

# PhD Thesis: “Supramolecular Scaffolds for Biomimetic Catalysis”

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## Abstract

This PhD thesis is concerned with the design, synthesis and the characterization of supramolecular scaffolds for biomimetic catalysis. Development of new organocatalytic systems based upon well-designed calix[4]arene derivatives was made and their application for on water catalysis<sup>1</sup> of the Vinylogous Mukaiyama Aldol Reaction<sup>2</sup> (VMAR) was explored. The obtained results showed that combination of high hydrophobicity<sup>3</sup> and synthetic versatility of calixarene macrocycles can be exploited for a kind of catalysis which permits the use of mild conditions and the choice of a reaction medium, water, different from organic solvents which are largely employed for the synthesis of fine chemicals and are responsible of large energy usage and industrial pollution<sup>4</sup>. So, calixarene macrocycles can be exploited to develop new environmentally oriented catalytic approaches. The target molecules bear a butenolide moiety substituted at  $\gamma$  position; this moiety represents a recurring motif in several compounds displaying a wide range of biological activities<sup>5</sup>. Moreover, thanks to the presence of functional groups typically involved in processes of molecular recognition through weak interactions, like hydroxyl and carbonyl functionalities, these products exhibit interesting features in their solid state assembly, showing that playing on non covalent interactions could be a good opportunity to build supramolecular architectures resembling the natural ones.

Resorcin[4]arene self-assembled capsules<sup>6</sup> were applied to catalyze the 1,3-dipolar cycloaddition between nitrones and unsaturated aldehydes and Friedel-Crafts reaction between aromatic (heteroaromatic) compounds and benzyl chloride. In both cases, the results indicated that resorcin[4]arene hexameric capsule is able to catalyze complex reaction thanks to its recognition<sup>7</sup>

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<sup>1</sup> Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassa, G. *Chem. Rev.* **2000**, *100*, 1929.

<sup>2</sup> (a) Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816; (b) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2005**, *44*, 3275.

<sup>3</sup> Neri, P.; Sessler, J. L.; Wang, M. –X.; *Calixarenes and Beyond*, Springer, Berlin, **2016**.

<sup>4</sup> Constable, D. J. C.; Jimenez-Gonzales, C.; Henderson, R. K. *Org. Process. Res. Dev.* **2007**, *11*, 133.

<sup>5</sup> Kalesse, M.; Cordes, M.; Symkenberg, G.; Lu, H.-H. *Nat. Prod. Rep.* **2014**, *31*, 563.

<sup>6</sup> (a) MacGillivray, L. R.; Atwood, J. L. *Nature* **1997**, *389*, 469; (b) Avram, L.; Cohen, Y. *J. Am. Chem. Soc.* **2002**, *124*, 15148.

<sup>7</sup> (a) Bräuer, T. M.; Zhang, Q.; Tifenbacher, K. *Angew. Chem. Int. Ed.* **2016**, *55*, 7698; (b) Caneva, T.; Sporni, L.; Strukul, G.; Scarso, A. *RSC Adv.* **2016**, *6*, 83505.

and Brønsted acidity<sup>8</sup>. The encapsulation of reagents into a confined environment, in the case of 1,3-dipolar cycloaddition, has made possible to obtain isoxazolidines with a certain grade of control on regio- and stereo-selectivity; in addition, nanoconfinement and hydrogen bonding by OH groups of the resorcinarene subunits allowed Friedel Crafts alkylation with a wide range of electrophiles. Products from 1,3-dipolar cycloaddition<sup>9</sup> and benzylated products from Friedel-Crafts alkylation<sup>10</sup> are, on different levels, a viable building block for preparation of natural compounds and in medicinal chemistry.

Considering these results, it's reasonable to think that mimicking at a certain level the *modus operandi* of natural enzymes can represent a turning point in the developing of new pathways in the field of the organocatalysis. Particularly, an enzyme-like catalysis can be obtained by exploiting calixarene hydrophobic cavity and their ability to recognize and to discriminate different substrates based on non-covalent interactions (particularly hydrogen bonding), or by making use of self-assembled resorcin[4]arene capsules.

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<sup>8</sup> Zhang, Q.; Tiefenbacher, K. *J. Am. Chem. Soc.* **2013**, *135*, 16213.

<sup>9</sup> Berthet, M.; Cheviet, T.; Dujardin, G.; Parrot, I.; Martinez, J. *Chem. Rev.* **2016**, *116*, 15235

<sup>10</sup> Rueping, M.; Nachtsheim, B. J. *Beilstein J. Org. Chem.* 2010, *6*, doi:10.3762/bjoc.6.6.