Catalytic approach for amide coupling for the development of nucleic acid-supported catalysts

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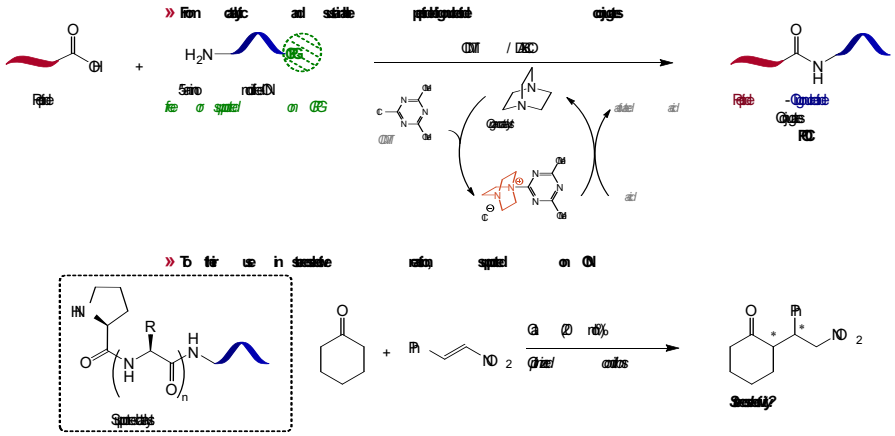
Oligonucleotide (ON) therapeutics have made remarkable progress in medicinal chemistry. Since the development of the first antisense ON in the late 1970s, 18 ON therapeutics (including antisense RNA and siRNA) have been approved by FDA, with an additional 130 in clinical trials.[1] Despite their growing applications, ON face some limitations, such as poor cellular uptake and instability in biological fluids.
To address this issue, cell penetrating peptides have been developed and conjugated to ON to enhance bioavailability and stability. This peptide–oligonucleotide conjugates (POC) can be prepared by linking a peptide and an ON through various chemical functions, including amide bonds.[2] In this context, we have developed a new sustainable catalytic approach for the direct preparation of amides from carboxylic acids and amines.[3] This method has been adapted for POC synthesis both in aqueous solution and on CPG solid support.[4]
We have used these POC as organocatalysts to promote enantioselective nitro-Michael addition. To the best of our knowledge, POC as organocatalyst has been poorly reported, to promote aldol reaction,[5] without any insight on stereochemistry. In this work, we present proof of concept demonstrating that POC could be used for the identification of the optimal chiral organocatalyst.



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