A Ball-Milling-Enabled Zinc-Mediated Reaction for the Synthesis of Fluorinated β-Amino Acids

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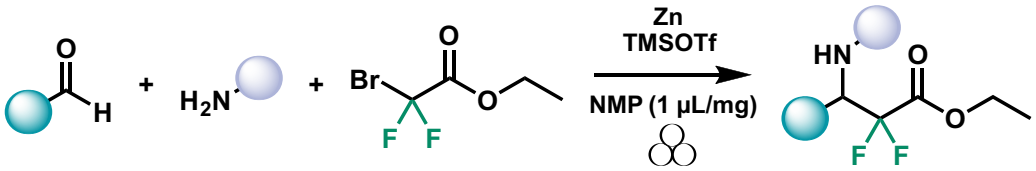
Fluorinated pseudo-amino acids are highly valuable building blocks in medicinal chemistry and peptide science, where fluorine incorporation can strongly modulate metabolic stability, lipophilicity, and conformational behavior.[1] However, their synthesis often relies on solution-based organometallic methods requiring dry solvents, inert atmosphere, and pre-activated metals, which limits operational simplicity and sustainability.[2]

To access this type of β-amino acids, a zinc-mediated carbonyl alkylative amination reaction was recently reported[3], enabling the synthesis of a broad range of substrates. Additionally, ball-milling has been studied for its applications to synthetic chemistry in the recent years since it can lead to solvent-minimized/free reactions, decreased reaction times, increased selectivity, or different reaction outcomes when compared to results obtained from solution-based reactions.[4] It has also been shown that carrying out zinc-mediated reactions by mechanochemistry needed no previous activation of the zinc powder and no need to exclude air or moisture from the reaction vessel.[5]

Herein, we have developed a ball-milling zinc-mediated carbonyl alkylative amination reaction enabling the access to fluorinated pseudo-amino acid derivatives *via* a two-step one-pot reaction which provides a practical and greener route to various fluorinated β-amino acids.



General scheme of our ball-milling zinc-mediated carbonyl alkylative amination reaction

References

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