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Histidine-Containing Peptide Catalysts Developed by a Facile Library Screening Method
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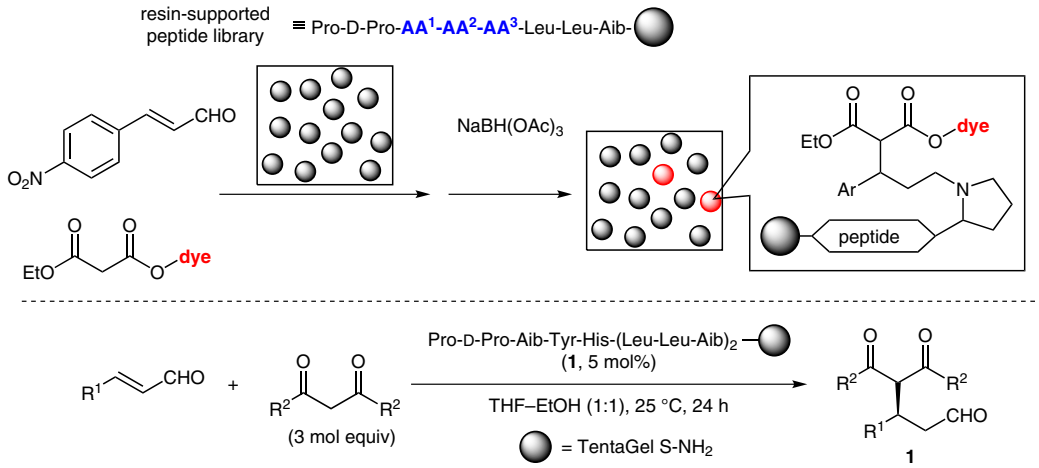
Supported Library-Based Screening of Peptide Catalysts



2a R^3 = NO_2, 89% yield, 98% ee
2b R^3 = Cl, 84% yield, 94% ee
2c R^3 = Br, 88% yield, 96% ee
2d R^3 = OMe, 82% yield, 92% ee

2e 80% yield, 94% ee

2f 83% yield, 94% ee

2g R^4 = NO_2, 70% yield, 98% ee (at 0 °C)
2h R^4 = OMe, 76% yield, 96% ee (at 0 °C)

Significance: A resin-supported peptide **1** [Pro-D-Pro-Aib-Try-His-(Leu-Leu-Aib)$_2$-TentaGel] was identified as an efficient peptide catalyst for the Michael addition of malonates to α,β-unsaturated aldehydes via a combinatorial approach using a resin-supported peptide library. Thus, the reaction of *para*-nitrocinnamaldehyde with the dye-anchored malonate was carried out with a resin-supported peptide library (100 members) during which a CHO group of the resulting Michael adduct condensed with the terminal prolyl unit of the library in situ. Through this screening protocol, a resin bead bearing a more catalytically active peptide was stained more strongly.

Comment: A resin-supported peptide **1** catalyzed the Michael reaction of dialkyl malonates and an α,β-unsaturated aldehydes to afford the corresponding products in up to 89% yield with up to 98% ee. The catalytic activity of **1** in which a histidine moiety was equipped at the fifth position was superior to that of [Pro-D-Pro-Aib-His-Phe-(Leu-Leu-Aib)]$_2$ and [Pro-D-Pro-Aib-Phe-His-(Leu-Leu-Aib)]$_2$. The authors indicated that the histidine moiety plays a critical role for accelerating the reaction by capturing the substrate.

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Category
Polymer-Supported Synthesis

Key words
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peptides
α,β-unsaturated aldehydes
heterogeneous catalysis