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Supramolecularly-Driven Mild Friedel-Crafts Reaction Inside the Hexameric Resorcinarene Capsule: C–Cl Bond Activation by H-Bonding with the Bridged Water Molecules

Pellegrino La Manna,[a] Carmen Talotta,[a] Giuseppe Floresta,[b,c] Margherita De Rosa,*,[a] Annunziata Soriente,[a] Antonio Rescifina,*,[c] Carmine Gaeta,*,[a] and Placido Neri [a]

Dedicated to Prof. Jerry L. Atwood on the occasion of his 75th birthday

Abstract: *A novel catalytical feature of the hexameric resorcinarene capsule (**C**) is here highlighted. The self-assembled cage **C** has been exploited to promote a mild Friedel-Crafts benzylation of several arenes and heteroarenes. In silico studies show the existence of a catalytically relevant H-bonding interaction between the bridged water molecules of the capsule and benzyl chloride, which is fundamental for the activation of the C–Cl bond. A supramolecular control of the capsule on the reaction outcome is evidenced. Inside the inner space of the capsule, N-methylpyrrole is preferentially benzylated in the unusual β-position, while mesitylene reacts faster than 1,3-dimethoxybenzene, despite the greater π-nucleophilicity of this latter.*

π-Nucleophiles represent useful building blocks in organic synthesis thanks to their use in carbon-carbon bond-forming reactions with electrophiles.[1] Among them, the Friedel-Crafts (FC) alkylation of arene and heteroarene with aliphatic and benzylic groups is particularly investigated.[2] Traditionally, this reaction is promoted by Lewis acids,[2] but recently, much attention has been focused on environmentally-oriented catalytic strategies based on metal free approaches.[3] Thus, Paquin and coworkers,[3a] reported a FC benzylation of arenes using benzyl fluoride in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as solvent. Their results evidenced a mechanism involving the activation of the C–F bond through an H-bonding interaction between the fluorine as H-bond acceptor and HFIP as H-bond donor. Analogously, Mayr and coworkers showed that the FC reaction between 4-methoxybenzyl halides and arenes occurs in 2,2,2-trifluoroethanol.[3b] Also, in this case, the authors remark the role of the hydroxylic solvent (CF_3CH_2OH) in the activation of the C–X bond.

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The hexameric capsule (**1**)$_6$•8H_2O (**C**)[4] which is obtained by self-assembly of six resorcinarene **1** units and eight water molecules[4a] (Figure 1), has been largely exploited as nanoreactor,[5] thanks to its capacity to host selectively the substrates and to accelerate the organic reactions with excellent chemo-, regio-, and stereoselectivity.[6] Examination of the literature data revealed that nanoreactor **C** shows some catalytically relevant features of interest for the catalysis of organic reactions. Inside the hexameric capsule have been accelerated a variety of organic reactions involving cationic intermediates and transition states thanks to their stabilization induced by the π-electron-rich aromatic cavity of **C**.[7] Moreover, nanoreactor **C** shows a remarkable Brønsted acidity (pK_a = 5.9 measured in water-saturated $CDCl_3$ and relative to the reported aniline pK_a-value in water) which has been exploited for the catalysis of chemical reactions.[8]

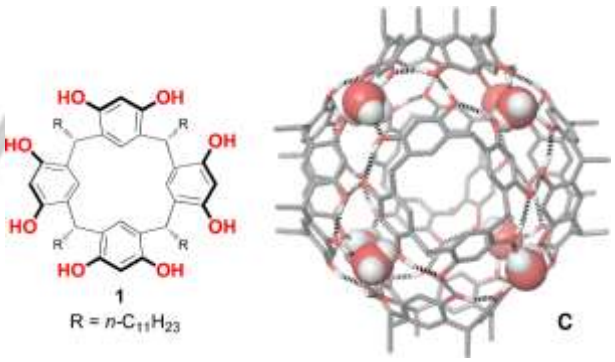

Figure 1. Chemical drawing of *C*-undecylresorcin[4]arene **1** (left) and a model of the hexameric capsule (**1**)$_6$•(H_2O)$_8$ (**C**) (right); undecyl chains and H-atoms have been removed for clarity, while bridged H_2O molecules are represented as CPK model.

Interestingly, very recently, we have shown the existence of catalytically relevant H-bonding interactions between the bridged water molecule (in CPK model in Figure 1) in **C** and substrates hosted inside the cavity.[6] On the basis of this considerations, and in accordance with the results previously reported by Paquin,[3a] we envisioned that the H-bond donor abilities of the bridged water molecules in **C**[6] could play a role in the catalysis of FC alkylation of π-nucleophiles through the H-bonding activation of the C–X bond.

Consequently, as a part of our ongoing project aimed at the exploration of the large possibilities offered by catalysis into

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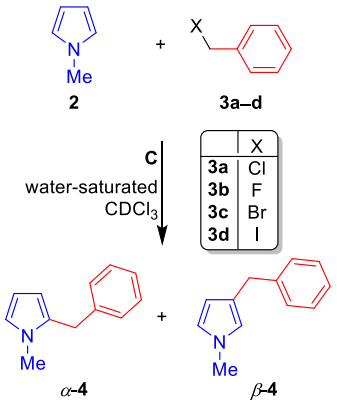
confined environments,[6] with particular regard to the C–C bond forming reactions,[9] we studied the FC benzylation of aromatic and heteroaromatic compounds with benzyl halides (Scheme 1) inside the hexameric capsule (Figure 1), and we wish to report here the results of our studies.



Scheme 1. Friedel-Crafts reaction between *N*-methylpyrrole and benzyl halides promoted by **C**.

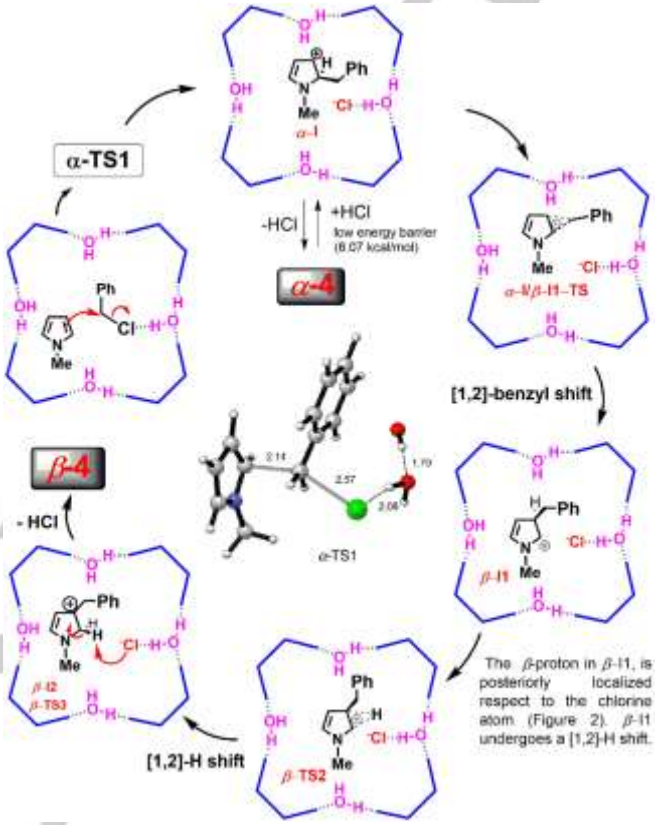
Initially, we investigated the reaction between *N*-methylpyrrole **2** and benzyl chloride **3a** in the presence of **C** (26%) (Scheme 1), using water-saturated[5] $CDCl_3$ as the solvent.[5] When the reaction mixture was stirred at 30 °C for 16 h the products **4** were obtained in 20% of total yield. Surprisingly the *β*-alkylated product *β*-**4** was favored with respect to the *α*-regioisomer *α*-**4** with a 90/10 ratio (Table 1, entry 2). This is an intriguing result since the benzylation at the 2-position of *N*-methylpyrrole,[10] under FC conditions, is usually the favored one.[11]

Table 1. Friedel-Crafts reaction between *N*-methylpyrrole **2** and benzyl halides promoted by hexameric resorcinarene capsule **C.**

Entry[a]	T (°C)	X	Equiv. of **2**	Capsule amount (mol%)	Yield (%)[b]	Ratio *β*-**4**/*α*-**4**[c]
1	30	Cl	1.5	0	0[d]	—
2	30	Cl	1.5	26	20	90/10
3[e]	30	Cl	1.5	26	0	—
4[f]	50	Cl	1.5	52	81	94/6
5[f]	50	Br	1.5	52	72	91/9
6[f]	50	F	1.5	52	75	85/15
7[f]	50	I	1.5	52	—	—

[a] Reaction conditions: **2** (0.22 M), **3** (0.15 M), **C** (0.076 M) in 1.1 mL of water-saturated $CDCl_3$, 16 h. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis (SI). [d] Analogous result was observed when the reaction was performed at 50 °C. [e] The reaction was performed in the presence of $Et_4N^+BF_4^-$ (0.76 M). [f]Only starting materials were recovered when the reaction was performed in the absence of capsule **C**.

However, some examples have been reported in which a 1:1 mixture of *α*/*β* regioisomers was obtained.[11c, 11e] Consequently, on the basis of this results we can conclude that the hexameric capsule **C** is able to drive the regiochemistry of the FC benzylation of *N*-methylpyrrole in Scheme 1 towards an unconventional route. Of course, this represents an interesting example of supramolecular control of a reaction outcome.[12]



Scheme 2. The mechanism proposed for the preferential formation of *β*-**4** inside the hexameric capsule **C**, as calculated through *in silico* studies (SI) of the FC reaction between **2** and **3a** inside the model capsule $\mathbf{C_R}$ having shorter feet. Inset: H-bonding interaction between the chlorine atom of **3a** and a bridged water molecule of **C** in the hetero-binary complex [**2**+**3a**]@$\mathbf{C_R}$. Only the atoms of the ONIOM high layer have been represented; the capsule has been schematized in blue. The chlorine atom is engaged in a hydrogen bond with a water molecule. The distances are given in Å. Carried out with CYLview.

When the reaction in Scheme 1 was performed in the absence of **C**, regardless of the kind of benzyl halide exploited, no hint of conversion of **2** and **3a** into **4** (Table 1, entry 1) was observed by NMR spectroscopy. These data strongly suggested that the reaction in Scheme 1 occurs inside **C**. This was confirmed by the finding that in the presence of $(Et)_4N^+BF_4^-$ (0.76 M), as a competitive guest,[13] no conversion of **2** and **3a** into **4** was observed (Table 1, entry 3). In addition, a ^{1}H NMR spectrum (SI, Figure S2) of the reaction mixture in the presence of $(Et)_4N^+BF_4^-$, showed the presence of shielded signals at negative values of chemical shifts attributable to tetraethyl cation inside the cavity of **C**. Furthermore, no hints of products **4** were detected when the reaction in Scheme 1 was performed in the presence of hydrogen-bond competitor solvents (*e.g.*, DMSO).

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As previously discussed **C** shows a strong affinity for cationic guests,[7] consequently, a question arises whether it is able or not to accommodate π-electron-rich aromatic nucleophiles. Detailed NMR studies (see EXSY, COSY, HSQC, and DOSY experiments in SI) clearly indicated that both *N*-methylpyrrole **2** and benzyl chloride **3a** were encapsulated inside the nanocontainer **C**.

Interestingly, by doubling the percentage of **C** (52%) and by increasing the reaction temperature at 50 °C, the products **4** were obtained in 81% of total yield with a marked regioselectivity for β-**4** (β-**4**/α-**4** = 94/6, entry 4 in Table 1). These results suggested a products inhibition[14] probably due to a high affinity of the benzylated products β-**4** for the capsule. In fact, the catalytic efficiency of **C** was dramatically lowered when the reaction in Scheme 1 was performed in the presence of products **4** (94/6 β-**4**/α-**4** mixture of regioisomers, SI pages S5–S7).

To get more insights into the reaction mechanism that lead to the preferential formation of β-**4** inside the hexameric capsule **C** (Scheme 2), we conducted a quantum chemical investigation of the effect of the capsule on the course of the FC reaction between **2** and **3a**, using a capsule model $\mathbf{C_R}$ with shorter feet and ONIOM method (Scheme 2 and SI, pages S30–S39). Our calculations clearly indicated that **C** is capable to host benzyl chloride **3a** followed by the *N*-methylpyrrole **2**. In fact, an enthalpic stabilization was calculated (Table S6) for the encapsulated reagent **3a** principally due to the formation of a hydrogen bonding interaction between the chlorine atom and a bridged water molecule in $\mathbf{C_R}$ (Figure S30 and MC in Figure 2). Interestingly, the pK_a calculation of all hydrogen atoms directly bonded to oxygens in the $\mathbf{C_R}$ model (Table S11), pointed out that there are four localized zones with a microenvironmental pK_a of ≈2.5 while the mean pK_a results of 6.1, in excellent agreement with the experimental datum (*vide supra*). In addition, a highly negative complexation enthalpy (Table S6) was observed for the formation of the hetero-binary complex [**2**+**3a**]@$\mathbf{C_R}$ (Figure S31). The calculations indicate that the reaction proceeds through α-TS1 (Figure S33, Scheme 2) which lead to the corresponding Wheland intermediate, α-I (Scheme 2 and Figure 2), located 1.2 kcal/mol below TS1 (SI, Table S7, and Figure S33). Finally, the loss of the hydrogen atom from the σ-complex α-I (Figures S30,S31) proceeds very easily thanks to a very low energetic barrier (Figure S33, 0.2 kcal/mol) and the obtained product α-**4** is located 9.40 kcal/mol (Figure S33) below the starting reagents making the reaction exergonic. At this point, the keystone to justify the marked preference for the product β-**4** is the [1,2]-benzyl shift (Scheme 2 and Figure 2) which rearranges the α-I adduct in the β-I1 through the transition state α-I/β-I1-TS with an activation energy of 25.4 kcal/mol. On the other hand, the σ-complex, β-I1, not being able to directly lose the β-proton (Scheme 2 and Figure 2), since posteriorly localized respect to the chlorine atom (Figure 2), undergoes a [1,2]-H shift, through β-TS2, to give the Wheland intermediate β-I2, more stable than β-I1 by 5.2 kcal/mol. From the σ-complex, β-I2, the product β-**4**, was obtained through a re-aromatization step with a very low energy barrier (Figure S32). Interestingly, the encapsulated product β-**4**@$\mathbf{C_R}$ is thermodynamically more stable than α-**4**@$\mathbf{C_R}$ by 2.8 kcal/mol. The calculations indicate that the retro-FC from α-**4** to α-I proceed with a low energy barrier (6.1 kcal/mol) and consequently, in the long run, the reaction exclusively provides the thermodynamic product β-**4.** Summarizing, the calculations confirm the catalytically relevant role of the capsule and particularly, the calculations highlight that the capsule exerts a supramolecular control on the reaction determining the preferential formation of the β-**4** product. In fact, from the results of the secondary-order perturbation theory (SOPT) analysis of the Fock matrix in NBO basis (Table S8 and Figure S34), clearly emerges that the σ-adducts α-I and β-I1 in Figure 2 are stabilized by a series of delocalizations, involving principally the chlorine atom of **3a** and the antibonding orbital of the O–H single bond of the capsule. This is in accordance with an enhanced transfer, at the Wheland intermediate, of the acidic water proton to the chlorine atom (Figure S32). Summarizing, the computational studies here reported clearly indicate a stabilization of the Wheland σ-complexes α-I and β-I1 inside the hexameric capsule with respect to those occurring in the bulk solvent, and consequently a lowering of the activation barrier of the FC reaction. In fact, comparison of the activation barrier Gibbs free energy of the rate-limiting step for the FC reaction revealed a very high value (α-TS1, $\Delta G^{\ddagger}$ = 50.5 kcal/mol, Table S7) when the reaction between **2** and **3a** occurred in the absence of the hexameric capsule. In addition, the calculations indicated that inside **C** the [1,2]-H shift and the [1,2]-benzyl shift can occur justifying the preference for β-**4.**

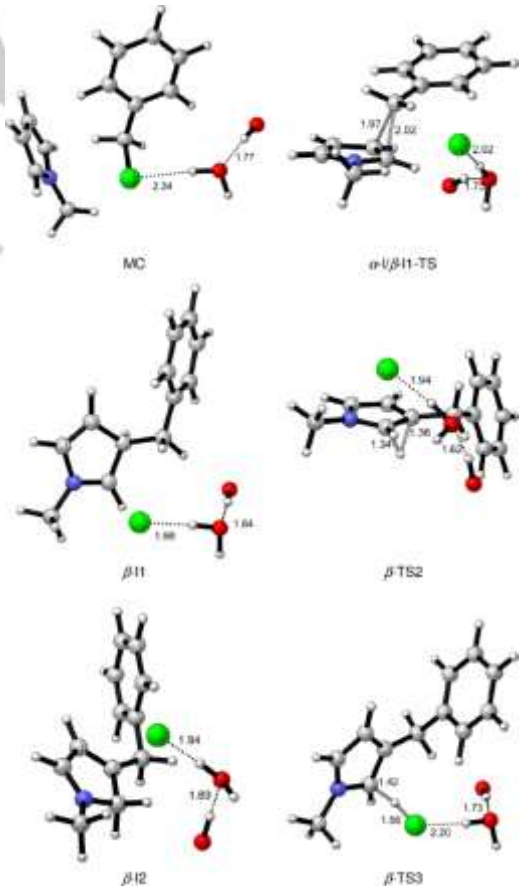
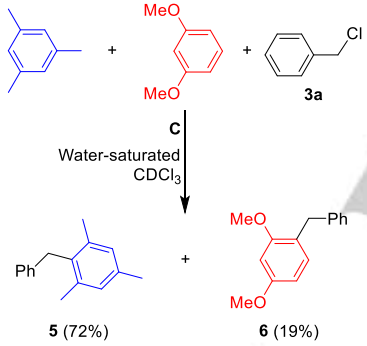


Figure 2. Geometries for all S and TS states associated with the path in Scheme 2 for the FC reaction. Only the atoms of the ONIOM high layer have been represented; the capsule has been omitted for clarity. Along the path, the chlorine atom of **3a** is always engaged in a hydrogen bond with a water molecule of $\mathbf{C_R}$. The distances are given in Å. Carried out with CYLview.

10.1002/anie.201801642

Finally, the calculations indicated a high affinity of β-**4** to the capsule (ΔH = –16.6) justifying the experimentally observed inhibition of the nanoreactor. From the comparison of the Wiberg bond indexes (Table S9) between the encapsulated reactants and the other intermediates up to the product, it is evident the formation of a catalytically relevant hydrogen bond between the Cl atom of **3a** and a bridged water molecule of $\mathbf{C_R}$, that reaches its maximum value at the α-I@$\mathbf{C_R}$ (0.135), β-I2@$\mathbf{C_R}$ (0.199), and α-I/β-I1-TS@$\mathbf{C_R}$ (0.154), accomplished by a change in the charge of the chlorine atom that reaches its maximum negative value at the same stationary points.

To corroborate the catalytic role of this H-bonding interaction, we studied the reaction in Scheme 2 using benzyl iodide **3d** as the substrate, because the iodine atom in **3d** is a weaker H-bond acceptor.[15] Interestingly, when *N*-methylpyrrole **2** was reacted with benzyl iodide **3d** in the presence of hexameric capsule **C**, no conversion to **4** was observed. Differently, by using benzyl fluoride **3b** and benzyl bromide **3c** the products **4** were obtained in 75 and 72% yield, with a β/α regioselectivity of 85/15 and 91/9, respectively. In addition, when D_2O-saturated $CDCl_3$ was used under the condition reported in Table 1, entry 4, the products **4** were obtained in 51% yield (Figure S1, bottom), a value significantly lower than that observed in the presence of H_2O (81%). This result is in full accordance with the deuterium isotope effect on H-bonding.[16]



Scheme 3. Competition FC benzylation experiment between mesitylene and 1,3-dimethoxybenzene promoted by **C** capsule. Reaction time, 4 h.

At this point, we studied the scope of the FC reaction promoted by **C** exploring a variety of π-nucleophiles. Previously, Mayr and coworkers reported a comparison of the nucleophilicity parameters of typical π-systems reacting with electrophiles.[3b] On the basis of the nucleophilicity scale reported by Mayr,[3b] we choose the series of aromatic substrates. First of all, our attention was focused on two arenes with different position along the Mayr's scale,[3b] such as mesitylene and 2,3-dimethoxybenzene. Surprisingly, when mesitylene was reacted with benzyl chloride **3a** at 50 °C in the presence of **C**, the benzylated product **5** was obtained in 92% yield after 4 h, whereas the 2,3-dimethoxybenzene afforded the 4-benzylated product **6** in only 40% yield under the same conditions. This surprising higher reactivity of mesitylene was in contrast with its position in the Mayr's scale of nucleophilicity with respect to 1,3-dimethoxybenzene[3b] and could be due to a stronger affinity of mesitylene for the capsule and consequently to its more efficient encapsulation. Another hypothesis could concern a possible product inhibition by **6**. To shed light on this aspects, we performed a competition experiment in which an equimolar mixture of 2,3-dimethoxybenzene (1.5 equiv) and mesitylene (1.5 equiv) was mixed with benzyl chloride (1.0 equiv) in the presence of **C** (52%) in water saturated $CDCl_3$ (Scheme 3).

Under these conditions, the products **5** and **6** were isolated by chromatographic column in 72% and 19% yield, respectively. This result excludes a product inhibition by **6** that would also inhibit the formation of **5**. In conclusion, when the FC reaction occurs inside the inner space of the self-assembled capsule **C**, the benzylation of mesitylene is favored with respect to the 2,3-dimethoxybenzene despite its greater nucleophilicity.

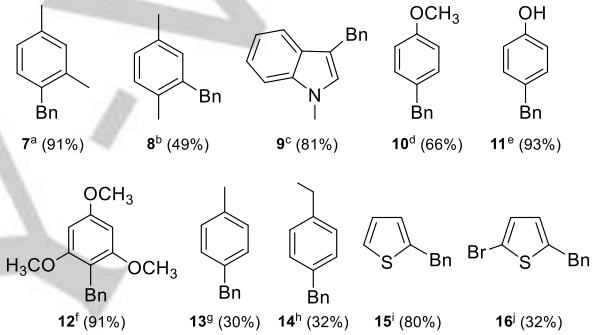


Figure 3. Products obtained by reactions of arenes with benzyl chloride in the presence of **C**. Reaction conditions: arene (0.22 M), **3a** (0.15 M), **C** (0.076 M) in 1.1 mL of water-saturated $CDCl_3$ at 50 °C, 16 h. Isolated yields (%). [a]From *m*-xylene. [b]From *p*-xylene. [c] From *N*-methylindole; contains 16% of the corresponding 2-isomer. [d]From anisole; contains 6% of the *ortho*-isomer. [e] From phenol; contains 35% of the *ortho*-isomer. [f] From 1,3,5-trimethoxybenzene; contains 6% of the di-substituted product. [g]From toluene; contains 18% of the *ortho*-isomer. [h] From ethylbenzene; contains 15% of the *ortho*-isomer. [i] From thiophene; contains 40% of the 3-isomer. [j] From 2-bromothiophene.

The hexameric capsule **C** was able to promote the benzylation of scarce π-nucleophiles such as toluene and ethylbenzene to give derivatives **13** and **14** with good regioselectivity (*para*/*ortho* ratio of 82/18 and 85/15 respectively). Analogously, when the *m*-xylene was reacted with benzyl chloride **3a** in the presence of **C**, at 50 °C for 16 h, the corresponding mono-benzylated product **7** (Figure 3) was obtained in high yield (91%). Differently, the *para*-xylene isomer was converted to **8** with a lower yield (49%, Figure 3). This is an interesting result since the benzylation of these scarce π-nucleophiles (toluene, ethylbenzene, xylenes) is reported in the presence of metal catalysts ($AlCl_3$, $FeCl_3$, $InCl_3$, etc.),[17] and generally occurs with low selectivity and requiring stoichiometric amounts of catalyst.[18] Regarding other arenes and heteroarenes systems, a high yield was observed also in the alkylation of *N*-methylindole with benzyl chloride in the presence of **C**, to give the benzylated derivative **9** in 81% yield. Anisole and phenol were efficiently benzylated to **10** and **11**, respectively. In the case of **11**, a 35% of the *ortho* isomer was detected in the crude product. When thiophene was mixed with benzyl chloride

3a in the presence of **C** in water-saturated $CDCl_3$ (Figure 3) the monobenzylated derivative **15** was obtained in high yield (80%). Differently by *N*-methylpyrrole **2**, in this case, the α-regioisomer was favored with a α/β regioselectivity ratio of 67/33.

In conclusion, we have here shown for the first time, that the H-bond donor ability of the bridged water molecules of hexameric resorcinarene capsule **C** can be exploited to promote the FC benzylation of several arenes and heteroarenes. **C** is able to exert a supramolecular control on the reaction at different levels. Inside the inner space of **C**, *N*-methylpyrrole was preferentially benzylated in the β position. The less π-nucleophilic mesitylene reacts faster than 1,3-dimethoxybenzene, because of its stronger affinity for the capsule. From these data, it is clear that the exploitation of H-bond donor ability of the bridged water molecules, here highlighted, opens up new potentialities in the supramolecular catalysis mediated by the fascinating self-assembled nanocontainer **C**.

Keywords: supramolecular catalysis • self-assembled capsule • Friedel-Crafts • resorcinarene • H-bond activation

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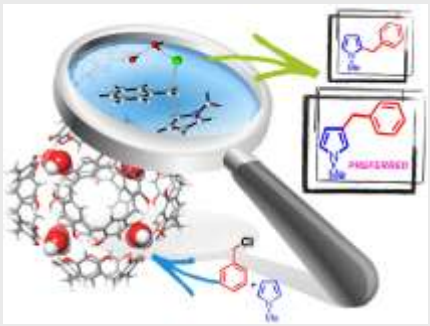
A little bit of water *is necessary to promote a Friedel-Crafts benzylation of π-nucleophiles inside the hexameric resorcinarene capsule. The activation of C-Cl bond of BnCl occurs through H-bonding interactions with the bridged water molecules of the capsule. A supramolecular control of the capsule on the reaction outcome is evidenced. Thus, N-methylpyrrole is preferentially benzylated in the unusual β-position, while mesitylene reacts faster than 1,3-dimethoxybenzene.*



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Page No. – Page No.

Supramolecularly-Driven Mild Friedel-Crafts Reaction Inside the Hexameric Resorcinarene Capsule: C-Cl Bond Activation by H-Bonding with the Bridged Water Molecules