RECENT ADVANCES IN RADICAL DEHALOGENATION REACTIONS USING PHOTOCHEMISTRY

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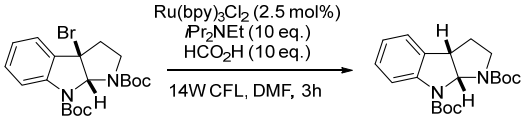
INTRODUCTION

Since Barton's seminal work in the 1970s, radical dehalogenations have been a mainstay in radical reactions and have been useful in the synthesis of many natural products by enabling C-H and C-C bond formation.[1-3] In one of Barton's initial reports, a modified Hunsdiecker reaction followed by radical reduction of the derived halide is performed using tributyltin hydride, yielding a decarboxylated hydrocarbon.[1] Although trialkyltin hydrides are versatile and effective as a hydrogen atom donor, tin reagents are toxic and have limited functional group tolerance and chemoselectivity.[4] To address these issues, research has focused on developing tin catalysts and tin hydride substitutes. Although useful, these modern methods still suffer from generating toxic byproducts and having limited reaction scope.

PHOTOREDOX-MEDIATED RADICAL DEHALOGENATION

To address issues with traditional radical reactions and to provide further selectivity, Stephenson and coworkers harnessed the power of photoredox catalysis.[5] Photoredox catalysis employs visible light and a photocatalyst to initiate a single electron transfer event, allowing access to transformations that would otherwise be challenging or inaccessible. By using the popular photoredox catalyst, tris(2,2'-bipyridyl)ruthenium-(II) chloride ($Ru(bpy)_3Cl_2$) and an amine as the hydrogen atom source, a reductive dehalogenation could be accomplished under mild reaction conditions and generated benign byproducts (Scheme 1). Tuning the hydrogen atom source resulted in a switch from C-H bond formation through reductive dehalogenation to C-C bond formation, allowing for functionalization of indoles and pyrroles.[6, 7]

Scheme 1. Stephenson's reductive radical dehalogenation.[4]



ENZYMATICALLY-MEDIATED RADICAL DEHALOGENATION

Although the use of photoredox catalysis has allowed access to reductive radical dehalogenations in a chemoselective and environmentally friendly manner, achieving high enantioselectivity still remains a challenge. Inspired by nature and the high enantioselectivity in which enzymes catalyze transformations, Hyster and coworkers hypothesized that radical reactions could be accessed in an enantioselective manner by harnessing the redox promiscuity of nicotinamide and flavin cofactors.[8] Certain enzymes, such as flavoenzymes, are known to promote one- and two-electron pathways, depending

on the presence and redox state of the cofactor. By tuning the redox state of the nicotinamide cofactors bound in the active site of ketoreductases using photoexcitation, Hyster and coworkers enabled novel reactivity of the enzyme through a single electron pathway, allowing for enantioselective radical dehalogenation of small molecule scaffolds (Figure 1). This method was the first example of photo-induced enzyme promiscuity and proceeded through an electron donor-acceptor (EDA) complex in the active site of the enzyme. To expand the reaction scope, other flavoenzymes were examined and 'ene'-reductases were found to be capable of catalytic, asymmetric radical cyclizations with high enantioselectivity.[9]

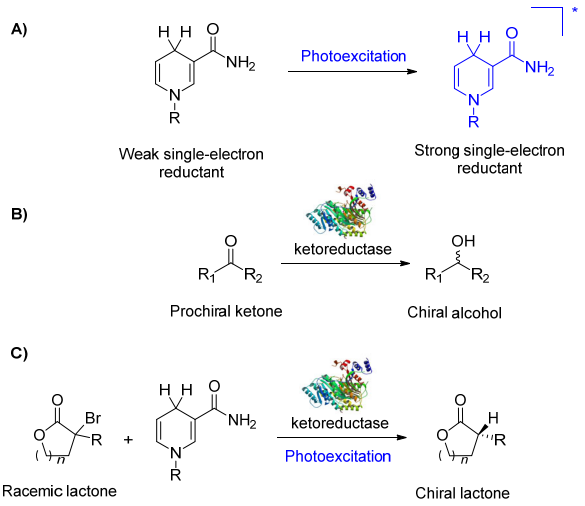


Figure 1. A) Photoexcitation of nicotinamide cofactors results in a potent single-electron reductant B) Natural reactivity of ketoreductases C) Photoexcitation of NAD(P)H bound to ketoreductase results in enantioselective radical dehalogenation[8]

SUMMARY AND OUTLOOK

Although radical dehalogenations have traditionally been performed with trialkyltin reagents, recent advances in organic methods have allowed access to radical transformations using photoredox catalysis and biocatalysis. As both these fields are in their infancy, progress is needed for the development of photoredox catalysts that can provide highly enantioselective reactions or that can be used biocatalytically with enzymes to access novel transformations.

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