

Ene Reductase Enabled Intramolecular β -C–H Functionalization of Substituted Cyclohexanones for Synthesis of Bridged Bicyclic Nitrogen Scaffolds

Background/Objective

While direct C–H functionalization of α -positions of carbonyl compounds is well-established, the more challenging direct β -C–H functionalization is under-explored. Meanwhile, compounds containing 6-azabicyclo[3.2.1]octane scaffolds have many applications in the chemical industry. Thus, developing an enzymatic strategy for efficient β -C–H functionalization of carbonyl compounds can potentially serve as a green and economic approach to access β -functionalized carbonyl compounds.

Approach

Researchers performed extensive enzyme screening and condition optimization for the photoenzymatic reactions to identify the best enzyme and reaction conditions. Following this, we tested various substrates with different substitutions to explore the substrate scope of the reaction. Then, we tested both chemical and enzymatic derivatizations of the chemoenzymatic product.

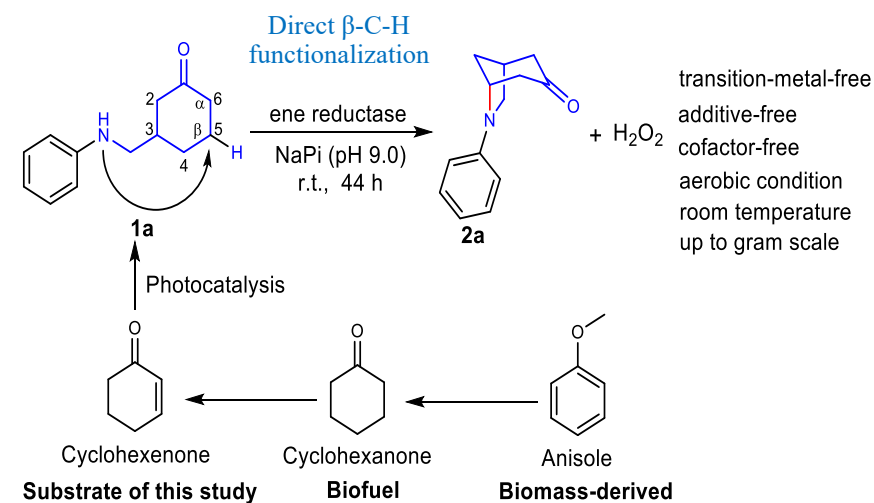
Results

- A direct transition-metal-free β -C–H functionalization strategy of carbonyl compounds is developed with ene reductases.
- Combining the β -C–H functionalization strategy with photocatalysis allows the synthesis of a series of 6-azabicyclo[3.2.1]octan-3-ones in one-pot reactions.
- The developed chemoenzymatic approach can be easily scaled up to gram scale, and the product can be derivatized to 6-azabicyclo[3.2.1]octan-3 α -ols.

Significance/Impacts

The cyclohexenones used in the study can be readily converted from biomass-derived biofuel cyclohexanones. When combined with the current photoenzymatic approach, it will allow us to develop a useful route for upgrading biomass to value-added chemicals.

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A potential novel chemoenzymatic route for upgrading biomass to value-added chemicals.