ENZYMATIC CATALYSIS IN TOTAL SYNTHESIS

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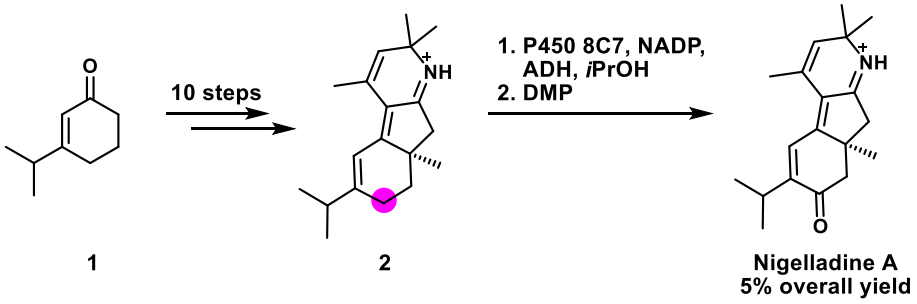
INTRODUCTION

The field of natural product synthesis has been driven by the admirable architecture and potential for desirable bioactivity. In the last twenty years, organic chemists have also sought inspiration from nature to overcome challenges in total syntheses.[1] This resulted in further development of a rapidly evolving field of biocatalysis, which utilized the power of enzymatic transformations to enable efficient selective catalytic reactions. The unique effectiveness and selectivity of enzymatic catalysis, often inaccessible by small molecule catalysts, provides unique disconnections that simplify the synthesis of complex natural products and their families.

ENABLING TOTAL SYNTHESES

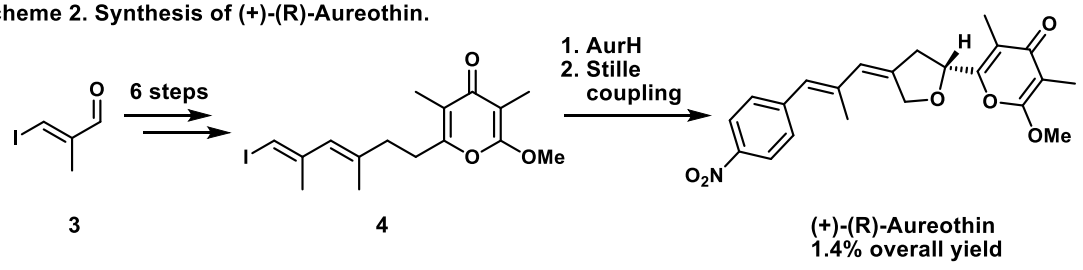
In 2017, Arnold and Stoltz reported the first enantioselective total synthesis of Nigelladine A (Scheme 1).[2] Starting with enone **1**, the chemical synthesis of iminium ion **2** was achieved in 10 steps by condensation of a free amine. While conventional chemical means of allylic oxidation failed to effect the desired oxidation selectively, an engineered P450 enzyme was able to selectively hydroxylate the position of interest and complete the total synthesis after an additional chemical oxidation.

Scheme 1. Synthesis of Nigelladine A.



Enzymatic catalysis has also been able to shorten syntheses and enable elusive asymmetric syntheses. For example, in 2004, Hertweck reported the first total synthesis of (+)-(*R*)-Aureothin (Scheme 2).[3] While many racemic syntheses have been reported,

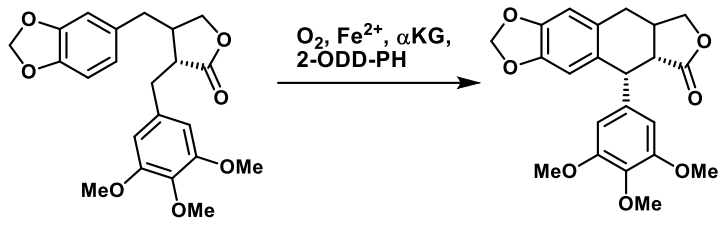
Scheme 2. Synthesis of (+)-(R)-Aureothin.



enantioselective syntheses were challenging due to the facile racemization. Starting with aldehyde **3**, the last intermediate **4** in the biosynthetic pathway of aureothin was synthesized in 6 steps. AurH, a cytochrome P450 monooxygenase, catalyzed the heterocycle formation and the enantioselective synthesis was realized after a Stille coupling.

By combining the tools of enzymatic catalysis and traditional organic syntheses, strategic disconnects during retrosynthetic design to allow for access families of natural products and/or allow for diversification to create analogues. For example, Renata has applied this concept to efficiently and enantioselectively access (-)-Podophyllotoxin and create derivatives.[4] Utilizing Baran's oxidative enolate coupling methodology allowed the synthesis of **5**, along with derivatives with varying substitution on the aryl rings. The key C-C bond formation was catalyzed by 2-ODD-PH (Scheme 3), and the natural product was achieved in two steps from **6**.

Scheme 3. Key enzymatic step in synthesis (-)-Podophyllotoxin.



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CONCLUSION AND FUTURE DIRECTIONS

By applying biosynthetic enzymology to traditional organic synthesis, chemists have been able to realize enantioselective syntheses, and utilize strategic disconnections to allow for access families of natural products and diversification. Recent discoveries in the identification and engineering of enzymes for C-H halogenation could eventually enable access to natural products with varying halogenation patterns. Furthermore, the ability to combine enzymes into a biocatalytic cascade has proved to be considerably advantageous, as seen in Merck's production of islatravir. Chemoenzymatic syntheses will continue to gain momentum in the field of total synthesis.

REFERENCES

1. Renata, H. *Biochemistry*. **2018**, *57,* 403-412.
2. Arnold, F. H.; Stoltz, B. M. *J. Am. Chem. Soc.* **2017**, *139,* 10196-10199.
3. Hertweck, C. *ChemBioChem* **2008**, *9*, 2064-2066.
4. Renata, H. *Angew. Chem. Int. Ed.* **2019**, *58*, 11657-11660.