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Biocatalytic, Intermolecular C–H Bond Functionalization for the Synthesis of Enantioenriched Amides  

Enzymatic Nitrene Insertion into C–H Bonds for Synthesis of Enantioenriched Amides

**Significance:** Hirschi, Arnold, and co-workers report a nitrene insertion into benzylic C–H bonds by using engineered heme enzymes. The evolved enzymes transfer nitrenes to various arene-substituted substrates to give the corresponding products in moderate to good total turnover numbers and with good to excellent enantioselectivities.

**Comment:** The amide group is widely distributed in various natural products, synthetic materials, and pharmaceutical products. In the highlighted method, the authors directly install amides onto alkanes as inexpensive feedstock chemicals. They obtain valuable enantioenriched products in an inexpensive and environmentally friendly way.

\[
\begin{align*}
R^1 & = \text{aromatic} \\
R^2 & = \text{Alk} \\
R^3 & = \text{Me, Et, OMe, CH}_2\text{Bn}
\end{align*}
\]

**Selected examples:**

- NHAc, er > 99.5:0.5, 1580 TTN with iAMD9
- NHAc, er > 99.5:0.5, 1365 TTN with iAMD8
- NHAc, er > 99.5:0.5, 1764 TTN with iAMD9
- NHAc, er > 99.5:0.5, 570 TTN with iAMD8
- NHAc, er = 88:12, 1500 TTN with iAMD8
- NHAc, er > 99.5:0.5, 83% isolated yield (4 mmol scale) with iAMD8
- NHAc, er > 99.5:0.5, 600 TTN with iAMD8-A74T
- NHAc, er > 99.5:0.5, 1600 TTN with iAMD8-A74T

**Proposed reaction pathway:**

<table>
<thead>
<tr>
<th>R^1</th>
<th>R^2</th>
<th>R^3</th>
<th>PivOH</th>
<th>Enz</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>R^2</td>
<td>R^3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Synfacts 2021, 17(12), 1379 Published online: 17.11.2021 1861-19581861-194X  
DOI: 10.1055/s-0040-1720019; Reg-No.: B09721SF