A longstanding question in molecular evolution is how genetic, structural, and biochemical alterations lead to new protein functions. Earlier work from my laboratory (Nature 455:363-368, 2008) demonstrated that a single amino acid substitution at the active site of a heme-dependent enzyme was necessary and sufficient to generate a novel activity. Here I will discuss our recent findings, which will show how nature has fine-tuned conformational fluctuations to evolve unusual catalysts.