Chiral Amine-urea Mediated Asymmetric Cycloadditions of Nitrile Oxides with $\omega$-Hydroxystyrenes and Their Computational Studies for Asymmetric Induction

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The nitrile oxide cycloadditions (NOCs) followed by reductive N-O bond cleavage sequence has been classically utilized for a number of natural product syntheses to construct stereogenic centers bearing nitrogen and oxygen functionalities. It is hence necessary to develop the enantioselective NOCs, as well as chiral substrate-based diastereoselective NOCs. However, up to date, only a few methodologies of enantioselective NOCs by using chiral Lewis acids [1] or metal catalysts [2] have been reported. This is probably due to their linear symmetrical structure that does not form an enantioface. Furthermore, enantioselective NOCs that involve organocatalytic variants or even in the presence of stoichiometric amount of chiral organic media have yet to be explored. To overcome the intrinsic challenge, we propose a novel dual-activation strategy involving LUMO activation by a Brønsted acid and HOMO activation by a Brønsted base in inverse electron-demand cycloadditions between nitrile oxides and $\omega$-hydroxystyrenes employing chiral amine-urea. In the congress, we describe the first example of cinchona alkaloid-based amine-urea-mediated asymmetric 1,3-dipolar cycloadditions between nitrile oxides and $\omega$-hydroxystyrenes, based on the dual activation methodology. In addition to stoichiometric asymmetric induction, catalytic amount of amine-urea enables the cycloadditions in an enantioselective manner. The high levels of asymmetric induction were strongly supported by DFT calculations of the energy differences between the anti-open TS (S) and anti-open TS (R). It has been also disclosed by the calculations that both the LUMO of nitrile oxides and HOMO of $\omega$-hydroxystyrenes can be activated by chiral amine-urea engaging the two reactants.

Dual activation strategy: inverse electron-demand 1,3-dipolar cycloadditions