Tetrahedron 68 (2012) 2657–2661

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Highly selective palladium-catalyzed aminocarbonylation and cross-coupling reactions on a cavitand scaffold

Zsolt Csók [a,*], Anikó Takátsy [b], László Kollár [a,*]

[a] Department of Inorganic Chemistry, University of Pécs, H-7624 Pécs, PO Box 266, Hungary
[b] Department of Biochemistry and Medical Chemistry, Medical School, University of Pécs, H-7624 Pécs, PO Box 266, Hungary

ARTICLE INFO

Article history:
Received 16 November 2011
Received in revised form 3 January 2012
Accepted 23 January 2012
Available online 28 January 2012

Keywords:
Cavitand
Aminocarbonylation
Cross-coupling
Carbon monoxide
Palladium

ABSTRACT

Palladium-catalyzed aminocarbonylation and cross-coupling reactions (Suzuki-, Sonogashira-, Stille-coupling) served as highly efficient synthetic tools for the synthesis of novel, functionalized deepened cavitands. Unexpectedly high chemoselectivities towards tetrafunctionalized cavitands have been observed for all of these reactions even using coupling partners much below the stoichiometric amount. No significant formation of either the mono-, di- or trifunctionalized products was observed.

1. Introduction

Cavitands[1] are a class of molecular hosts representing a conformationally rigid, bowl-shaped structure. Enlarging the inner cavity of such molecular containers is essential considering their potential applications as sensors, nanoreactors and drug delivery systems.[2] Deepening the molecular pocket of cavitands was principally accomplished by conventional organic reactions[3]; nevertheless homogeneous catalytic cross-coupling reactions were sparsely employed as well.[4] In a previous paper, we described a methodology based on Williamson etherification that provided easy access to a wide variety of deepened cavitands, including a tetraiodo derivative.[5] Tetraiodocavitand (**1**), bearing four excellent leaving groups, served as a key intermediate for further extension of the cavitand structure as demonstrated in its utilization in a Suzuki-reaction. In this study, we aimed to broaden the scope of palladium-catalyzed homogeneous catalytic reactions on this cavitand scaffold.

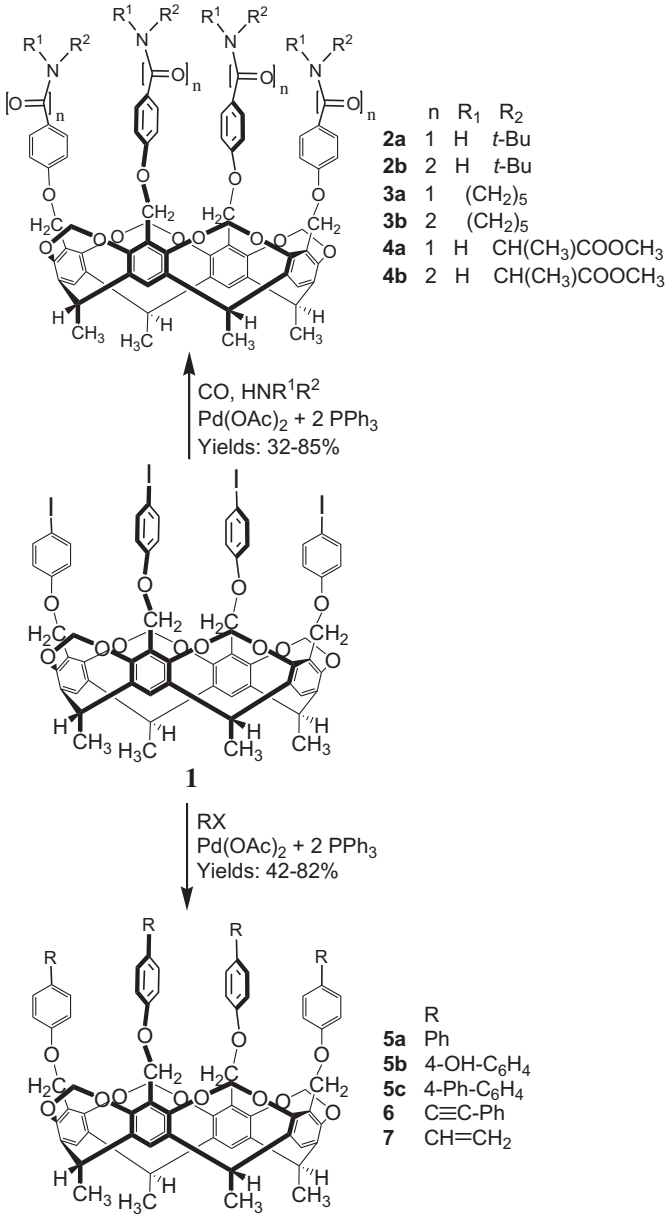
Carboxamide functionalities were previously introduced into the cavitand skeleton by acylation of the corresponding aminocavitands.[6] Palladium-catalyzed carbonylation reactions serve as an important synthetic tool in the hands of organic chemists.[7] In aminocarbonylation, organohalides (preferably iodoalkenes and iodoarenes) can readily be converted into the corresponding carboxamides by using carbon monoxide and various amines as nucleophiles, in the presence of a palladium(0) catalyst.[8] The synthetic applicability of these catalytic reactions is due to the ease in structural variation of amides both on the amide nitrogen and on the carboxylic acid moieties. That is, instead of the conventional carboxylic acid—acyl chloride—amide route, the direct carbonylation of haloaromatics or haloalkenes as well as those of the corresponding triflate surrogates can be used.[9] It is worth mentioning that aminocarbonylation has shown high tolerance towards both the structure of the primary and secondary amine and that of the organic halide derivative. This straightforward synthetic method has been successfully applied to a range of substrates, including simple model compounds, heterocyclic compounds[10] and biologically important skeletons such as tropane[11] and steroidal backbones.[12] However, to the best of our knowledge, there are no examples of palladium-catalyzed carbonylation reactions performed on cavitands or related macrocycles.

2. Results and discussion

Aminocarbonylation as well as cross-coupling (Suzuki-, Sonogashira-, Stille-coupling) reactions were chosen to introduce various functionalities on the rim of the cavitand scaffold in the presence of $Pd(OAc)_2$+2PPh_3 in situ catalytic systems (Scheme 1). The tetraiodo-cavitand (**1**), used as a substrate, was synthesized by an improved methodology (see Experimental).

* Corresponding authors. E-mail addresses: zscsok@gamma.ttk.pte.hu (Z. Csók), kollar@ttk.pte.hu (L. Kollár).

0040-4020/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2012.01.065



Scheme 1. Selective functionalization of **1** via aminocarbonylation and cross-coupling reactions.

Besides a primary (*tert*-butyl-amine) and a secondary amine (piperidine), a chiral amino acid (D-alanine methyl ester hydrochloride) was employed as *N*-nucleophile for the preparation of the novel carboxamidocavitands (n=1, **2a**–**4a**) in aminocarbonylation. Depending on the reaction conditions, the insertion of a second CO also permits the formation of ketocarboxamides (n=2, **2b**–**4b**).

We noticed that increasing the molar equivalents of the amine reagents resulted in the preferential formation of tetrakis(2-ketocarboxamide)cavitands (n=2) in the product distribution (Table 1, entries 1 and 2 for **2b**, 7 and 8 for **3b**, and entries 15–17 for **4b**, respectively). Furthermore, higher CO pressure generated also, as expected, a superior chemoselectivity towards these derivatives (entries 2, 4, 6 for **2b**, entries 8, 9, 11 for **3b**, and entries 14, 15 for **4b**, respectively). Generally, both higher molar equivalents of the amine reactants and higher CO pressure provided better yields. It is important to note that none of these tetrakis(2-ketocarboxamide) derivatives contained any mono-, bis- or tris(carboxamide) impurities.

To our surprise, when the molar equivalents of the amine reactants were decreased below 4, i.e., less than a stoichiometric amount of the

Table 1
Palladium-catalyzed aminocarbonylation of **1**[a]

Entry	Amine	Amine (mol equiv)	p[CO] (bar)	Conversion[b] (%)	Chemoselectivity[c] (%)	Isolated yield[d] (%)
1	*t*-Bu-amine	4	1	55	**2a** (100)	32 (**2a**)
2	*t*-Bu-amine	18	1	100	**2a** (70), **2b** (30)	n.d.
3	*t*-Bu-amine	2	30	46[g]	**2a** (100)	18 (**2a**)
4	*t*-Bu-amine	18	30	89	**2b** (100)	65 (**2b**)
5	*t*-Bu-amine	1	90	22[h]	**2a** (100)	13 (**2a**)
6	*t*-Bu-amine	18	90	83	**2b** (100)	78 (**2b**)
7	Piperidine	4	1	96	**3a** (100)	56 (**3a**)
8	Piperidine	18	1	100	**3a** (87), **3b** (13)	n.d.
9	Piperidine	18	30	90	**3a** (29), **3b** (71)	n.d.
10	Piperidine	2	90	42[g]	**3a** (40), **3b** (60)	n.d.
11	Piperidine	18	90	80	**3b** (100)	69 (**3b**)
12[e]	Piperidine	18	30	29	**3b** (100)	25 (**3b**)
13[f]	Piperidine	18	30	90	**3b** (100)	85 (**3b**)
14	D-Ala–OMe	4	1	100	**4a** (86), **4b** (14)	n.d.
15	D-Ala–OMe	4	30	100	**4a** (76), **4b** (24)	n.d.
16	D-Ala–OMe	8	30	100	**4a** (52), **4b** (48)	n.d.
17	D-Ala–OMe	16	30	100	**4a** (9), **4b** (91)	n.d.
18	D-Ala–OMe	8	90	100	**4a** (49), **4b** (51)	n.d.
19[e]	D-Ala–OMe	8	30	29	**4a** (44), **4b** (56)	n.d.

[a] Reaction conditions: **1**/$Pd(OAc)_2$/PPh_3/base=1:0.15:0.3:12, 60 °C.
[b] (Moles of converted **1**)/(moles of initial **1**)×100.
[c] Determined on the crude reaction mixture by means of ^{1}H and ^{13}C NMR spectroscopy (before column chromatography) as described in Experimental (4.3).
[d] Isolated yields of pure products.
[e] Tris(2,4,6-trimethoxyphenyl)phoshine was used as ligand.
[f] Tributylphosphine tetrafluoroborate was used as a ligand precursor.
[g] In the case of selective tetrasubstitution the highest conversion that could be achieved is 50%.
[h] In the case of selective tetrasubstitution the highest conversion that could be achieved is 25%.

N-nucleophile was used, only the same tetrafunctionalized products (**2a**–**4a** and **2b**–**4b**) could be isolated along with unreacted starting tetraiodocavitand (**1**) (entries 3, 5 and 10). Therefore, during the course of the reactions, the composition of the reaction mixtures was carefully checked both by in situ ^{1}H and ^{13}C NMR. Again, neither the formation of mono-, di- or trifunctionalized products nor that of the 'mixed-substituted' carboxamido-ketocarboxamido-cavitands was observed even at lower amine/substrate molar ratios. Hence, it has been proved by detailed NMR investigations, carried out on crude reaction mixtures, that two types of tetrafunctionalised aminocarbonylated products such as carboxamidocavitands **2a**–**4a** and ketocarboxamidocavitands **2b**–**4b** were almost exclusively formed. The total of the side products (that is, the total amount of the 'mixed-substituted' iodo-carboxamido-cavitands or that of the carboxamido-ketocarboxamido-cavitands) was less than 3% according to the NMR analyses.

A catalytic system containing bulkier ligand (tris(2,4,6-trimethoxyphenyl)phosphine) provided even higher chemoselectivity towards **3b**, however, it showed less catalytic activity compared to the $Pd(OAc)_2$+2PPh_3 catalyst system (entries 9 and 12). Very good activity and excellent chemoselectivity were observed in the presence of the catalyst containing the more basic tributylphosphine (added as a tetrafluoroborate salt)[13] instead of PPh_3 (entry 13).

The structure of carboxamides **2a**–**4a** was confirmed by ^{1}H and ^{13}C NMR spectroscopy and MS measurements, all other novel cavitands were isolated as pure compounds and fully characterized (Experimental). Cavitands **4a** and **4b** could only be isolated as mixtures. Tetrakis(amidocavitands) bearing amide N–H protons (**2** and **4**) showed remarkably different ^{1}H NMR spectra in DMSO-d_6 and in $CDCl_3$ (see Fig. 1 for **4**). The ^{1}H NMR spectrum of the mixture of **4a** and **4b** in DMSO-d_6, a media competitive for hydrogen bonds, clearly indicated a monomeric, C_4 symmetrical species, where the N–H doublet appeared at 8.58 and 9.28 ppm, respectively. In contrast, the spectrum, in the less polar $CDCl_3$, no longer showed the

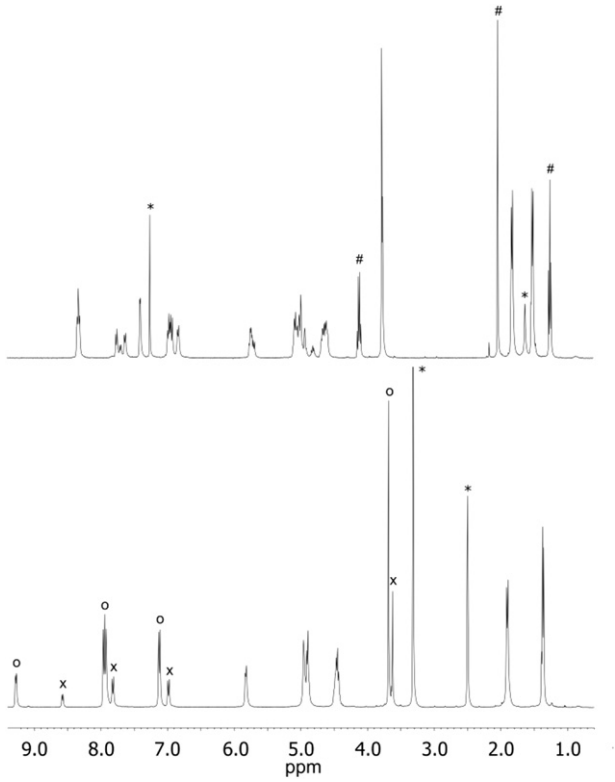
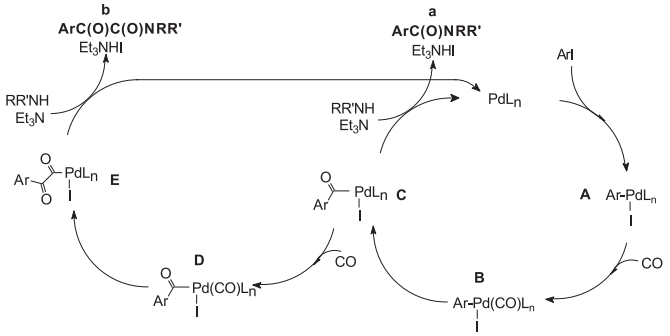


Fig. 1. ^{1}H NMR spectra of the mixture of **4a** and **4b** in $CDCl_3$ (top) and in DMSO-d_6 (bottom), × and o denote the protons of **4a** and **4b**, respectively (* stands for the protons of the corresponding NMR solvents, # designates residual EtOAc).

features of a symmetrical structure. This suggests the presence of hydrogen bonded dimeric forms of **2** or **4** in nonpolar solvents.[4a] Furthermore, the ^{1}H NMR spectra of **3** in both DMSO-d_6 and in $CDCl_3$ displayed highly symmetrical, monomeric species owing to the absence of amide N–H protons capable of making intermolecular hydrogen bonds. The characteristic, low-field ArC=O chemical shifts appeared in all ^{13}C NMR spectra of the tetra(2-ketocarboxamide)cavitands (188.89 ppm for **2b**, 190.31 ppm for **3b** and 188.57 ppm for **4b**) along with the signal for N(H)C=O (165.73 ppm for **2b**, 165.55 ppm for **3b** and 165.52 ppm for **4b**).

The formation of the mono and double-carbonylated products (**a** and **b**, respectively) can be rationalized as follows (Scheme 2). The iodoarene substrate is oxidatively added to the Pd(0) centre forming the aryl-iodo intermediate (**A**), which is able to coordinate carbon monoxide as a terminal carbonyl ligand (**B**). The insertion of carbon monoxide provides the palladium(II)–acyl intermediate (**C**), which undergoes aminolysis forming carboxamides (**a**). A further carbon monoxide could also be coordinated forming an acyl–carbonyl complex (**D**). The insertion of the 'second' carbon



Scheme 2. A simplified catalytic cycle of mono and double-carbonylation leading to **a** and **b**, respectively.

monoxide results in the formation of the arylglyoxyloyl complex (**E**), which provides ketocarboxmides (**b**). It should be noted that the formation of the latter product via reductive elimination from acyl–carbamoyl–palladium(II) species cannot be excluded.[14]

It has been proved that neither carboxamides can be carbonylated to 2-ketocarboxamides nor 2-ketocarboxamides decarbonylated to carboxamides under the reaction conditions used. That is, the chemoselectivity of the reaction is determined during the carbon monoxide insertion steps (**B**→**C**, and **D**→**E**) followed by aminolysis.

We have previously described a Suzuki-reaction using $PhB(OH)_2$,[5] and now we have broadened the scope of cross-coupling reactions on this cavitand platform. Besides two novel deepened cavitands obtained by Suzuki-coupling (**5b** and **5c**), Sonogashira- (**6**) and Stille-reactions (**7**) were also exploited (Scheme 1). It should be noted that **5c** exhibits very low solubilities in most organic solvents. As described for aminocarbonylation, decreasing the molar equivalents of the coupling reagents (boronic acids, phenylacetylene or tributylvinylstannane) below 4, the exclusive formation of tetrafunctionalized products (**5a**, **5b**, **5c**, **6**, **7**) was observed while the corresponding amount of unreacted starting tetraiodocavitand (**1**) was recovered.

To find a reasonable explanation for the very high chemoselectivities towards tetrafunctionalized products, some novel catalytic features of the palladium-catalyst have to be supposed. It is worth noting, that Reinhoudt and Sherburn reported on various organic reactions between cavitands having appropriate functionalities and less than 4 mol equiv of reactants. As expected, these reactions resulted in the generation of *statistical mixtures* of up to five partially substituted products.[15] In contrast, we noticed unexpectedly high chemoselectivities towards tetrafunctionalized cavitands in homogeneous palladium-catalyzed reactions. Although these selectivities have been proved by in situ NMR and catalytic investigations, as well as by the isolation of two-component mixtures and analytically pure compounds in high yields, the rationalisation of the formation of '*well-defined cavitands*' needs further investigations. Quantum chemical calculations, kinetic and coordination chemistry studies are in progress.

3. Conclusion

Palladium-catalyzed cross-coupling reactions (Suzuki-, Sonogashira-, Stille-coupling) served as highly efficient synthetic tools for the synthesis of electron-rich, extended cavitands. Furthermore, the easily available and varied amine reactants make aminocarbonylation a powerful synthetic methodology for the functionalization of deepened cavitands. Remarkable chemoselectivities were achieved towards tetracarboxamido- and tetrakis(ketocarboxamido)cavitands, which exhibit great stability and good solubility in most organic solvents. All of these deepened cavitands might serve as flexible binding pockets in 'host–guest' chemistry.

4. Experimental

4.1. General procedures

All reagents and solvents were purchased from Aldrich and used as received. Toluene and THF were distilled from sodium/benzophenone. ^{1}H and ^{13}C NMR spectra were recorded at 25 °C in $CDCl_3$ (or in DMSO-d_6) on a Varian Inova 400 spectrometer at 400.13 MHz and 100.62 MHz, respectively. The ^{1}H chemical shifts (δ), reported in parts per million (ppm) downfield, are referenced to the residual protons (7.26 ppm for $CDCl_3$ and 2.50 for DMSO-d_6). The ^{13}C chemical shifts are referenced to the carbon resonance of $CDCl_3$ (77.00 ppm) or to that of DMSO-d_6 (39.52 ppm), respectively. MALDI-TOF spectra were obtained on an Autoflex II TOF/TOF

spectrometer (Bruker Daltonics) in positive ion modes, using a 337 nm pulsed nitrogen laser (accelerating voltage: 20.0 kV, matrix: 2,5-dihydroxybenzoic acid). Cavitand **5a** was prepared as previously described.[5]

4.2. Improved synthesis of tetrakis(4-iodo-phenoxymethyl)-cavitand (1)

To a solution of 4-iodophenol (10.4 g, 0.047 mol) in THF (60 mL) was added a solution of aqueous NaOH (0.47 M, 100 mL), then the solution was stirred for 30 min. This solution was then slowly added to a solution of tetrakis(bromomethyl)cavitand (5.2 g, 5.37 mmol) in THF (100 mL).[16] The reaction mixture was stirred at 70 °C for 16 h, then the precipitated product was collected by filtration and dried in vacuo. Yield: 5.302 g (65%). The spectroscopic data corresponded to those reported.[5]

4.3. A typical procedure for aminocarbonylation experiments

Method A (for cavitands **2**, **3**): Compound **1** (250 mg, 0.164 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), PPh_3 (13.1 mg, 0.05 mmol) and K_2CO_3 (272 mg, 1.97 mmol) were weighed and placed under an inert atmosphere into a 100 mL autoclave. Dry toluene (20 mL) and the corresponding amount of amine (given in Table 1) were added, and then the reaction mixture was placed under CO pressure. The reaction mixture was stirred at 60 °C for 40 h, the precipitate was filtered, and the filtrate was evaporated to dryness. The residue was treated with MeOH (5 mL), the resulting precipitate was collected by filtration and dried in vacuo. An analytically pure sample of **3b** was obtained by column chromatography (silica gel; eluent: CH_2Cl_2/EtOAc=1:1, R_f=0.51). *Method B* (for cavitands **4**): Compound **1** (250 mg, 0.164 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), and PPh_3 (13.1 mg, 0.05 mmol) were weighed and placed under an inert atmosphere into a 100 mL autoclave. Dry DMF (20 mL), NEt_3 (275 μL, 1.97 mmol) and the corresponding amount of D-alanine methyl ester hydrochloride (given in Table 1) were added. The reaction mixture was then placed under CO pressure. The reaction mixture was stirred at 60 °C for 40 h, the precipitate was filtered, and the filtrate was evaporated to dryness. The residue was treated with MeOH (5 mL), the resulting precipitate was collected by filtration, and purified by column chromatography (silica gel; eluent: CH_2Cl_2/EtOAc=1:1; R_f=0.80).

4.4. A typical procedure for Suzuki (5) and Sonogashira (6) cross-coupling reactions

Compound **1** (250 mg, 0.164 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), PPh_3 (13.1 mg, 0.05 mmol) and 1.31 mmol of the corresponding coupling reagent (4-hydroxyphenylboronic acid for **5b**, 4-biphenylboronic acid for **5c** and phenylacetylene for **6**) were weighed, placed under an inert atmosphere into a Schlenk-tube, and deoxygenated THF (10 mL) was added. (For the synthesis of **6**, CuI (31 mg, 0.164 mmol) was also added.) K_2CO_3 (272 mg, 1.97 mmol) was dissolved in deoxygenated water (5 mL), and was added to the reaction mixture. The reaction mixture was then stirred at 70 °C for 16 h. (During the preparation of **5c**, the product precipitated from the reaction mixture, thus no further purification was required.) The reaction mixture was partitioned between CH_2Cl_2 (10 mL) and water (10 mL). The organic phase was separated, and the aqueous phase was extracted with another portion of CH_2Cl_2 (10 mL). The combined organic phases were washed with water (10 mL), dried over $MgSO_4$, and evaporated to dryness. The residue was treated with MeOH (5 mL), the resulting precipitate was collected by filtration, and dried in vacuo. An analytically pure sample of **6** was obtained by column chromatography (silica gel; eluent: benzene; R_f=0.90).

4.5. A typical procedure for Stille (7) cross-coupling reaction

Into a Schlenk-tube, **1** (250 mg, 0.164 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), PPh_3 (13.1 mg, 0.05 mmol), CuI (31 mg, 0.164 mmol) and KF (115 mg, 1.97 mmol) were weighed, and placed under an inert atmosphere. Anhydrous DMF (15 mL) and tributyl(vinyl)tin (383 μL, 1.312 mmol) were added, and then the reaction mixture was stirred at 70 °C for 2 days. The precipitation was filtered, the filtrate was evaporated to dryness, and the residue was treated with MeOH (5 mL). The resulting precipitate was collected by filtration, and purified by column chromatography (silica gel; eluent: benzene; R_f=0.68).

4.6. Characterizations of the products

*4.6.1. Cavitand **2a**.* Viscous material (75 mg, 32%). Found: C, 71.22; H, 6.71, N, 3.77. $C_{84}H_{92}N_4O_{16}$ requires C, 71.37; H, 6.56; N, 3.96%. R_f (CH_2Cl_2) 0.95; ν_{max}(KBr): 1655 cm^{-1}; δ_H (400.1 MHz, DMSO-d_6): 1.36 (36H, s, *t-Bu*), 1.90 (12H, d, *J* 7.2 Hz, CH_3CH), 4.48 (4H, d, *J* 7.2 Hz, inner of OCH_2O), 4.82–4.96 (12H, br m, $CHCH_3$ overlapping with $ArCH_2O$), 5.81 (4H, d, *J* 7.2 Hz, outer of OCH_2O), 6.92 (8H, d, *J* 8.4 Hz, Ar), 7.52 (4H, s, N*H*), 7.74 (8H, d, *J* 8.4 Hz, Ar), 7.91 (4H, s, Ar). δ_C (100.6 MHz, DMSO-d_6): 16.1 (CH_3CH), 28.7 ((CH_3)$_3$C), 31.3 (CH_3CH), 50.6 ((CH_3)$_3$*C*), 60.5 ($ArCH_2O$), 99.4 (OCH_2O), 113.7, 122.1, 122.5, 128.4, 129.1, 139.1, 153.1, 160.3, 165.6 (C=O). MS: 1435.49 $[M+23]^+$.

*4.6.2. Cavitand **2b**.* White powder (195 mg, 78%), mp 273–277 °C. Found: C, 69.42; H, 5.98; N, 3.38. $C_{88}H_{92}N_4O_{20}$ requires C, 69.28; H, 6.08; N, 3.67%. R_f (CH_2Cl_2) 0.86; ν_{max}(KBr): 1662 cm^{-1}; δ_H (400.1 MHz, DMSO-d_6): 1.36 (36H, s, *t-Bu*), 1.90 (12H, d, *J* 7.2 Hz, CH_3CH), 4.47 (4H, d, *J* 7.2 Hz, inner of OCH_2O), 4.90 (4H, q, *J* 7.2 Hz, $CHCH_3$), 4.94 (8H, s, $ArCH_2O$), 5.82 (4H, d, *J* 7.2 Hz, outer of OCH_2O), 7.11 (8H, d, *J* 8.4 Hz, Ar), 7.86 (8H, d, *J* 8.4 Hz, Ar), 7.92 (4H, s, Ar), 8.40 (4H, s, N*H*). δ_C (100.6 MHz, DMSO-d_6): 16.1 (CH_3CH), 28.3 ((CH_3)$_3$C), 31.3 (CH_3CH), 51.1 ((CH_3)$_3$*C*), 60.8 ($ArCH_2O$), 99.4 (OCH_2O), 114.8, 122.1, 122.7, 126.0, 132.0, 139.1, 153.2, 163.1, 165.7 (N(H)C=O), 188.9 (ArC=O). MS: 1547.60 $[M+23]^+$.

*4.6.3. Cavitand **3a**.* Viscous material (135 mg, 56%). Found: C, 72.17; H, 6.44; N, 3.59. $C_{88}H_{92}N_4O_{16}$ requires C, 72.31; H, 6.34; N, 3.83%. R_f (50% EtOAc/$CHCl_3$) 0.42; ν_{max}(KBr): 1607 cm^{-1}; δ_H (400.1 MHz, $CDCl_3$): 1.52–1.72 (24H, br m, (CH_2)$_3$), 1.82 (12H, d, *J* 7.2 Hz, CH_3CH), 3.53 (16H, br s, N(CH_2)$_2$), 4.64 (4H, d, *J* 7.2 Hz, inner of OCH_2O), 4.92 (8H, s, $ArCH_2O$), 5.09 (4H, q, *J* 7.2 Hz, $CHCH_3$), 5.76 (4H, d, *J* 7.2 Hz, outer of OCH_2O), 6.91 (8H, d, *J* 8.0 Hz, Ar), 7.33 (8H, d, *J* 8.0 Hz, Ar), 7.40 (4H, s, Ar). δ_C (100.6 MHz, $CDCl_3$): 16.1 (CH_3CH), 24.6, 26.2 (br), 31.2 (CH_3CH), 43.3 (br), 48.8 (br), 60.6 ($ArCH_2O$), 100.0 (OCH_2O), 114.2, 120.7, 122.3, 128.8, 129.2, 138.9, 154.0, 159.5, 170.0 (*C*=O). MS: 1483.60 $[M+23]^+$.

*4.6.4. Cavitand **3b**.* White powder (219 mg, 85%), mp 190–193 °C. Found: C, 70.43; H, 5.81; N, 3.31. $C_{92}H_{92}N_4O_{20}$ requires C, 70.21; H, 5.89; N, 3.56%. R_f (50% CH_2Cl_2/EtOAc) 0.51; ν_{max}(KBr): 1635, 1672 cm^{-1}; δ_H (400.1 MHz, $CDCl_3$): 1.54 (8H, br s, CH_2), 1.68 (16H, br s, (CH_2)$_2$), 1.82 (12H, d, *J* 7.2 Hz, CH_3CH), 3.28 (8H, br s, NCH_2), 3.68 (8H, br s, NCH_2), 4.59 (4H, d, *J* 7.2 Hz, inner of OCH_2O), 4.98 (8H, s, $ArCH_2O$), 5.07 (4H, q, *J* 7.2 Hz, $CHCH_3$), 5.75 (4H, d, *J* 7.2 Hz, outer of OCH_2O), 6.98 (8H, d, *J* 8.8 Hz, Ar), 7.41 (4H, s, Ar), 7.89 (8H, d, *J* 8.8 Hz, Ar). δ_C (100.6 MHz, $CDCl_3$): 16.1 (CH_3CH), 24.3, 25.4, 26.2, 31.2 (CH_3CH), 42.1, 47.1, 60.9 ($ArCH_2O$), 99.8 (OCH_2O), 114.6, 121.0, 121.7, 126.8, 132.1, 139.1, 153.9, 163.5, 165.5 (NC=O), 190.3 (ArC=O). MS: 1595.68 $[M+23]^+$.

*4.6.5. Cavitand **4a** (isolated as a mixture of **4a** and **4b**).* White powder (180 mg, ca. 68% (combined yield)). R_f (50% CH_2Cl_2/EtOAc) 0.80; ν_{max}(KBr): 1661, 1774 cm^{-1}; δ_H (400.1 MHz, DMSO-d_6): 1.38

(12H, d, *J* 7.2 Hz, COOC*H*$_3$), 1.90 (12H, d, *J* 7.2 Hz, C*H*$_3$CH), 3.63 (12H, s, NC(H)C*H*$_3$), 4.40–4.54 (8H, m, inner of OC*H*$_2$O overlapping with NC*H*(CH$_3$)), 4.91 (4H, q, *J* 7.2 Hz, C*H*CH$_3$), 4.96 (8H, s, ArC*H*$_2$O), 5.83 (4H, d, *J* 7.2 Hz, outer of OC*H*$_2$O), 6.99 (8H, d, *J* 8.8 Hz, Ar), 7.82 (8H, d, *J* 8.4 Hz, Ar), 7.92 (4H, s, Ar), 8.58 (4H, d, *J* 6.8 Hz, N*H*). MS: 1555.28 $[M+23]^+$.

4.6.6. Cavitand ***4b*** *(isolated as a mixture of* ***4a*** *and* ***4b****).* White powder (180 mg, ca. 68% (combined yield)). R_f (50 % CH_2Cl_2/EtOAc) 0.80; ν_{max}(KBr): 1661, 1774, 970, 1254 cm^{-1}; δ_H (400.1 MHz, DMSO-d_6): 1.37 (12H, d, *J* 7.2 Hz, COOC*H*$_3$), 1.90 (12H, d, *J* 7.2 Hz, C*H*$_3$CH), 3.69 (12H, s, NCH(C*H*$_3$)), 4.40–4.54 (8H, m, inner of OC*H*$_2$O overlapping with NC*H*(CH$_3$)), 4.91 (4H, q, *J* 7.2 Hz, C*H*CH$_3$), 4.96 (8H, s, ArC*H*$_2$O), 5.83 (4H, d, *J* 7.2 Hz, outer of OC*H*$_2$O), 7.12 (8H, d, *J* 8.8 Hz, Ar), 7.92 (4H, s, Ar), 7.96 (8H, d, *J* 8.4 Hz, Ar), 9.28 (4H, d, *J* 5.2 Hz, N*H*). δ_C (100.6 MHz, DMSO-d_6): 16.0 (*C*H$_3$CH), 16.5 (NC(H)*C*H$_3$), 31.3 (CH$_3$*C*H), 47.5 (N*C*(H)CH$_3$), 52.1 (COO*C*H$_3$), 60.8 (Ar*C*H$_2$O), 99.4 (O*C*H$_2$O), 114.8, 122.7, 125.9, 132.2, 139.1, 153.1, 160.8, 163.4, 165.5 (N(H)*C*=O), 172.3 (*C*OOCH$_3$), 188.6 (Ar*C*=O); MS: 1667.68 $[M+23]^+$.

4.6.7. Cavitand ***5b****.* White powder (96 mg, 42%), mp >350 °C (dec). Found: C, 76.42; H, 5.12. $C_{88}H_{72}O_{16}$ requires C, 76.29; H, 5.24%. ν_{max}(KBr): 973, 1244 cm^{-1}; δ_H (400.1 MHz, DMSO-d_6): 1.91 (12H, d, *J* 7.2 Hz, C*H*$_3$CH), 4.56 (4H, d, *J* 7.2 Hz, inner of OC*H*$_2$O), 4.82–5.02 (12H, m, C*H*CH$_3$ overlapping with ArC*H*$_2$O), 5.82 (4H, d, *J* 7.2 Hz, outer of OC*H*$_2$O), 6.79 (8H, d, *J* 8.0 Hz, Ar), 6.95 (8H, d, *J* 8.4 Hz, Ar), 7.35 (8H, d, *J* 8.0 Hz, Ar), 7.43 (8H, d, *J* 8.4 Hz, Ar), 7.92 (4H, s, Ar), 9.50 (4H, s, O*H*). δ_C (100.6 MHz, DMSO-d_6): 16.1 (*C*H$_3$CH), 31.3 (CH$_3$*C*H), 60.4 (Ar*C*H$_2$O), 99.4 (O*C*H$_2$O), 115.0, 115.7, 122.3, 122.9, 127.0, 127.1, 130.5, 133.0, 139.0, 153.1, 156.6, 157.3. MS: 1407.45 $[M+23]^+$.

4.6.8. Cavitand ***5c****.* White powder (114 mg, 43%), mp >350 °C (dec). Found: C, 82.96; H, 5.28. $C_{112}H_{88}O_{12}$ requires C, 82.74; H, 5.46%. ν_{max}(KBr): 974, 1260 cm^{-1}; δ_H (400.1 MHz, $CDCl_3$): 1.86 (12H, d, *J* 7.2 Hz, C*H*$_3$CH), 4.76 (4H, d, *J* 7.2 Hz, inner of OC*H*$_2$O), 5.00 (8H, s, ArC*H*$_2$O), 5.13 (4H, q, *J* 7.2 Hz, C*H*CH$_3$), 5.82 (4H, d, *J* 7.2 Hz, outer of OC*H*$_2$O), 6.99 (8H, d, *J* 9.2 Hz, Ar), 7.30–7.60 (48H, m, Ar). MS: 1647.60 $[M+23]^+$.

4.6.9. Cavitand ***6****.* White powder (125 mg, 54%), mp >300 °C (dec). Found: C, 81.62; H, 4.98. $C_{96}H_{72}O_{12}$ requires C, 81.34; H, 5.12%. R_f (benzene) 0.90; ν_{max} (KBr): 975, 1246 cm^{-1}; δ_H (400.1 MHz, $CDCl_3$): 1.85 (12H, d, *J* 7.2 Hz, C*H*$_3$CH), 4.66 (4H, d, *J* 7.2 Hz, inner of OC*H*$_2$O), 4.96 (8H, s, ArC*H*$_2$O), 5.11 (4H, q, *J* 7.2 Hz, C*H*CH$_3$), 5.79 (4H, d, *J* 7.2 Hz, outer of OC*H*$_2$O), 6.88 (8H, d, *J* 8.5 Hz, Ar), 7.28–7.53 (32H, m, Ar). δ_C (100.6 MHz, $CDCl_3$): 16.2 (*C*H$_3$CH), 31.2 (CH$_3$*C*H), 60.6 (Ar*C*H$_2$O), 88.3 (C≡*C*), 89.1 (*C*≡C), 100.1 (O*C*H$_2$O), 114.6, 116.0, 120.7, 122.5, 123.5, 127.9, 128.3, 131.5, 133.2, 139.0, 154.0, 158.6. MS: 1440.81 $[M+23]^+$.

4.6.10. Cavitand ***7****.* White powder (150 mg, 82%), mp >270 °C (dec). Found: C, 77.38; H, 5.58. $C_{72}H_{64}O_{12}$ requires C, 77.12; H, 5.75%. R_f (benzene) 0.68; ν_{max}(KBr): 972, 1246 cm^{-1}; δ_H (400.1 MHz, $CDCl_3$): 1.83 (12H, d, *J* 7.5 Hz, C*H*$_3$CH), 4.67 (4H, d, *J* 7.2 Hz, inner of OC*H*$_2$O), 4.92 (8H, s, ArC*H*$_2$O), 5.07–5.15 (8H, m, C*H*CH$_3$ overlapping with CH=C*H*$_a$H$_b$), 5.60 (4H, d, *J* 17.6 Hz, CH=CH$_a$*H*$_b$), 5.76 (4H, d, *J* 7.2 Hz, outer of OC*H*$_2$O), 6.65 (4H, dd, *J* 17.6, 10.8 Hz, C*H*=CH$_2$), 6.86 (8H, d, *J* 8.7 Hz, Ar), 7.30 (8H, d, *J* 8.7 Hz, Ar), 7.40 (4H, s, Ar). δ_C (100.6 MHz, $CDCl_3$): 16.2 (*C*H$_3$CH), 31.2 (CH$_3$*C*H), 60.6 (Ar*C*H$_2$O), 100.1 (O*C*H$_2$O), 111.8, 114.6, 120.6, 122.7, 127.4, 130.9, 136.1, 138.9, 154.0, 158.5. MS: 1142.6 $[M+22]^+$.

Acknowledgements

The authors thank the Hungarian Research Fund (CK78553) and Developing Competitiveness of Universities in the South Transdanubian Region (SROP-4.2.1.B-10/2/KONV-2010-0002) for the financial support and Johnson Matthey for the generous gift of palladium(II) acetate. Z.C. thanks the Bolyai Grant of the Hungarian Academy of Sciences.

Supplementary data

^{1}H and ^{13}C NMR spectra (as pdf files) are available via the Internet at http://www.journals.elsevier.com/tetrahedron for all isolated cavitands. Supplementary data related to this article can be found in the online version, at doi:10.1016/j.tet.2012.01.065.

References and notes

1. Cram, D. J.; Karbach, S.; Kim, H. E.; Knobler, C. B.; Maverick, E. F.; Ericson, J. L.; Helgeson, R. C. *J. Am. Chem. Soc.* **1988**, *110*, 2229–2237.
2. Cram, D. J.; Cram, J. M. *Container Molecules and their Guests*; Royal Society of Chemistry: Cambridge, 1994.
3. (a) Moran, J. R.; Ericson, J. L.; Dalcanale, E.; Bryant, J. A.; Knobler, C. B.; Cram, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 5707–5714; (b) Tucci, F. C.; Rudkevich, D. M.; Rebek, J., Jr. *J. Org. Chem.* **1999**, *64*, 4555–4559; (c) Li, X.; Upton, T. G.; Gibb, C. L. D.; Gibb, B. C. *J. Am. Chem. Soc.* **2003**, *125*, 650–651.
4. (a) Ma, S.; Rudkevich, D. M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1998**, *120*, 4977–4981; (b) Aakeröy, C. B.; Schultheiss, N.; Desper, J. *Org. Lett.* **2006**, *12*, 2607–2610.
5. Csók, Z.; Kégl, T.; Párkányi, L.; Varga, Á.; Kunsági-Máté, S.; Kollár, L. *Supramol. Chem.* **2011**, *23*, 710–719.
6. (a) Rudkevich, D. M.; Hilmersson, G.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1998**, *119*, 9911–9912; (b) Rudkevich, D. M.; Hilmersson, G.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1998**, *120*, 12216–12225; (c) Chang, T.-Y.; Paek, K. *Bull. Korean Chem. Soc.* **2008**, *29*, 1857–1859.
7. (a) Beller, M.; Bolm, C. *Transition Metals for Organic Synthesis*; Wiley-VCH: Weinheim, 1998; Vol. I–II; (b) *Modern Carbonylation Methods*; Kollár, L., Ed.; Wiley-VCH: Weinheim, 2008.
8. Skoda-Földes, R.; Kollár, L. *Lett. Org. Chem.* **2010**, *7*, 621–633.
9. (a) Skoda-Földes, R.; Kollár, L. *Curr. Org. Chem.* **2002**, *6*, 1097–1119; (b) Brennführer, A.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 4114–4133; (c) Cornils, B.; Herrmann, W. A. In *Applied Homogeneous Catalysis with Organometallic Compounds*; Wiley-VCH: Weinheim, 1996; (d) Beller, M.; Bolm, C. *Transition Metals for Organic Synthesis*; Wiley-VCH: Weinheim, 1998; Vols. I–II; (e) Arcadi, A. Carbonylation of enolizable ketones (enol triflates) and iodoalkenes. In *Modern Carbonylation Methods*; Kollár, L., Ed.; Wiley-VCH: Weinheim, 2008; Chapter 9, pp 223–250.
10. Takács, A.; Szilágyi, A.; Ács, P.; Márk, L.; Peixoto, A. F.; Pereira, M. M.; Kollár, L. *Tetrahedron* **2011**, *67*, 2402–2406.
11. Horváth, L.; Berente, Z.; Kollár, L. *Lett. Org. Chem.* **2007**, *4*, 236–238.
12. (a) Balogh, J.; Mahó, S.; Háda, V.; Kollár, L.; Skoda-Földes, R. *Synthesis* **2008**, 3040–3042; (b) Ács, P.; Takács, A.; Szilágyi, A.; Wölfling, J.; Schneider, G.; Kollár, L. *Steroids* **2009**, *74*, 419–423 and references cited therein.
13. Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295–4298.
14. (a) Ozawa, F.; Sugimoto, T.; Yamamoto, T.; Yamamoto, A. *Organometallics* **1984**, *3*, 692–697; (b) Son, T.; Yanagihara, H.; Ozawa, F.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1251–1258.
15. (a) Boerrigter, H.; Verboom, W.; van Hummel, G. J.; Harkema, S.; Reinhoudt, D. N. *Tetrahedron Lett.* **1996**, *37*, 5167–5170; (b) Barrett, E. S.; Irwin, J. L.; Picker, K.; Sherburn, M. S. *Aust. J. Chem.* **2002**, *55*, 319–325.
16. Sorrell, T. N.; Pigge, F. C. *J. Org. Chem.* **1993**, *58*, 784–785.