

Complimentary and personal copy

[www.thieme.com](http://www.thieme.com)

## SYNFACTS Highlights in Chemical Synthesis

This electronic reprint is provided for non-commercial and personal use only: this reprint may be forwarded to individual colleagues or may be used on the author's homepage. This reprint is not provided for distribution in repositories, including social and scientific networks and platforms.

Publishing House and Copyright:  
© 2023 by  
Georg Thieme Verlag KG  
Rüdigerstraße 14  
70469 Stuttgart  
ISSN 1861-1958

Any further use  
only by permission  
of the Publishing House

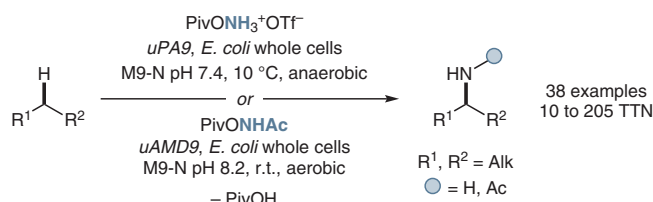
 **Thieme**

S. V. ATHAVALE\*, S. GAO, A. DAS, S. C. MALLOJJALA, E. ALFONZO, Y. LONG, J. S. HIRSCHI\*, F. H. ARNOLD\* (CALIFORNIA INSTITUTE OF TECHNOLOGY, PASADENA AND BINGHAMTON UNIVERSITY, USA)

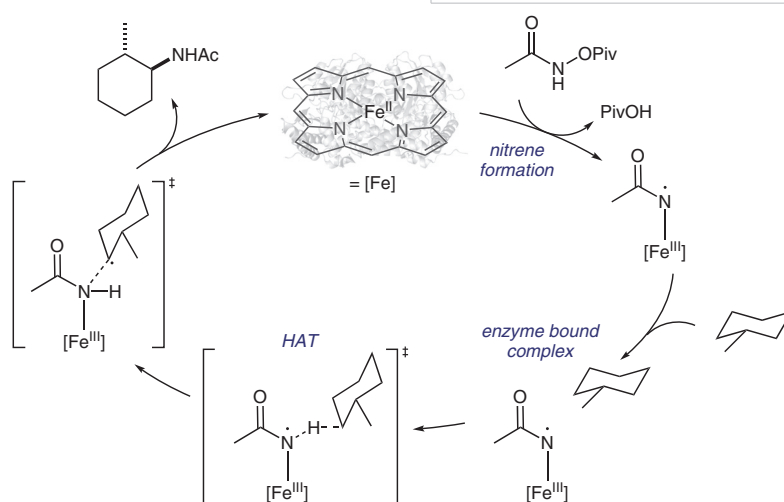
Enzymatic Nitrogen Insertion into Unactivated C–H Bonds

*J. Am. Chem. Soc.* **2022**, *144*, 19097–19105, DOI: 10.1021/jacs.2c08285.

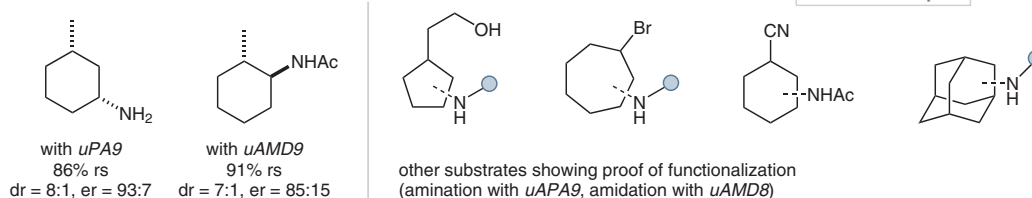
# Enzymatic Amination and Amidation of Unactivated Csp<sup>3</sup>–H Sites



Proposed mechanism for catalyzed amidation



Selected examples



**Significance:** Arnold and co-workers disclose the cytochrome P450-catalyzed nitrogen insertion into unactivated Csp<sup>3</sup>–H bonds. The desymmetrizations of methyl- and ethylcyclohexane serve as spectacular examples of the excellent site- and enantioselectivity of the utilized biocatalysts. The evolved enzymes can be considered as the nitrogen counterparts of P450 monooxygenases, where a hydroxylamine derivative is used as a nitrogen atom source to modify unreacted substrates. Mechanistic studies suggest a stepwise radical pathway involving an enantiodetermining hydrogen atom transfer (HAT).

**Comment:** While enzymatic oxygenation and halogenation of unactivated Csp<sup>3</sup>–H bonds are well established, the analogous nitrogen incorporation was still unknown. Herein, underdeveloped heme-containing nitrene transferases subjected to directed evolution show evidence of functionalization toward a variety of substituted hydrocarbons. We look forward to a further expansion of the scope of this methodology.

**SYNFACTS Contributors:** Benjamin List, Marian Guillén  
*Synfacts* 2023, 19(01), 0081 Published online: 16.12.2022  
DOI: 10.1055/s-0042-1751781; Reg-No.: B00323SF

© 2023, Thieme. All rights reserved.  
Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Category

Organo- and Biocatalysis

Key words

nitrogen insertion  
C–H bond amination  
C–H bond amidation  
cytochrome P450  
Fe-nitrenoid