Category

Organo- and Biocatalysis

Key words

desymmetrization

peptide catalysis

enzyme mimic

acetylation

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Remote Desymmetrization at Near-Nanometer Group Separation Catalyzed by a Miniaturized Enzyme Mimic
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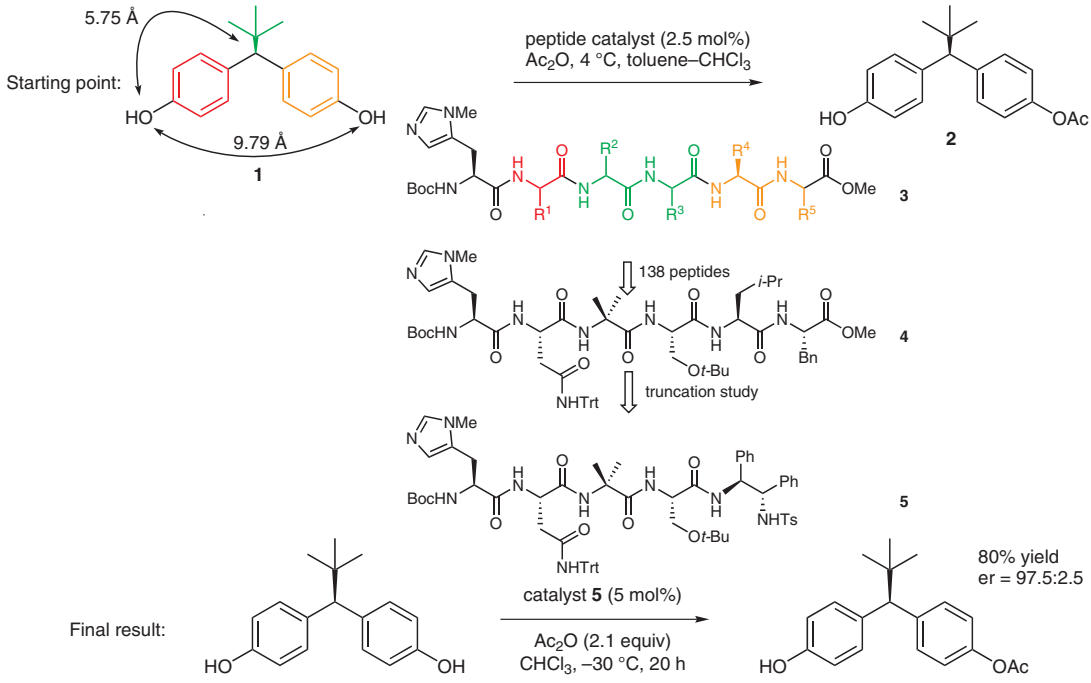
Remote Desymmetrization: Peptide versus Enzyme Catalysis



Significance: A catalytic protocol for the unprecedented remote asymmetric desymmetrization of bis(phenol) **1** via peptide-catalyzed monoacetylation has been developed. Since the desired site of functionalization is >5.7 Å from the 'prochiral' stereogenic center and the enantiotopic oxygen atoms are separated by a near-nanometer span, bis(phenol) **1** represents a particulary challenging substrate. After an examination of libraries of hexameric peptides **3**, whose residue pattern was chosen as a mirror image of the alternating aromatic–aliphatic–aromatic nature of substrate **1**, and followed by a truncation study of lead catalyst **4**, tetramer **5** was identified as the best catalyst, delivering monoacetylated product **2** in 80% yield and with an er of 97.5:2.5.

Comment: Often enzymes are employed as chiral catalysts when facing a challenging problem for enantioselective catalysis. Due to their molecular complexity they are able to induce chirality over substantial distances. In the present example, however, the small tetramer **5** was superior to more than 450 enzymes screened in the asymmetric hydrolysis of the bis(acetate) of **1**. In contrast to enzymatic catalysis, which leads to reasonable enantioselectivities only through secondary kinetic resolution of monoacetate **2**, the selectivity in the peptide-catalyzed version is dominated by enantiotopic group discrimination. Potential for enantioselective recognition, a property typically inherent in enzymes, was observed by ^{1}H NMR spectroscopy. Association of peptide catalyst **5** with bis(phenol) **1** caused the loss of degeneracy of the phenol moieties.

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