Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Chemical Biology

Biocatalytic hydrogen atom transfer: an invigorating approach to free-radical reactions

Yuji Nakano, Kyle F Biegasiewicz and Todd K Hyster

Initiating and terminating free-radical reactionis via hydrogen atom transfer (HAT) is an attractive means of avoiding substrate prefunctionalization. Small molecule catalysts and reagents, however, struggle to execute this fundamental step with useful levels of diastereoselectivity and enantioselectivity. In contrast, nature often carries out HAT with exquisite levels of selectivity for even electronically unactivated carbon–hydrogen bonds. By understanding how enzymes exploit and control this fundamental step, new strategies can be developed to address several long-standing challenges in free-radical reactions. This review will cover recent discoveries in biocatalysis that exploit a HAT mechanism to either initiate or terminate novel one-electron reactions.

Address
Department of Chemistry, Princeton University, Princeton, NJ 08544, USA

Corresponding author: Hyster, Todd K (thyster@princeton.edu)

Current Opinion in Chemical Biology 2019, **49**:16–24

This review comes from a themed issue on **Biocatalysis and biotransformation**

Edited by **Kylie A Vincent** and **Bettina Nestl**

https://doi.org/10.1016/j.cbpa.2018.09.001

Introduction

Reactions involving open-shell radical intermediates provide complementary reactivity to classic two-electron pathways [1]. Unfortunately, traditional approaches to radical formation often require preactivation strategies that complicate synthetic designs. Alternatively, abstraction of a hydrogen atom from a substrate's carbon–hydrogen (C–H) bond offers a more streamlined approach to radical formation as it mitigates the need for substrate preactivation [2]. Controlling hydrogen atom transfer (HAT) can, however, be problematic on substrates containing electronically unbiased C–H bonds [3]. Conversely, termination of carbon-centered radicals is often accomplished by HAT to provide a new C–H bond. While the selective delivery of a hydrogen atom can determine the product's stereoconfiguration, it is currently challenging to control using small molecules [4]. In order to overcome these obstacles we propose searching beyond small molecule catalysts and reagents.

Biocatalysis offers an approach for overcoming the aforementioned barriers. Many of nature's transformations, such as anaerobic metabolism [5] and DNA repair [6], are understood to proceed by radical mechanisms. Additionally, metal-cofactor dependent enzymes (such as P450s and non-heme iron/α-ketoglutarate-dependent enzymes) that catalyze highly selective C–H functionalizations (such as hydroxylation, amination or halogenation) are known to initiate by the abstraction of a hydrogen atom from substrate [7]. Enzymes are also capable of differentiating prochiral intermediates with exclusive selectivity [8], making them suitable catalysts for the stereoselective delivery of hydrogen atoms to radicals. Developing biocatalytic protocols that draw inspiration from nature promises to afford general solutions to these fundamental problems.

This review will cover biocatalytic HAT transformations reported in the last two years (2016–2018) with an emphasis on newly uncovered enzymes or reactivity. To ensure concise coverage, attention will be given to transformations generating chiral products and omitting processes involving HAT with heteroatom–hydrogen sites. Though relevant, the chemistry of cytochrome P450 monooxygenase has been recently covered elsewhere [9] and will not be discussed herein.

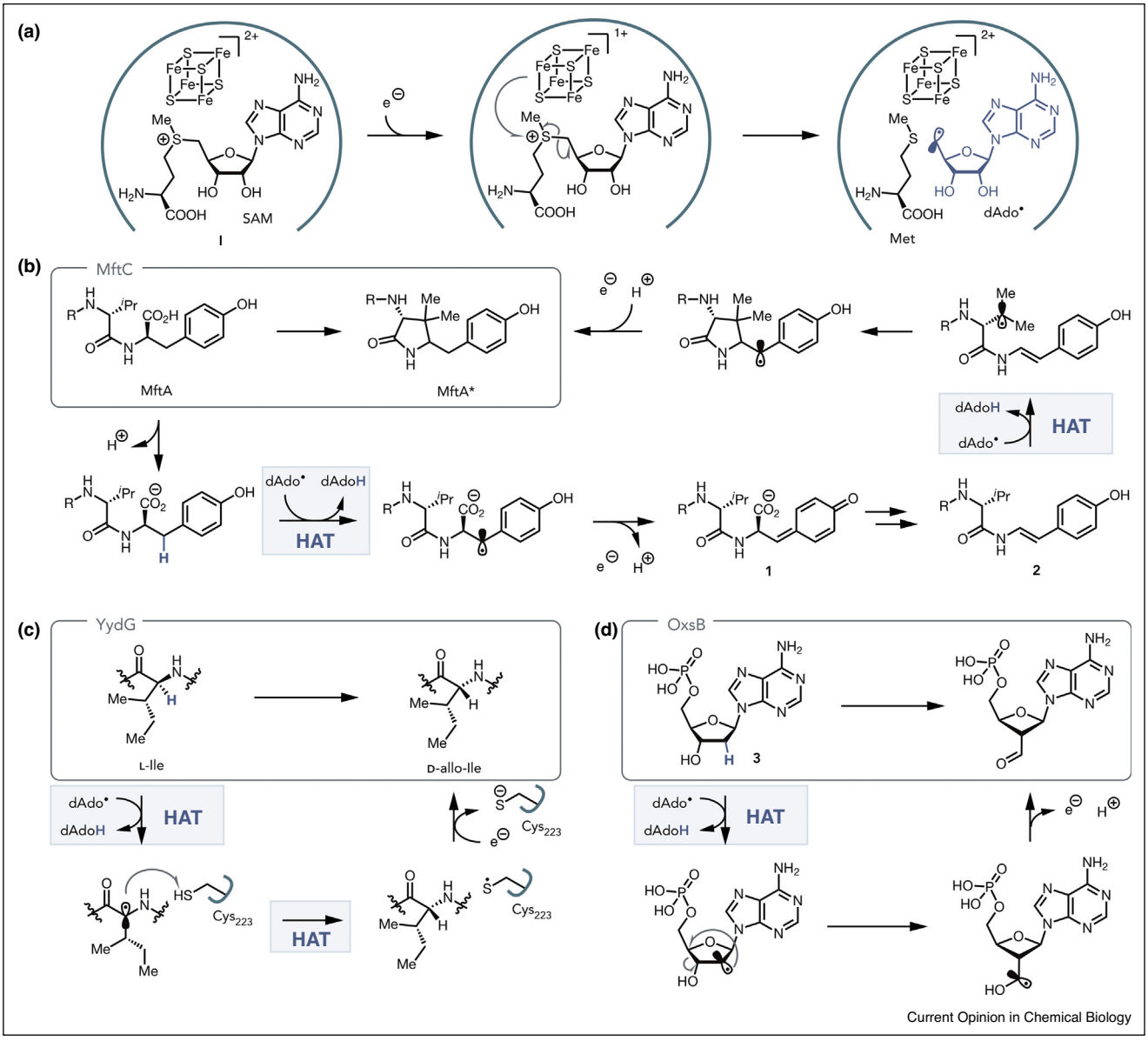
Biocatalytic transformations initiated by HAT

Radical *S*-adenosyl-L-methionine dependent enzymes

The largest enzyme superfamily, with over 100 000 annotated members, is the radical *S*-adenosyl-L-methionine (SAM) family [10]. Structurally they are defined by the presence of an iron–sulfur cluster $[4Fe–4S]^{2+}$ and SAM cofactor (as in **I**, Figure 1). Delivery of an electron results in $[4Fe–4S]^{1+}$ mediated homolytic cleavage of the S–C5′ bond, expelling methionine (Met) and unmasking the 5′-deoxyadenosyl radical (dAdo$^{\bullet}$) [11] that serves as the catalytically competent intermediate in radical SAM transformations (Figure 1a). The dAdo$^{\bullet}$ radical most frequently instigates HAT on a C–H bond on the substrate, producing dAdoH as by-product, and a substrate-centered radical that can undergo rearrangements, cyclizations, addition reactions or fragmentation reactions [12].

Peptides constitute a significant portion of natural products identified in a wide variety of microorganisms. Of these, ribosomally synthesized post-translationally

Figure 1



(a) Formation of dAdo• from SAM and [4Fe–4S] cluster. **(b)** MftC effects peptide modification of MftA to MftA•. **(c)** Epimerase YydG mechanism. **(d)** OxsB-catalyzed ring contraction of 2′-deoxyadenosylphosphate.

modified peptides (RiPPs) have garnered significant attention with whole-genome sequencing technologies allowing rapid identification of gene clusters encoding for both precursor peptides and modification enzymes. Many of these biosynthetic clusters have been found to encode for radical SAM enzymes [13]. For example, Bandarian and Bruender showed that MftC effects decarboxylation at the C-terminus of the MftA peptide in the biosynthetic pathway to mycofactotcin [14•]. Here, the dAdo• radical is implicated in a HAT with the C–H bond at the C_β-position on the terminal tyrosine residue. Following a second oxidation event, unsaturated *para*-quinone **1** is generated whereupon decarboxylation forms enamine **2**. Another equivalent of the dAdo• radical then facilitates a second HAT event at a neighbouring valine residue, with a 5-exo-trig cyclization installing the γ-butyrolactam moiety in MftA* (Figure 1b). Isotopic labelling and spectroscopic experiments by the Latham group provided support for this mechanism [15].

Beyond HAT at the C_β-position of peptide residues, the C_α-position may also be modified by radical SAM to provide RiPPs. Berteau *et al.* found that non-natural D-amino acids identified in a post-translationally modified