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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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Dedication ((optional))

Abstract: The simple tetraminocalix[4]arene **1**, bearing weak H-bond donor NH_2 groups, is 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”, thanks to the hydrophobic amplification of weak interactions. The catalytic efficiency of calixarene catalyst **1** is closely related to its recognition abilities toward the reactants **5** and **6** through a multipoint recognition model. The proposed model provides good explanations for the differences on the reaction rate acceleration and on the stereoselectivity observed with different substrates.

Introduction

From their birth to now, calixarenes[1] have gradually gained a prominent position in a wide range of supramolecular applications, including molecular recognition and sensing,[2] self-assembly processes,[3] and 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] thanks to which reactive catalytic groups can be introduced on both rims, and to their recognition abilities, which offer the possibility to discriminate among 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 it has become an attractive topic in current organocatalysis.[9,10] In comparison to organic solvents, water as medium provides promising benefits with respect to environmental impact, reaction rate acceleration,[7-10] and switching of the stereo- and regio-selectivity.[9a,11] Subsequently, Sharpless firstly introduced 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 in water of the reacting species and catalyst is 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] thus amplifying the secondary interactions between them and favoring the molecular collisions. Although water as solvent can interfere in the formation of H-bonds between catalyst and substrate, many examples have been reported of hydrogen bonding[14] promoted organocatalysis under on-water conditions,[15] in which a hydrophobic amplification of the H-bonds between the catalyst and the substrate permits the activation of this 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 under ""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" has been neglected.[7]

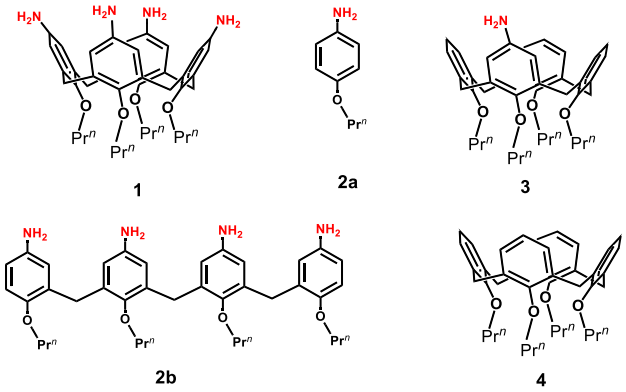

Figure 1. Structure of screened catalysts **1-4.**

Recently, we have investigated the catalysis under "on-water conditions" of the Vinylogous[18a-g] Mukaiyama Aldol Reaction (VMAR)[18h-l] using thioureido-calixarene organocatalysts.[7] We have shown that the reaction rate acceleration is closely related to the hydrophobicity of the calixarene scaffold, in conjunction with its ability to recognise the substrate via H-bonding

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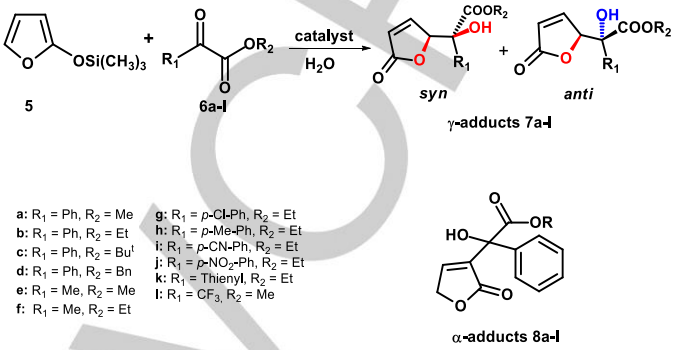
interactions with the thioureido group.

On this basis it is probable that, thanks to the amplification commonly observed under "on-water conditions", even weaker H-bond donor groups could be able to 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) bearing weak H-bond donor groups. Thus, we envisioned that under "on-water conditions", even the weak H-bond donor NH_2 groups of **1** should be effective to activate the substrate **6** in the VMAR (Scheme 1), on the basis of the hydrophobic amplification, and we wish to report here the results of our study.

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 containing tertiary hydroxy groups, as useful building blocks for biological and pharmaceutical products.[23]



a: R_1 = Ph, R_2 = Me
b: R_1 = Ph, R_2 = Et
c: R_1 = Ph, R_2 = Bu^t
d: R_1 = Ph, R_2 = Bn
e: R_1 = Me, R_2 = Me
f: R_1 = Me, R_2 = Et
g: R_1 = *p*-Cl-Ph, R_2 = Et
h: R_1 = *p*-Me-Ph, R_2 = Et
i: R_1 = *p*-CN-Ph, R_2 = Et
j: R_1 = *p*-NO_2-Ph, R_2 = Et
k: R_1 = Thienyl, R_2 = Et
l: R_1 = CF_3, R_2 = Me

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

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

Entry[a]	Catalyst	Medium	Time (h)	Conversion to **7a** [%][b]	Dr (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: **6a** (0.23 mmol), **5** (0.34 mmol) and 5.0 mol % of catalyst **1** in 1 mL of medium 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 using a reciprocal shaker with an agitation speed = 1400 rpm. [g] The reaction was performed in the presence of 20 mol % of catalyst. [h] See reference 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-regioselectivity between **5** and **6a** in the presence of catalyst **1** (Table 1).

Interestingly, using water as medium for 4 hours (entry 3, Table 1), an almost quantitative conversion (99 %) of **6a** to the γ-adduct **7a** was observed, with a *syn/anti* ratio of 63/37, while no trace of the α-adduct **8a** was detected. Under these conditions, the reactants **5** and **6a** and the catalyst **1** were insoluble, and therefore, the suspension was vigorously stirred magnetically.

When the above "on-water" VMAR was performed in the absence of catalyst **1**, 28 % of conversion to **7a** was observed after 14 h (entry 1, Table 1), with a switch of the stereoselectivity in favor of the *anti* adduct (*syn/anti* ratio of 32/68). This result clearly indicated that the presence of **1** accelerates the rate of conversion of **5** and **6a** to **7a** thanks 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 transition state (**I**) proposed in Figure 2. It is very likely that the H-bonds (in red in Figure 2) between the amino group of **1** and the carbonyl group of **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 **6a** from the *Re* face of **5** is favored, probably thanks to the stabilization of the ternary complex **5**·**1**·**6a**, (see the proposed model obtained by molecular mechanics calculations, Figure 2) induced by a multipoint recognition of **5** and **6a** via H-bonds (see Figure 2).

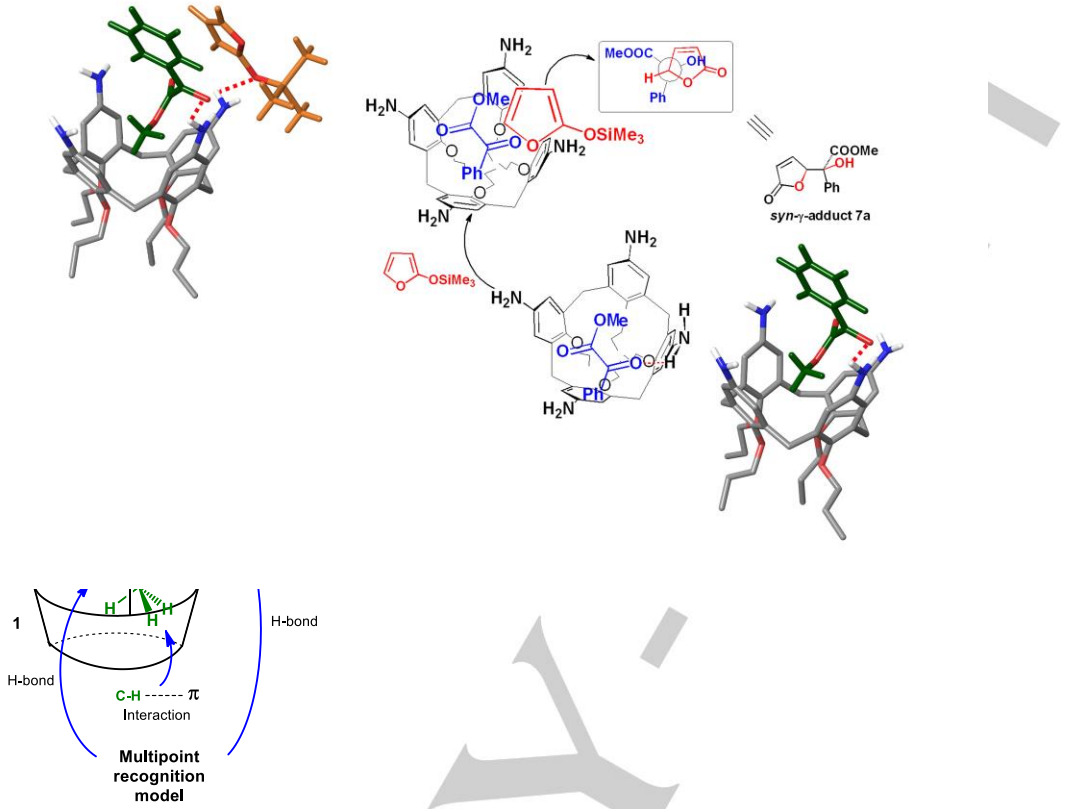


Figure 2. Plausible catalytic cycle for the VMAR catalyzed by calixarene catalyst **1**. (a) Model of the complex **6a**·**1** obtained by molecular mechanics calculations (AMBER force field). (b) Model of the ternary complex **5**·**1**·**6a** obtained by molecular mechanics calculations and multipoint recognition model proposed for the activation of the substrate **6a**. (c) Proposed transition states for the on-water VMAR of **5** and **6a** catalyzed by **1**. (b and c) In green α-ketoester **6a**, in orange2-(trimethylsilyloxy)furan **5**, the dotted lines in red indicate H-bonds.

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

The addition of **6a** to the solution of **1** caused a slight downfield shifts of the NMR signal of the aromatic hydrogen atoms in *ortho* to NH_2 groups of **1** (Figure S23). This indicated that the NH_2 groups were engaged in H-bonding interactions with the carbonyl group of **6a** (Figure 2) with a fast complexation equilibrium. A nonlinear least-squares fitting for the ArH signal gave an association constant value of 35±5 M^{-1} for the complexation of **6a** with **1** in accordance with the weak H-bond-donating abilities of the NH_2 groups. Similar results were obtained with substrate **6i** (Figure S24) with an association constant value of 78±7 M^{-1}. Finally, we have performed DFT calculations with the aim to evaluate the H-bond strenght between the NH_2 groups of **1** and the carbonyl groups of **6a.**
In details, the H-bond strengths was estimated through the magnetically induced currents[26] adopting a computational protocol recently reported.[26] The DFT calculation at the B3LYP/6-31G* level of theory, indicated an energy value of 2.5 kcal/mol for the Calix–NH-H···O=C(Ph)COOMe H-bond; a value significantly lower (< 1 kcal/mol) was found for the H-bonding interaction between NH_2 group of **1** and carbonyl ester of **6a**. In

conclusion, DFT calculations indicated that the H-bonding interaction between the amino group of **1** and the ketone carbonyl group of **6a** is classifiable as a weak H-bonding interaction.[27]

Table 2. Optimization of the reaction conditions for VMAR of **5** with **6a** catalyzed by **1** under "on-water conditions"

Entry[a]	1 (mol%)	Additive (mol %)	T (°C)	Conversion to 7a [%][b]	Dr (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**	nd	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**	nd	1

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

When the VMAR between **5** and **6a** in the presence of **1** as catalyst was performed in organic solvents, such as CH_2Cl_2 (entry 4, Table 1), Toluene (entry 5, Table 1), or THF (entry 6, Table 1), the conversion to **7a** was lowered to 50, 43, and 64 %, after 14 h, respectively, thus supporting the concept of hydrophobic amplification. Further supporting evidence was obtained by performing the VMAR between **5** and **6a** in the presence of **1** in D_2O as medium.

Under these conditions (entry 8, Table 1) a 34 % of conversion of **6a** to **7a** was observed after 34 h. This lower efficiency with respect to H_2O (99 % after 4 h) 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 **5** and **6a** was conducted in the presence of the monomeric counterpart **2a** as catalyst under on-water conditions, then a 48 % of conversion to **7a** was obtained after 4 h (entry 10, Table 1) and a slight improvement was observed with prolonged reaction times (entry 11, Table 1), indicating a significantly lower catalytic efficiency with respect to **1** (99 % after 4 h).

Additionally, it is noteworthy that the use of the linear tetramer **2b**[28] as catalyst was considerably less efficient than **1**, under the same reaction conditions, leading to a conversion similar to that obtained in the absence of any catalyst (30 % after 4h, entry 12, Table 1). Clearly, this latter result highlight the importance of the calixarene cavity and indicates that the catalytic efficiency of **1** is also related to the preorganization[29] of the catalyst. In fact, differently by the conformationally mobile catalyst **2b**, the calix[4]arene **1,** as is known,[19a] is blocked (preorganized) in the cone-structure and in this way facilitating the formation of H-bond interactions between the amino-groups at the upper rim of **1** and the substrate, in accord with the multipoint recognition model proposed in Figure 2.

In addition, when the reaction was performed in the presence of 20 % of catalyst **3** (Figure 1), bearing a single-amino group at the calix[4]arene upper rim, the aldol adduct **7a** was obtained in 77 % after 14 h, while 5 % of **1** is already sufficient to give a 99 % of conversion after 4 h (entries 13 and 3, Table 1). The 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 to optimize the reaction conditions, we studied the VMAR between **5** and **6a** in the presence of **1** under on-water conditions by changing the reaction time, the percentage of catalyst, and the temperature. By shortening the reaction time from 4 to 2 h, a drop in the yield from 99 to 74 % was observed (entry 1, Table 2). A lower percentage of catalyst **1** led to a worsening of conversion to **7a** (80 % after 14 h, entry 3 in Table 2). Analogously, an increase of the reaction temperature from 30 to 50 °C led to a lower conversion (53 % after 14 h, entry 6 in Table 2).

It has been reported that the protonation of the amino groups in 2,2'-diamino-1,1'-binaphthyl organocatalyst[24] leads to an improvement of 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. Prompted by these results,[24] we studied the catalytic efficiency of **1** toward the VMAR in Scheme 1 in the presence of acid co-catalysts (entries 7–10, Table 2). From our screening, it was clear that the combination of catalyst **1** with acid additives (entries 7-10, Table 2) did not imply any improvements, likely because the formation of anilinium species leads to an higher cation hydration and/or water-solubility of **1**. Finally, we have compared the catalytic efficiency of tetraminocalix[4]arene **1** toward the VMAR in Scheme 1 with that of $Cu(OTf)_2$, recently reported.[20] The reaction between **6** and **5a** (1.5 equiv) in presence of $Cu(OTf)_2$ (5.0 % mol, in 1 mL of wate rat 30 °C under rapid and vigorus magnetic stirring) revealed a moderate catalytic efficiency with a conversion of 48 % after 4 h significantly lower than that achieved using tetraminocalix[4]arene catalyst **1** (99% after 4h, entry 3, Table 1). Furthermore, using $Cu(OTf)_2$ a reversal of diastereoselectivity in favor of the *anti* adduct was observed with a *syn/anti* ratio of 21/79 compared to 64/36 in the presence of catalyst **1**. Thus,

this result highlight the potentialities of calixarene **1** as organocatalyst under on-water conditions in terms of high efficiency and stereoselectivity.

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

Table 3. Evaluation of substrate scope for VMAR between TMSOF **5** and ketoesters **6a-l** for VMAR catalyzed by **1** under "on-water conditions".

Entry[a]	6	Product	Time (h)	Yield [%][b]	Dr (*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: **6** (0.23 mmol), **6** (0.34 mmol) and 5.0 mol % of catalyst **1** in 1 mL of medium at 30°C and under rapid and vigorous magnetic stirring.[b] Combined yield of isolated diastereomers after column chrromatography. [c] Determined by ^{1}H NMR analysis of crude mixturereaction according to literature data[20-22]; in parentheses, dr of the product after column chromatography.

With these conditions in hand, we next studied the VMAR with a variety of substrates (Table 3). In detail, when ethyl, *tert*-butyl, and benzyl esters **6b**–**d** were used as the substrate in the presence of **1**, then conversions to the corresponding derivatives **7b**–**d** of 74, 85, and 86 %, respectively (entries 2-4, Table 3), were observed, indicating a lower efficiency with respect to methyl ester **6a**, while the preference for the *syn* diastereoisomer was respected in all cases, in addition no trace of the α-adducts **8b**–**d** was detected. In order to rationalize these data, we performed molecular mechanics calculations (AMBER force field) to investigate the structure of the complexes between the calix[4]arene catalyst **1** and the α-ketoester substrates **6.**

A close inspection of the minimized structure **6a▪1** in Figure 2 reveals that the methyl group of ketoester **6a** is included in the aromatic cavity of **1** optimally oriented to establish C-H···π interactions (average distance C-H···$\pi^{centroid}$ = 2.76 Å)[30] (see Figure 3). In addition, weak H-bonding interactions were detected between two NH_2 groups of **1** and the two carbonyl group of **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 the complexes only due to weak H-bonds between amino and carbonyl groups, while the alkyl groups of the ester moiety of **6b**–**c** are too large to occupy the calix-cavity of **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.

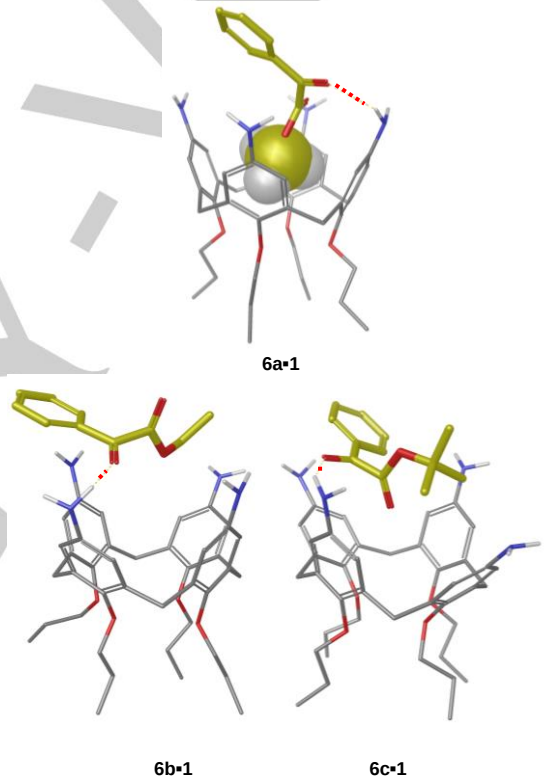


Figure 3. Optimized structure of the **6a**–**c▪1** complexes obtained by molecular mechanics calculations (AMBER force field).

The substitution of the phenyl group of benzoylformate **6a** with a methyl group in acetyl formate **6e** has no influence on the catalytic efficiency of **1**. In fact, the conversion to **7e** was 99 % after 4 h, perfectly matching the value found for the conversion of **6a** to **7a**. Surprisingly, with substrate **6e** a switch of the stereoselectivity was observed, with a 61/39 *anti*/*syn* ratio (entry 5, Table 3). The model of the complex **6e·1** (Figure 4) shows that **6e** is lying on the upper rim of **1,** establishing H-bonding interactions between carbonyl and amino groups. In the transition state (Figure 4), a ternary complex **5·1·6e** is formed in which the carbonyl group of **6e** is activated by a H-bond with the

amino group of **1**, while a proximal amino group forms a H-bond with the oxygen of the silyloxy group of **5.** The ternary complex **5·1·6e** (Figure 4) is further stabilized by C-H▪▪▪π interactions between the α-methyl group of **6e** and the furan ring of **5**, favoring thus the attack at the activated carbonyl group of **6e** from the *Re* face of **5**. Analogous results were found for the corresponding ethyl acetylformate substrate **6f**, which gave similar experimental results (entry 6, Table 3).

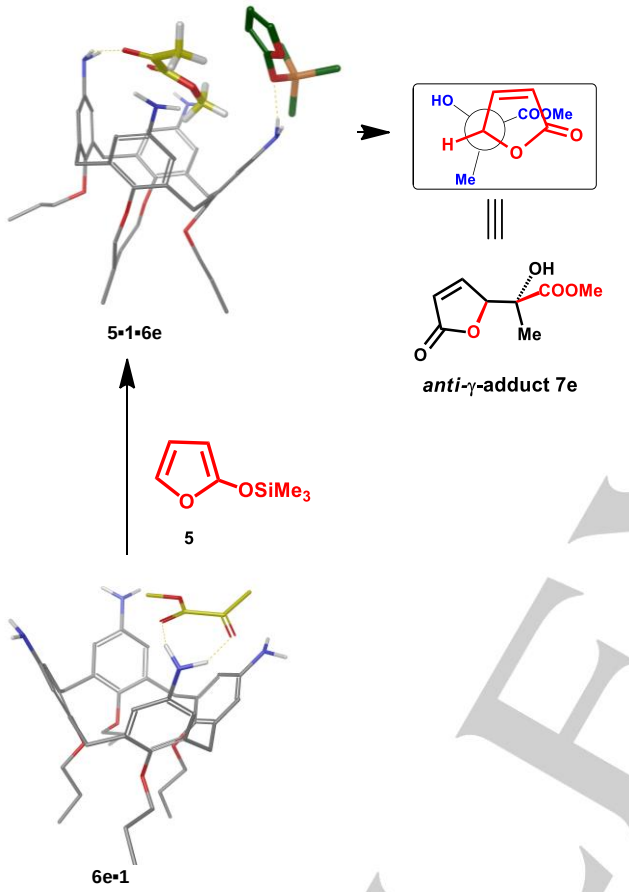


Figure 4. Plausible catalytic cycle for the VMAR catalyzed by calixarene catalyst **1**. (a) Model of the complex **6e·1** obtained by molecular mechanics calculations (AMBER force field). (b) Model of the ternary complex **5·1·6e** obtained by molecular mechanics calculations (AMBER force field). (c) Proposed transition states for the on water VMAR of **5** and **6e** catalyzed by **1**. (b and c) In green 2-trimethyl silyloxyfuran **5, in** yellowα-keto ester **6e**, the dotted lines in red indicate the hydrogen bonds.

When ethyl 4-ciano-benzoylformate **6i** was reacted with **5** in the presence of **1** under on-water conditions, a conversion of 99 % was already reached after 36 min. and, surprisingly, a *syn*/*anti* ratio of 99/1 (entry 9, Table 3) was observed. Analogously, an excellent *syn*-preference was observed with the substrate ethyl 4-nitro-benzoylformate **6j** (entry 10, Table 3), which showed a 99 % conversion to **7j** after 4 h with a *syn*/*anti* ratio of 95/5.

Probably, the high *syn*-preference observed with the substrates **6i** and **6j** are due to more a compact transition state[31] leading to the *syn*-isomer. In fact, a close inspection of the minimized structure of 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-bonding interactions with proximal amino groups of **1** (Figures 5a and 5c). It is likely that the multipoint H-bonding interactions between **6i** and **1** leads to a higher complex stabilization, providing a more compact transition state after the attack of the furanone **5** (Figures 5d,e).In a similar way, the minimized structure of the complex **6j·1** (Figure 5b) reveals a multipoint recognition of the substrate **6j** in which both NO_2 and C=O groups are engaged in H-bonding interactions with proximal amino groups of **1** (Figure 5c). Interestingly, when the para position of **6** was occupied by non-H-bond-interacting groups, such as the CH_3 of 4-methyl-benzoylformate **6h**, then the VMAR led to a lower *syn*/*anti* ratio (70/30, entry 7 in Table 3).

At this point, the question arises as to whether the high *syn*-preference observed for **7i** and **7j** (entries 9 and 10 in Table 3) could be alternatively determined by the electron-withdrawing effect of the ciano and nitro groups in **6i** and **6j**. Thus, we decided to investigate the VMAR on trifluoroacetylformate substrate **6l** bearing an electron-withdrawing trifluoromethyl group. In this instance, the minimized structure indicates that substrate **6l** is too short to match with the multipoint recognition model proposed in Figure 5c, thus predicting a lower *syn*-preference. We were delighted to experimentally see that after 4 h a 99 % of conversion to **7l** was reached with a "normal" *syn*/*anti* ratio of 60/40. Analogously, with ethyl 4-chloro-benzoylformate **6g,** after 14 h a 99 % of conversion to **7g** (entry 7 Table 3) was reached with a *syn*/*anti* ratio of 70/30. These results lend a strong support to the multipoint recognition of the substrate **6i** and **6j** leading to a more compact transition state during the attack of furanone **5** and determining a higher *syn* preference.

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

Conclusions

On the basis of the known hydrophobic amplification of weak interactions between catalyst and substrate under "on-water conditions", we have designed a simple tetraminocalix[4]arene **1**, bearing weak H-bond donor NH_2-groups. We have then

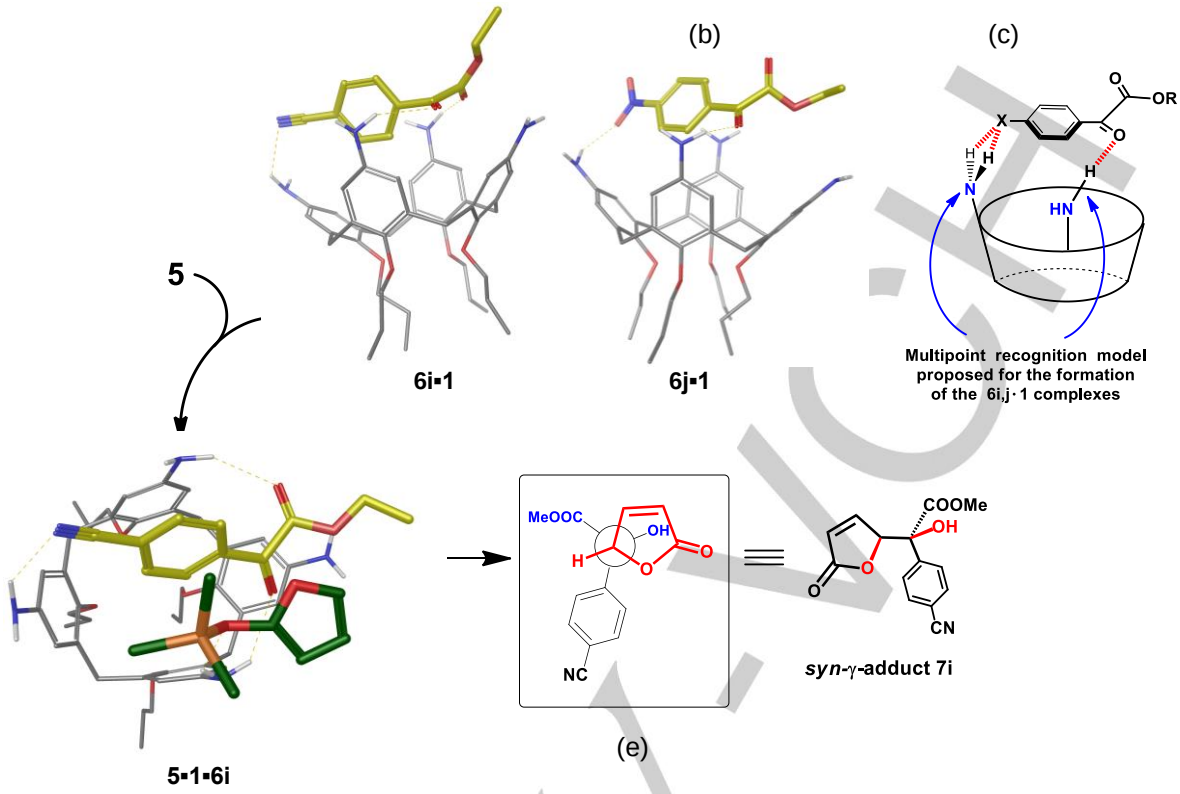


Figure 5. (a and b) Minimized structures (molecular mechanics calculations, AMBER force field) of the **6i·1** and **6j·1** complexes. (c) Multipoint recognition model proposed for the activation of the substrates **6i** and **6j**. Plausible catalytic cycle for the VMAR catalyzed by calixarene catalyst **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 **5** and **6i**catalyzed by **1**. (a,b and d) In green 2-trimethyl silyloxyfuran **5,** inyellowα-keto esters **6i** and **6j**, the dotted lines in yellow indicate the hydrogen bonds.

demonstrated that under "on-water conditions" **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 corresponding catalytic performance in organic solvents. Our studies indicate that in the catalytic cycle, **1** establishes H-bonding interactions, via its amino groups, with the substrate **6** and furanone **5** through a multipoint recognition model. This model well explains the differences on the reaction rate acceleration and on the stereoselectivityobserved with different substrates.

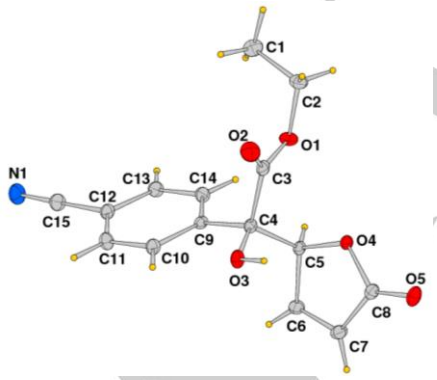


Figure 6. ORTEP representation of the assymetric unit of compound (*R,S*)-*syn*-**7i**. Ellipsoids are displayed at 50% probability. CCDC 1523707.

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

Experimental Section

All 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 sprying 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 [600.13 MHz (^{1}H) and 150.03 MHz (^{13}C)], Bruker Avance-400 spectrometer [400 (^{1}H) and 100.57 MHz (^{13}C)], Bruker Avance-300 spectrometer [300 (^{1}H) and 75.48 MHz (^{13}C)], or Bruker Avance-250 spectrometer [250 (^{1}H) and 62.80 MHz (^{13}C)]; chemical shifts are reported relative to the residual solvent peak ($CHCl_3$: δ 7.26, $CDCl_3$: δ 77.23). Derivatives: **1**[19a], **2**,[32] **3**[19b] **4**[33] and ketoesters **6c**[34]and **6d**[35], **2b**[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 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 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 using a NaTFA solution in positive ion mode. A linear calibration was applied. All final compounds purity was determined by elemental analysis on a Flash EA 1112 Series with Thermal Conductivity Detector, for C, H, N and S. The final compounds was found to be >95% when analyzed. Molecular mechanics calculations was performed with MacroModel-9.0/Maestro-4.1 using AMBER force field.[36]

X-Ray Crystallography

Single crystal diffraction data for the structural determination of compound **7i** was collected with the rotating-crystal method using synchrotron radiation at the XRD1 beam-line 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 using the XDS[37] package and the resulting data sets were scaled using XSCALE.[38] The crystal structures were determined by VLD Phasing with SIR-2014[39] and refined with SHELX-14,[40] operating through the WinGX GUI.[41] Thermal parameters of all non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed at the geometrically calculated positions and refined using the riding model. Crystallographic data and refinement details are reported in Table S2.

General procedurefor on water catalysis of VMAR in presence of calixarene catalyst.

A mixture of appropriate *α*-ketoester **6a-l** (0.23 mmol) and catalyst **1**–**3** (0.011 mmol), was vigorously stirred in presence of 2-(trimethylsilyloxy)furan (TMSOF) **5** (0.053 g, 0.34 mmol) in 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), then extracted with ethyl acetate (3 x 5 mL), (except for the reaction with α-ketoester **5i** were chloroform was used). Organic layers were collected and dried over Na_2SO_4, then filtered and evaporated under reduced pressure. Diastereoisomeric ratios and percentages of conversion of the*γ*-adducts **7a-h**, **7j-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* diastereomers.

Derivatives 7a, 7c, 7d, 7e, 7f, 7l

Prepared according to the general procedure using the appropriate α–ketoesters, 2-(trimethylsilyloxy)furan **5** in presence of catalyst **1**. The residue was purified by flash chromatography on silica gel (Hexane/EtOAc = 80:20) to give *anti* and *syn* diastereomers. Yields are listed in Table 3. Diastereomeric ratios are reported in Table 3. Spectroscopic data of *anti* and *syn* diastereomers matched those reported in literature.[20-22]

Derivative 7b

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

Anti–**7b**: Isolated as a white solid. The spectroscopic data for *anti*–**7b** 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): δ 1.35 (t, 3H, *J* = 7.1 Hz, -OCH_2CH_3), 3.89 (s, 1H, OH), 4.29-4.43 (m, 2H, -OCH_2CH_3), 5.77 (s, 1H, -CH), 6.16 (d, 1H, *J* = 5.6 Hz, =CH), 6.96 (d, 1H, *J* = 6.0 Hz, =CH), 7.39-7.44 (m, 1H, ArH), 7.41 (d, 2H, *J* = 7.6 Hz),7.70 (d, 2H, *J* = 7.6 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ 14.2, 63.9, 77.4, 86.4, 124.0, 125.7, 129.0, 129.2, 136.5, 151.6, 171.8, 172.8. **HRMS (ESI-FTICR)**, calcd. for $C_{14}H_{14}O_5Na$: 285.07334 [*M* + Na^+], found : 285.07355. **EA** (%) for $C_{14}H_{14}O_5$: calc. C 64.12, H 5.38, found C 64.03, H 5.29.

Derivative 7g

Prepared according to the general procedure using **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* diastereomers. Yield: 99% (combined yield of isolated diastereomers); *dr* = 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): δ 1.35 (t, 3H, *J* = 7.2 Hz, -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, 1H, J_2 = 2.1 Hz, J_1 = 5.8 Hz, =CH), 6.95 (dd, 1H, J_2 = 1.5 Hz, J_1 = 5.8 Hz, =CH), 7.39 (d, 2H, *J* = 8.8 Hz), 7.65(d, 2H, *J* = 8.8 Hz). **^{13}C NMR** (75 MHz, $CDCl_3$, 298 K): δ 14.2, 64.1, 77.4, 86.2, 124.3, 127.3, 129.2, 135.0, 135.4, 151.2, 171.4, 172.5. **HRMS (ESI-FTICR)**, calcd for $C_{14}H_{13}ClO_5Na$: 319.03437 [*M* + Na^+], found : 319.03436. **EA** (%) for $C_{14}H_{13}ClO_5$: calc. 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* diastereomers. Yield: 36% (combined yield of isolated diastereomers); *dr* = 30/70 (28/72 after chromatography).

Anti–**7h***:* Isolated as a white solid.The spectroscopic data for *anti*-**7h** diastereomer 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): δ 1.35 (t, 3H, J = 7.1 Hz, -OCH$_2$*CH$_3$*), 2.37 (s, 3H, -CH$_3$), 3.86 (bs, 1H, OH), 4.29-4.41 (m, 2H,-O*CH$_2$*CH$_3$), 5.75-5.76 (m, 1H, -CH), 6.16 (dd, 1H, J_2 = 1.9 Hz , J_1 = 5.8 Hz , =CH), 6.98 (dd, 1H, J_2 = 1.4 Hz, J_1 = 5.8 Hz, =CH), 7.23 (d, 2H, J = 8.1 Hz, ArH), 7.57 (d, 2H, J = 8.3 Hz, ArH). **^{13}C NMR** (150 MHz, $CDCl_3$, 298 K): δ 14.2, 21.2, 63.8, 77.4, 86.4, 123.9, 125.5, 129.7, 133.5, 139.1, 151.7, 171.9, 172.8. **HRMS (ESI-FTICR)**, calcd for $C_{15}H_{16}O_5Na$: 299.08899 [M + Na$^+$], found : 299.08917.**EA** (%) for $C_{15}H_{16}O_5$: calc. 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* diastereomer. Yield: 99%, *dr*> 1/99.

Syn–**7i***:* Isolated as a white solid. M.p.: 154-155 °C. **^{1}H NMR** (400 MHz, $CDCl_3$, 298 K): δ 1.36 (t, 3H, J = 7.2 Hz, -OCH$_2$*CH$_3$*), 4.07 (s, 1H, OH), 4.32-4.44 (m, 2H, -O*CH$_2$*CH$_3$), 5.70 (br m, 1H,-CH), 6.20 (dd, 1H, J_2 = 1.9 Hz, J_1 = 5.8 Hz, =CH), 6.91 (dd, 1H, J_2 = 1.5 Hz, J_1 = 5.8 Hz, =CH), 7.73 (d, 2H, J = 8.7 Hz, ArH), 7.87 (d, 2H, J = 8.7 Hz, ArH). **^{13}C NMR** (100 MHz, $CDCl_3$, 298 K): δ 14.2, 64.5, 77.4, 85.9, 113.3, 118.3, 124.6, 126.8, 132.7, 141.6, 150.6, 170.7, 172.2. **HRMS (ESI-FTICR)**, calcd for $C_{15}H_{13}NO_5Na$: 310.06859 [M + Na$^+$], found : 310.06972. **EA** (%) for$C_{15}H_{13}NO_5$: calc. 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* diastereomers. Yield: 98% (combined yield of isolated diastereomers); *dr* = 5/95 (>1/99 after chromatography).

The spectroscopic data for *anti*–**7j** isomer matched those reported in literature.[20] Isolated as a yellow oil.

The spectroscopic data for *syn*–**7j** isomer matched those reported in literature.[20] Isolated as an orange solid.

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* diastereomers. Yield: 80% (combined yield of isolated diastereomers); *dr* = 46/54 (unchanged after chromatography).

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

Syn–**7k**: Isolated as a white solid. M.p.: 95-96 °C. **^{1}H NMR** (300 MHz, $CDCl_3$, 298 K): δ 1.37 (t, 3H, J = 7.1 Hz, -OCH$_2$*CH$_3$*), 4.22 (s, 1H, OH), 4.34-4.44 (m, 2H, -O*CH$_2$*CH$_3$), 5.62 (br, 1H, -CH), 6.20 (dd, 1H, J_2 = 2.0 Hz, J_1 = 5.8 Hz, =CH), 7.05 (dd, 1H, J_2 = 3.7 Hz, J_1 = 5.1 Hz, =CH), 7.13 (dd, 1H, J_2 = 1.5 Hz, J_1 = 5.8 Hz, =CH), 7.24-7.26 (m, overlapped with residual signal of $CHCl_3$ in $CDCl_3$), 7.34 (dd, 1H, J_2 = 1.2 Hz, J_1 = 5.1Hz, =CH). **^{13}C NMR** (75 MHz, $CDCl_3$, 298 K): δ 14.1, 64.1, 77.4, 86.4, 124.1, 125.3, 126.6, 127.8, 140.5, 151.3, 170.8, 172.4. **HRMS (ESI-FTICR)**, calcd for $C_{12}H_{12}O_5SNa$: 291.02976 [M + Na$^+$], found : 291.02979. **EA** (%) for $C_{12}H_{12}O_5SNa$: calc. C 53.72, H 4.51, S 11.95, found C 53.81, H 4.45, S 12.83.

Acknowledgements ((optional))
Acknowledgements Text.

Keywords: keyword 1 • keyword 2 • keyword 3 • keyword 4 • keyword 5

[1] (a) C. D. Gutsche, *Calixarenes, An Introduction*, Royal Society of Chemistry, Cambridge, UK, **2008**. (b) P. Neri, J. L. Sessler, M. –X. Wang (Eds)**,** *Calixarenes and Beyond*, Springer, Dordrecht, **2016**; (c) C. D. Gutsche, Calixarenes, *An Introduction,* Royal Society ofChemistry, Cambridge, UK, **2008;** (d**)** Z. Asfari, V. Böhmer**,** J. Harrowfield, J. Vicens, (Eds.), *Calixarenes 2001*, Kluwer, Dordrecht, **2001**; (e) J. Vicens, J. Harrowfield, (Eds.), *Calixarenes in the Nanoworld*, Springer, Dordrecht, **2007**.

[2] (a) Y. Sun, Y. Mei, J. Quan, X. Xiao, L. Zhang, D. Tian, H. Li, *Chem. Commun.* **2016**, DOI: 10.1039/c6cc07956c; (b) E. Brunetti, S. Moerkerke; J. Wouters; K. Bartik; I. Jabin, *Org. Biomol. Chem.* **2016**, *14*, 10201−10207; (c) Y. Yeon, S. Leem, C. Wagen, V. M. Lynch, S. K. Kim, J. L. Sessler, *Org. Lett.* **2016**, *18*, 4396−4399; (d) C. Gaeta, C. Talotta, F. Farina, G. Campi, M. Camalli, P. Neri, *Chem. Eur. J.* **2012,** *18*, 1219−1230.

[3] (a) D. M. Rudkevic in *Calixarenes 2001* (Eds. : Z. Asfari, V. Bohmer, J. Harrowfield, J. Vicens), Kluwer. Dordrecht, **2001**, pp. 155-180. (b) J. Jr. Rebek, *Chem. Commun.* **2000**, 637−643; (c)A. Diaz-Moscoso, F. A. Arroyave, P. Ballester, *Chem. Commun.* **2016**, *52*, 3046−3049; (d)C. Talotta, C. Gaeta, Z. Qi, C. A. Schalley, P. Neri, *Angew. Chem. Int. Ed.* **2013**, *52*, 7437−7441; (e) C. Gaeta, C. Talotta, P. Della Sala, L. Margarucci, A. Casapullo, P. Neri, *J. Org. Chem.* **2014**, *79*, 3704−3708.

[4] (a) C. Talotta, N. A. De Simone, C. Gaeta, P. Neri, *Org. Lett.* **2015**, *17*, 1006−1009; (b) C. Gaeta; C. Talotta, S. Mirra, L. Margarucci, A. Casapullo, P. Neri, *Org. Lett.* **2013**, *15*, 116−119; (c) G. Orlandini, V. Zanichelli, A. Secchi, A. Arduini, G. Ragazzon, A. Credi, M. Venturi, S. Silvi, *Supramol. Chem.* **2016**, *28*, 427−435; (d) A. Arduini, R. Ferdani, A. Pochini, A. Secchi, F. Ugozzoli, *Angew. Chem. Int. Ed.* **2000**, *39*, 3453−3456; (e)C. Gaeta, C. Talotta, L. Margarucci, A. Casapullo, P. Neri, *J. Org. Chem.* **2013**, *78*, 7627−7638;(f) A. Arduini, G. Orlandini, A. Secchi, A. Credi, S. Silvi, M. Venturi in Calixarenes and Beyond (Eds.: P. Neri, J. L. Sessler, M.−X. Wang), Elsevier, Oxford, **2016**, pp.761−781; (g) C. Gaeta, C. Talotta, M. De Rosa, A. Soriente, P. Neri in *Calixarenes and Beyond* (Eds.: P. Neri, J. L. Sessler, M.−X. Wang), Elsevier, Oxford, **2016**, pp.783−809.

[5] (a) D. H. Homden, C. Redshaw, *Chem. Rev.* **2008**, *108*, 5086−5130; (b) M. Yilmaz, S. Sayn, in *Calixarenes and Beyond* (Eds.: P. Neri, J. L. Sessler, M. –X. Wang) Springer, Dordrecht, **2016**, pp. 719-741; (c) Z.-Y. Li, J.-W. Chen, Y. Liu, W. Xia, L. Wang, *Curr. Org. Chem.* **2011**, *15*, 39-61; (d) R. Cacciapaglia, L. Mandolini, Calixarene based catalytic system. In *Calixarene in action;* L. Mandolini; R. Ungaro, (Eds); Imperial College Press: Singapore, **2000**; ch. 10, pp. 241- 264. (e) A. Soriente, M. Fruilo, L. Gregoli, P. Neri, *Tetrahedron. Lett.* **2003**, *44*, 6195−6198; (f) A. Soriente, M. De Rosa, M. Fruilo, L. Lepore, C. Gaeta, P. Neri, *Adv. Synth. Catal*. **2005**, *347*, 816−824; (g) S. Meninno, A. Parrella, G. Brancatelli, S. Geremia, C. Gaeta, C. Talotta, P. Neri, A. Lattanzi, *Org. Lett.* **2015**, *17*, 5100−5103.

[6] (a) C. D. Gutsche, *Tetrahedron* **1986,** *42*, 1633**−**1640; (b) K. Iwamoto, K. Araki, S. Shinkai, *Tetrahedron* **1991**, *47*, 4325−4342; (c) W. Verboom, A. Durie, R. J. M. Egberink, Z. Asfari, D. N. Reinhoudt, *J. Org. Chem.* **1992**, *57*, 1313−1316; (d) M. Martino, C. Gaeta, L. Gregoli, P. Neri, *Tetrahedron Lett.* **2002**, *43*, 9521−9525; (e) M. De Rosa, A. Soriente, G. Concilio, C. Talotta, C. Gaeta, P. Neri, *J. Org. Chem.* **2015**, *80*, 7295−7300.

[7] M. De Rosa, P. La Manna, A. Soriente, C. Gaeta, C. Talotta, P. Neri, *RSC Adv.* **2016**, *6*, 91846−91851.

[8] (a) D.C. Rideout, R. Breslow,*J. Am. Chem. Soc.* **1980**, *102*, 7816-7817; (b) R. Breslow, *Acc. Chem. Res.* **1991**, *24*, 159-164; (c) Breslow, R. *Acc. Chem. Res.* **2004**, *37*, 471-478.

[9] (a) M. C. Pirrung, K. Das Sarma, *Tetrahedron* **2005**, *61*, 11456−11472; (b) M. C. Pirrung, *Chem. Eur. J.* **2006**, *12*, 1312−1317. (c) M. U. Lindström, *Organic Reactions in Water*; Blackwell Publishing: Oxford, UK, **2007**.

[10] C.-J Li, T.-H Chan, *Comprehensive organic reactions in aqueous media* 2nd ed.; John Wiley & Sons, Hoboken **2007**.

[11] (a) U. M. Lindström, *Chem. Rev*. **2002**, *102*, 2751-2772; (b) M. Woyciechowska, G. Forcher, S. Buda, J. Mlynarski, *Chem. Commun*. **2012**, *48*, 11029-11031.

[12] (a) S. Narayan, J. Muldoon, M. J. Finn, V. V. Fokin, H. Kolb, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2005**, *44*, 3275-3279; (b) R. N. Butler, A. G. Coyne, *Chem. Rev.* **2010**,*110*, 6302-6337; (c) A. Chanda, V. V. Fokin, *Chem. Rev.* **2009**,*109*, 725-748; (d) R. Breslow; K. Groves, M. U. Mayer, *Pure & Appl. Chem.* **1998**, *70*, 1933-1938; (e) F. Biedermann, W. N. Nau, H.-J Schneider, *Angew. Chem. Int. Ed.* **2014**, 11158-11171.

[13] As suggested by a referee, we emphasize here the difference between the catalysis under on-water conditions with respect to the phase-transfer catalysis (PTC), where the catalyst acts in a heterogeneous system between reactants located in different immiscible phases. The catalyst function is to favor the migration of a reactant from one phase into another phase where the reaction takes place. In particular, when they are used for accelerating reactions between water insoluble and water soluble reactants, their role is to transfer a reactant from the aqueous phase to the organic phase. The reaction reported here is performed under “on-water” conditions, where all the reactants are insoluble in water, including the catalyst.

[14] J. E. Klijn, J. B. F. N. Engberts, *Nature* **2005**, *436*, 746−747.

[15] (a) C. M. Kleiner, P. R. Schreiner, *Chem. Commun.* **2006**, 4315−4317; (b) M. Rueping, T. Theissmann, *Chem. Sci.* **2010,** *1*, 473−476; (c) H. Y. Bae, S. Some, J. S. Oh, Y. S. Lee, C. E. Song, *Chem. Commun.* **2011,** *47*, 9621−9623: (d) F. Cruz-Costa, P. de Armas, F. Garcia-Tolledo, *Chem. Eur. J.* **2013**, *19*, 16550−16554; (e) H. Y. Bae, C. E. Song, *ACS Catal.* **2015**, *5*, 3613−3619.

[16] (a) P. Sarkar, C. Mukhopadhyay, *Green Chem.* **2016**, *18*, 442-451; (b) S. Sayin, M. Yilmaz, *RSC Adv.* **2014**, *4*, 2219-2225; (c) Y.-L. Lu, L. Liu, Y.-L. Wang, Y.-C. Han, D. Wang, Y.-J. Chen, *Green Chem.* **2008**, *10*, 635-640; (d) S. Shimizu, N. Shimada,Y. Sasaki, *Green Chem.* **2006**, *8*, 608-614.

[17] (a) L. Zu, J. Wang, H. Li, W. Wang, *Org. Lett.* **2006**, *8*, 3077-3079; (b) K. Surendra, N. S. Krishnaveni, A. Manesh, K. R. Rao, *J. Org. Chem*. **2006**, *71*, 2532-2534

[18] The term "vinylogy" was introduced by Fuson in 1935 and it indicates the ability to transmit electronic effects through a conjugated π–system [see: (a) R. C. Fuson, *Chem. Rev.* **1935**, *16*, 1–27]. Over the years, the principle has been applied to different polar reactions where it allows the extension of the electrophilic or nucleophilic character of a functional group through the π-system of a C=C double bond [see: (b) G. Casiraghi, F. Zanardi, *Chem. Rev.* **2000**, *100*, 1929–1972; (c) S. E. Denmark, J. R. Heemstra Jr., G. L. Beutner, *Angew. Chem. Int. Ed.* **2005**, *44*, 4682-4698]. In the aldol reaction the use of a γ-enolizable α,β-unsaturated carbonyl substrate as an "extended enolate" (a dienolate) allows a “vinylogous” extension of the reaction. Therefore, 2-(trimethylsilyloxy)furan **6** is the activated silicon dienolate precursor of furan-2-(5H)-one [see: (d) Y. Wang, F. Xing, M. Xue, G.-F Du, X.-H. Guo, K.-W. Huang, B. Dai, *Synthesis* **2016**, 48, 79-84; (e) A. Adamkiewicz, M. Woyciechowska, J. Mlynarski, *Eur. J. Org. Chem.* **2016**, 2897-2901; (f) M. Woyciechowska, G. Forcher, S. Buda, J. Mlynarski, *Chem. Comm.* **2012**,*48*, 11029-11031; (g) M. Frings, I. Atodiresei, Y. Wang, J. Runsik, G. Raabe, C. Bolm, *Chem. Eur. J.* **2010**, *16*, 4577-4587]. For some general examples regarding the catalysis of the VMAR, see: (h) M. De Rosa, S. Di Marino, A. M. D'Ursi, M. Strianese, A. Soriente, *Tetrahedron* **2012**, *68*, 3086-3091; (i) M. De Rosa, A. Soriente, *Tetrahedron* **2011**, *67*, 5949-5955; (j) G. Cafeo, M. De Rosa, F. H. Kohnke, A. Soriente, C. Talotta, L. Valenti, *Molecules* **2009**, *14*, 2594-2601; (k) G. Cafeo, M. De Rosa, F. H. Kohnke, P. Neri, A. Soriente, L. Valenti, *Tetrahedron Lett.* **2008**, *49*, 153-155; (l) M. De Rosa, C. Talotta, A. Soriente, *Lett. Org. Chem.* **2009**, *6*, 301-305.

[19] (a) R. A. Jakobi, V. Böhmer, C. Gruttner, D. Kraft, W. Vogt, *New J. Chem.* **1996**, *20*, 493−501; (b) A. M. A. Wageningen, E. Snip, W. Verboom, D. N. Reinhoudt, H. Boerrigter, *Liebigs Ann. Recueil* **1997**, 2235- 2245; (c) R. Zadmard, T. Schrader, *J. Am. Chem. Soc.* **2005**, *127*, 904−915.

[20] M. Frings, I. Atodiresei, J. Runsink, G. Raabe, C. Bolm, *Chem. Eur. J.* **2009**, *15*, 1566-1569.

[21] Y. Wang, F. Xing, M. Xue, G.-F. Du, X.-H. Guo, K.-W. Huang, B. Dai, *Synthesis* **2016**, *48*, 79- 84.

[22] (a) D. A. Evans, C. S. Burgey, M. C. Kozlowski, S. W. Tregay,*J. Am. Chem. Soc*., **1999**, *121*, 686- 699. (b) J. Luo, H. Wang, X. Han, L. –W. Xu, J. Kwiatkowski, K.-W. Huang, Y. Lu, *Angew. Chem. Int. Ed.***2011**, *50*, 1861- 1864

[23] (a) T. Janecki, (Ed.) *Natural Lactones and Lactams: synthesis, occurrence and biological activity*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, **2013**; (b) M. De Rosa, A. Zanfardino, E. Notomista,T. A. Wichelhaus, C. Saturnino, M. Varcamonti, A. Soriente, *Eur. J. Med. Chem.* **2013,** *69*, 779-785; (c) M. Grimaldi, M. De Rosa, S. Di Marino, M. Scrima, B. Posteraro, M. Sanguinetti, G. Fadda, A. Soriente, A. M. D’Ursi, *Biorg. & Med. Chem.* **2010**, *18*, 7985-7990; (d) Y. Hayashi, H. Yamaguchi, M. Toyoshima, K. Okado, T. Toyo, M. Shoji, *Chem. Eur. J.***2010,** *16*,10150-10159; (e) D. A. Nicewicz, A. D. Satterfield, D. C. Schimitt, J. S. Johnson, *J. Am. Chem. Soc.* **2008**, *130,* 17281-17283.

[24] A. Sakakura, K. Kazuhiko, K. Ishihara, *Org. Lett.* **2006**, *8,* 2229−2232.

[25] (a) K. Hirose, in Analytical Methods in Supramolecular Chemistry (Ed.: C. A. Schalley), Wiley-VCH, Weinheim, 2007, pp. 17– 54. (b) K. A. Connors, in Binding Constants-the measurement of molecular complex stability, John Wiley & Sons, New York, Chichester, 1987. See ESI for further details.

[26] (a) H. Fliegl, O. Lehtonen, D. Sundholm, V. R. I. Kaila, *Phys. Chem. Chem. Phys.* **2011**,*13*, 434-437; (b) G. Monaco, P. Della Porta, M. Jabloński, R. Zanasi, *Phys. Chem. Chem. Phys.* **2015**, *17*, 5966-5972.

[27] T. Steiner, *Angew. Chem. Int. Ed.* **2002**, *41*, 48-76.

[28] S.E. Matthews, M. Saadioui, V. Böhmer, S. Barboso, F. Arnaud-Neu, M.-J. Schwing-Weill, A. Garcia Carrera, J.-F. Dozol, *J. Prakt. Chem.* **1999**, *341*, 264-273.

[29] As is known by the preorgaization principle introduced by Cram, the more highly hosts are preorganized and more stable will be their host–guest complexes, see: D. J. Cram, *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1009–1020.

[30] H. Suezawa, S. Ishihara, Y. Umezawa, S. Tsuboyama, M. Nishio, *Eur. J. Org. Chem.* **2004**, 4816−4822.

[31] See the outcome of the Mukaiyama aldol reaction in an aqueous medium: Y. Yamamoto, K. Maruyama, K. Matsumoto, *J. Am. Chem. Soc.* **1983**, *105*, 6963−6965

[32] I.T. Ho, J. H. Chu, W. S. Chung, *Eur. J. Org. Chem.* **2011**, 1472-1481.

[33] C.D. Gutsche, L.-G. Lin, *Tetrahedron* **1986**, *42*, 1633−1640.

[34] W. J. Quan, D. Q. Man, W. Liang, X. Kai, W. Hao, L. Ren-Rong, G. Jian-Rong, J. Yi-Xia, *Org. Lett*. **2014**, *16*, 776-779.

[35] N. J. A. Martin, X. Cheng, B. List, *J. Am. Chem. Soc*.**2008**, *130*, 13862-13863.

[36] MacroModel-9.0/Maestro-4.1 program: F.Mohamadi, N. G. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson, W. C. Still, *J. Comput. Chem.* **1990**, *11*, 440−467.

[37] W.Kabsch, *Acta Crystallogr., Sect. D: Biol. Crystallogr.* **2010**, *66*, 125−132.

[38] W. Kabsch, *Acta Crystallogr., Sect. D: Biol. Crystallogr*. **2010**, *66*, 133−144.

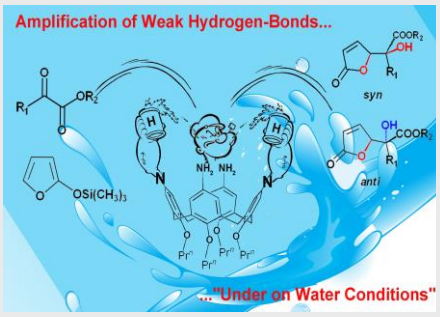
[39] M. C. Burla, R. Caliandro, B. Carrozzini, G. L. Cascarano, C. Cuocci, C. Giacovazzo, M. Mallamo, A. Mazzone, G. Polidori, *J. Appl. Crystallogr.* **2015**, *48*, 306−309.

[40] G. M. Sheldrick, *Acta Cryst.* **2008**, *A64*, 112−122.

[41] L. J. Farrugia, *J. Appl. Cryst.* **2012**, *45*, 849−854.

FULL PAPER

The hydrophobic amplification of weak H-bonding interactions makes the simple tetraminocalix[4]arene **1** a highly efficient organocatalyst "under on-water conditions" for the Vinylogous Mukaiyama Aldol Reaction (VMAR) of 2-(trimethylsilyloxy)furan **5** with α-ketoesters **6a-l.**



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