

# Site-selective indole oxidation catalyzed by a Mn-containing artificial metalloenzyme

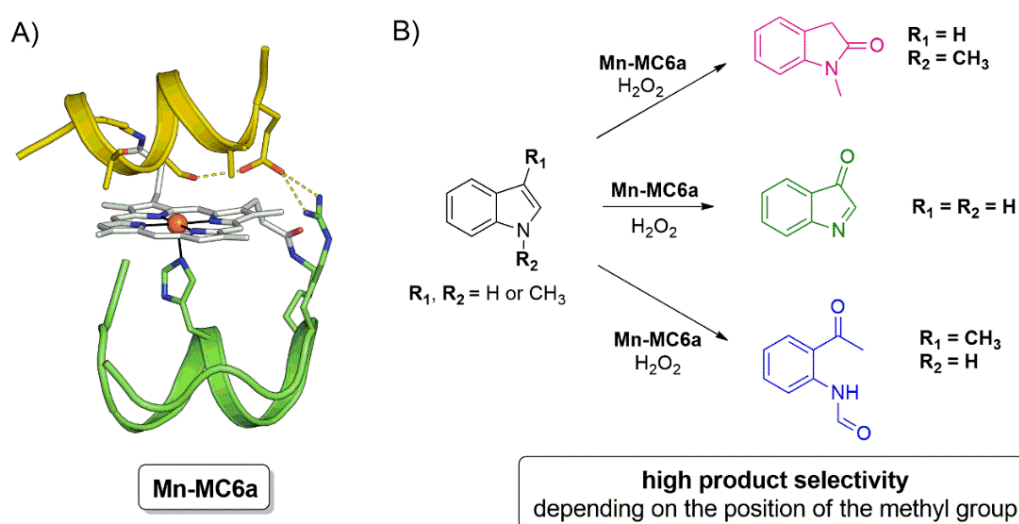
Linda Leone<sup>a</sup>, Giorgia Iovinella<sup>a</sup>, Daniele D'Alonzo<sup>a</sup>, Marco Chino<sup>a</sup>, Ornella Maglio<sup>a,b</sup>,  
Flavia Nastri<sup>a</sup>, Vincenzo Pavone<sup>a</sup> and Angela Lombardi<sup>a</sup>

<sup>a</sup>Department of Chemical Sciences, University "Federico II" of Napoli, Via Cintia, 80126, Napoli, Italy;

<sup>b</sup>IBB-CNR, Via Mezzocannone 16, 80134, Napoli, Italy; email: [linda.leone@unina.it](mailto:linda.leone@unina.it)

Metalloenzymes have become attractive tools for application in oxidation catalysis, since a complex protein environment exerts a highly specific control on the reactivity of the metal center.<sup>1</sup> Compared to synthetic catalysts, enzymes cover only a limited repertoire of reactions and substrates. The development of hybrid catalysts, obtained by anchoring catalytic metal complexes to native or artificial biomolecular scaffolds, is aimed at merging the advantages of both systems while overcoming the drawbacks.<sup>2,3</sup> In this area, our research is devoted to the development of peptide-porphyrin conjugates resembling natural heme-proteins, called "Mimochromes".<sup>3,4</sup> Among them, Mimochrome VIa (MC6a) is the most promising catalyst, thanks to its robust but flexible scaffold (Figure 1A). MC6a, in its Mn<sup>III</sup> complex, (Mn-MC6a) is an efficient catalyst with enzyme-like properties, because fast and chemoselective reactions with a peroxygenase-like mechanism were found in the oxidation of thioethers. Even more remarkably, Mn-MC6a selectively exhibits either peroxygenase- or catalase-like activity depending on the reaction conditions.

Here we present the oxidation of indole and its derivatives catalyzed by Mn-MC6a, with the aim of exploiting the catalytic properties of this artificial enzyme in reactions with potential synthetic applications.



**Figure 1:** A) Designed model of Mn-MC6a; B) oxidation of methyl-substituted indoles catalyzed by Mn-MC6a.

Indole is one of the most common heterocyclic scaffolds available in nature. It occurs in several natural compounds (such as alkaloids and plant hormones) and is part of many pharmaceuticals.<sup>5-8</sup> Despite the structural simplicity of this molecule, indole oxidation leads to a large number of products, including mono- and di-oxygenated compounds. Indole oxidation has been studied with both biological<sup>5,6</sup> and synthetic<sup>7,8</sup> catalysts. In all the approaches described so far, no or weak selectivity toward any of the oxidation products has been reported.<sup>5-8</sup> Conversely, Mn-MC6a is able to oxidize indole under unprecedented site-selective conditions, yielding to 3-oxindolenine as single product. Additionally, the reaction selectivity is dramatically altered when 1- or 3-methyl-substituted indoles are used as substrates (Figure 1B). A detailed mechanistic analysis will help to rationalize the outstanding selectivity of the catalyst.

#### References:

1. Sheldon, R. A. and Woodley, J. M. *Chem. Rev.* **2018**, *118*, 801–838.
2. Schwizer, F. *et al. Chem. Rev.* **2018**, *118*, 142-231.
3. Chino, M. *et al. Biopolymers* **2018** (doi: 10.1002/bip.23107).
4. Natri, F. *et al. Chem. Soc. Rev.*, **2016**, *45*, 5020-5054.
5. Kuo, H. H. and Mauk, A. G.; *Proc. Natl. Acad. Sci. U. S. A.* **2012**, *109*, 13966–13971.
6. Barrios, D. A. *et al. J. Am. Chem. Soc.* **2014**, *136*, 7914-7925.
7. Linhares, M. *et al. Appl. Catal. A.* **2014**, *470*, 427–433.
8. Poon L. C.-H. *et al. J. Am. Chem. Soc.* **2011**, *133*, 1877–1884.