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Enzyme-mediated C-N Bond Formation via Ene Reactions and Diels-Alder Cycloadditions

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PURPOSE OF THE ABSTRACT

The incorporation of nitrogen into organic building blocks through C-N bond forming reactions represents one of the most crucial methodology goals in modern organic chemistry. Especially nitrogen-containing heterocycles, an absolute go-to motif in today's pharmaceuticals, pose a critically important synthetic target. Biocatalytic methodologies to facilitate C-N bond formations are therefore highly desireable. However, Nature's repertoire to introduce nitrogen moieties into molecular frameworks is generally limited to direct functional group interconversions. Here, the toolbox of synthetically valuable biocatalytic methods has been expanded steadily in the past years through a number of nitrogen-fixation strategies based on reductive aminations and additions catalyzed by transaminases, imine reductases, and amine dehydrogenases, to name a few.[1] In a complementary approach mimicking chemistry by biological means, most recently the biocatalytic imitation of non-natural but synthetically relevant reactions was moved into the spotlight,[2] and nitrene insertion-based transformations utilizing engineered heme proteins introduced whole new pathways for the biocatalytic C?N bond formation.[3]

As a yet untapped template from the world of traditional synthesis, another attractive alternative approach for selective C-N bond formations engages reactive nitroso. First explored in the 1960´s for the synthesis of allylamines using nitrosobenzene, nitroso ene reactions, and the related nitroso-Diels-Alder cycloadditions, are nowadays found in a wide variety of synthetic strategies towards natural products and pharmaceuticals.[4] In this study, we highlight the potential of established oxidoreductase systems as biological mediators for the generation of reactive nitroso species. The biocatalytic oxidation of acylated hydroxylamines enables the direct and selective introduction of nitrogen functionalities via activation of allylic C-H bonds or [4+2]-cycloaddition with dienes.[5] Utilizing either laccases or an oxidase/peroxidase couple for the formal dehydrogenation of N-hydroxycarbamates and hydroxamic acids with air as terminal oxidant, acylnitroso species are generated under particularly mild aqueous conditions. The reactive intermediates undergo C-N bond formation through an ene-type mechanism and provide high yields both in intramolecular and intermolecular enzymatic aminations. Alternatively, hetero-Diels-Alder cycloadditions offer access to six-membered N,O-heterocycles. In addition to extensive studies on the product scope and stereoselectivity aspects, investigations on different pathways of the two biocatalytic systems and labelling studies provide more insights into this unprecedented promiscuity of classical oxidoreductases as catalysts for nitroso-based transformations.

FIGURES

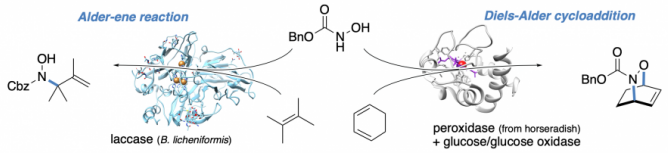

FIGURE 1

Figure 1

Ene reactions and Diels-Alder cycloadditions catalyzed by oxidoreductases

FIGURE 2

KEYWORDS

promiscuity | ene reaction | amination | heterocycles

BIBLIOGRAPHY