Supplementary Information

Exploiting the Hydrophobicity of Calixarene Macrocycles for Catalysis Under "On-Water" Conditions

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**General Methods.** Flash chromatography was performed on Merck silica gel (60, 40-63 µm). 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 spraying with H$_2$SO$_4$-Ce(SO$_4$)$_2$ or phosphomolybdic acid. 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: 10$^1$, 12$^2$, 11$^3$, 7a$^4$, 7d$^5$, and 7c$^6$ were synthesized according to literature procedures. Melting points were measured with a Stuart melting point apparatus (SMP3).

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General procedure for on water catalysis of VMAR in the presence of calixarene catalyst. A mixture of the appropriate $\alpha$-ketoester 7a-d (0.22 mmol) and catalyst (0.011 mmol) was stirred in the presence of 2-(trimethylsilyloxy)furan (TMSOF) 6 (0.33 mmol) in deionized water (1 mL) as medium. The reaction mixture was kept under magnetic stirring (1400 rpm) at 30 °C for the appropriate time (see Table 3), then it was extracted with ethyl acetate (3 x 5 mL). Organic layers were collected and dried over Na$_2$SO$_4$, then filtered and evaporated under reduced pressure. Diastereoisomeric ratios and percentage of conversion to $\gamma$-adducts 8a, 8b, and 8d were determined by integration of the $^1$H NMR signals of the crude reaction mixtures in comparison with the literature values.$^{4-7}$ In the case of 8c, the crude reaction mixture was purified by flash chromatography on silica gel using a gradient from $n$-hexane to a mixture of $n$-hexane/ethyl acetate (90/10) to give syn and anti diastereomers of 8c. The relative configuration of 8c was assigned in analogy to other derivatives 8a, 8b, and 8d$^{20a}$ by comparison $^1$H-NMR chemical shifts of the characteristic -CH and =CH signals of the $\gamma$-hydroxybutenolide ring (see page S37).

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Synthesis of catalyst 1

Scheme S1. Synthesis of 1.

To a solution of 10 (0.14 g, 0.23 mmol) in dry CH$_2$Cl$_2$ (7 mL) 3,5-bis(trifluoromethyl)phenylisothiocyanate (0.07 g, 0.26 mmol) was added. The reaction mixture was stirred under a nitrogen atmosphere for 16 h at rt. The solvent was removed under reduced pressure and the crude mixture was purified by flash chromatography on silica gel (hexanes/CHCl$_3$, 80/20) to give derivative 1 as a light yellow solid (0.16 g, 0.18 mmol, 78.3 %). $^1$H NMR (250 MHz, CDCl$_3$, 298 K): $\delta$ 0.88-1.14 (overlapped, -OCH$_2$CH$_2$CH$_3$, 12H), 1.86-2.03 (overlapped, -OCH$_2$CH$_2$CH$_3$, 8H), 3.14 (d, $J = 13.2$ Hz, 2H, ArCH$_2$Ar), 3.17 (d, $J = 13.2$ Hz, 2H, ArCH$_2$Ar), 3.63-3.75 (overlapped, -OCH$_2$CH$_2$CH$_3$, 4H), 3.98-4.08 (m, -OCH$_2$CH$_2$CH$_3$, 4H), 4.43 (d, $J = 13.2$ Hz, 2H, ArCH$_2$Ar), 4.49 (d, $J = 13.2$ Hz, 2H, ArCH$_2$Ar), 5.94 (br t, ArH, 1H), 6.06 (d, ArH, $J = 7.3$ Hz, 2H), 6.18 (s, ArH, 2H), 6.90-7.10 (overlapped, ArH + NH, 7H), 7.61 (s, NH,
\( ^{1}H \), 7.71 (s, CF\textsubscript{3}ArH, 1H), 7.78 (s, CF\textsubscript{3}ArH, 2H). \(^{13}C\) NMR (63 MHz, CDCl\textsubscript{3}, 298 K): \( \delta \) 9.7, 10.56, 10.61, 22.8, 23.3, 30.8, 30.9, 76.5, 77.1, 77.3, 119.6, 120.9, 122.4, 124.0, 125.1, 126.2, 127.1, 128.5, 128.9, 129.3, 131.4, 133.6, 135.8, 136.3, 136.9, 139.6, 155.1, 155.5, 157.3, 179.1. HRMS (MALDI-FTICR), calcd for C\textsubscript{49}H\textsubscript{52}N\textsubscript{2}O\textsubscript{4}S [M + H\textsuperscript{+}]: 879.36205, found: 879.36198. M.p: 117-118 °C.

**Synthesis of catalyst 2**

To a solution of 11 (0.10 g, 0.66 mmol) in dry CH\textsubscript{2}Cl\textsubscript{2} (10 mL) 3,5-bis(trifluoromethyl)phenyl isothiocyanate (0.21 g, 0.79 mmol) was added under N\textsubscript{2}. The solution was stirred under nitrogen atmosphere for 16 h at rt. Then, the solvent was removed under reduced pressure and the crude mixture was purified by flash chromatography on silica gel (hexanes/CHCl\textsubscript{3}, 65/35) to give 2 as an ocher solid (0.22 g, 0.52 mmol, 79.0 %). \(^{1}H\) NMR (250 MHz, CDCl\textsubscript{3}, 298 K): \( \delta \) 1.05 (t, \( J = 7.4 \) Hz, 3H, -OCH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}), 1.84 (m, 2H, -OCH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}), 3.95 (t, \( J = 6.5 \) Hz, 2H, -OCH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{3}), 7.00 (d, \( J = 8.9 \) Hz, 2H, ArH), 7.25 (d, \( J = 8.9 \) Hz, 2H, ArH), 7.57 (s, 1H, NH), 7.66 (s, 1H, CF\textsubscript{3}ArH), 7.99 (s, 2H, CF\textsubscript{3}ArH), 8.16 (s,1H, NH). \(^{13}C\) NMR (63, CDCl\textsubscript{3}, 298 K): \( \delta \) 10.4, 22.3, 69.8, 116.1, 119.2, 120.7, 124.4, 127.2, 127.8, 131.0, 131.8, 139.6, 159.2, 180.1. HRMS (MALDI-FTICR), calcd for C\textsubscript{18}H\textsubscript{17}F\textsubscript{6}N\textsubscript{2}OS [M + H\textsuperscript{+}]: 423.09603, found: 423.09608. M.p: 121-122 °C.
Synthesis of catalyst 4


Derivative 13
To a solution of 12 (0.43 g, 0.31 mmol) in dry CH$_2$Cl$_2$ (7 mL), at -13 °C, HNO$_3$ (69.5%, 0.035 mL) and H$_2$SO$_4$ (96%, 0.035 mL) were added under N$_2$. After 5 minutes the reaction mixture was quenched with H$_2$O (20 mL) and extracted with CH$_2$Cl$_2$ (3 x 10 mL). The organic layers were collected and dried over Na$_2$SO$_4$, filtered and evaporated under reduced pressure to give a yellow crude solid, which was purified by flash chromatography on silica gel (hexanes/CHCl$_3$, 70/30) to give derivative 13 as a yellow solid (0.32 g, 0.23 mmol, 74.2%). $^1$H NMR (300 MHz, TCDE, 363 K): δ 0.69-1.65 (overlapped, -OCH$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$ + -C(CH$_3$)$_3$, 100H), 3.07-3.76 (overlapped, -OCH$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$ + ArCH$_2$Ar, 22H), 6.64-6.69 (overlapped, ArH, 4H), 6.78 (s, ArH, 2H), 6.91 (s, ArH, 2H), 7.02 (s, ArH, 2H), 7.84 (s, NO$_2$-ArH, 2H), 8.62 (bs, OH, 1H). $^{13}$C NMR (75 MHz, TCDE, 363 K): δ 13.7, 22.2, 22.3, 22.5, 25.5, 25.6, 29.6, 30.3, 30.5, 31.2, 31.3, 31.4, 31.6, 31.9, 33.8, 72.9, 73.5, 73.8, 124.6, 124.9, 125.8, 126.8, 127.0, 128.1, 129.9, 131.6, 131.8, 133.3, 133.4, 140.3, 144.5, 144.9, 146.4, 151.5, 153.3, 159.4. HRMS (MALDI-FTICR), calcd for C$_{92}$H$_{135}$NO$_8$K [M + K$^+$]: 1421.98531, found: 1421.98945. M.p: 181-182°C.

Derivative 14
Cs₂CO₃ (0.75 g, 2.31 mmol) was added to a suspension of derivative 13 (0.32 g, 0.23 mmol) in acetone (20 mL). The reaction mixture was refluxed for 2 hours, then was allowed to cool slowly to room temperature. 1-Iodohexane (0.98 g, 4.62 mmol) was added and the reaction mixture was refluxed for 36 hours, then it was cooled to rt and concentrated under vacuum. The crude product was dissolved in CH₂Cl₂ (50 mL), washed with aqueous 1N HCl (20 mL) and the organic layer was dried over Na₂SO₄, filtered and the crude product was evaporated to dryness and then purified by flash chromatography on silica gel using a gradient of n-Hexane/CHCl₃ (from 90/10 to 75/25) to give derivative 14 (0.29 g, 0.20 mmol, 87.0 %). ¹H NMR (300 MHz, TCDE, 363 K): δ 0.71-1.80 (overlapped, -OCH₂CH₂CH₂CH₂CH₃ + -C(CH₃), 111H), 3.18-3.80 (overlapped, -OCH₂CH₂CH₂CH₂CH₃ + ArCH₂Ar, 24H), 6.58 (bs, ArH, 2H), 6.73 (bs, ArH, 2H), 6.86-7.04 (overlapped, ArH, 6H), 7.56 (s, NO₂-ArH, 2H). ¹³C NMR (75 MHz, TCDE, 363 K): δ 13.8, 22.4, 22.5, 25.9, 29.6, 30.1, 30.2, 30.5, 31.2, 31.4, 31.6, 31.7, 31.8, 33.7, 33.8, 33.9, 73.0, 73.3, 73.5, 73.7, 123.2, 124.9, 125.3, 126.2, 126.5, 127.7, 131.2, 132.5, 132.8, 132.9, 133.5, 135.8, 143.6, 145.0, 145.6, 152.8, 153.7, 160.3. HRMS (MALDI-FTICR), calcd for C₉₈H₁₄₇NO₈Na [M + Na⁺]: 1490.10527, found: 1490.10384. M.p: 243-244 °C.

Derivative 15
Raney nickel (cat. amounts) was added to a solution of derivative 14 (0.42 g, 0.29 mmol) in hot DMF (230 mL). The resulting black suspension was stirred under H₂ (1 atm) at rt for 18 hours, then was filtered through a celite pad. Concentration of the filtrate to dryness gave a crude product, which was purified by flash chromatography on silica gel (hexanes/CH₂Cl₂, 80/20) to give derivative 15 (0.36 g, 0.25 mmol, 86.2 %). ¹H NMR (300 MHz, TCDE, 363 K): δ 0.39-1.78 (overlapped, OCH₂CH₂CH₂CH₂CH₂CH₃ + -C(CH₃), 111H), 3.63-3.77 (overlapped, ArCH₂Ar + OCH₂CH₂CH₂CH₂CH₂CH₃, 24 H), 6.73-7.07 (overlapped, ArH, 12H). ¹³C NMR (75 MHz, TCDE, 363 K): δ 13.3, 13.4, 25.2, 25.3, 25.4, 29.9, 30.6, 30.9, 31.0, 31.2, 31.4, 33.4, 73.6, 113.5 (broad), 125.5 (broad), 132.4 (broad), 145.0, 145.2, 154.0 (broad). HRMS (ESI-FTICR), calcd for C₉₈H₁₅₀NO₆ [M + H⁺]: 1438.14915, found: 1438.12274. Decomposes to light red oil at 151.5 °C.

Catalyst 4
3,5-bis(trifluoromethyl)phenyl isothiocyanate (0.08 g, 0.30 mmol) was added to a solution of derivative 15 (0.32 g, 0.22 mmol) in dry CH₂Cl₂ (15 mL). The reaction mixture was stirred for 24 hours at rt under N₂ atmosphere, then other isothiocyanate (0.03 g, 0.11 mmol) was added. After another 12 hours, solvent was evaporated to give a brown oil, which was purified by flash column chromatography on silica gel (hexanes) to obtain catalyst 4 as a white solid (0.32 g, 0.19 mmol, 86.4 %). 

\[ ^{1}H\text{ NMR (300 MHz, TCDE, 363 K):}\]
\[ \delta \quad 0.31-1.82 \quad (\text{overlapped, } \text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3 + -\text{C(CH}_3)_2, \quad 111\text{H}), \quad 3.48-3.75 \quad (\text{overlapped, } \text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3 + \text{ArCH}_2\text{Ar}, \quad 24\text{H}), \quad 6.80-7.42 \quad (\text{overlapped, } \text{ArH} + \text{CF}_3\text{ArH}, \quad 13\text{H}), \quad 8.10 \quad (s, \quad \text{CF}_3\text{ArH}, \quad 2\text{H}). \]

\[ ^{13}C\text{ NMR (75 MHz, TCDE, 363 K):}\]
\[ \delta \quad 13.7, \quad 22.4, \quad 25.6, \quad 30.0, \quad 31.0, \quad 31.4, \quad 33.8, \quad 126.2 \quad (broad), \quad 133.1 \quad (broad), \quad 145.6 \quad (broad), \quad 154.0 \quad (broad). \]


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**Derivative 8c**

Prepared according to the general procedure from 7c, 2-(trimethylsilyloxy)furan 6 and catalyst 1. The residue was purified by flash column chromatography on silica gel using a gradient from n-hexane to a mixture of n-hexane/ethyl acetate (90/10) to give anti and syn diastereomers. **Anti isomer** (isolated as a colorless oil) (0.012 g, 0.037 mmol, 16.7%): 

\[ ^{1}H\text{ NMR (600 MHz, CDCl}_3, \quad 298 \text{ K):}\]
\[ \delta \quad 3.60 \quad (\text{broad, } 1\text{H, OH}), \quad 5.25 \]
(d, 1H, J = 12.1 Hz, CH$_2$ benz ), 5.32 (d, J = 12.1 Hz, 1H, CH$_2$ benz), 5.55 (s, 1H, -CH), 6.10 (dd, $J_2$ = 1.8 Hz, $J_1$ = 5.4 Hz, 1H, =CH), 7.18 (dd, $J_2$ = 1.2 Hz, $J_1$ = 5.4 Hz, 1H, =CH), 7.32-7.37 (overlapped, ArH, 8H), 7.57-7.59 (overlapped, ArH, 2H). $^{13}$C NMR (150 MHz, CDCl$_3$, 298 K): $\delta$ 69.0, 78.4, 85.8, 124.1, 126.0, 128.75, 128.76, 129.0, 129.1, 129.2, 134.4, 136.8, 152.1, 171.4, 172.4. Syn isomer (isolated as a colorless oil) (0.010 g, 0.031 mmol, 14.2%): $^1$H NMR (400 MHz, CDCl$_3$, 298 K): $\delta$ 3.88 (s, 1H, OH), 5.28 (d, 1H, J = 12.1 Hz, CH$_2$ benz), 5.34 (d, 1H, J = 12.1 Hz, CH$_2$ benz), 5.78-5.79 (m, 1H, -CH), 6.16 (dd, $J_2$ = 2.0 Hz, $J_1$ = 6.0 Hz, 1H, =CH), 6.95 (dd, $J_2$ = 1.6 Hz, $J_1$ = 5.6 Hz, 1H, =CH), 7.31-7.42 (overlapped, ArH, 8H), 7.66-7.69 (overlapped, ArH, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$, 298 K): $\delta$ 69.4, 77.6, 86.3, 124.1, 125.7, 128.5, 128.9, 129.0, 129.1, 129.3, 134.5, 136.3, 151.5, 171.7, 172.7. HRMS (ESI-FTICR), calcd for C$_{19}$H$_{16}$O$_5$Na : 347.08999 [$M + Na^+$], found : 347.08931.
Copies of $^1$H NMR, $^{13}$C NMR and MS spectra of synthesized derivatives

Figure S1. $^1$H NMR spectrum of catalyst 1 (250 MHz, CDCl$_3$, 298 K).
Figure S2. $^{13}$C NMR spectrum of catalyst 1 (63 MHz, CDCl$_3$, 298 K).

Figure S3. DEPT 135 spectrum of catalyst 1 (63 MHz, CDCl$_3$, 298 K).
Figure S4. MALDI MS spectrum of catalyst 1.
Catalyst 2

Figure S5. $^1$H NMR spectrum of catalyst 2 (250 MHz, CDCl$_3$, 298 K).

Figure S6. $^{13}$C NMR spectrum of catalyst 2 (63 MHz, CDCl$_3$, 298 K).
Figure S7. MALDI MS spectrum of catalyst 2.
Derivative 13

Figure S8. $^1$H NMR spectrum of derivative 13 (300 MHz, TCDE, 363 K).
Figure S9. $^{13}$C NMR spectrum of derivative 13 (75 MHz, TCDE, 363 K).
Figure S10. DEPT 135 spectrum of derivative 13 (75 MHz, TCDE, 363 K).
Figure S11. MALDI MS spectrum of derivative 13.
Derivative 14

Figure S12. $^1$H NMR spectrum of derivative 14 (300 MHz, TCDE, 363 K).
Figure S13. $^{13}$C NMR of derivative 14 (75 MHz, TCDE, 363 K).
Figure S14. DEPT 135 spectrum of derivative 14 (300 MHz, TCDE, 363 K).
Figure S15. MALDI MS spectrum of derivative 14.
Derivative 15

Figure S16. $^1$H NMR spectrum (300 MHz, TCDE, 363 K) of derivative 15.
Figure S17. $^{13}$C NMR of derivative 15 (75 MHz, TCDE, 363 K).
Figure S18. ESI MS spectrum of derivative 15.
Catalyst 4

Figure S19. $^1$H NMR spectrum of catalyst 4 (300 MHz, TCDE, 363 K).
Figure S20. $^{13}$C NMR spectrum of catalyst 4 (75 MHz, TCDE, 363 K).
Figure S21. ESI MS spectrum of catalyst 4.
Derivative 8c

Anti Isomer

Figure S22. $^1$H NMR spectrum of *anti* isomer of derivative 8c (600 MHz, CDCl$_3$, 298 K).
Figure S23. $^{13}$C NMR spectrum of *anti* isomer of derivative $8c$ (150 MHz, CDCl$_3$, 298 K).
Figure S24. $^1$H NMR spectrum of syn isomer of derivative 8c (400 MHz, CDCl$_3$, 298 K).
Figure S25. $^{13}$C NMR spectrum of syn isomer of derivative 8c (100 MHz, CDCl$_3$, 298 K).
Figure S26. ESI Mass Spectrum of derivative 8c.

Found Exact Mass for derivative 8c
(C_{19}H_{16}NaO_{5})

Calcd Exact Mass for derivative 8c
(C_{19}H_{16}NaO_{5})
Determination of the relative configuration of 8c based on the comparison $^1$H-NMR data with known 8a and 8d

Figure S27. Representative sections of $^1$H-NMR spectra (400 MHz, CDCl$_3$, 298 K) : a) crude VMAR reaction mixture of 8a; b) crude VMAR reaction mixture of 8d; c) isolated syn-8c; d) isolated anti-8c. The relative configuration of 8c was assigned based on the comparison of $^1$H-NMR characteristic chemical shifts of -CH methine resonances (anti and syn diastereomers were indicated with green and blue triangles, respectively), and CH olefinic protons (anti and syn diastereomers were indicated with blue squares).
$^1$H NMR titrations of 7a and 7b with catalyst 1

The following standard procedure was used.

**Host solution.** A 3.2 mM CDCl$_3$ solution of catalyst 1 was prepared (2.00 mL).

In 0.5 mL of host solution, derivative 7a was dissolved (solution 7a).

0.4 mL of host solution, in a NMR tube, was titrated with solution 7a in the concentration range indicated below.

$[1] = 3.2$ mM. [7a] concentration range during titration: 0.00-2.50 mM.

In 0.5 mL of host solution, derivative 7b was dissolved (solution 7b).

0.4 mL of host solution, in a NMR tube, was titrated with solution 7b in the concentration range indicated below.

$[1] = 3.2$ mM. [7b] concentration range during titration: 0.00-2.50 mM.

The titration data were analyzed by nonlinear least-squares fitting procedures$^8$ and in all cases a good fit of the experimental data with the theoretical model confirmed the 1:1 stoichiometry of the complexes.

$^8$Connors, K. A. *Binding Constants*; John Wiley & Sons: Chichester, 1987
Figure S28. (a) Plots of \( \delta \) for NH proton of 1 as a function of the concentration of 7a (CDCl\(_3\), 25 °C, 400 MHz). (b) Titration of 1 with 7a. Aromatic region of the \( ^1H \) NMR spectrum (400 MHz, 298 K) of 1 after addition of 7a ([7a] concentration range during titration: 0.00-2.50 mM, from bottom to top) (in red the NH signals of 1).

Figure S29. (Top) Plot of the chemical shift of a NH proton of catalyst 1 (3.2 mM in 0.5 mL CDCl\(_3\) at 298 K) versus [7b]/10^{-3} at 25 °C in CDCl\(_3\). (Bottom) Titration of 1 with 7b. Aromatic region of the \( ^1H \) NMR spectrum (400 MHz, 298 K) of 1 after addition of 7b ([7b] concentration range during titration: 0.00-2.50 mM, from bottom to top) (in red the NH signals of 1).
Figure S30. Aromatic region of the $^1$H NMR spectrum (400 MHz, CD$_3$CN) : (a) of 1; (b) of 7a; (c) of 1 after added of 4 equiv of 7a; (d) of 1 after added of 8 equiv of 7a.