

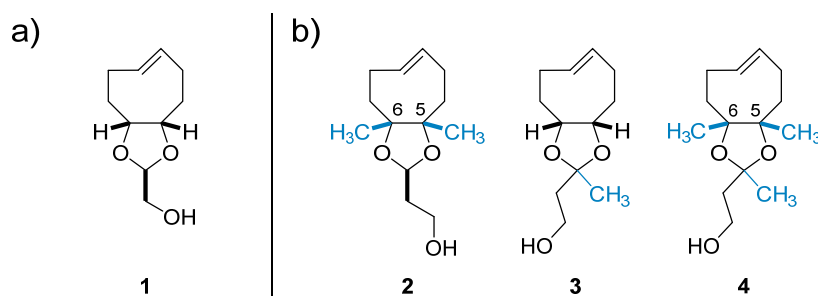
HIGHLY REACTIVE DIENOPHILES FOR BIOORTHOGONAL TETRAZINE LIGATIONS

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The reactions between 1,2,4,5-tetrazines and *trans*-cyclooctenes (TCO), known as “tetrazine ligations”, are the fastest bioorthogonal reactions reported so far with second order rate constants of up to $3.3 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$ [1]. The conformationally strained *trans*-cyclooctene d-TCO (**1**) introduced by Fox and coworkers (Figure 1a) [1] is an additionally strained and thus more reactive TCO that still show moderate stability, in contrast to highly reactive *s*-TCO [2] with only very limited *in vivo* stability.

The aim of this work is the development of structurally enhanced d-TCO derivatives by introducing methyl groups at key positions in the core structure to increase reactivity while still maintaining sufficient stability (Figure 1b). Bis-methylation at positions 5 and 6 of the TCO core structure (compounds **2** and **4**) and methylation of the acetal carbon (compounds **3** and **4**) have been considered. Based on computational studies compounds **2** and **4** are expected to be significantly more reactive compared to the parent TCO **1**. In addition, the introduced methyl groups are also expected to be beneficial for stability. Results of computational and experimental investigations will be presented.



[1] A. Darko, S. Wallace, O. Dmitrenko, M. M. Machovina, R. A. Mehl, J. W. Chin, J. M. Fox, *Chem. Sci.* **2014**, *5*, 3770–3776.

[2] M. T. Taylor, M. L. Blackman, O. Dmitrenko, J. M. Fox, T. Ligation, *J. Am. Chem. Soc.* **2011**, *133*, 9646–9649.