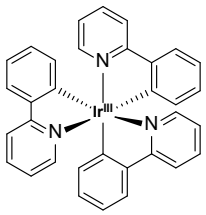
PHOTOREDOX-MEDIATED OXIDATIVE RADICAL/POLAR CROSSOVER

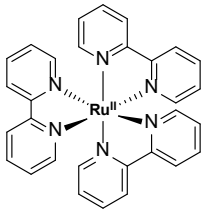
Reported by Nick Wade October 31st, 2023

INTRODUCTION

Photoredox catalysis has emerged as a powerful and versatile tool that harnesses the power of visible light to impart energy into numerous chemical reactions.[1] This methodology employs a photoexcited catalyst to initiate and propagate electron transfer processes without the need for external chemical oxidants or reductants. As a result, light-mediated synthesis has gained considerable prominence over the last two decades as synthetic organic chemists have searched for atom-economical and mild methods for performing challenging transformations.[1a] By exploiting the multifaceted nature of photoactive catalysts as light-absorbing species, single electron donors and single electron oxidants (**Figure 1**), photoredox catalysis has enabled reactions that were previously elusive due to high enthalpic barriers and poor functional group compatibility.[2,3]

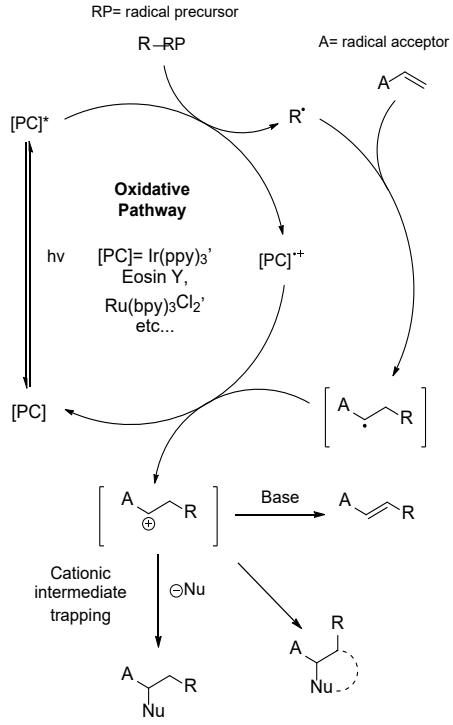


$E_{1/2}(M+/M^*)$= -1.73 V
$E_{1/2}(M+/M)$= 0.78 V



$E_{1/2}(M+/M^*)$= -0.81 V
$E_{1/2}(M+/M)$= 1.29 V

Figure 1. Common photocatalysts used in photoredox reactions and their experimental redox potentials.



Scheme 1. Radical Polar crossover catalytic cycle via oxidative radical quenching.

Net-neutral, photoredox-mediated oxidative radical polar crossover (ORPCO) reactions represent a subset of photoredox reactions where a high oxidation state photocatalyst oxidizes a carbon centered radical into a carbocation.[4] This mode of reactivity leverages the synergy between photocatalysis, radical propagations, and polar intermediates to transform simple radical precursors into structurally complex, densely functionalized compounds. In ORPCO reactions, a delicate balance is struck between the generation of radical species and their conversion into polar intermediates (**Scheme 1**). Managing the precise thermodynamics and kinetics of ORPCO reactions is a significant challenge synthetic chemists are working to overcome in the field to this day.

RADICAL GENERATION AND NUCLEOPHILE TRAPPING

The initial single-electron transfer SET event from an excited photocatalyst fragments the radical precursor into a stable anionic leaving group, and a carbon centered radical. These radical precursors

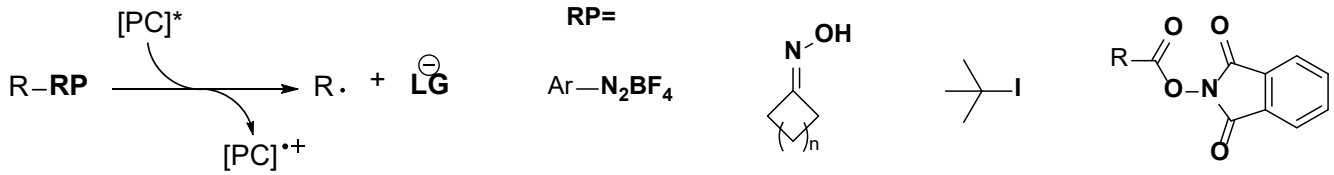


Figure 2. Common radical precursors in oxidative radical polar crossover (ORPCO) reactions.

generally require low redox potentials and irreversible formation of a leaving group. As a result, initial attempts at ORPCO utilized reactive diazonium tetrafluoroborate salts as radical precursors due to the evolution of nitrogen gas after single-electron reduction.[5a-d] However, recent advances have utilized phthalimide based photoredox active esters,[6a] oximes[6b] and alkyl halides[6c] as radical precursors (**Figure 2**) to expand the scope of viable substrate scaffolds used in ORPCO. To preclude undesired reactivity, early reports of cationic radical polar crossover mainly focused on intramolecular trapping or elimination of Wheland intermediates to afford cyclized or rearomatized compounds.[5a, 5b]

FATE OF POLAR SPECIES: EXTERNAL NUCLEOPHILE TRAPPING

Trapping with external nucleophiles (i.e. solvent, or anionic nucleophiles) changes the precise timing of the ORPCO catalytic cycle and allows for reactivity orthogonal to that of intramolecular cation trapping.[7a] ORPCO reactions in MeOH, H_2O or MeCN allow for cation capture to form methyl ethers, alcohols, or N-acyl amines in tandem radical polar crossover-Ritter reactions.[7b] Common methods using solvent for trapping cationic intermediates universally applies to Radical-Polar crossover systems. Additionally, use of various fluoride salts has allowed for nucleophilic fluorination, complementary to radical based electrophilic fluorination methods.[8a] Using a similar methodology, Doyle and coworkers demonstrated ^{18}F fluorination into medicinally relevant compounds.[6a] Given the mild conditions and application to the synthesis of biologically active molecules, ORPCO has become a premier methodology for building and derivatizing complex racemic substrates.

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