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Stereoselective Construction of β-, γ- and δ-Lactam Rings via Enzymatic C-H Amidation
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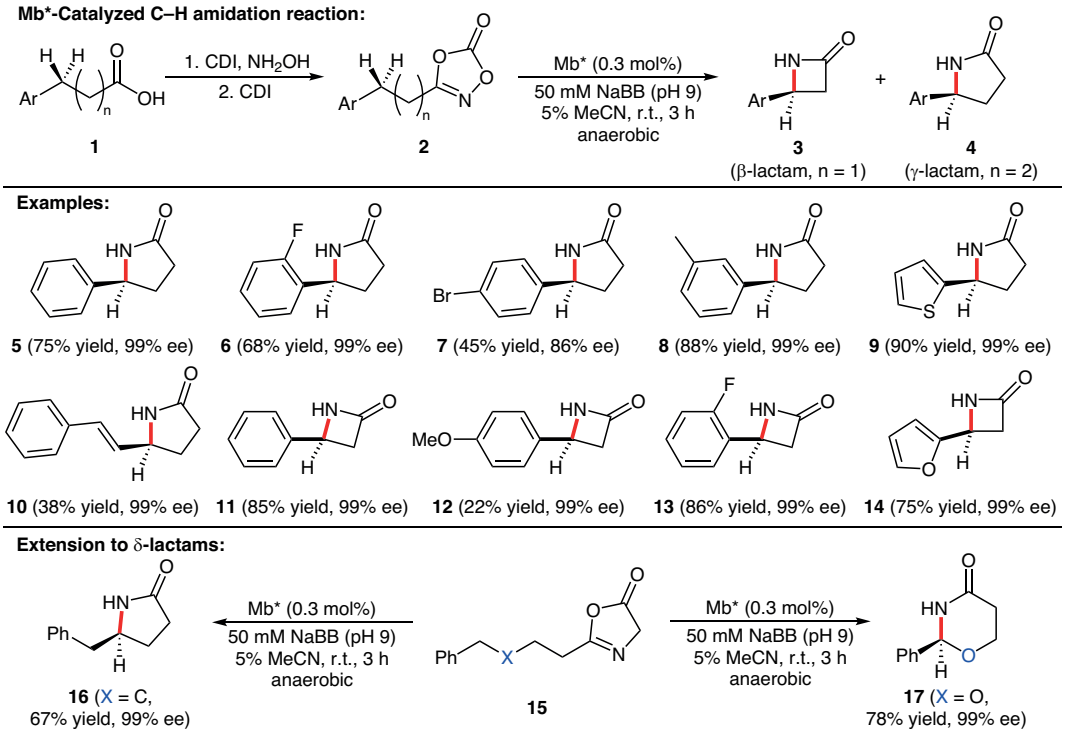
Biocatalytic, Enantioselective Synthesis of Lactams



Significance: Metal-mediated amination of aliphatic C–H bonds has been achieved using reactive metal-nitrenoid species, though while numerous cyclic systems have been accessed through this approach, the formation of the cyclic amides (lactams) presents a challenge owing to the instability of the requisite acyl-nitrene intermediates that can competitively decompose to isocyanates through a Curtius-type rearrangement. Only rare examples of Ir-mediated lactam formation have been reported, with the current scope limited to γ-lactams (*Science* **2018**, *359*, 1016). The current report exploits the use of stable dioxazolones as nitrene precursors for the enantioselective, biocatalyzed C–H amidation for the formation of β-, γ- and δ-lactams.

Comment: Various heme-containing enzymes and proteins were initially screened as potential biocatalysts for the transformation, and while many led to predominant formation of the acyclic amide, a modified myoglobin (Mb) derivative featuring an H64V mutation led to trace yields of the desired γ-lactam with high levels of enantioselectivity. Screening of a broader panel of engineered Mb variants led to the identification of Mb (H64V, V68A denoted as Mb*) as the best biocatalyst for the system with a broad scope demonstrated for the synthesis of both γ- and β-lactams in high yields and with excellent enantiopurities for the *S* enantiomer. Interestingly, an alternative Mb variant (L29T, H64T, V68L) provided the γ-lactams with the opposite stereochemistry. For δ-lactams, obtaining selectivity was challenging, though could be overcome through substrate modification (**15**).

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Category
Synthesis of Heterocycles

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