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Repurposing EREDs for Regioselective Radical Cross-Coupling

AUTHORS

Mark PETCHEY / ASTRAZENECA, COMPOUND SYNTHESIS AND MANAGEMENT, DISCOVERY SCIENCES BIOPHARMACEUTICALS R&D, ASTRAZENECA PEPPAREDSLEDEN 1, MÖLNDAL
Yuxuan YE / CORNELL UNIVERSITY, DEPARTMENT OF CHEMISTRY AND CHEMICAL BIOLOGY, CORNELL UNIVERSITY, ITHACA
Victor SPELLING / ASTRAZENECA, 3EARLY CHEMICAL DEVELOPMENT, PHARM SCI, BIOPHARMA R&D, ASTRAZENECA PEPPAREDSLEDEN 1, MÖLNDAL
Magnus JOHANSSON / ASTRAZENECA, 4MEDICINAL CHEMISTRY, RESEARCH AND EARLY DEVELOPMENT, CARDIOVASCULAR, RENAL AND METABOLISM (CVRM) BIOPHARMACEUTI-CALS R&D, ASTRAZENECA PEPPAREDSLEDEN 1, MÖLNDAL
Martin HAYES / ASTRAZENECA, 1COMPOUND SYNTHESIS AND MANAGEMENT, DISCOVERY SCIENCES BIOPHARMACEUTICALS R&D, ASTRAZENECA PEPPAREDSLEDEN 1, MÖLNDAL
Todd HYSTER / CORNELL UNIVERSITY, DEPARTMENT OF CHEMISTRY AND CHEMICAL BIOLOGY, CORNELL UNIVERSITY, ITHACA

PURPOSE OF THE ABSTRACT

Single-electron radical cross coupling reactions display unique reactivity, expediting the requirement for protecting group chemistry, functional group interconversions and unproductive redox cycling.(1) However, using traditional small-molecule catalysts, regio- and stereoselective radical C-C bond formation is challenging due to the inherent short-lived nature of highly reactive radical species.(2,3) Nature has evolved biocatalysts, such as radical S-adenosyl (SAM) enzymes and cobalamin, to catalyze these transformations in the synthesis of structurally complex natural products. However, the high specificity of these enzymes often militates against their application for small molecule synthesis, due to their limited substrate scope. The introduction of abiological transformations to natural proteins can serve as a powerful tool to advance enzymatic catalysis to reaction landscapes unexplored by natural evolution.

Pioneering work by the Hyster group showed that flavoenzymes could be reprogrammed for non-natural single electron transfer mechanisms, coupling α-halo ketones and amides with styrenyl derivatves. In these examples the chiral centre is set via asymmetric hydrogen atom transfer (HAT) from the flavin.(4, 5) By investigating a diverse range of radical precursors and coupling partners, we have discovered that FMN-dependent ‘ene'-reductases (EREDs) are also able to catalyse regioselective radical cross-coupling additions. Rational enzyme engineering was used to probe the enantio- and regioselectivity, revealing how radical termination is intricately controlled by hydride transfer from the flavin cofactor.

FIGURES

FIGURE 1

FIGURE 2

KEYWORDS

Radical C-C bond formation | Enzyme engineering | FMN dependent EREDs | New-to-nature chemistry

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