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Urea-based foldamer catalyst for C-C bond forming in asymmetric Michael reaction : a DFT investigation

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Bioinspired urea-based oligomers that fold with high fidelity (foldamers (**F**)) have been proven¹ as robust alternatives to metal based asymmetric catalysis, able to catalyze challenging C-C bond forming reactions with high enantioselectivity, and loadings as low as 1:10000 chiral catalyst/substrates molar ratios. However, studies developed at the atomistic level are necessary to understand the characteristics and function of the foldamers as catalysts. A DFT based Global Optimization procedure has been performed to find the low lying molecular arrangement in the conjugate addition of dimethylmalonate (**M**) to (1E)-3-methyl-1-nitrobut-1-ene (**N**) (see Figure below). It was found that **N** prefer the second site as H-bond donor, and **M** the first site. The interactions stabilizing the system are mainly electrostatic and noncovalent, with a set of Van der Waals interactions well defined between **N** and the phenyl group in **F**. Further investigations have been made in the Transition States, and the enantiomer **R** was predominant over the enantiomer **S**, which is coincident with the experimental observations. The enantiocontrol is identified to be related with specific geometrical parameters of the catalyst. These results rationalize the structure-properties relationship of the catalyst, and present for the first time a conclusive identification of its function. Further improvements to the catalytic properties of **F**-like foldamers are now possible.

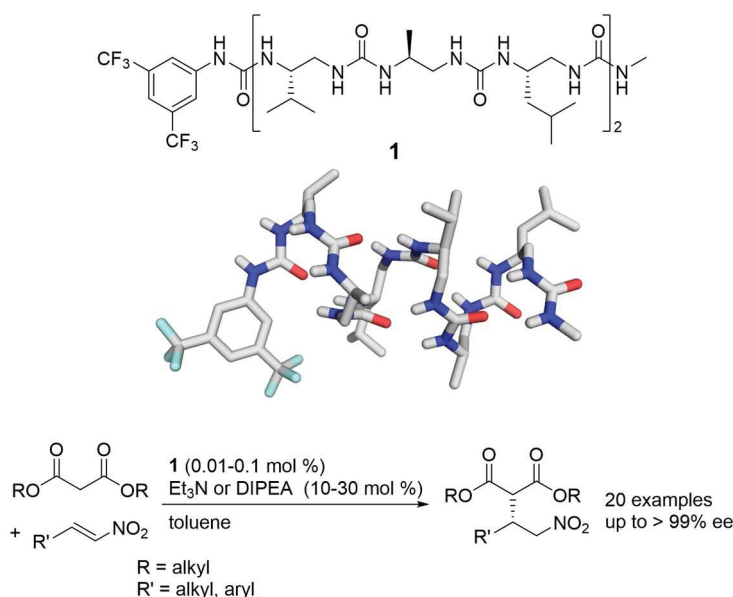


Figure 1. Representation of the foldamer and the substrates under study in our investigation.

¹ *J. Am. Chem. Soc.* **2017**, 139, 36, 12524–12532