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PII: S0040-4020(14)01514-2

DOI: 10.1016/j.tet.2014.10.063

Reference: TET 26133

To appear in: *Tetrahedron*

Received Date: 28 August 2014

Revised Date: 15 October 2014

Accepted Date: 27 October 2014

Please cite this article as: Uyanik A, Bayrakci M, Eymur S, Yilmaz M, Upper rim functionalized calix[4]arene-based *L*-proline as organocatalyst for direct asymmetric aldol reactions in water and organic media, *Tetrahedron* (2014), doi: 10.1016/j.tet.2014.10.063.

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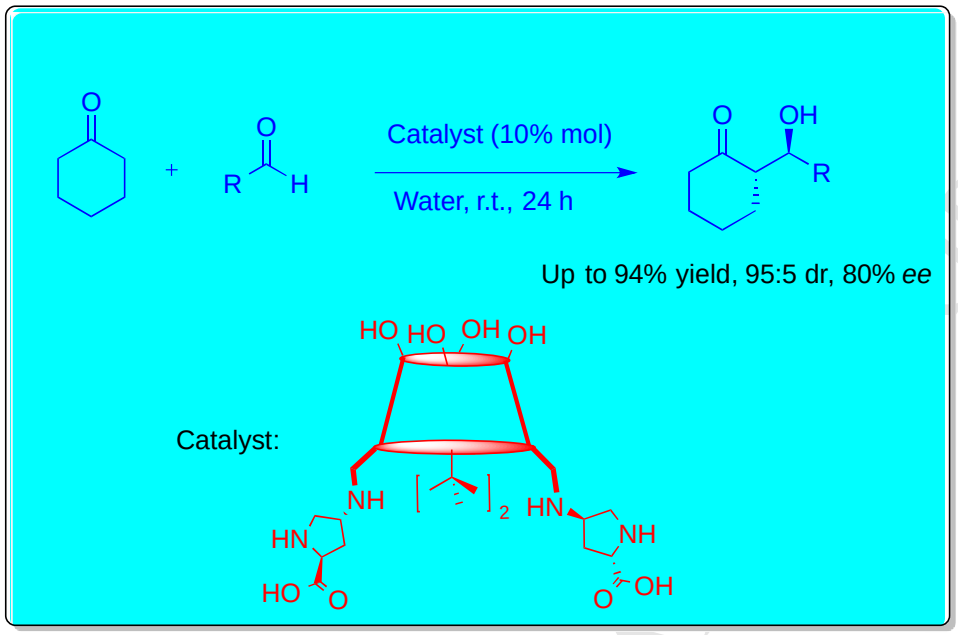
Graphical Abstract:



Upper rim functionalized calix[4]arene-based *L*-proline as organocatalyst for direct asymmetric aldol reactions in water and organic media

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Abstract

The synthesis of upper rim-functionalized calix[4]arene-based *L*-proline was described, and its catalytic efficiency as organocatalyst for the enantioselective aldol reaction in water was investigated. The results showed that the nature of the hydrophobic cavity of calixarene is critical for catalytic activity in water. The products of the reaction between various ketones and aldehydes with *anti*-configuration were obtained in high yields (up to 94%) with high diastereo- (up to 95:5 dr) and enantioselectivities (up to 80% *ee*).

1. Introduction

The synthesis of enantiomerically pure compounds has attracted extensive interest in academic and especially commercial communities because enantiomers of the same compound can show different biological activities.[1] In recent years, enantioselective C-C bond formation reactions catalyzed by organocatalysts have been recognized as powerful tools for creating practical protocols for asymmetric organic synthesis.[2] The organocatalytic aldol reaction is one of the most powerful C-C bond-forming processes, yielding 1,3-dioxygenated compounds, which are important structural motifs found in biologically active molecules.[3] After the seminal contributions of List *et al.* in the early 2000s,[4] *L*-proline and its various structural derivatives were shown to be powerful catalysts in asymmetric aldol reactions.[5]

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Over the past few decades, the use of water as a reaction medium for enantioselective transformations has attracted significant attention from a synthetic point of view, because water possesses unique and attractive properties as a solvent that alter the reactivity of catalysts and help generate intermediate transition states during catalytic processes.[6] Although *L*-proline derivative-catalyzed organocatalytic aldol reactions are typically performed in polar organic solvents such as DMSO or DMF, it has been demonstrated that the addition of a small amount of water has a positive effect on the reaction.[7] However, the use of an excess amount of water decreases the reactivity and stereocontrol of the reaction.[8] Therefore, the investigation of novel chiral molecules capable of promoting enantioselective aldol reactions in water remains an important goal. For this purpose, the catalytic efficiency of *L*-proline derivatives bearing large apolar substituents and amine catalysts bearing hydrophobic alkyl chains for highly diastereo- and enantioselective direct aldol reactions in water have recently been investigated by several research groups.[9]

Calixarenes are macrocyclic, basket-like compounds that are important in supramolecular chemistry mostly due to their potential ability to exist in a cone conformation, and the ease with which their lower and upper rims can be functionally modifed.[10] In particular, calix[4]arene derivatives have been used successfully in the areas of ion and molecular recognition, host-guest chemistry, catalysis, enzyme mimicry, interaction with biomolecules, ion extraction and selective ion transport systems.[11]

We have recently reported a direct aldol reaction in water using *p-tert*-butylcalix[4]arene-based chiral organocatalysts bearing a chiral proline moiety at the lower rim of the calix[4]arene units (**1**, Figure 1).[12] We postulated that a hydrophobic region and a hydrophilic region can be generated by the formation of hydrogen bonds between the free OH groups of interfacial water molecules and the OH groups of the calix[4]arene moiety, and catalyst **1** should assemble with hydrophobic reactants in water and isolate the transition state from water. When considering the catalytic inefficiency of the monomeric analog of compound **1** for the aldol reaction in water, we can easily assume that the hydrophobic part of the lower rim-functionalized calix[4]arene of compound **1** is responsible for the observed reactivity and selectivity in water. In this study, we aimed to synthesize a novel upper rim-functionalized calix[4]arene-based *L*-proline compound **2** to catalyze direct aldol reactions between cyclohexanone and aromatic aldehydes in water.

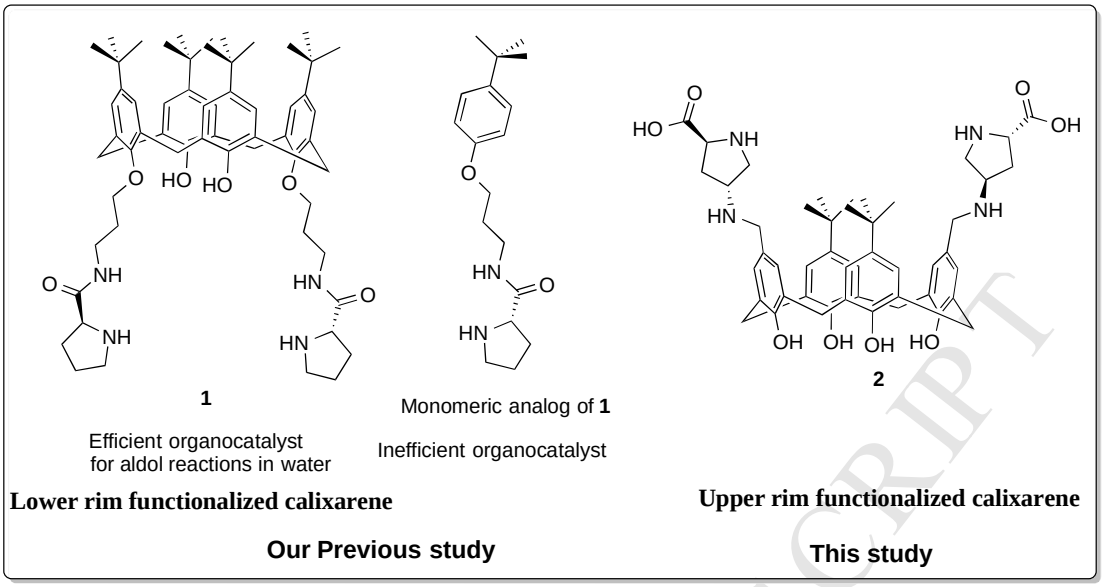


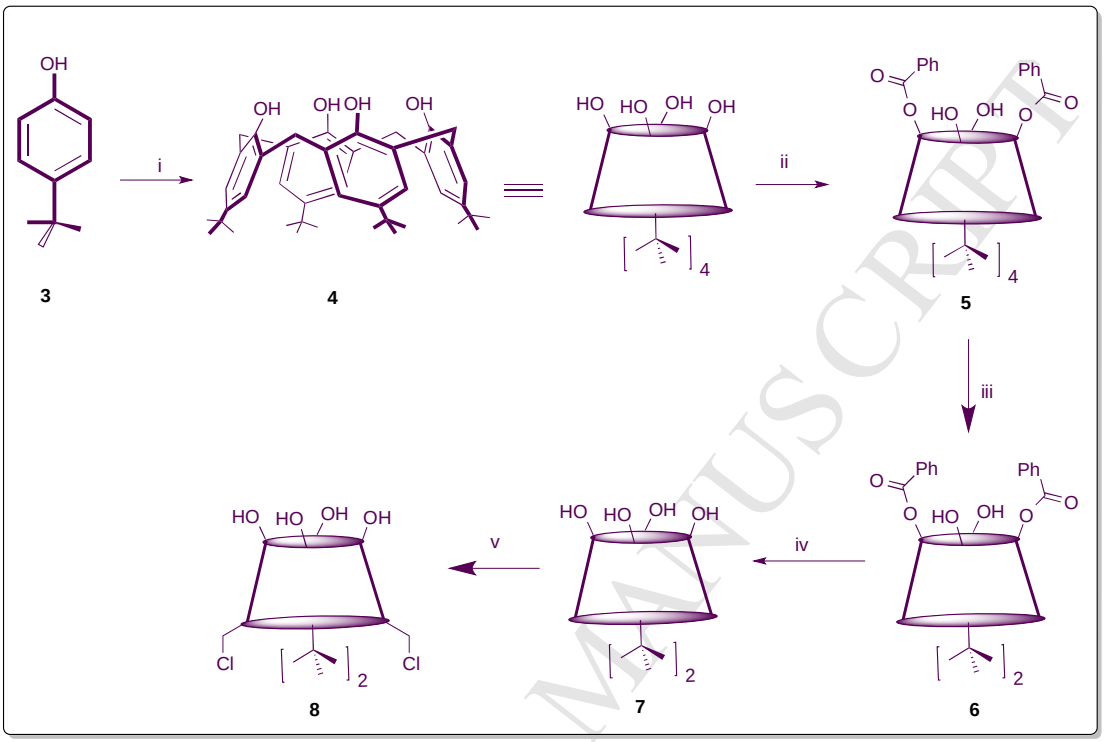
Figure 1. Structure of proline-substituted calixarene derivatives as catalysts for aldol reactions in water.

2. Results and discussion

We have a keen interest in asymmetric aldol reactions that can be promoted by calix[4]arene-based organocatalysts. In this study, our aim was to develop a novel upper rim-functionalized calix[4]arene-based organocatalyst for enantioselective aldol reactions in water. As far as we know, there has been only one report of a compound of this class in the literature,[13] in which an *L*-proline moiety was introduced selectively at the upper rim of conformationally rigid calix[4]arenes. This organocatalyst had been evaluated in enantioselective aldol reactions in the presence of only small amounts of water, affording moderate enantiomeric excesses (*ee*s up to 49%). Therefore, the investigation of novel calixarene-based organocatalysts for aldol reactions in water is still emerging and deserves more attention. Encouraged by our previous experience with direct asymmetric aldol reactions catalyzed by lower rim-functionalized calixarenes in water,[12] we hypothesized that an upper rim-functionalized calix[4]arene-based *L*-proline might also be a simple and efficient catalyst for aldol reactions in water. In the work presented here, we report a direct catalytic asymmetric aldol reaction with cyclohexanone as the aldol donor catalyzed by upper rim-functionalized calix[4]arene-based organocatalyst **2**.

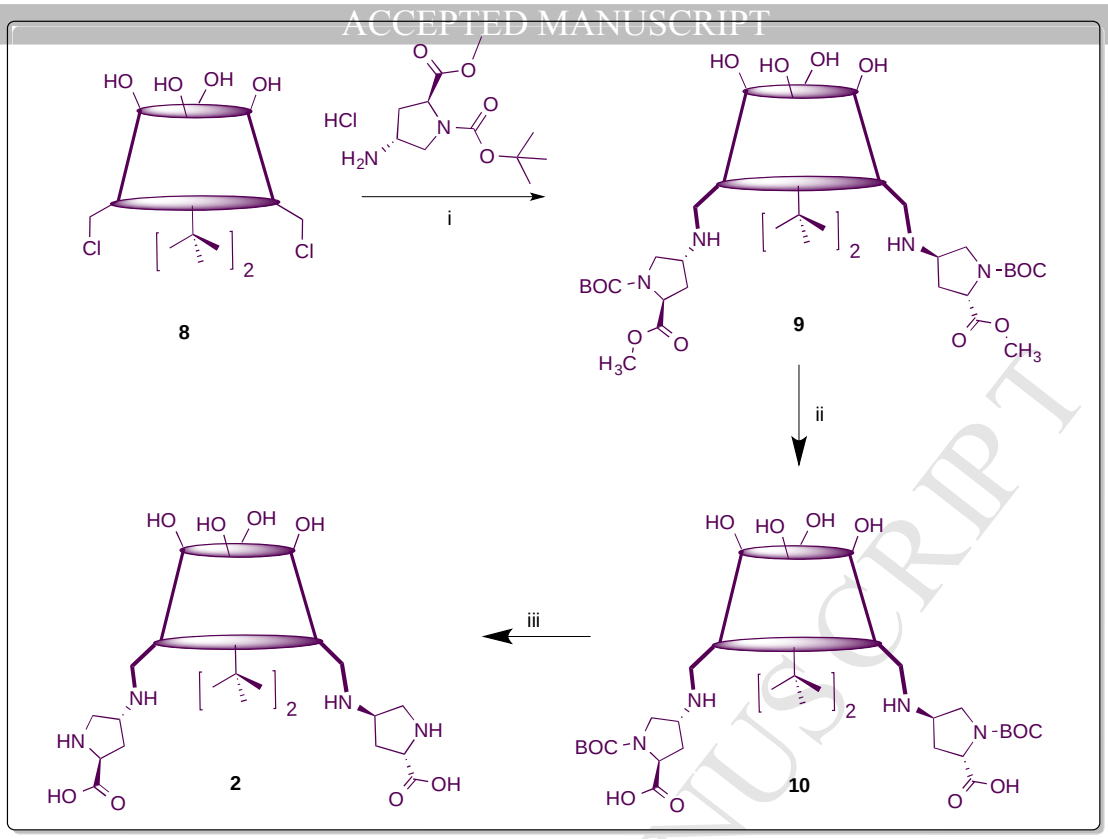
2.1 Synthesis of Catalyst 2

The synthesis of organocatalyst **2** investigated in this study is summarized in Schemes 1 and 2. The required starting materials **4-8** were obtained according to published procedures as shown in Scheme 1.[14-16]



Scheme 1. Synthesis of the compound **8** Reaction conditions: (*i*): HCOH, NaOH, 2h, 110-120 °C, (*ii*): K_2CO_3, benzoyl chloride, CH_3CN, 4h, 80 °C, (*iii*): $AlCl_3$, toluene, 2h, room temperature, (*iv*): NaOH, ethanol/water, 12h, reflux, (*v*): $C_8H_{17}OCH_2Cl$, $SnCl_4$, chloroform, -10 °C.

Next, *L*-proline-substituted calix[4]arene derivatives **9**, **10** and **2** were obtained in three steps (Scheme 2); these derivatives have not been synthesized previously. As shown below, chloromethylated compound **8** was stirred overnight with N-Boc-trans-4-amino-*L*-proline methyl ester hydrochloride in the presence of triethylamine to obtain the corresponding Boc-protected proline methyl ester of calix[4]arene **9**. In the second step, the methyl ester of calix[4]arene **9** was subsequently converted into the carboxylic acid analogue **10** by the reaction of the Boc-protected proline methyl ester of calix[4]arene **9** with NaOH and methanol at room temperature under a dry atmosphere. Finally, the Boc groups of calixarene **10** were converted to the final compound **2** by the controlled hydrolyzation of crude product **10** with trifluoroacetic acid (TFA).



Scheme 2. Synthesis of the compound **2** Reaction conditions: (*i*): TEA, dichloromethane, overnight, room temperature, (*ii*): 2M NaOH, MeOH, 15h, room temperature, (*iii*): TFA, CH_2Cl_2, overnight, room temperature.

All of the compounds were fully characterized by ^{1}H, ^{13}C NMR, FT-IR (ATR) spectroscopy and elemental analyses. The ^{1}H NMR spectra of newly synthesized compounds **2, 8, 9,** and **10** showed two sets of doublets corresponding to the bridging methylene protons. A typical AX pattern was observed around 3.20-3.40 ppm and 4.10-4.20 ppm, corresponding to the methylene bridge $ArCH_2Ar$ protons for compounds **9**, **10** and **2**. The high field doublets around 3.20–3.40 ppm for compounds **9**, **10**, and **2** were assigned to the equatorial protons of the methylene groups, whereas the low field signals around 4.10–4.20 ppm were assigned to the axial protons. This NMR data demonstrated that these compounds were in the cone conformation. Furthermore, this conclusion was supported by ^{13}C NMR data showing $ArCH_2Ar$ resonance signals between 31.0 and 31.4 ppm. The IR spectra revealed that synthesized compound **9,** although bearing proline methyl ester units, showed characteristic ester peaks around 1744 cm^{-1}, whereas the same peaks were not observed for synthesized compound **10,** bearing proline carboxylic acid units in the region 1740-1750 cm^{-1}. These data can be used to monitor the proline binding and de-

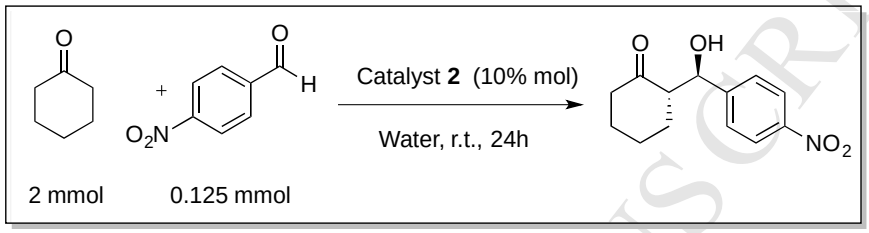
esterification reaction progress for calixarene compounds **9** and **10**. Although the ^{1}H NMR spectra of the newly synthesized calixarene compound **9** showed one singlet peak assigned to the methyl ester protons of proline units around 3.70 ppm, as expected, the same peak disappeared for carboxylic acid derivative **10** after the hydrolization of the proline methyl ester of calix[4]arene **9**. This data demonstrated that de-esterification of the proline methyl ester protons of compounds **9** with NaOH was complete. Furthermore, the new peaks for compounds **9** and **10** seen as singlets around 1.40 ppm were attributed to the *tert*-butyl groups of the Boc-protected units; however, the same peaks were not observed for compound **2**. These data are consistent with the hydrolysis of the Boc-protected units of calixarene compound **10** with TFA and the formation of the final compound **2**. In the ^{13}C NMR spectra of these proline-based calixarenes, it is obvious that compounds **9**, **10**, and **2** possess certain symmetry elements, and therefore the number of signals observed in the ^{13}C NMR is less than the number of C atoms in ligands **9**, **10**, and **2**. Furthermore, all other data were in agreement with the proposed structures of compounds **9**, **10**, and **2**.

2.2 Optimization of the aldol reactions

Our initial screening efforts focused on the efficiency of compound **2** for catalyzing the aldol reaction of cyclohexanone (**13**) with 4-nitrobenzaldehyde (**14**) in water at room temperature (Table 1). Compound **2** could efficiently catalyze this aldol reaction with high conversion values, high diastereoselectivities, and good enantioselectivities. At the outset, the aldol reaction of cyclohexanone (0.125 mmol) and 4-nitrobenzaldehyde (2 mmol) was studied by using 10 mol % catalyst **2** in different amounts of water (Table 1, entries 1-4). The reaction was complete within 24 h in 0.25 mL water at room temperature, and the product was obtained in 99% conversion, 94/6 *dr*, and 77% *ee* (Table 1, entry 4). When the aldol reaction was performed with 20 mol % catalyst, the product was also obtained in high diastereo- and good enantioselectivities (70% ee) (Table 1, entry 5). It should be noted that a decrease in the catalyst loading from 10% to 5% did not significantly affect the diastereoselectivity or the conversion but did reduce the enantioselectivity (Table 1, entry 6). Because the highest enantioselectivity was obtained in water with 10 mol % loading, we also investigated the effect of different additives on the aldol reaction. We selected readily available acids as additives in the compound **2**-catalyzed aldol reaction. We found that the addition of these acids had no significant effect on the

enantioselectivity or diastereoselectivity (Table 1, entries 7-10). Under these conditions, the highest enantiomeric excess was obtained by using 0.25 mL of water. These initial screening results demonstrated that this new upper rim-functionalized calix[4]arene-based compound **2** could be used as an effective organocatalyst for an enantioselective aldol reaction in water.

Table 1 Catalytic aldol reactions between cyclohexanone and 4-nitrobenzaldehydes catalyzed by **2** in water



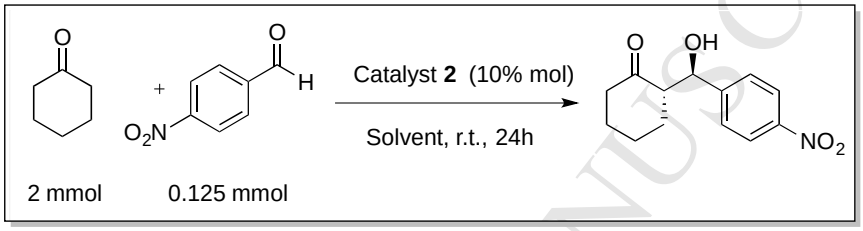
Entry	Water (mL)	Catalyst: (% mol)	Additive	Conv. (%)[a]	*anti:syn*[a]	*ee* (%)[b]
1	1.0	10%	-	90	91:9	71
2	0.50	10%	-	95	95:5	75
3	0.25	10%	-	98	94:6	77
4	0.125	10%	-	99	94:6	76
5	0.25	20%	-	98	92:8	70
6	0.25	5%	-	96	91:9	63
7	0.25	10%	$ClCH_2COOH$	77	93:7	74
8	0.25	10%	CH_3COOH	98	94:6	75
9	0.25	10%	PhCOOH	90	89:11	73
10	0.25	10%	PTSA	99	94:6	55

a. Determined by ^1H NMR spectroscopy of crude mixture.
b. The *ee* value of anti-isomer was determined by chiral HPLC analysis in comparison with authentic racemic material.

We further examined the ability of compound **2** to promote the enantioselective aldol reaction of cyclohexanone and 4-nitrobenzaldehyde in organic solvents, and the results are summarized in Table 2. When DMF was used as the solvent, the corresponding aldol product was obtained with high conversion (97%) after 24 h (Table 2, entry 1). The reaction with DMSO proceeded efficiently and gave the desired product with good conversion (73%), but the enantioselectivity was low

(64%) (Table 2, entry 2). $CHCl_3$ and THF were also shown to afford the corresponding product with good conversions and high enantioselectivities (entries 3 and 4). We also found that the volume of DMF did not have much effect on the enantioselectivity. Our solvent screening studies clearly demonstrated that compound **2** could efficiently catalyze the asymmetric aldol reaction in polar organic solvents. Furthermore, different additives had almost no effect on the enantioselectivity of the reaction (Table 2, entries 7-8).

Table 2 Catalytic aldol reactions between cyclohexanone and 4-nitrobenzaldehyde catalyzed by compound **2** in organic solvents



Entry	Solvent	Amount of solvent	Additive	Conv. (%)[a]	*anti:syn*[a]	*ee* (%)[b]
1	DMF	0.50	-	97	86:14	84
2	DMSO	0.50	-	73	78:22	64
3	$CHCl_3$	0.50	-	88	87:13	81
4	THF	0.50	-	98	82:18	83
5	DMF	0.25	-	87	87:13	80
6	DMF	0.125	-	76	85:15	77
7	DMF	0.50	CH_3COOH	74	70:30	75
8	DMF	0.50	PhCOOH	67	86:14	84

a. Determined by ^1H NMR spectroscopy of crude mixture.

b. The *ee* value of anti-isomer was determined by chiral HPLC analysis in comparison with authentic racemic material.

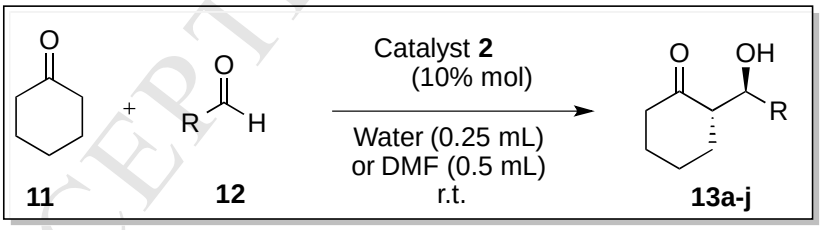
2.2 Direct asymmetric aldol reactions catalyzed by compound 2

The scope of this aldol reaction using upper rim-functionalized calix[4]arene-based compound **2** as a catalyst in the presence of a large amount of water was studied, and the results are summarized in Table 3 (Method A). The results demonstrated the catalytic efficiency of compound **2**. It catalyzed the aldol reaction of a variety of substituted aromatic aldehydes, with cyclohexanone affording aldol products **13a** to **13j** in moderate to good enantioselectivity and high

diastereoselectivity. The *p*-substituted benzaldehydes **12a**, **12d**, **12g**, **12h**, **12i**, and **12j** afford the aldol product in *ee* of >75% (Table 3, entries 1, 5, 8, 9, and 10). In contrast, the reaction with *o*-substituted benzaldehydes (**12c** and **12f**) and *m*-substituted benzaldehydes (**12b** and **12e**) provided lower enantioselectivity than that of *p*-substituted donors. In all of the cases, the reactions proceeded smoothly at room temperature, and diastereoselectivity ranged from good to excellent.

Having established the optimal reaction conditions for the reaction in organic solvents (Table 2), we then tested the catalytic efficiency of compound **2** in the enantioselective aldol reaction between cyclohexanone and a variety of substituted benzaldehydes in DMF (Table 3, Method B). In most cases, the aldol products were obtained in high yields and with good enantioselectivities. Among these aldehydes, nitro-substituted benzaldehydes offered the best enantioselectivity, and the desired aldol products were obtained in good chemical yields with *anti*- diastereoselectivity. For example, when *o*-nitrobenzaldehyde was used, the *anti*-aldol adduct **13c** was obtained in 90% chemical yield with 92:8 *dr* and 84% *ee*. As seen in Table 3, we observed that the use of DMF has a positive effect on the enantioselectivity but negative effect on the diastereoselectivity of the rection.

Table 3 Direct aldol reaction between various benzaldehydes and cyclohexanone with compound **2**



Entry	Aldehyde (R)[a]	Yield (%)[b]	*anti:syn*[c]	*ee* (%)[d]
1	4-NO_2Ph (A) (B)	93 91	94:6 86:14	77 84
2	3-NO_2Ph (A) (B)	70 91	95:5 87:13	70 84
3	2-NO_2Ph (A) (B)	87 90	73:27 92:8	70 84
4	4-ClPh (A) (B)	91 87	61:39 80:20	80 80
5	3-ClPh (A) (B)	94 96	68:32 60:40	74 80
6	2-ClPh (A)	92	90:10	76

	(B)	82	86:14	83
7	4-BrPh (A) (B)	93 82	88:12 73:27	76 75
8	4-FPh (A) (B)	93 91	60:40 67:33	75 73
9	4-CNPh (A) (B)	94 79	91:9 85:15	77 81
10	4-CF_3Ph (A) (B)	94 91	89:11 70:30	77 60

a. (A): Method A (in water), (B): Method B (in DMF).
b. Isolated yield after flash column chromatography on silica gel.
c. Determined by ^{1}H NMR spectroscopy of crude mixture.
d. The *ee* value of anti-isomer was determined by chiral HPLC analysis in comparison with authentic racemic material.

Together, the abovementioned results led us to suggest a mechanism based on general enamine catalysis for the compound **2** catalyzed aldol reaction performed in water. As shown in Fig. 2, we hypothesized that under our reaction conditions, a hydrophilic region and a hydrophobic region can be created by the formation of hydrogen bonds between the free OH groups of interfacial water molecules and the OH and NH groups of the calix[4]arene moiety, which improve the activity of organic catalysis in water. The transition state of the reaction can be described according to a Houk-List model.[17]

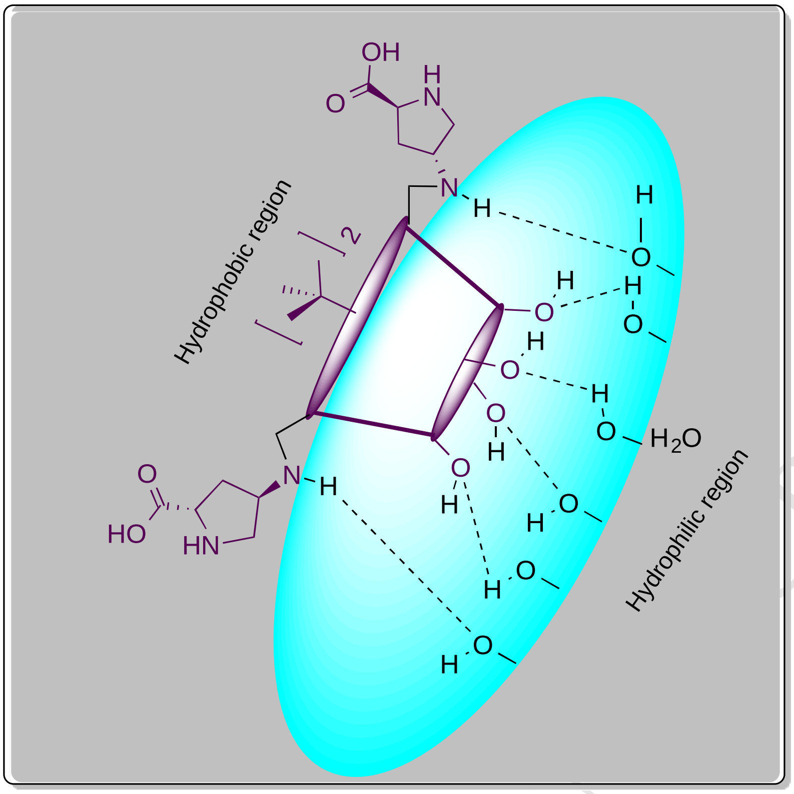


Figure 2. Proposed structure of catalyst **2** in the water

3. Conclusion

In summary, we developed a practical synthesis of compound **2**, a novel organocatalyst containing an *L*-proline on the upper side of the calix[4]arene scaffolds, and evaluated its ability to catalyze enantioselective aldol reactions between substituted benzaldehydes and cyclohexanone. Considering the catalytic inefficiency of *L*-proline for the aldol reaction in water, the results presented here clearly demonstrate the enormous effect of the hydrophobic part of the calix[4]arene of compound **2** on the reactivity and selectivity in water. We demonstrated that compound **2** was able to promote enantioselective aldol reactions directly in the presence of excess amounts of water in high yields (up to >94%) with good enantioselectivities (up to >80%) and diastereoselectivities (up to 95:5). We also found that organocatalyst **2** can catalyze direct aldol reactions in DMF with good diastereoselectivities (up to 92:8) and good enantioselectivities (up to 84%). More detailed studies on the mechanism and synthetic applications of these *L*-proline-functionalized calixarene derivatives in catalytic asymmetric synthesis are currently in

progress in our laboratory.

4. Experimental

4.1 General

All chemical reagents, starting materials, and solvents were purchased from Aldrich, Fluka and Merck. Flash column chromatography (FC) was performed by using glass columns with flash grade silica gel (Merck Silica Gel 60). Reactions were monitored by thin layer chromatography (TLC) using pre-coated silica gel plates. All organic extracts were dehydrated over oven dried $MgSO_4$ and concentrated by using rotary evaporator before being subjected to FC. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian 400 MHz spectrometer using $CDCl_3$ as the solvent. Chemical shifts values are reported in ppm from tetramethylsilane. FTIR spectra were evaluated on a Perkin Elmer spectrum 100 FTIR spectrometer. Elemental analyses were performed using a Leco CHNS-932 analyzer. Enantiomeric excess (*ee*) values of chiral adducts were detected by a HPLC (Agilent 1200 Series) system using a Chiralcel OD-H column. Melting points were determined on an EZ-Melt apparatus in a sealed capillary.

4.2 Synthesis of 5,17-Bis(N-Boc-trans-4-amino-L-proline metyl ester)-11,23-di-*tert*-butylcaliks[4]aren (9)

To a stirred solution of 5,17-bis(chloromethyl)-11,23-di-*tert*-butylcaliks[4]aren (**8**) (0.50 g, 0.79 mmol) and triethylamine (0.66 mL, 4.74 mmol) in dry dichloromethane (20 mL), N-Boc-trans-4-amino-L-proline methyl ester hydrochloride (0.47 g, 1.66 mmol) in dry dichloromethane (10 mL) mixture containing triethylamine (0.23 mL, 1.66 mmol) was added drop wise at room temperature and under N_2. The reaction mixture was allowed to stand overnight at room temperature. After filtration, the solution was evaporated to dryness. The residue was washed with water and dried over $MgSO_4$. Then, the product was recrystallized from CH_2Cl_2 and MeOH to obtain pure compound (**9**) in 90% yield as a pale yellow solid with mp >300 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (s, 18H, But), 1.40 (s, 18H, $OC(CH_3)_3$), 1.82-1.90 (m, 2H, ProC5), 2.28-2.49 (m, 2H, ProC5), 3.22-3.31 (bm, 6H, ProC4 and $ArCH_2Ar$), 3.49-3.51 (bm, 4H, ProC5), 3.71 (s, 6H, $COOCH_3$), 3.74-3.75 (m, 4H, $C\underline{H_2}NH$), 4.17-4.28 (m, 6H, ProC1 and $ArCH_2Ar$), 6.94 (s, 4H, ArH), 7.05 (s, 4H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 154.3, 153.7, 147.9, 146.8, 133.1, 128.7, 128.5, 127.4, 125.8, 80.1, 67.8, 58.1, 55.1, 52.1, 45.9, 34.1, 32.2, 31.5, 29.7, 28.2. FTIR (ATR)

(characteristic frequencies): 2952, 2869, 1744, and 1696 cm^{-1}; Anal.Calc. for (%) $C_{60}H_{80}N_4O_{12}$: C, 68.68; H, 7.68; N, 5.34; Found: C, 68.73; H, 7.61; N, 5.37.

4.3 5,17-Bis(N-Boc-trans-4-amino-L-proline carboxylic acid)-11,23-di-*tert*-butylcaliks[4]aren (10)

Compound **9** (0.50 g, 0.48 mmol) was stirred in methanol (10 mL) for 30 min. To this mixture a 2M NaOH (2.65 mL, 5.31 mmol) solution was added and stirred at room temperature for 15 hours. Next, 0.5 M hydrochloride acid (40 mL) was added to this stirred mixture. The aqueous solution was extracted with dichloromethane (2x50 mL) and ethyl acetate (2x20 mL) respectively. Organic phases were combined and dried over $MgSO_4$. After evaporating of residue, 0.22 g of pure compound **10** was obtained as a white solid in 44% yield with m.p. >300 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24 (s, 18H, But), 1.40 (s, 18H, $OC(CH_3)_3$), 1.80-1.90 (m, 2H, ProC5), 2.30-2.44 (m, 2H, ProC5), 3.22-3.37 (bm, 6H, ProC4 and $ArCH_2Ar$), 3.50-3.58 (bm, 4H, ProC5), 3.65-3.73 (m, 4H, $C\underline{H_2}NH$), 4.17-4.30 (m, 6H, ProC1 and $ArCH_2Ar$), 6.95 (s, 4H, ArH), 7.07 (s, 4H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 153.7, 148.1, 146.6, 144.4, 127.8, 127.6, 127.2, 126.0, 125.7, 80.1, 67.8, 58.2, 55.1, 45.7, 34.0, 32.5, 31.4, 29.7, 28.2. FTIR (ATR) (characteristic frequencies): 3170, 2957 and 1672 cm^{-1}; Anal.Calc. for (%) $C_{58}H_{76}N_4O_{12}$: C, 68.21; H, 7.50; N, 5.49; Found: C, 68.19; H, 7.55; N, 5.47.

4.4 5,17-Bis(trans-4-amino-L-proline carboxylic acid)-11,23-di-*tert*-butylcaliks[4]aren (2)

To a solution of compound **10** (0.50 g, 0.49 mmol) in dry dichloromethane (30 mL), trifluoroacetic acid (TFA) (1.52 mL) was added and stirred at room temperature overnight. Then, the solution was evaporated to dryness and the residue was dissolved in dry dichloromethane (100 mL). Organic phases were extracted with 5% $NaHCO_3$ (2x20 mL). The aqueous phase was extracted by ethyl acetate (2x20 mL). All organic phases were combined and dried over $MgSO_4$. After evaporating of organic residue, pure compound was obtained with quantitative yield m.p. >300 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (s, 18H, But), 2.30-2.50 (m, 2H, ProC5), 3.10-3.19 (m, 2H, ProC5), 3.20-3.40 (bm, 6H, ProC4 and $ArCH_2Ar$), 3.65-3.98 (bm, 8H, ProC5 and $C\underline{H_2}NH$), 4.19-4.42 (m, 6H, ProC1 and $ArCH_2Ar$), 7.05-7.21 (bs, 8H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 147.9, 146.6, 144.7, 132.6, 128.9, 128.5, 127.4, 125.9, 67.8, 58.0, 55.0, 46.0, 34.1, 32.1, 31.5, 29.7. FTIR (ATR) (characteristic frequencies): 2960, 2849 and 1663 cm^{-1}; Anal.Calc. for (%) $C_{48}H_{60}N_4O_8$: C, 70.22; H, 7.37; N, 6.82; Found: C, 70.19; H, 7.44; N, 6.77.

4.5 General procedure for the enantioselective direct aldol reaction

The following procedure for the reaction of cyclohexanone with 4-nitrobenzaldehyde in brine is representative.

To a solution of cyclohexanone (2.0 mmol) in water (0.25 mL) was added 4-nitro benzaldehyde (0.25 mmol) and compound **2** (0.025 mmol). Upon consumption of 4-nitrobenzaldehyde (monitored by TLC), the reaction mixture was extracted with EtOAc. Then the organic layers were combined, dried with anhydrous MgSO4, concentrated to dryness under reduced pressure, and subjected to column chromatography using 1:3 EtOAc : Hexanes as the eluent to afford the product **13a** purified by preparative TLC.

4.5.1 (*S*)-2-((*R*)-Hydroxy(4-nitrophenyl)methyl)cyclohexan-1-one (**13a**).[18a,b] It was obtained in a maximum of 93% yield and 77% *ee*. *anti/syn*: 94:6, *anti*-diastereomer; ^{1}H NMR (400 MHz, $CDCl_3$ δ ppm): 1.24-2.02 (m, 6H), 2.28-2.40 (m, 2H), 2.51-2.60 (m, 1H), 4.12 (s, 1H), 4.78 (d, *J* = 8.4 Hz, 1H), 7.46 (d, *J* = 8.0 Hz, 2H), 8.18 (d, *J* = 8.4 Hz, 2H). The optical purity was determined by HPLC on Chiralpak OD-H column [hexane/2-propanol 80:20, 254 nm, flow rate 0.5 mL/min], anti: t_{minor} = 26.0 min and t_{major} = 33.2 min.

4.5.2 (*S*)-2-((*R*)-Hydroxy(3-nitrophenyl)methyl)cyclohexan-1-one (**13b**).[18a] It was obtained in a maximum of 70% yield and 70% *ee*. *anti/syn*: 95:5, *anti*-diastereomer; ^{1}H NMR (400 MHz, $CDCl_3$ δ ppm): 1.34-2.13 (m, 6H), 2.30-2.54 (m, 2H), 2.61-2.63 (m, 1H), 4.12 (s, 1H), 4.84 (d, *J* = 8.4 Hz, 1H), 7.54 (t, *J* = 7.9 Hz, 1H), 7.68 (t, *J* = 7.6 Hz, 1H), 8.18 (d, *J* = 7.9 Hz, 1H), 8.26 (d, *J* = 1.6 Hz, 1H). The optical purity was determined by HPLC on Chiralpak OD-H column [hexane/2-propanol 80:20, 254 nm, flow rate 0.5 mL/min], *anti*: t_{major} = 23.6 min and t_{minor} = 28.8 min.

4.5.3 (*S*)-2-((*R*)-Hydroxy(2-nitrophenyl)methyl)cyclohexan-1-one (**13c**).[18a] It was obtained in a maximum of 87% yield and 70% *ee*. *anti/syn*: 73:27, *anti*-diastereomer; ^{1}H NMR (400 MHz, $CDCl_3$ δ ppm): 1.48-1.70 (m, 6H), 2.23-2.38 (m, 2H), 2.68-2.70 (m, 1H), 4.02 (s, 1H), 5.43 (d, *J* = 7.2 Hz, 1H), 7.31 (t, *J* = 7.9 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 1H). The optical purity was determined by HPLC on Chiralpak OD-H column [hexane/2-propanol 80:20, 254 nm, flow rate 0.5 mL/min], *anti*: t_{major} = 24.3 min and t_{minor} = 26.1 min.

4.5.4 (*S*)-2-((*R*)-Hydroxy(4-chlorophenyl)methyl)cyclohexan-1-one (**13d**).[18c] It was obtained in a maximum of 91% yield and 80% *ee*. *anti/syn*: 61:39, *anti*-diastereomer; ^{1}H NMR (400 MHz, $CDCl_3$ δ ppm): 1.22-2.10 (m, 6H), 2.33-2.53 (m,

2H), 2.55-2.63 (m, 1H), 3.62 (s, 1H), 4.77 (d, *J* = 8.4 Hz, 1H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.7 Hz, 2H). The optical purity was determined by HPLC on Chiralpak OD-H column [hexane/2-propanol 95:5, 220 nm, flow rate 1.0 mL/min], *anti*: t_{minor} = 21.9 min and t_{major} = 25.8 min.

4.5.5 (*S*)-2-((*R*)-Hydroxy(3-chlorophenyl)methyl)cyclohexan-1-one (**13e**).[18d] It was obtained in a maximum of 94% yield and 74% *ee*. *anti/syn*: 68:32, anti-diastereomer; ^{1}H NMR (400 MHz, $CDCl_3$ δ ppm): 1.28-2.04 (m, 6H), 2.31-2.40 (m, 3H), 3.94 (s, 1H), 4.80 (d, *J* = 8.8 Hz, 1H), 7.20-7.25 (m, 3H, Ar), 7.32 (s, 1H, Ar). The optical purity was determined by HPLC on Chiralpak OD-H column [hexane/2-propanol 96:4, 220 nm, flow rate 1.0 mL/min], *anti*: t_{major} = 23.2 min and t_{minor} = 25.8 min.

4.5.6 (*S*)-2-((*R*)-Hydroxy(2-chlorophenyl)methyl)cyclohexan-1-one (**13f**).[18d] It was obtained in a maximum of 92% yield and 76% *ee*. *anti/syn*: 90:10, *anti*-diastereomer; ^{1}H NMR (400 MHz, $CDCl_3$ δ ppm): 1.52-2.10 (m, 6H), 2.25-2.42 (m, 2H), 2.60-2.68 (m, 1H), 3.89 (s, 1H), 5.30 (d, *J* = 8.0 Hz, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 7.6 Hz, 1H), 7.28 (d, *J* = 8.1 Hz, 1H), 7.50 (d, *J* = 7.5 Hz, 1H). The optical purity was determined by HPLC on Chiralpak OD-H column [hexane/2-propanol 95:5, 220 nm, flow rate 1.0 mL/min], anti: t_{minor} = 17.0 min and t_{major} = 21.9 min.

4.5.7 (*S*)-2-((*R*)-Hydroxy(4-bromophenyl)methyl)cyclohexan-1-one (**13g**).[18a,b] It was obtained in a maximum of 93% yield and 76% *ee*. *anti/syn*: 88:12, *anti*-diastereomer; ^{1}H NMR (400 MHz, $CDCl_3$ δ ppm): 1.20-1.31 (m, 1H), 1.49-1.78 (m, 4H), 2.02-2.10 (m, 1H), 2.28-2.52 (m, 3H), 4.04 (d, *J* = 2.7 Hz, 1H), 4.71 (dd, *J* = 8.7, 2.6 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H). The optical purity was determined by HPLC on Chiralpak OD-H column [hexane/2- propanol 90:10, 220 nm, flow rate 0.5 mL/min], *anti*: t_{minor} = 32.9 min and t_{major} = 39.3 min.

4.5.8 (*S*)-2-((*R*)-Hydroxy(4-fluorophenyl)methyl)cyclohexan-1-one (**13h**).[18c] It was obtained in a maximum of 93% yield and 75% *ee*. *anti/syn*: 60:40, *anti*-diastereomer; ^{1}H NMR (400 MHz, $CDCl_3$ δ ppm): 1.22-1.30 (m, 1H), 1.50-1.78 (m, 4H), 2.01-2.13 (m, 1H), 2.30-2.55 (m, 3H), 4.01 (s, 1H), 4.76 (d, *J* = 8.8 Hz, 1H), 7.01-7.08 (m, 2H), 7.28-7.33 (m, 2H). The optical purity was determined by HPLC on Chiralpak OD-H column [hexane/2-propanol 95:5, 220 nm, flow rate 0.5 mL/min], *anti*: t_{minor} = 41.6 min and t_{major} = 47.1 min.

4.5.9 (*S*)-2-((*R*)-Hydroxy(4-cyanophenyl)methyl)cyclohexan-1-one (**13i**).[18d] It was obtained in a maximum of 94% yield and 77% *ee*. *anti/syn*: 95:5, *anti*-diastereomer;

^{1}H NMR (400 MHz, $CDCl_3$ δ ppm): 1.30-1.41 (m, 1H), 1.42-1.70 (m, 3H), 1.72-1.86 (m, 1H), 2.02-2.15 (m, 1H), 2.40 (td, *J* = 12.9, 6.0 Hz, 1H), 2.44–2.62 (m, 2H), 4.12 (d, *J* = 3.0 Hz, 1H), 4.82 (dd, *J* = 8.1, 3.0 Hz, 1H), 7.43 (d, *J* = 8.1 Hz, 2H), 7.62 (d, *J* = 8.1 Hz, 2H). The optical purity was determined by HPLC on Chiralpak OD-H column [hexane/2-propanol 95:5, 220 nm, flow rate 1 mL/min], *anti*: t_{minor} = 54.4 min and t_{major} = 68.4 min.

4.5.10 (S)-2-((R)-Hydroxy(4-trifluoromethhylphenyl)methyl)cyclohexan-1-one (13j).[18d] It was obtained in a maximum of 94% yield and 77% *ee*. *anti/syn*: 89:11, *anti*-diastereomer; ^{1}H NMR (400 MHz, $CDCl_3$ δ ppm): 1.22-1.46 (m, 1H), 1.48-1.80 (m, 4H), 2.05–2.13 (m, 1H), 2.33 (td, *J* = 12.9, 4.8 Hz, 1H), 2.45-2.55 (m, 1H), 2.68-2.80 (m, 1H), 4.01 (t, *J* = 3.0 Hz, 1H), 4.85 (d, J = 8.7 Hz, 1H), 7.42 (t, *J* = 7.2 Hz, 1H) 7.53–7.75 (m, 3H). The optical purity was determined by HPLC on Chiralpak OD-H column [hexane/2-propanol 95:5, 220 nm, flow rate 1 mL/min], *anti*: t_{minor} = 17.0 min and t_{major}= 21.9 min.

Acknowledgements

The financial support the Scientific and Technological Research Council of Turkey (TUBITAK grant no.112T349 and CMST COST Action CM1005), and the Research Foundation of Selcuk University (BAP) is gratefully acknowledged.

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