BIOCATALYSIS

Biocatalytic Friedel–Crafts alkylation

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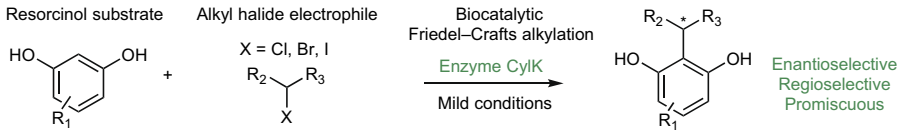

The Friedel–Crafts alkylation is widely used in organic chemistry for alkylation of arenes and heteroarenes. However, many Friedel–Crafts alkylation reactions in organic chemistry face limitations and challenges concerning regioselectivity, stereoselectivity and unwanted polyalkylation. Most importantly, the regioselectivity in this reaction commonly originates from the nature of the arene nucleophile, restricting the synthetic variability of classical Friedel–Crafts alkylation reactions.

Thus, a biocatalytic Friedel–Crafts alkylation reaction is desired whereby the enzyme allows alternative control over regioselectivity and stereoselectivity. However, common biocatalytic Friedel–Crafts reactions require the use of alkylating agents that are not prevalent in organic chemistry labs.

Recently, a team led by Emily P. Balskus at Harvard University discovered that the enzyme CylK employs a secondary alkyl chloride — commonly used by organic chemists in these reactions — as an alkylating agent for Friedel–Crafts reactions in nature. However, the substrate scope concerning non-native substrates of this enzyme remained unclear.

Now, Balskus and co-workers expand their work by exploring the substrate scope of wild-type CylK. The results indicate that the wild-type enzyme is limited to arenes that contain a resorcinol moiety — which is also found in the natural substrate. However, the enzyme tolerated the introduction of diverse functional groups at position 4 and 5 of the aromatic ring. Furthermore, the authors showed that CylK can also use secondary alkyl bromides and iodides as alkylating agents, rather than being limited to secondary alkyl chlorides.

Importantly, the enzyme specifically mediates alkylations at the 2-position of the resorcinol ring — a substitution found in many bioactive compounds — whereas the classical Friedel–Crafts reaction favours alkylation at the 4-position. In addition, the enzyme performs the reaction in a stereospecific and stereoselective manner.

Overall, this work confirms that CylK is a promising enzyme for organic chemistry. It offers several desired synthetic features, and the wild-type enzyme shows a good degree of promiscuity. Mechanistic and structural studies as well as directed evolution are anticipated to expand the utility of this enzyme and the understanding of its catalytic mode.

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