps in total 95% yield. Nitration of **10** with 100% nitric acid and then reduction gave the corresponding amine, which was further methylated by HCHO and acetic acid in the presence of $NaBH_3CN$, and then followed by deprotection to provide the target molecule **11** in total 87% yield for the four steps.

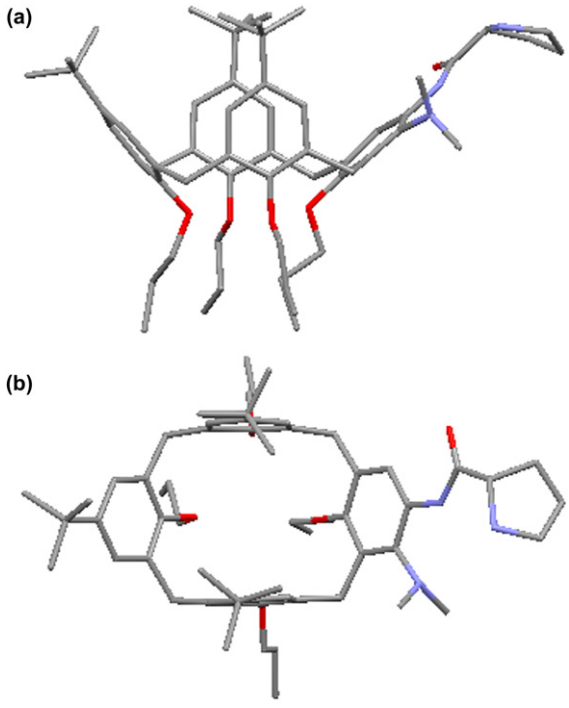
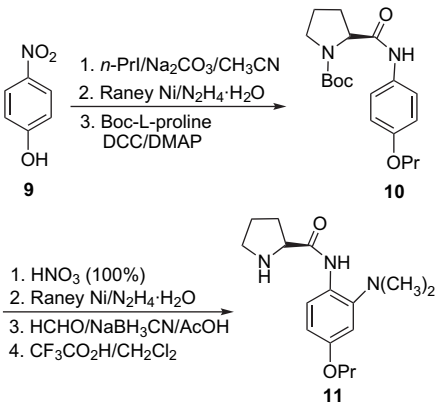


Figure 1. (a) Side view and (b) top view of crystal structure of compound **8a**. Methanol molecule and hydrogen atoms are omitted for clarity.



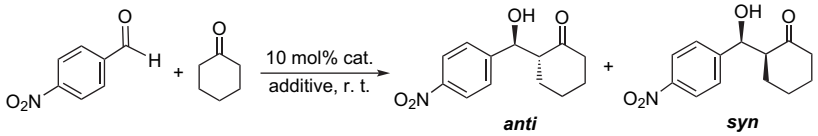
Scheme 2. Synthesis of compound **11**.

2.2. Direct aldol reaction of 4-nitrobenzaldehyde with cyclohexanone catalyzed by 8a and 8b

With the optical pure calix[4]arene derivatives **8a** and **8b** in hand, we then tested their catalytic efficiencies in the enantioselective aldol reaction between 4-nitrobenzaldehyde and cyclohexanone. As shown in entries 1 and 2 in Table 1, with 10 mol% of catalyst **8a** or **8b**, the direct aldol reaction of 4-nitrobenzaldehyde and cyclohexanone could be completed within 10 h at room temperature to give the aldol product in a high yield and the *anti*-isomer in moderate ee value. It has been reported that the enantioselective direct aldol reaction catalyzed by an organocatalyst could be significantly influenced by the acidic additive.[16] So, we first tested the aldol reaction catalyzed by **8a** or **8b** in the presence of 20 mol% CF_3SO_3H, and found that a large decrease in the catalytic activities and the stereoselectivities was observed (Table 1, entries 3 and 4). Even when we prolonged the reaction time, low yield of the product and low diastereoselectivity were only obtained (Table 1, entries 5 and 6). These results might be attributed to the protonation of the catalyst to lower their nucleophilicity. However, we found that the decrease in the acidity of the additive could accelerate the aldol reaction (Table 1, entries 7–12). As a result, the reaction could be completed in 6 h with an obvious improved enantioselectivity in the presence of 20 mol% AcOH (Table 1, entries 13 and 14). Moreover, it was also found that decreasing the amount of AcOH to 10 mol% could affect the selectivity but not the yield and the reaction time (Table 1, entries 15 and 16). These observations suggested that the catalytic system of 10 mol% of catalyst and 20 mol% of AcOH could be the optimal reaction conditions.

The solvent effects on the aldol reaction of 4-nitrobenzaldehyde and cyclohexanone catalyzed by **8a** and **8b** were then evaluated, and the results were shown in Table 2. It was found that the reaction medium could affect not only the catalytic activities but also the stereoselectivities of the process. When the reaction was carried out in DMSO, the enantioselectivity could be significantly improved in the case of both **8a** and **8b**, but the reaction rate was very slow (Table 2, entries 1 and 2). Changing the solvent to DMF or THF, both the reaction rate and the chemical yield were significantly increased, while a little decrease in the stereoselectivity was observed (Table 2, entries 3–6). When the reaction was carried out in an aqueous solvent, a significant increase in the reaction rate was found (Table 2, entries 7–12), which is consistent with a recent report[17] that the addition of an amount of water to the solvent accelerated the reaction rate. Moreover, we also found that the reaction could be completed in 20 h in pure water (Table 2, entries

Table 1
Aldol reaction of 4-nitrobenzaldehyde and cyclohexanone catalyzed by **8a** or **8b**[a]



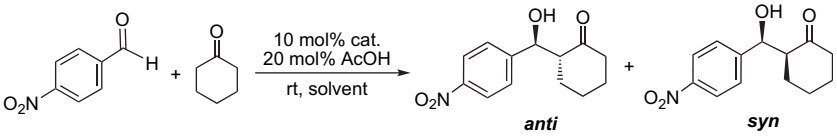
Entry	Catalyst	Additive	Time (h)	Yield[b] (%)	dr[c] (*anti*/*syn*)	ee[d] (%, *anti*)
1	**8a**	—	10	98	78:22	44
2	**8b**	—	10	99	81:19	44
3	**8a**	CF_3SO_3H	36	30	29:71	8
4	**8b**	CF_3SO_3H	36	Trace	—	—
5	**8a**	CF_3CO_2H	76	34	56:44	37
6	**8b**	CF_3CO_2H	76	26	64:36	48
7	**8a**	Cl_2CHCO_2H	44	90	80:20	13
8	**8b**	Cl_2CHCO_2H	44	85	76:24	9
9	**8a**	*m*-NO_2–$PhCO_2H$	10	98	73:27	32
10	**8b**	*m*-NO_2–$PhCO_2H$	10	98	71:29	23
11	**8a**	$PhCO_2H$	20	99	69:31	48
12	**8b**	$PhCO_2H$	20	99	73:27	47
13	**8a**	CH_3CO_2H	6	99	73:27	58
14	**8b**	CH_3CO_2H	6	99	76:24	63
15	**8a**	CH_3CO_2H[e]	6	99	70:30	56
16	**8b**	CH_3CO_2H[e]	6	99	75:25	40

[a] The reactions were conducted with **8a** or **8b** (10 mol %), additive (20 mol %), aldehyde (0.25 mmol), and ketone (0.2 mL).
[b] Isolated yield.
[c] Determined by NMR.
[d] Determined by HPLC; the configuration was assigned as 2*R*,1′*S* by comparison of retention times.
[e] Acetic acid (10 mol %) was used.

13 and 14), in which a negative effect on the enantioselectivity but no obvious effect on the diastereoselectivity of the process was observed (entries 7–14).

In order to improve the enantioselectivity of the process, we further explored temperature effects on the aldol reaction. As shown in Table 3, when **8a** was used as the catalyst, the enantioselectivity was increased from 58% (Table 3, entry 1) at room temperature to 75% at −20 °C (Table 3, entry 5). However, with **8b** as the catalyst, a little decrease in the enantioselectivity was observed under the same conditions (Table 3, entries 2, 4, and 6). Moreover, it was also found that the presence of 10 equiv H_2O at low temperature displayed no much better catalytic efficiency than the ones without water (Table 3, entries 7–10). These observations implied that the stereochemical pathway of the reaction could be controlled to some extent by the inherently chiral element of the aminocalix[4]arene moiety, and catalyst **8a** could be the matched diastereomer for this transformation at low temperature.

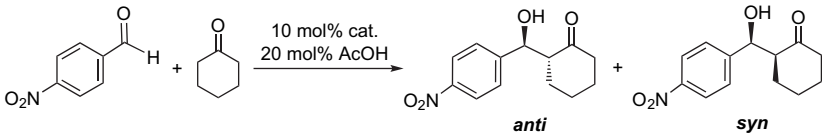
Table 2
Solvent effects on the aldol reaction catalyzed by **8a** or **8b**[a]



Entry	Catalyst	Solvent	Time (h)	Yield[b] (%)	dr[c] (*anti*/*syn*)	ee[d] (%, *anti*)
1	**8a**	DMSO	144	80	72:28	72
2	**8b**	DMSO	144	81	69:31	77
3	**8a**	DMF	44	95	65:35	64
4	**8b**	DMF	70	95	68:32	69
5	**8a**	THF	3.5	90	71:29	63
6	**8b**	THF	3.5	90	61:39	63
7	**8a**	DMSO/H_2O[e]	3.5	99	82:18	64
8	**8b**	DMSO/H_2O[e]	3.5	99	81:19	51
9	**8a**	DMF/H_2O[e]	3.5	99	83:17	57
10	**8b**	DMF/H_2O[e]	3.5	99	84:16	46
11	**8a**	THF/H_2O[e]	3.5	99	83:17	57
12	**8b**	THF/H_2O[e]	3.5	99	84:16	56
13	**8a**	H_2O[f]	20	99	85:15	49
14	**8b**	H_2O[f]	20	99	85:15	48

[a] The reactions were conducted with **8a** or **8b** (10 mol %), acetic acid (20 mol %), aldehyde (0.25 mmol), and ketone (0.2 mL) in solvent (0.2 mL).
[b] Isolated yield.
[c] Determined by NMR.
[d] Determined by HPLC; the configuration was assigned as 2*R*,1′*S* by comparison of retention times.
[e] 1:1 (v/v).
[f] 10 equiv.

Table 3
Temperature effects on the aldol reaction catalyzed by **8a** or **8b**[a]



Entry	Catalyst	Temperature (°C)	H_2O (equiv)	Yield[b] (%)	dr[c] (*anti*/*syn*)	ee[d] (%, *anti*)
1	**8a**	25	—	99	73:27	58
2	**8b**	25	—	99	76:24	63
3	**8a**	−10	—	87	84:16	59
4	**8b**	−10	—	86	78:22	58
5	**8a**	−20	—	75	86:14	75
6	**8b**	−20	—	76	79:21	58
7	**8a**	−10	10	88	86:14	67
8	**8b**	−10	10	87	87:13	55
9	**8a**	−20	10	79	89:11	60
10	**8b**	−20	10	76	85:15	65

[a] The reactions were conducted with **8a** or **8b** (10 mol %), acetic acid (20 mol %), aldehyde (0.25 mmol), and ketone (0.2 mL) at the indicated temperature.
[b] Isolated yield.
[c] Determined by NMR.
[d] Determined by HPLC; the configuration was assigned as 2*R*,1′*S* by comparison of retention times.

As comparison, we further investigated the catalytic efficiency of L-prolinamide derivative **11** in the aldol reaction of 4-nitrobenzaldehyde with cyclohexanone under the optimal reaction conditions described above. As shown in Table 4, when the aldol reaction proceeded at room temperature, catalyst **11** gave a slight higher enantioselectivity while a lower reactivity than those of **8a** and **8b** (Table 4, entries 1–3). However, compared with the reaction catalyzed by **11** at −20 °C, the catalyst **8a** gave a significant high enantioselectivity (75% ee) while **8b** showed a low enantioselectivity (Table 4, entries 4–6). These results suggested that the *cS*-inherently chiral moiety and the *S*-stereogenic central moiety in **8a** could be matched to each other in this catalytic process. As a result, the inherently chiral moiety might play an important role in helping to stereocontrol the reaction at low temperature.

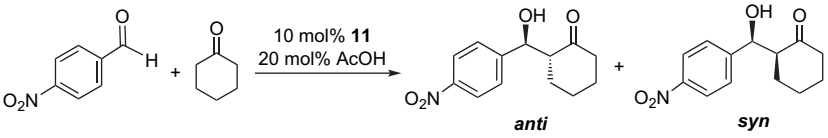
2.3. Scope and limitations for the aldol reaction catalyzed by 8a

Under the optimal conditions, a range of aromatic aldehydes and different ketones including cyclic and acyclic ketones were further examined to evaluate the generality of **8a** in catalyzing direct aldol reactions, and the results were listed in Table 5. As shown in entries 1–3, the *para*- and *ortho*-nitrobenzaldehyde gave better enantioselectivity than *meta*-nitrobenzaldehyde with cyclohexanone. For 4-cyanobenzaldehyde (Table 5, entry 4), it was found that not only its yield but the diastereo- (up to 94:6 dr) and enantioselectivity (79%) are higher than those of 4-nitrobenzaldehyde with cyclohexanone. However, low yields and enantioselectivities were achieved for the direct aldol reactions of biphenyl-4-carbonaldehyde and 1-naphthaldehyde with cyclohexanone catalyzed by **8a** (Table 5, entries 5 and 6). In the case of aromatic aldehydes bearing strong electron-rich substituents, no aldol products were isolated (Table 5, entries 7 and 8). Moreover, the reaction of 4-nitrobenzaldehyde with other cyclic and acyclic ketones was also investigated to examine the scope of the aldol donors. Consequently, it was found that acetone and butanone gave the products in high yields but low enantioselectivities (24% and 57% ee, respectively). However, for cyclopentanone, the diastereoselectivity is low but a quantitative overall yield and the highest enantioselectivity up to 94% ee were obtained (Table 5, entry 11).

3. Conclusions

In conclusion, we have synthesized two *meta*-substituted inherently chiral calix[4]arene catalysts **8a** and **8b** by two routes, determined their absolute configuration by X-ray crystallographic

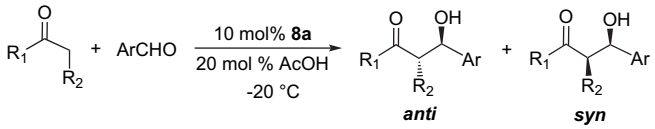
Table 4
The aldol reactions promoted by different catalysts[a]



Entry	Catalyst	Temperature (°C)	Time (h)	Yield[b] (%)	dr[c] (*anti*/*syn*)	ee[d] (%, *anti*)
1	**11**	25	24	70	76:24	68
2	**8a**	25	6	99	73:27	58
3	**8b**	25	6	99	76:24	63
4	**11**	−20	36	77	78:22	64
5	**8a**	−20	36	75	86:14	75
6	**8b**	−20	36	76	79:21	58

[a] The reactions were conducted with the catalyst (10 mol %), acetic acid (20 mol %), aldehyde (0.25 mmol), and ketone (0.2 mL).
[b] Isolated yield.
[c] Determined by NMR.
[d] Determined by HPLC; the configuration was assigned as 2*R*,1′*S* by comparison of retention times.

Table 5
Aldol reactions of aromatic aldehydes with different ketones catalyzed by **8a**[a]



Entry	R_1, R_2	Ar	Time (h)	Yield[b] (%)	dr[c] (*anti*/*syn*)	ee[d] (%)
1	$-(CH_2)_4-$	4-$NO_2C_6H_4$	24	75	86:14	75 (2*R*,1′*S*)
2	$-(CH_2)_4-$	2-$NO_2C_6H_4$	24	68	84:16	76 (2*R*,1′*S*)
3	$-(CH_2)_4-$	3-$NO_2C_6H_4$	24	65	84:16	63 (2*R*,1′*S*)
4	$-(CH_2)_4-$	4-CNC_6H_4	24	93	94:6	79 (2*R*,1′*S*)
5	$-(CH_2)_4-$	Ph–Ph	48	40	83:17	56 (2*R*,1′*S*)
6	$-(CH_2)_4-$	1-Naphthyl	48	35	90:10	50 (2*R*,1′*S*)
7	$-(CH_2)_4-$	4-$CH_3C_6H_4$	36	—[e]	—	—
8	$-(CH_2)_4-$	4-$CH_3OC_6H_4$	36	—[e]	—	—
9	CH_3, H	4-$NO_2C_6H_4$	24	96	—	24 (*R*)
10	CH_3, CH_3	4-$NO_2C_6H_4$	36	80[f]	87:13	57 (*R*)
11	$-(CH_2)_3-$	4-$NO_2C_6H_4$	15	100	56:44	94 (2*R*,1′*S*)

[a] The reactions were conducted with **8a** (10 mol %), acetic acid (20 mol %), aldehyde (0.25 mmol), and ketone (0.2 mL) at −20 °C.
[b] Isolated yield.
[c] Determined by NMR.
[d] Determined by HPLC; the configuration was assigned by comparison of retention times.
[e] No products were isolated.
[f] Linear products (15%).

analysis, and further evaluated their abilities as bifunctional organocatalysts to catalyze the enantioselective aldol reaction between aromatic aldehydes and ketones. It was found that both of the catalysts could promote the aldol reaction between 4-nitrobenzaldehyde and cyclohexanone in the presence of acetic acid in high yields and good enantioselectivities. Consequently, under the optical conditions of 10% of **8a**, 20% of acetic acid, and −20 °C, the product in 94:6 *anti*/*syn* ratio could be obtained when 4-cyanobenzaldehyde was used as aldol donor, while a high enantioselectivity up to 94% ee for the *anti*-isomer was achieved for the reaction of cyclopentanone with 4-nitrobenzaldehyde. Moreover, by studies of temperature effect on the aldol reaction and comparison with L-prolinamide derivative **11** as the catalyst, we also found that the inherently chiral calixarene skeleton with (*cS*)-conformation in **8a** was identified as the matched configuration of the stereogenic elements, and the inherently chiral moiety might play an important role in helping to stereocontrol the reaction. The results we presented here provided a practical example for asymmetric catalysis of inherently chiral calixarene derivatives with high efficiencies. More applications of the inherently chiral calixarenes in catalytic asymmetric synthesis are currently under investigation in our group.

4. Experimental

4.1. General

Melting points were measured with an X-4 digital indicating melting point apparatus. ^1H and ^{13}C NMR spectra were recorded using a Bruker Spectrospin AV300 instrument. Tetramethylsilane (TMS) was used as an internal standard, with chemical shifts expressed in parts per million (ppm) downfield from the standard. Mass spectra were determined by MALDI-TOF technique. Elementary analysis was performed in the Analytic Laboratory of this Institute. Flash column chromatography was carried out with silica gel (160–200 mesh). Other reagents and solvents were purchased from common commercial sources and were used as received or purified by distillation from appropriate drying agents.

4.1.1. Synthesis of **3**

Hydrazine hydrate (4.0 mL) was added dropwise to a suspension of **2** (1.32 g, 1.53 mmol) and a catalytic amount of Raney Ni in THF (30 mL). After the mixture was refluxed 2 h under argon, the Raney Ni was filtered over Hyfro and the solvent was evaporated. The residue was taken up in CH_2Cl_2 (50 mL), washed with H_2O (30 mL) and brine (30 mL), and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was obtained and used without further purification. A mixture of the residue and aqueous formaldehyde (37%, 1.34 mL) in THF (28 mL) was stirred for 15 min. Then $NaBH_3CN$ (597 mg, 9.50 mmol) was added and stirred for another 15 min, following by adding AcOH (1.79 mL). The resulting solution was stirred for 7 h at room temperature, 1 N NaOH aqueous solution was then added to adjust the solution pH≈7. The reaction mixture was extracted by CH_2Cl_2 (3×50 mL) and the combined organic phases were washed with saturated brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography with petroleum ether/ethyl acetate (10:1, v/v) as an eluent to afford **3** (1.05 g, 80%) as a white solid. Mp: 107–109 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.76 (s, 1H), 6.83–6.51 (m, 6H), 4.46–4.42 (m, 2H), 4.36 (d, J=12.8 Hz, 1H), 4.24 (d, J=13.2 Hz, 1H), 3.99–3.67 (m, 8H), 3.39 (d, J=13.3 Hz, 1H), 3.16–3.12 (m, 3H), 2.84 (s, 3H), 2.52 (s, 3H), 2.10 (s, 3H), 2.05–1.78 (m, 8H), 1.26–0.73 (m, 39H). MALDI-TOF MS: m/z 861.2 (M^+), 884.2 ($[M+Na]^+$), 900.2 ($[M+K]^+$). Anal. Calcd for $C_{56}H_{80}O_5N_2$: C, 78.10; H, 9.36; N, 3.25. Found: C, 77.75; H, 9.43; N, 3.15.

4.1.2. Synthesis of racemic **4**

To a solution of NaO*t*-Bu (731 mg, 7.62 mmol) in *n*-BuOH (65 mL)/DMSO (3.80 mL) was added **3** (328 mg, 0.38 mmol), and the reaction mixture was refluxed for about 48 h. After removal of the solvent under reduced pressure, 10% HCl (30 mL) was added, and the mixture was then extracted with CH_2Cl_2 (3×30 mL). The combined organic phase was washed with H_2O and dried over anhydrous Na_2SO_4 and concentrated. The residue was separated by column chromatography (silica gel; petroleum ether/CH_2Cl_2, 2:1) to give compound **4** as a white solid (297 mg, 95%). Mp: 96–98 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 6.90 (s, 1H), 6.82–6.79 (m, 3H), 6.65 (s,

1H), 6.51 (s, 1H), 6.04 (s, 1H), 4.48–4.43 (m, 2H), 4.35 (d, J=12.6 Hz, 1H), 4.15 (d, J=12.7 Hz, 1H), 4.04–3.65 (m, 8H), 3.40 (d, J=12.7 Hz, 1H), 3.16–3.10 (m, 2H), 2.98 (d, J=12.7 Hz, 1H), 2.79 (s, 3H), 2.26 (s, 3H), 2.01–1.89 (m, 8H), 1.19 (s, 9H), 1.14 (s, 9H), 1.05–0.86 (m, 21H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.4, 154.3, 153.8, 149.9, 144.1, 144.0, 143.1, 139.9, 135.4, 134.4, 134.1, 134.0, 133.8, 133.5, 132.0, 126.3, 125.5, 125.1, 124.9, 123.9, 115.8, 77.1, 77.0, 76.2, 42.8, 42.6, 33.93, 33.90, 33.7, 31.7, 31.6, 31.3, 30.7, 28.3, 23.5, 23.4, 23.1, 22.6, 10.6, 10.5, 10.3, 10.1. MALDI-TOF MS: m/z 819.1 (M^+), 842.1 ([M+Na]$^+$), 858.1 ([M+K]$^+$). Anal. Calcd for $C_{54}H_{78}O_4N_2$: C, 79.17; H, 9.60; N, 3.42. Found: C, 78.93; H, 9.61; N, 3.32.

4.1.3. Synthesis of *7a*

To a solution of racemic **4** (297 mg, 0.36 mmol) in dried CH_2Cl_2 (30 mL) were added L-Boc-proline (82 mg, 0.38 mmol), DCC (112 mg, 0.54 mmol), and DMAP (22 mg, 0.18 mmol), respectively. The mixture was stirred at room temperature for 10 h, and the insoluble DCU formed was then removed by filtration. The filtrate was concentrated, and the residue was purified by column chromatography with petroleum ether/ethyl acetate (15:1 v/v) as an eluent to afford compounds **7a** (178 mg, 48%) and **7b** (176 mg, 48%) both as a white solid. Mp: 90–92 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.38 (br s, 0.5H), 7.82 (br s, 0.5H), 7.25 (s, 1H), 6.91–6.50 (m, 6H), 4.46–4.15 (m, 5H), 4.00–3.65 (m, 8H), 3.65–3.35 (m, 3H), 3.20–3.08 (m, 3H), 2.80 (s, 3H), 2.60–1.85 (m, 5H), 1.85–1.72 (m, 10H), 1.55–0.83 (m, 48H). MALDI-TOF MS: m/z 1016.3 (M^+), 1039.3 ([M+Na]$^+$), 1045.3 ([M+K]$^+$). Anal. Calcd for $C_{64}H_{93}O_7N_3$: C, 75.63; H, 9.22; N, 4.13. Found: C, 76.05; H, 9.47; N, 4.07.

4.1.4. Synthesis of *8a*

A solution of **7a** (360 mg, 0.35 mmol) and TFA (0.54 mL) in dried CH_2Cl_2 (20 mL) were stirred under nitrogen atmosphere at room temperature for 15 h. After removal of the solvent under reduced pressure, the residue was taken up in CH_2Cl_2 (50 mL), washed with 5% $NaHCO_3$ (2×30 mL), and dried over anhydrous Na_2SO_4. After evaporation of the solvent, **8a** (320 mg) was obtained in a quantitative yield as a white solid, which was used without further purification. Mp: 130–132 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.56 (s, 1H), 7.64 (s, 1H), 6.94 (s, 1H), 6.90 (s, 1H), 6.82 (m, 2H), 6.62 (s, 1H), 6.46 (s, 1H), 4.47–4.37 (m, 3H), 4.20 (d, J=12.8 Hz, 1H), 4.02–3.63 (m, 10H), 3.40 (d, J=12.8 Hz, 1H), 3.20–2.90 (m, 5H), 2.75 (s, 3H), 2.26–1.60 (m, 14H), 1.20 (s, 9H), 1.16 (s, 9H), 1.06–0.76 (m, 21H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.1, 154.3, 153.7, 153.3, 144.4, 143.9, 143.1, 138.6, 134.4, 134.2, 133.9, 133.6, 133.5, 132.1, 131.7, 126.2, 125.6, 125.5, 125.3, 125.1, 123.6, 120.3, 77.2, 76.9, 76.1, 61.1, 47.2, 43.0, 42.7, 33.94, 33.86, 33.6, 31.7, 31.6, 31.2, 31.1, 30.84, 30.75, 26.2, 23.45, 23.38, 23.1, 22.5, 10.6, 10.4, 10.3, 10.0. HRMS calcd for $C_{59}H_{85}N_3O_5$: [M]$^+$ 916.3233, found: 916.6546.

4.1.5. Synthesis of *8b*

According to the above method for synthesis of **8a**, hydrolyzing **7b** (275 mg, 0.27 mmol) gave **8b** as a white solid (247 mg). Mp: 128–130 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.40 (s, 1H), 7.53 (s, 1H), 7.02 (s, 1H), 6.97 (s, 1H), 6.89 (m, 2H), 6.57 (s, 1H), 6.37 (s, 1H), 4.47–4.38 (m, 3H), 4.21 (d, J=12.7 Hz, 1H), 4.10–3.58 (m, 10H), 3.37 (d, J=12.8 Hz, 1H), 3.23–2.85 (m, 5H), 2.76 (s, 3H), 2.22–1.64 (m, 14H), 1.25 (s, 9H), 1.21 (s, 9H), 1.11–0.83 (m, 21H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3, 154.5, 153.5, 153.3, 144.5, 143.7, 143.1, 139.0, 134.3, 134.0, 133.9, 133.3, 133.1, 131.7, 131.5, 126.5, 125.7, 125.6, 125.5, 125.1, 123.5, 121.0, 77.1, 76.9, 75.9, 61.1, 47.3, 43.0, 42.6, 34.0, 33.9, 33.6, 31.8, 31.6, 31.3, 31.2, 30.9, 30.6, 26.3, 23.5, 23.4, 23.2, 22.4, 10.7, 10.6, 10.2, 10.0. HRMS calcd for $C_{59}H_{85}N_3O_5$: [M]$^+$ 916.3233, found: 916.6564.

4.1.6. Synthesis of *11*

A mixture solution of **9** (1.07 g, 7.68 mmol) and *n*-PrI (3.74 mL, 38.39 mmol) in dried CH_3CN (100 mL) in the presence of Na_2CO_3 (4.07 g, 38.39 mmol) was refluxed for 6 h under nitrogen atmosphere. After removal of the solvent under reduced pressure, 10% HCl (100 mL) was added, and the mixture was then extracted with CH_2Cl_2 (3×40 mL). The combined organic phase was washed with H_2O and dried over anhydrous Na_2SO_4 and concentrated to obtain the etherified product, which was reduced by hydrazine hydrate in the presence of a catalytic amount of Raney Ni, and then acetylated by L-Boc-proline in the presence of DCC and DMAP to give the compound **10** in total 95% yield for three steps. Starting from **10**, the prolinamido-derivative **11** as a colorless liquid was obtained in total 87% yield for four steps according to the same procedure as described in route B for synthesis of **8a** and **8b**.

Compound **10**. Mp: 136–138 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.29 (br s, 1H), 7.40 (d, J=8.9 Hz, 2H), 6.83 (d, J=7.7 Hz, 2H), 4.45 (br s, 1H), 3.88 (t, J=6.6 Hz, 2H), 3.60–3.20 (m, 2H), 2.51 (br s, 1H), 2.01–1.71 (m, 5H), 1.49 (s, 9H), 1.02 (t, J=7.4 Hz, 3H). MS (ESI): m/z 348.08 [M]$^+$. Anal. Calcd for $C_{19}H_{28}O_4N_2$: C, 65.49; H, 8.10; N, 8.04. Found: C, 64.45; H, 8.04; N, 7.81.

Compound **11**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.10 (s, 1H), 8.26 (d, J=2.5 Hz, 1H), 6.68 (d, J=2.5 Hz, 1H), 6.60 (dd, J=8.9, 2.5 Hz, 1H), 3.92–3.84 (m, 4H), 3.12–2.95 (m, 2H), 2.65 (s, 6H), 2.26–2.00 (m, 2H), 1.84–1.72 (m, 4H), 1.03 (t, J=7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.8, 155.5, 144.9, 125.9, 120.4, 108.2, 106.9, 69.65, 61.4, 47.4, 44.1, 30.9, 26.3, 22.6, 10.5. HRMS calcd for $C_{16}H_{25}N_3O_2$: [M]$^+$ 291.3886, found: 291.2013.

4.2. Crystal data for 8a

$C_{60.5}H_{92}N_3O_7$, M=973.37, trigonal, space group $P3_221$, a=12.9528(18), b=12.9528(18), c=59.907(12) Å, α=90.00°, β=90.00°, γ=120.00°, V=8704.3(5) Å^3, Z=6, ρ_{calcd}=1.114 cm^{-3}, Mo Kα radiation, λ=0.71073 Å, μ=0.072 mm^{-1}, T=113(2) K, R_{int}=0.0637, R_1=0.0642 ($I>2\sigma(I)$). Crystallographic data for the structure have been deposited with Cambridge Crystallographic Database as supplementary publication number CCDC 686801.

4.3. A general procedure for aldol reactions

To a stirred solution of 10 mol % catalyst in ketones (0.2 mL) at a given temperature after 15 min, the aldehyde (0.25 mmol) was added. The mixture was allowed to stir for a given time, then the solvent was evaporated and the crude product analyzed. If necessary, the crude products were purified by flash chromatography with hexane/ethyl acetate mixture as eluents.

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