A Simple Tetraminocalix[4]arene as a Highly Efficient Catalyst under "On-Water" Conditions through Hydrophobic Amplification of Weak Hydrogen Bonds

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Abstract: The simple tetraminocalix[4]arene **1**, which contains weak H-bond-donor NH_2 groups, is reported to be a highly efficient organocatalyst for the Vinylogous Mukaiyama Aldol Reaction (VMAR) of 2-(trimethylsilyloxy)furan **5** with α-ketoesters **6a–l** under "on-water" conditions owing to the hydrophobic amplification of weak H-bond interactions. The catalytic efficiency of calixarene catalyst **1** was shown to be closely related to its recognition abilities towards the reactants **5** and **6** through a multipoint recognition model. The proposed model provided good explanations for the differences on the reaction rate acceleration and on the stereoselectivity observed with different substrates.

Introduction

From their discovery to now, calixarenes[1] have gradually gained a prominent position in a wide range of supramolecular applications, which includes molecular recognition and sensing,[2] self-assembly processes,[3] and the synthesis of (pseudo)rotaxanes and catenanes.[4] Recently, much effort has been focused on the application of calixarene derivatives as catalysts.[5] This is mainly due to the ease of functionalization of the calixarene macrocycles,[6] which is facilitated by the range of reactive catalytic groups that can be introduced on both rims, and to their recognition abilities, which offer the ability to discriminate between different substrates.[7]

Since the early work of Breslow on the feasibility of the Diels–Alder reaction in water,[8] the great potential of this reaction medium has been recognized and has become an attractive topic in current organocatalysis.[9,10] In comparison with organic solvents, water as a reaction medium provides promising benefits with respect to environmental impact, reaction rate acceleration,[7–10] and the ability to switch the stereo- and regioselectivity of a reaction.[9a,11] Subsequently, Sharpless was the first to introduce the expression "on-water" conditions[12a] to highlight the increase of acceleration of an organic reaction when an aqueous suspension of reactants and catalyst was vigorously stirred. Thanks to the results of Sharpless and coworkers,[12] it was clear that the insolubility of the reacting species and catalyst in water was not a critical aspect for the reaction efficiency. In fact, under "on-water" conditions, the hydrophobic effect drives the reactants and the catalyst to aggregate,[13] which thus amplifies the secondary interactions between them and favors molecular collisions. Although water as a solvent can interfere in the formation of H bonds between the catalyst and the substrate, many examples have been reported of hydrogen-bond-promoted organocatalysis[14] under "on-water" conditions,[15] in which a hydrophobic amplification of the H bonds between the catalyst and the substrate permits the activation of the latter.

Naturally, the synthetic versatility of calixarene macrocycles combined with their hydrophobic character make them ideal candidates for the design of simple calixarene-based organocatalysts for applications that use "on-water" conditions.[7] Surprisingly, to date, many examples of catalysis with water-soluble calixarene derivatives[16] ("in-water" conditions[17]) have been reported, whereas their catalysis under "on-water" conditions have been neglected.[7]

Recently, we have investigated the catalysis under "on-water" conditions of the Vinylogous[18a–g] Mukaiyama Aldol Reaction (VMAR)[18h–l] by using thioureido–calixarene organocatalysts.[7] We reported that the reaction rate acceleration is closely related to the hydrophobicity of the calixarene scaffold in

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conjunction with its ability to recognize the substrate through H-bond interactions with the thioureido group.

On this basis, it is probable that, owing to the amplification that is commonly observed under "on-water" conditions, even weaker H-bond-donor groups could catalyze organic reactions under "on-water" conditions. Thus, as a part of our ongoing program on the use of calixarene-based organocatalysts under "on-water" conditions, we designed the simple aminocalix[4]arene derivatives **1**[19a] and **3**[19b](Figure 1), which bear weak H-bond-donor groups. We envisioned that, under "on-water" conditions, even the weak H-bond-donor NH_2 groups of calixarene **1** should be effective in activating the substrate **6** in the VMAR (Scheme 1) through hydrophobic amplification, and we report the results of our study here.

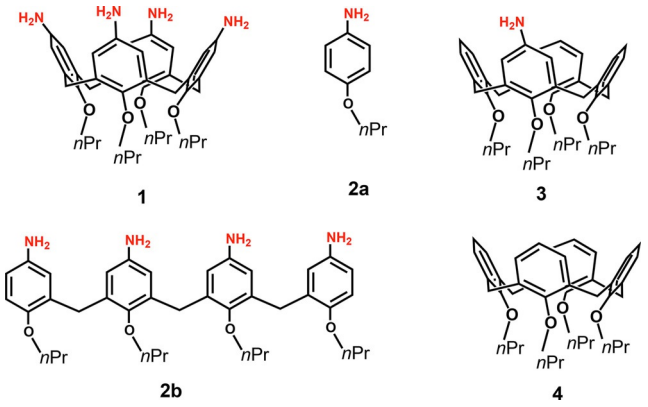
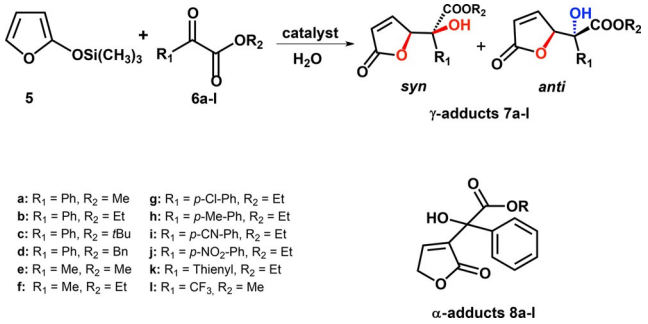


Figure 1. Structure of screened catalysts **1**–**4**.



Scheme 1. VMAR between 2-(trimethylsilyloxy)furan **5** and α-ketoesters **6a**–**l**.

On the basis of our previous experience with vinylogous reactions,[7,18] we selected the VMAR of 2-(trimethylsilyloxy)furan **5** with α-ketoesters **6a**–**l** as a model reaction for the study of the catalytic activity of tetraminocalix[4]arene **1** under "on-water" conditions (Scheme 1 and Table 1). This reaction represents a convenient approach to the synthesis of functionalized γ-butenolides that contain tertiary hydroxy groups, which are useful building blocks for biological and pharmaceutical products.[23]

Table 1. Solvent screening for the VMAR of compounds **5** and **6a**.

Entry[a]	Catalyst	Medium	Time [h]	Conversion to **7a** [%][b]	d.r. (*anti*/*syn*)[c]
1	–	H_2O[d]	14	28	68:32
2	**1**	H_2O[d]	2	74	33:67
3	**1**	H_2O[d,i]	4	99	37:63
4	**1**	CH_2Cl_2[e]	14	50	48:52
5	**1**	Toluene[e]	14	43	31:69
6	**1**	THF[e]	14	64	50:50
7	**1**	CH_3OH[e]	14	70	65:35
8	**1**	D_2O	2	34	34:66
9	**1**	H_2O[f]	4	37	21:79
10	**2a**	H_2O[d,g]	4	48	38:62
11	**2a**	H_2O[d,g]	14	65	40:60
12	**2b**	H_2O[d]	4	30	60:40
13	**3**	H_2O[d,g]	14	77	54:46
14	**4**	H_2O[h]	24	23	50:50

[a] General conditions: Compounds **6a** (0.23 mmol), **5** (0.34 mmol) and catalyst **1** (5.0 mol%) in medium (1 mL) at 30 °C and under rapid and vigorous magnetic stirring. [b] Determined by ^{1}H NMR analysis. [c] Determined by ^{1}H NMR analysis according to literature data.[20–22] [d] Deionized water. [e] Anhydrous solvent. [f] The reaction was performed by using a reciprocal shaker, agitation speed = 1400 rpm. [g] The reaction was performed in the presence of 20 mol% of catalyst. [h] See ref. [7]. [i] Catalyst was recovered and reused for five consecutive runs under these reaction conditions without appreciable changes in the yield and diastereoselectivity.

Results and Discussion

In an initial screening, we investigated the influence of the medium on the reaction rate acceleration and on the stereo- and regioselectivity of the reaction of compounds **5** and **6a** in the presence of catalyst **1** (Table 1). Interestingly, by using water as a reaction medium (entry 3), an almost quantitative conversion (99%) of substrate **6a** to the γ-adduct **7a** was observed after 4 h with a *syn*/*anti* ratio of 63:37, and no trace of the α-adduct **8a** was detected. Under these conditions, the reactants **5** and **6a** and the catalyst **1** were insoluble; therefore, the suspension was vigorously stirred magnetically.

When the above "on-water" VMAR was performed in the absence of catalyst **1**, we observed a yield of 28% of γ-adduct **7a** after 14 h as well as a switch of the stereoselectivity in favor of the *anti* adduct (*syn*/*anti* ratio of 32:68; Table 1, entry 1). This result clearly indicated that the presence of catalyst **1** accelerates the rate of conversion of substrates **5** and **6a** into the desired product **7a** owing to the combined effects of hydrophobic interactions with the calix[4]arene skeleton and H-bonding interactions with the NH_2 groups of catalyst **1**.

The stereochemical outcome of the above VMAR (Scheme 1) can be rationalized through the model of the proposed transition state **I** (Figure 2, obtained by molecular mechanic calculations). It is very likely that the H bonds (red dashes) between the amino group of catalyst **1** and the carbonyl group of substrate **6a** in the complex **6a·1** play a key role in the activation of the substrate. Thus, the attack at the *Si* face of the activated carbonyl group of compound **6a** from the *Re* face of compound **5** is favored owing to the stabilization of the ternary

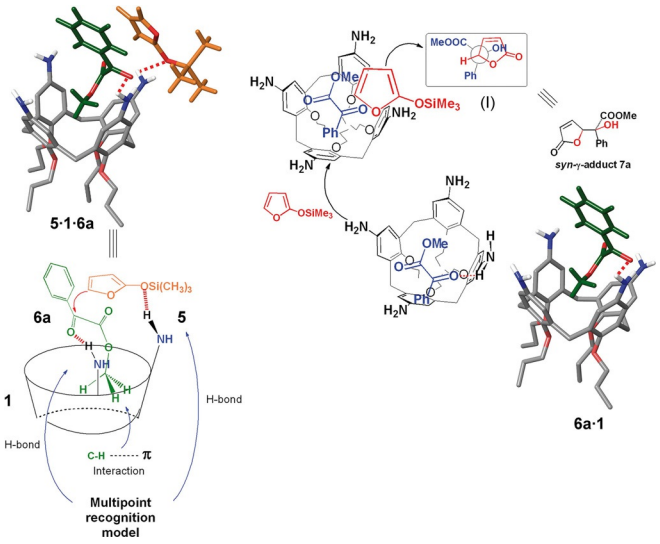


Figure 2. Plausible catalytic cycle for the VMAR that is catalyzed by calixarene **1**. a) Model of the complex **6a·1** obtained by molecular mechanics calculations (AMBER force field). b) Model of the ternary complex **5·1·6a** obtained by molecular mechanics calculations and a multipoint recognition model proposed for the activation of the substrate **6a**. c) Proposed transition states for the "on-water" VMAR of substrates **5** and **6a** in the presence of catalyst **1**. Green: α-ketoester **6a**; orange: 2-(trimethylsilyloxy)furan **5**; dotted red lines: H-bonds.

complex **5·1·6a**, which is induced by a multipoint recognition of compounds **5** and **6a** through H bonds.

In particular, we have proposed a ternary complex **5·1·6a** in which an amino group of catalyst **1** establishes an H bond with the carbonyl group of compound **6a**, and a proximal NH_2 group forms an H bond with the silyloxy group of compound **5** (Figure 2). Some interesting examples in which the amino groups are effective H-bond donors in organocatalytic processes have been previously reported in the literature.[24] In addition, we have previously reported[7] that, when compounds **5** and **6a** were suspended in water and stirred in the presence of *p*-H-calix[4]arene (**4**), a conversion of 23% to product **7a** was observed after 24 h (Table 1, entry 14), which is significantly lower than that obtained in the presence of *p*-NH_2-calix[4]arene (**1**) (99%, entry 3). These results clearly support the hypothesis that the weak H-bond-donor NH_2 groups of catalyst **1** are very effective in the catalysis of the VMAR that is shown in Scheme 1 under "on-water" conditions. To confirm our hypothesis about the presence of H-bonding interactions between catalyst **1** and compound **6a**, we performed ^{1}H NMR titration experiments in $CDCl_3$[25] in which the concentration of catalyst **1** was kept constant and the concentration of compound **6a** was varied (see the Supporting Information, Figure S23).

The addition of compound **6a** to the solution of catalyst **1** caused a slight downfield shift of the NMR signal of the aromatic hydrogen atoms that were *ortho* to NH_2 groups of catalyst **1** (see the Supporting Information, Figure S23). This indicated that the NH_2 groups were engaged in H-bonding interactions with the carbonyl group of compound **6a** through a fast complexation equilibrium (Figure 2). A nonlinear least-squares fitting for the ArH signal gave an association constant value of $35 \pm 5\ M^{-1}$ for the complexation of compound **6a** with catalyst **1** in accordance with the weak H-bond-donor abilities of the NH_2 groups. Similar results were obtained with substrate **6i**, which had an association constant value of $78 \pm 7\ M^{-1}$ (see the Supporting Information, Figure S24).

Finally, we performed DFT calculations to evaluate the H-bond strength between the NH_2 groups of catalyst **1** and the carbonyl groups of compound **6a**. The H-bond strengths were estimated through the magnetically induced currents[26] by adopting a recently reported computational protocol.[26] The DFT calculation at the B3LYP/6-31G* level of theory indicated an energy value of 2.5 kcal mol^{-1} for the Calix–N(H)–H···O=C(Ph)COOMe H bond; a significantly lower value was found for the H-bond interaction between the NH_2 group of catalyst **1** and the carbonyl ester group of compound **6a** (< 1 kcal mol^{-1}). In conclusion, DFT calculations indicated that the H-bond interaction between the amino group of catalyst **1** and the ketone carbonyl group of compound **6a** can be classified as a weak H-bonding interaction.[27]

When the VMAR between compounds **5** and **6a** in the presence of catalyst **1** was performed in organic solvents, such as CH_2Cl_2, toluene, or THF (Table 1 entries 4, 5, and 6), the conversion to product **7a** was lowered to 50, 43, and 64% after 14 h, respectively, which supports the concept of hydrophobic amplification. Further supporting evidence was obtained by repeating the same reaction in D_2O as the medium (entry 8); under these conditions, a 34% of conversion of substrate **6a** into product **7a** was observed after 2 h. This lower efficiency, with respect to the reaction that used H_2O as the medium (99% after 4 h, entry 3), can be ascribed to the higher viscosity of D_2O (about 20%), which reduces the mixing efficiency and consequently the hydrophobic effect.[15e]

The role played by the calix[4]arene scaffold on the catalytic efficiency was also investigated. In particular, when the VMAR between compounds **5** and **6a** was conducted in the presence of the monomeric counterpart **2a** as the catalyst under "on-water" conditions, a 48% conversion of the substrates into the desired product **7a** was obtained after 4 h (entry 10), and only a slight improvement was observed with prolonged reaction times (entry 11); this indicates a significantly lower catalytic efficiency for monomer **2a** than calixarene **1** (99% after 4 h).

Notably, the use of the linear tetramer **2b**[28] as the catalyst under the same reaction conditions was considerably less efficient than catalyst **1** and led to a conversion similar to that obtained in the absence of any catalyst (30% after 4 h, entry 12). Clearly, the latter results highlight the importance of the calixarene cavity in catalytic activity and indicate that the catalytic efficiency of calixarene **1** is also related to the preorganization[29] of the catalyst. In fact, in contrast to the conformationally mobile catalyst **2b**, the calix[4]arene **1** is known to be blocked (preorganized) in the cone-structure,[19a] which can facilitate the formation of H-bond interactions between the amino groups at its upper rim and the substrate; this is in accord with the multipoint recognition model proposed in Figure 2.

In addition, when the reaction was performed in the presence of catalyst **3** (20 mol%; Figure 1), which bears a single amino group at the calix[4]arene upper rim, the aldol adduct **7a** was obtained in 77% after 14 h, whereas just 5 mol% of catalyst **1** was sufficient to give a 99% conversion to the product after only 4 h (Table 1, entry 13 vs. 3). These results strongly suggest that, in accordance with the multipoint recognition model proposed in Figure 2, two adjacent amino groups strongly promote the reaction. With the aim of optimizing the reaction conditions, we studied the VMAR between compounds **5** and **6a** in the presence of catalyst **1** under "on-water" conditions by altering the reaction time, catalyst amount, and reaction temperature. By shortening the reaction time from 4 to 2 h, a drop in the yield from 99 to 74% was observed (Table 2, entry 1). A lower percentage of catalyst **1** led to a reduced degree of conversion to the product **7a** (80% after 14 h, entry 3). Furthermore, an increase of the reaction temperature from 30 to 50 °C led to a lower conversion (53% after 14 h, entry 6).

Table 2. Optimization of the reaction conditions for VMAR of compounds **5** with **6a** in the presence of catalyst **1** under "on-water" conditions.

Entry[a]	**1** [mol%]	Additive [mol%]	*T* [°C]	Conversion to **7a** [%][b]	d.r. (*anti*/*syn*)[c]	*V* [mL]
1[d]	5	–	30	74	33:67	1
2	5	–	30	99	37:63	1
3[e]	2.5	–	30	80	53:47	1
4	5	–	30	66	30:70	0.5
5	5	–	30	68	36:64	1.5
6[e]	5	–	50	53	31:69	1
7[e]	5	CF_3COOH (10)	30	traces	n.d.	1
8	5	PhCOOH (10)	30	82	36:64	1
9	5	PhCOOH (20)	30	83	38:62	1
10[e]	5	HCl (10)	30	traces	n.d.	1

[a] General conditions: All reactions were carried out by using compounds **6a** (0.23 mmol, 1 equiv.), **5** (1.5 equiv.), and catalyst **1** (5.0 mol%) in medium (1 mL) at 30 °C under rapid and vigorous magnetic stirring; it was stopped, if not specified, after 4 h. [b] Determined by ^{1}H NMR analysis. [c] Determined by ^{1}H NMR analysis according to literature data.[21] [d] Reaction time: 2 h. [e] Reaction time: 14 h.

It has been reported that the protonation of the amino groups in 2,2′-diamino-1,1′-binaphthyl organocatalyst[24] led to an improvement in the catalytic efficiency of a Diels–Alder reaction between α-acyloxyacroleins with cyclic dienes, because the ammonium group is a stronger H-bond donor than the amino group.[24] Prompted by these results, we studied the catalytic efficiency of calixarene **1** towards the VMAR shown in Scheme 1 in the presence of acid co-catalysts (Table 2, entries 7–10). From our screening, it was clear that the combination of catalyst **1** with acid additives did not lead to any improvements; this is likely to be because the formation of an anilinium species leads to a higher cation hydration and/or water solubility of calixarene **1**. Finally, we have compared the catalytic efficiency of tetraminocalix[4]arene **1** towards the VMAR in Scheme 1 with that of the recently reported $Cu(OTf)_2$.[20] The reaction between compounds **6** and **5a** (1.5 equiv) in presence of $Cu(OTf)_2$ (5.0% mol, in 1 mL of water at 30 °C under rapid and vigorous magnetic stirring) revealed a moderate catalytic efficiency with a conversion of 48% after 4 h; this is significantly lower than that achieved by using tetraminocalix[4]arene **1** as the catalyst (99% after 4 h, Table 1, entry 3). Furthermore, in the reaction with $Cu(OTf)_2$, a reversal of diastereoselectivity in favor of the *anti* adduct was observed (*syn*/*anti* ratio of 21:79 compared with 64:36 for the reaction with catalyst **1**). Therefore, this result highlights the superiority, in terms of high efficiency and stereoselectivity, of calixarene **1** as an organocatalyst for "on-water" conditions.

Finally, the influence of the amount of water was also evaluated. In a reaction performed under "on-water" conditions, the amount of water provides the medium for efficient mixing of the reactants, but it does not affect the substrate concentrations.[10] When the VMAR between compounds **5** and **6a** in the presence of catalyst **1** was conducted in the presence of a lower amount of water (0.5 vs. 1.0 mL) a lower conversion to product **7a** of 66% was obtained after 14 h (Table 2, entry 4). A similarly low degree of conversion to product **7a** was observed when the amount of water was increased to 1.5 mL (entry 5). Accordingly, our experiments showed that the optimized conditions for the VMAR that is shown in Scheme 1 are 1 mL of pure water, 30 °C, and 5 mol% of catalyst.

With these conditions in hand, we next studied the VMAR with a variety of substrates (Table 3). When ethyl, *tert*-butyl, and benzyl esters **6b–d** were used as substrates alongside furan **5** in the presence of catalyst **1**, we observed conversions to the corresponding derivatives **7b–d** of 74, 85, and 86%, respectively (Table 3, entries 2–4), all of which correspond to a lower efficiency than the methyl ester substrate **6a**. However, the preference for the *syn* diastereoisomer was respected in all cases, and no trace of the α-adducts **8b–d** was detected. To rationalize these data, we performed molecular mechanics calculations (AMBER force field) to investigate the structure of the

Table 3. Evaluation of substrate scope for VMAR between TMSOF **5** and ketoesters **6a–l** in the presence of catalyst **1** under "on-water" conditions.

Entry[a]	**6**	Product	Time [h]	Yield [%][b]	d.r. (*anti*/*syn*)[c]
1	**a**	**7a**	4	99	36:64 (36:64)
2	**b**	**7b**	14	74	38:62 (37:63)
3	**c**	**7c**	14	85	35:65 (35:65)
4	**d**	**7d**	14	86	33:67 (33:67)
5	**e**	**7e**	4	99	61:39 (61:39)
6	**f**	**7f**	4	99	62:38 (62:38)
7	**g**	**7g**	14	99	30:70 (28:72)
8	**h**	**7h**	14	36	30:70 (28:72)
9	**i**	**7i**	0.3	98	>1:99 (>1:99)
10	**j**	**7j**	4	98	5:95 (>1:99)
11	**k**	**7k**	14	80	46:54 (46:54)
12	**l**	**7l**	4	99	40:60 (40:60)

[a] General conditions: compounds **6** (0.23 mmol), **5** (0.34 mmol), and catalyst **1** (5.0 mol%) in medium (1 mL) at 30 °C under rapid and vigorous magnetic stirring. [b] Combined yield of isolated diastereoisomers after column chromatography. [c] Determined by ^{1}H NMR analysis of crude reaction mixture according to literature data;[20–22] in parentheses: d.r. of the product after column chromatography.

complexes between the calix[4]arene catalyst **1** and the α-ketoester substrates **6**.

A close inspection of the minimized structure **6a·1** (Figure 2) revealed that the methyl group of ketoester **6a** is included in the aromatic cavity of catalyst **1** and is optimally oriented to establish C–H···π interactions (average C–H···$\pi^{centroid}$ distance = 2.76 Å)[30] (Figure 3). In addition, weak H-bond interactions

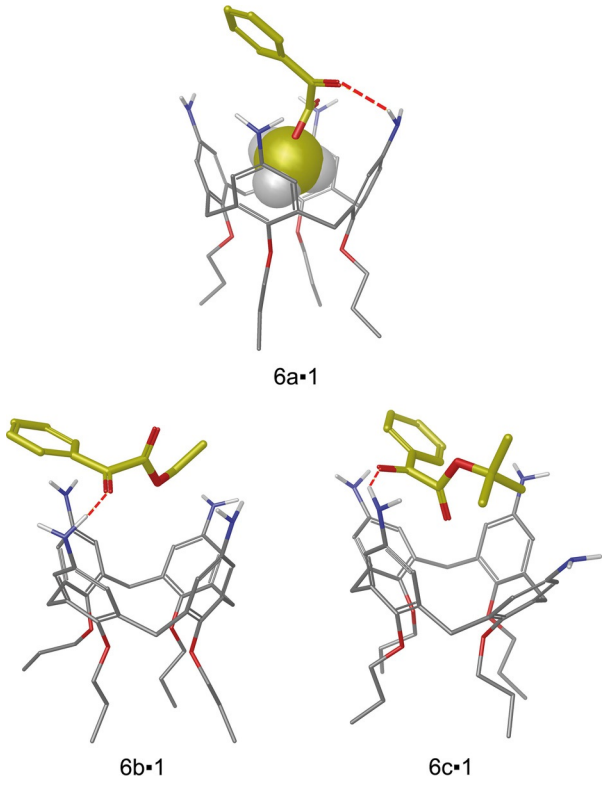


Figure 3. Optimized structure of the **6a**–**c·1** complexes obtained by molecular mechanics calculations (AMBER force field).

were detected between two NH_2 groups of catalyst **1** and the two carbonyl groups of compound **6a** with a mean N···O distance of 3.21 Å. An inspection of the minimized structures of the complexes **6b·1** and **6c·1** (Figure 3) evidenced a lower stabilization of these complexes, which was due to weak H bonds between the corresponding amino and carbonyl groups; furthermore, the alkyl groups of the ester moiety of compounds **6b**–**c** were too large to occupy the calixarene cavity of catalyst **1**. Thus, in accordance with our previous results,[7] the calixarene catalysts are able to discriminate between different substrates in the VMAR reaction under "on-water" conditions.

The substitution of the phenyl group of benzoylformate **6a** with a methyl group in acetyl formate **6e** had no influence on the catalytic efficiency of calixarene **1**. In fact, the conversion to product **7e** was 99% after 4 h, which perfectly matched the value found for the conversion of substrate **6a** to product **7a**. Surprisingly, with substrate **6e**, a switch in the stereoselectivity was observed (*anti*/*syn* 61:39, Table 3, entry 5). The model of the complex **6e·1** (Figure 4) showed that substrate **6e** lies on the upper rim of calixarene **1** such that H-bond interactions

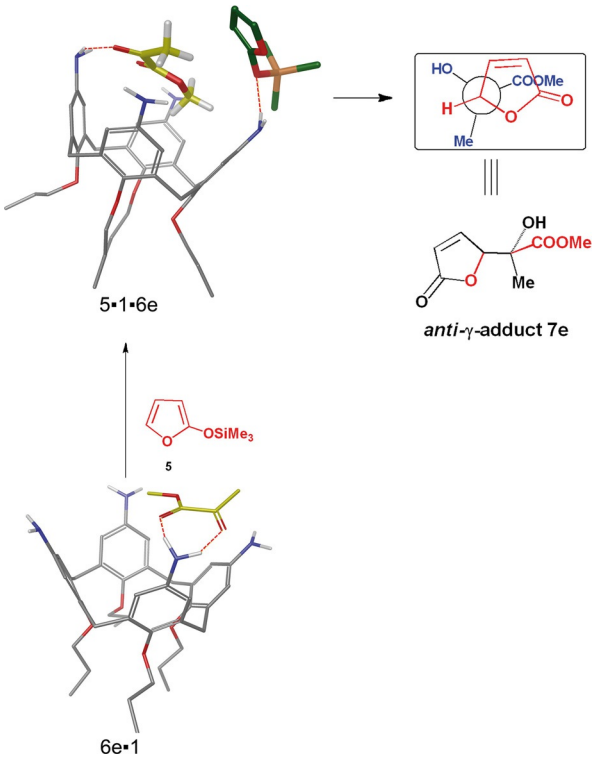


Figure 4. Plausible catalytic cycle for the VMAR that is catalyzed by calixarene catalyst **1**. a) Model of the complex **6e·1** obtained by molecular mechanics calculations (AMBER force field). b) Model of the ternary complex **5·1·6e** obtained by molecular mechanics calculations (AMBER force field). c) Proposed transition states for the "on-water" VMAR of substrates **5** and **6e** in the presence of catalyst **1**. Green: 2-trimethyl silyloxyfuran **5**; yellow: α-keto ester **6e**; dotted red lines: hydrogen bonds.

between the carbonyl and amino groups are established. In the transition state, a ternary complex **5·1·6e** (Figure 4) was formed, in which the carbonyl group of substrate **6e** was activated by a H bond with the amino group of calixarene **1** and a proximal amino group forms a H bond with the oxygen atom of the silyloxy group of compound **5**. The ternary complex **5·1·6e** is further stabilized by C–H···π interactions between the α-methyl group of compound **6e** and the furan ring of compound **5**, which leads to the favorable attack at the activated carbonyl group of compound **6e** from the *Re* face of furan **5**. Analogous results were found for the corresponding ethyl acetylformate substrate **6f**, which gave similar experimental results under the VMAR conditions (Table 3, entry 6).

When ethyl 4-cyano-benzoylformate **6i** was reacted with furan **5** in the presence of catalyst **1** under "on-water" conditions, a conversion of 99% was reached after just 36 min. Surprisingly, a *syn*/*anti* ratio of 99:1 was observed (entry 9). Analogously, a high *syn* preference was observed with the substrate ethyl 4-nitro-benzoylformate **6j**, which showed a 99% conversion to product **7j** after 4 h with a *syn*/*anti* ratio of 95:5 (entry 10).

The high preference for the *syn* diastereoisomer that was observed with the substrates **6i** and **j** was most likely due to the more compact transition state[31] that leads to the *syn* isomer. In fact, a close inspection of the minimized structure of

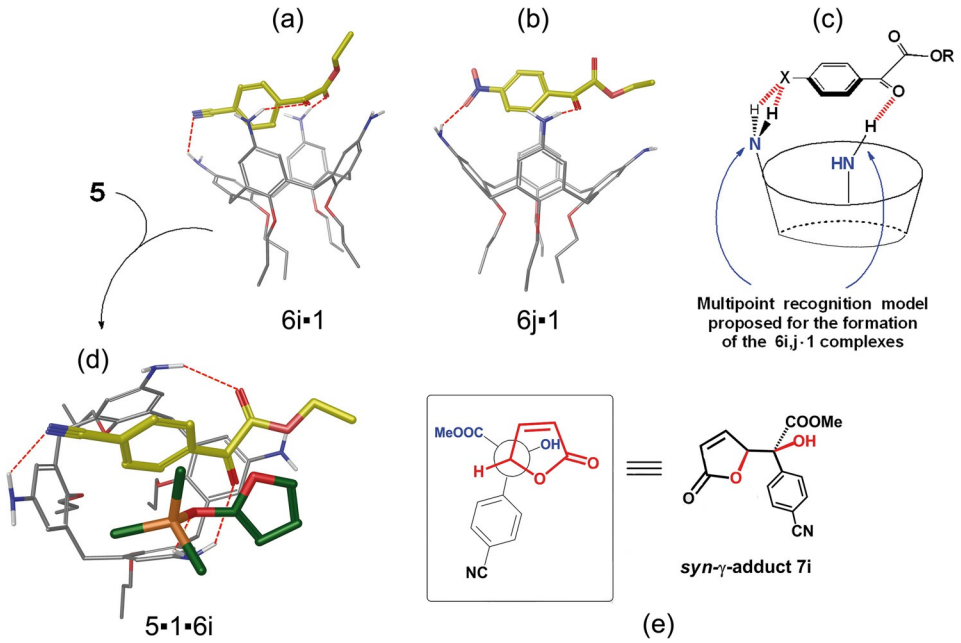


Figure 5. a), b) Minimized structures (molecular mechanics calculations, AMBER force field) of the **6i·1** and **6j·1** complexes. c) Multipoint recognition model proposed for the activation of the substrates **6i** and **j**. Plausible catalytic cycle for the VMAR catalyzed by calixarene **1**. d) Model of the ternary complex **5·1·6i** obtained by molecular mechanics calculations. (e) Proposed transition states for the "on-water" VMAR of substrates **5** and **6i** in the presence of catalyst **1**. Green: 2-trimethyl silyloxyfuran **5**; yellow: α-keto esters **6i** and **j**; dotted yellow lines: hydrogen bonds.

the complex **6i·1** (Figure 5a) revealed a multipoint recognition (Figure 5c) of the substrate **6i**, in which both CN and C=O groups are engaged in H-bond interactions with proximal amino groups of calixarene **1**. It is likely that the multipoint H-bonding interactions between compound **6i** and calixarene **1** lead to a higher degree of stabilization, which provides a more compact transition state after the attack of the furanone **5** (Figures 5d and e). In a similar way, the minimized structure of the complex **6j·1** (Figure 5b) revealed a multipoint recognition of the substrate **6j**, in which both NO_2 and C=O groups were engaged in H-bonding interactions with proximal amino groups of calixarene **1** (Figure 5c). Interestingly, when the *para* position of compound **6** was occupied by a non-H-bonding group, such as the CH_3 of 4-methyl-benzoylformate **6h**, the VMAR led to a lower *syn*/*anti* ratio (70:30, Table 3, entry 7).

At this point, the question as to whether the high *syn* preference that was observed in products **7i** and **j** (Table 3, entries 9 and 10) could be alternatively determined by the electron-withdrawing effect of the cyano and nitro groups in substrates **6i** and **j** was considered. Therefore, we investigated the VMAR on trifluoroacetylformate substrate **6l**, which contained an electron-withdrawing trifluoromethyl group. In this instance, the minimized structure indicated that substrate **6l** was too short to match with the multipoint recognition model proposed in Figure 5c, which would predict a lower *syn* preference. After a reaction time of 4 h, we were delighted to observed that a 99% of conversion to product **7l** was reached with a "normal" *syn*/*anti* ratio of 60:40 (entry 12). Analogously, with ethyl 4-chloro-benzoylformate **6g**, a 99% conversion to product **7g** was also achieved after 4 h (entry 7) with a *syn*/*anti* ratio of 70:30. These results lend a strong support to the multipoint recognition of the substrate **6i** and **j**, which lead to a more compact transition state during the attack of furanone **5** and display a higher *syn* preference.

Single crystal X-ray analysis

For γ-butenolide derivative **7i**, crystals that were suitable for X-ray analysis were obtained from $CH_3OH/CHCl_3$.Consistently with the aforementioned result, the structure determination by VLD methods indicated that compound **7i** crystallized in a polar space group ($Pn2_1a$).The high-quality diffraction data, which was collected from a frozen crystal with brilliant synchrotron radiation, permitted the unambiguous determination of the absolute structure of the crystal. The structure refinement revealed that the mounted crystal corresponded to the *syn*-**7i** diastereoisomers (Figure 6). The relative stereochemistry of derivative**7i** was assigned accordingly, whereas for derivatives **7a–h,j–l**, the *syn*/*anti* stereochemistry was assigned on the basis of the reported NMR spectral data.[20–22]

Conclusion

On the basis of the known hydrophobic amplification of weak interactions between catalyst and substrate under "on-water" conditions, we have designed a simple calixarene **1**, that bears weak H-bond-donor NH_2 groups. We demonstrated that, under "on-water" conditions, compound **1** is a highly efficient organocatalyst for the Vinylogous Mukaiyama Aldol Reaction (VMAR) of 2-(trimethylsilyloxy)furan **5** with α- ketoesters **6a–l**. Interestingly, this "on-water" catalytic activity is superior to the

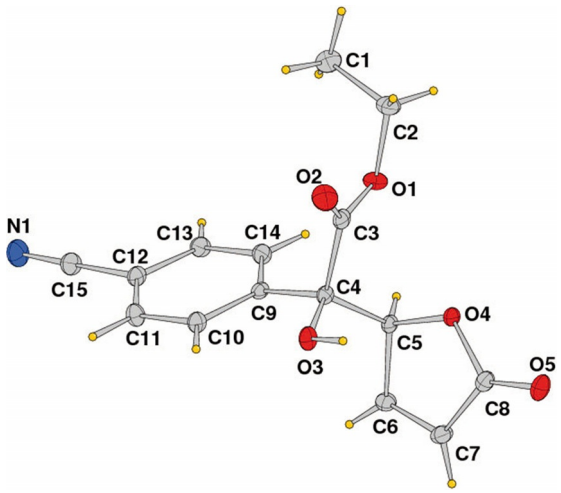


Figure 6. ORTEP representation of the asymmetric unit of compound (*R,S*)-*syn*-**7 i**. Ellipsoids are displayed at 50% probability. CCDC 1523707 (**7 i**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

corresponding catalytic performance in organic solvents. Our studies indicate that in the catalytic cycle, calixarene **1** establishes H-bonding interactions through its amino groups with the substrate **6** and furanone **5** through a multipoint recognition model. This model explains the differences in the reaction rate acceleration and the stereoselectivity observed with different substrates.

The results reported here can be considered an interesting example of "on-water" hydrophobic amplification of organocatalytic activity and could allow the development of new environmentally orientated catalytic approaches. It is expected that the hydrophobicity and the synthetic versatility of calixarene macrocycles could play further important roles for the design of novel supramolecular organocatalysts.

Experimental Section

General

Chemicals were reagent grade and were used without further purification. Anhydrous solvents were purchased from Aldrich. Reaction temperatures were measured externally. Reactions were monitored by TLC on Merck silica gel plates (0.25 mm) and visualized by UV light and spraying with H_2SO_4–$Ce(SO_4)_2$ or phosphomolibdic acid. Flash chromatography was performed on Merck silica gel (60, 40–63 μm). NMR spectra were recorded on Bruker Avance-600 spectrometer (^{1}H: 600.13 MHz, ^{13}C: 150.03 MHz), Bruker Avance-400 spectrometer (^{1}H: 400 MHz, ^{13}C: 100.57 MHz), Bruker Avance-300 spectrometer (^{1}H: 300 MHz, ^{13}C: 75.48 MHz), or Bruker Avance-250 spectrometer (^{1}H: 250 MHz, ^{13}C: 62.80 MHz); chemical shifts are reported relative to the residual solvent peak ($CHCl_3$: $\delta = 7.26$ ppm, $CDCl_3$: $\delta = 77.23$ ppm). Derivatives **1**,[19a] **2**,[32] **3**,[19b] **4**[6a] and ketoesters **6 c**,[33] **6 d**,[34] and **2 b**[27] were synthetized according to literature procedures. Melting points were measured on a Stuart melting point apparatus (SMP3). High-resolution mass spectra (HRMS) were acquired by using a Bruker solariX XR Fourier transform ion cyclotron resonance mass spectrometer equipped with a 7 T refrigerated actively-shielded superconducting magnet. The samples were ionized in positive ion mode by using the ESI ion source (Bruker Daltonik GmbH, Bremen, Germany). The mass range was set to *m/z* 150–3000. The mass spectra were calibrated externally by using a NaTFA solution in positive-ion mode. A linear calibration was applied. The purity of all final compounds was determined by elemental analysis on a Flash EA 1112 Series with Thermal Conductivity Detector, for C, H, N, and S. The final compounds were found to be >95% pure when analyzed. Molecular mechanics calculations were performed with MacroModel-9.0/Maestro-4.1 by using AMBER force field.[35]

X-ray crystallography

Single-crystal diffraction data for the structural determination of compound **7 i** was collected with the rotating-crystal method by using synchrotron radiation at the XRD1 beamline of the Elettra Synchrotron, Trieste, Italy. A moist single crystal was attached to a loop and flash-frozen to 100 K in a stream of N_2 vapour.

Cryoprotection was not employed. Diffraction images were indexed and integrated by using the XDS[36] package and the resulting data sets were scaled by using XSCALE.[37] The crystal structures were determined by VLD Phasing with SIR-2014[38] and refined with SHELX-14,[39] which was operated through the WinGX GUI.[40] Thermal parameters of all non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed at the geometrically calculated positions and refined by using the riding model. Crystallographic data and refinement details are reported in Table S2 (see the Supporting Information).

General procedure for on water catalysis of VMAR in the presence of a calixarene catalyst

A mixture of the appropriate α-ketoester **6 a**–**l** (0.23 mmol) and catalyst **1**–**3** (0.011 mmol) was vigorously stirred in the presence of 2-(trimethylsilyloxy)furan (TMSOF, **5**, 0.053 g, 0.34 mmol) in the appropriate solvent (H_2O, D_2O, or organic solvent, 1 mL). The reaction mixture was kept under magnetic stirring (1400 rpm) at 30 °C for the appropriate time (see Table 3) and then extracted with ethyl acetate (3×5 mL) (except for the reaction with α-ketoester **5 i** for which chloroform was used). The combined organic phases were dried over Na_2SO_4, the solids were removed by filtration, and the filtrate was concentrated under reduced pressure. Diastereoisomeric ratios and percentages of conversion of the γ-adducts **7 a**–**h**, **7 j**–**l** were determined by integration of the ^{1}H NMR signals of the crude reaction mixtures in comparison with the literature values.[20–22] The crude reaction mixture was purified by flash chromatography on silica gel to give *syn* and *anti* diastereoisomers.

Derivatives 7 a, c, d, e, f, and l: They were prepared in accordance with the general procedure by using the appropriate α-ketoesters and 2-(trimethylsilyloxy)furan (**5**) in the presence of catalyst **1**. The residue was purified by flash chromatography on silica gel (hexane/EtOAc, 80:20) to give *anti* and *syn* diastereoisomers. Yields and diastereoisomeric ratios are listed in Table 3. Spectroscopic data of *anti* and *syn* diastereoisomers matched those reported in literature.[20–22]

Derivative 7 b: Prepared according to the general procedure from **6 b**, 2-(trimethylsilyloxy)furan (**5**), and catalyst **1**. The residue was purified by flash chromatography on silica gel (hexane/EtOAc, 80:20) to give *anti* and *syn* diastereoisomers. Yield: 74% (combined yield of isolated diastereoisomers); d.r. = 38:62 (37:63 after chromatography).

anti-***7 b***: Isolated as a white solid. The spectroscopic data for *anti*-**7 b** isomer matched those reported in literature.[20]

syn-**7b**: Isolated as a white solid; m.p. 115–116 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): $\delta = 1.35$ (t, $J = 7.1$ Hz, 3H; OCH_2CH_3), 3.89 (s, 1H; OH), 4.29–4.43 (m, 2H; OCH_2CH_3), 5.77 (s, 1H; C*H*), 6.16 (d, $J = 5.6$ Hz, 1H; =C*H*), 6.96 (d, $J = 6.0$ Hz, 1H; =C*H*), 7.39–7.44 (m, 1H; Ar*H*), 7.41 (d, $J = 7.6$ Hz, 2H; Ar*H*), 7.70 ppm (d, $J = 7.6$ Hz, 2H; Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): $\delta = 14.2$ (CH_3), 63.9(CH_2), 77.4 (C), 86.4 (CH), 124.0 (CH), 125.7 (2C, $C_{Ar}H$), 129.0 (2C, $C_{Ar}H$), 129.2 ($C_{Ar}H$), 136.5 ($C_{Ar}C$), 151.6 (CH), 171.8 (C), 172.8 ppm (C); HRMS (ESI-FTICR): *m/z* calcd for $C_{14}H_{14}O_5Na$: 285.07334 [*M*+Na^+]; found: 285.07355; elemental analysis calcd (%) for $C_{14}H_{14}O_5$ (MW = 262.26): C 64.12, H 5.38; found C 64.03, H 5.29.

Derivative 7g: Prepared according to the general procedure from **6g**, 2-(trimethylsilyloxy)furan **5**, and catalyst **1**. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 85:15) to give *anti* and *syn* diastereoisomers. Yield: 99% (combined yield of isolated diastereoisomers); d.r. = 30:70 (28:72 after chromatography).

anti-**7g**: Isolated as a white solid. The spectroscopic data for *anti*-**7g** matched those reported in literature.[21]

syn-**7g**: Isolated as a white solid; m.p. 124.5–126.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): $\delta = 1.35$ (t, $J = 7.2$ Hz, 3H; OCH_2CH_3), 3.93 (s, 1H, OH), 4.29–4.43 (m, 2H, OCH_2CH_3), 5.69–5.70 (m, 1H, CH), 6.18 (dd, $^4J = 2.1$ Hz, $^3J = 5.8$ Hz, 1H; =CH), 6.95 (dd, 1H, $^4J = 1.5$ Hz, $^3J = 5.8$ Hz; =CH), 7.39 (d, $J = 8.8$ Hz, 2H; Ar*H*), 7.65 ppm (d, $J = 8.8$ Hz, 2H; Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$, 298 K): $\delta = 14.2$ (CH_3), 64.1 (CH_2), 77.4 (C), 86.2 (CH), 124.3 (CH), 127.3 (2C, $C_{Ar}H$), 129.2 (2C, $C_{Ar}H$), 135.0 ($C_{Ar}C$), 135.4 ($C_{Ar}C$), 151.2 (CH), 171.4 (C), 172.5 ppm (C); HRMS (ESI-FTICR): *m/z* calcd for $C_{14}H_{13}ClO_5Na$: 319.03437 [*M*+Na^+]; found: 319.03436; elemental analysis calcd (%) for $C_{14}H_{13}ClO_5$ (MW = 296.70): C 56.67, H 4.42; found C 56.75, H 4.33.

Derivative 7h: Prepared according to the general procedure from **6h**, 2-(trimethylsilyloxy)furan **5**, and catalyst **1**. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 85:15) to give *anti* and *syn* diastereoisomers. Yield: 36% (combined yield of isolated diastereoisomers); d.r. = 30:70 (28:72 after chromatography).

anti-**7h**: Isolated as a white solid. The spectroscopic data for *anti*-**7h** diastereoisomer matched those reported in literature.[21]

syn-**7h**: Isolated as a white solid; m.p. 98–100 °C; ^{1}H NMR (600 MHz, $CDCl_3$, 298 K): $\delta = 1.35$ (t, $J = 7.1$ Hz, 3H; OCH_2CH_3), 2.37 (s, 3H, CH_3), 3.86 (bs, 1H, OH), 4.29–4.41 (m, 2H, OCH_2CH_3), 5.75–5.76 (m, 1H, CH), 6.16 (dd, $^4J = 1.9$ Hz, $^3J = 5.8$ Hz, 1H; =CH), 6.98 (dd, $^4J = 1.4$ Hz, $^3J = 5.8$ Hz, 1H; =CH), 7.23 (d, 2H, $J = 8.1$ Hz, Ar*H*), 7.57 ppm (d, 2H, $J = 8.3$ Hz, Ar*H*); ^{13}C NMR (150 MHz, $CDCl_3$, 298 K): $\delta = 14.2$ (CH_3), 21.2 (OCH_2CH_3), 63.8 (CH_2), 77.4 (C), 86.4 (CH), 123.9 (CH), 125.5(2C, $C_{Ar}H$), 129.7 (2C, $C_{Ar}H$), 133.5 (Ar-C), 139.1 (Ar-C), 151.7 (CH), 171.9 (C), 172.8 ppm (C); HRMS (ESI-FTICR): *m/z* calcd for $C_{15}H_{16}O_5Na$: 299.08899 [*M*+Na^+]; found : 299.08917; elemental analysis calcd (%) for $C_{15}H_{16}O_5$ (MW = 276.29): C 65.21, H 5.84, found C 65.33, H 5.76.

Derivative 7i: Prepared according to the general procedure from **6i**, 2-(trimethylsilyloxy)furan **5**, and catalyst **1**. The residue was purified by flash column chromatography on silica gel ($CHCl_3$) to give the single *syn* diastereoisomer. Yield: 99%, d.r. > 1:99.

syn-**7i**: Isolated as a white solid; m.p. 154–155 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): $\delta = 1.36$ (t, $J = 7.2$ Hz, 3H; OCH_2CH_3), 4.07 (s, 1H, OH), 4.32–4.44 (m, 2H, OCH_2CH_3), 5.70 (br m, 1H, CH), 6.20 (dd, $^4J = 1.9$ Hz, $^3J = 5.8$ Hz, 1H; =CH), 6.91 (dd, $^4J = 1.5$ Hz, $^3J = 5.8$ Hz, 1H; =CH), 7.73 (d, $J = 8.7$ Hz, 2H; Ar*H*), 7.87 ppm (d, $J = 8.7$ Hz, 2H; Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): $\delta = 14.2$ (CH_3), 64.5 (CH_2), 77.4 (C), 85.9 (CH), 113.3 (Ar-CN), 118.3 (CH), 124.6 (2C, $C_{Ar}H$), 126.8 (2C, $C_{Ar}H$), 132.7 (Ar-C), 141.6 (Ar-C), 150.6 (CH), 170.7 (C), 172.2 ppm (C); HRMS (ESI-FTICR): *m/z* calcd for $C_{15}H_{13}NO_5Na$: 310.06859 [*M*+Na^+]; found: 310.06972; elemental analysis calcd (%) for $C_{15}H_{13}NO_5$ (MW = 287.27): C, 62.72, H, 4.56, N, 4.88; found C, 62.80, H, 4.47, N, 4.91.

Derivative 7j: Prepared according to the general procedure from **6j**, 2-(trimethylsilyloxy)furan **5**, and catalyst **1**. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 80:20) to give *anti* and *syn* diastereoisomers. Yield: 98% (combined yield of isolated diastereoisomers); d.r. = 5:95 (> 1:99 after chromatography).

The spectroscopic data for *anti*-**7j** (yellow oil) and *syn*-**7j** (orange solid) isomer matched those reported in literature.[20]

Derivative 7k: Prepared according to the general procedure from **6k**, 2-(trimethylsilyloxy)furan **5**, and catalyst **1**. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 85:15) to give *anti* and *syn* diastereoisomers. Yield: 80% (combined yield of isolated diastereoisomers); d.r. = 46:54 (unchanged after chromatography).

anti-**7k**: Isolated as a yellow oil. The spectroscopic data for *anti*-**7k** isomer matched those reported in the literature.[21]

syn-**7k**: isolated as a white solid; m.p. 95–96 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): $\delta = 1.37$ (t, $J = 7.1$ Hz, 3H, OCH_2CH_3), 4.22 (s, 1H, OH), 4.34–4.44 (m, 2H, OCH_2CH_3), 5.62 (br, 1H, CH), 6.20 (dd, $^4J = 2.0$ Hz, $^3J = 5.8$ Hz, 1H; =CH), 7.05 (dd, $^4J = 3.7$ Hz, $^3J = 5.1$ Hz, 1H; =CH), 7.13 (dd, $^4J = 1.5$ Hz, $^3J = 5.8$ Hz, 1H; =CH), 7.24–7.26 (m, overlapped with residual signal of $CHCl_3$ in $CDCl_3$), 7.34 ppm (dd, $^4J = 1.2$ Hz, $^3J = 5.1$ Hz, 1H; =CH); ^{13}C NMR (75 MHz, $CDCl_3$, 298 K): $\delta = 14.1$ (CH_3), 64.1 (CH_2), 77.4 (C), 86.4 (CH), 124.1 (CH), 125.3 (CH), 126.6 (CH), 127.8 (CH), 140.5 (C), 151.3 (CH), 170.8 (C), 172.4 ppm (C). HRMS (ESI-FTICR): *m/z* calcd for $C_{12}H_{12}O_5SNa$: 291.02976 [*M*+Na^+]; found: 291.02979; elemental analysis calcd (%) for $C_{12}H_{12}O_5S$ (MW = 268.28): C 53.72, H 4.51, S 11.95, found C 53.81, H 4.45, S 12.83.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: aldol reaction · calixarenes · hydrophobic effect · organocatalysts · supramolecular chemistry

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