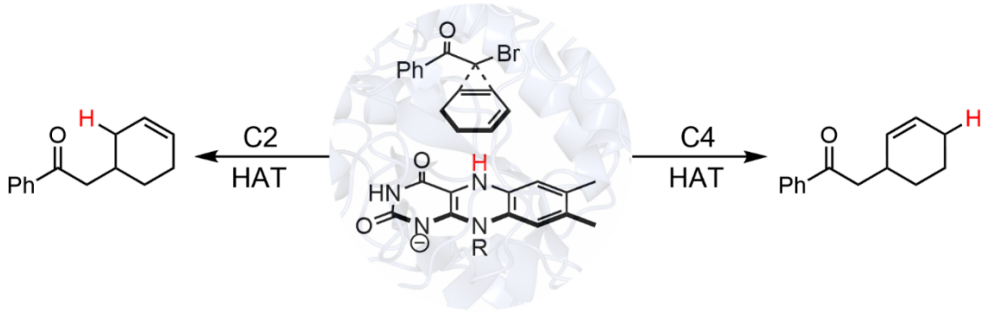
Expanding Nature's Catalytic Machinery

Mark R. Petchey[a], Yuxuan Ye[b], Victor Spelling[c], James D. Finnigan[d], Samantha Gittings[d], Magnus J. Johansson[e], Martin A. Hayes[a] and Todd K. Hyster[b]

[a]Compound Synthesis and Management, Discovery Sciences BioPharma R&D, AstraZeneca Pepparedsleden 1, 431 83, Mölndal, Sweden
[b]Department of Chemistry and Chemical Biology, Cornell University, Ithaca, New York 14850, United States
[c]Early Chemical Development, Pharm Sci, BioPharma R&D, AstraZeneca Pepparedsleden 1, 431 83, Mölndal, Sweden
[d]Prozomix Ltd, Building 4, West End Ind. Estate, Haltwhistle NE49 9HA, U.K.
[e]Medicinal Chemistry, Research and Early Development, CVRM, BioPharma R&D, AstraZeneca Pepparedsleden 1, 431 83, Mölndal, Sweden
mark.petchey@astrazeneca.com

The Hyster lab has been able to expand the reactivity profiles of enzymes by exploiting the use of common biological redox active co-factors for non-natural electron transfer mechanisms. This methodology has been successfully applied to the coupling of α-acyl radicals with monoalkenes, typically styrenes, forming a new C–C bond. Hydrogen atom transfer (HAT) from the flavin semiquinone (FMN_{sq}) terminates the substrate-centred radical and sets the stereocenter in the product. While this step occurs with high enantioselectivity, it has not been used to control the regioselectivity of HAT. In this respect, 1,3-dienes present a unique selectivity challenge because the resulting allylic radical can be terminated at two possible positions, forming a mixture of constitutional isomers. This type of selectivity represents a significant synthetic endeavour as it involves precisely positioning the diene over the N5 position of the flavin co-factor, favouring formation of a single constitutional isomer. We have discovered that flavin-dependent ene-reductases (EREDs) can catalyse the C–C bond-forming hydroalkylation of α-bromo ketones with unactivated dienes. Two EREDs were engineered to enable the synthesis of both constitutional isomers and the substrate scope explored. A mechanistic rationale for the improvement in selectivity could be determined using deuterium labelling experiments and induced fit docking studies. Overall, this work demonstrates how enzymes can control challenging mechanistic steps that enable more selective and efficient chemical synthesis.[1]



Engineering Enzyme-Templated
Regioselective Radical Termination
20 examples up to 99:1 regioisomeric ratio

---

(1) Petchey, M. R.; Ye, Y.; Spelling, V.; Finnigan, J. D.; Gittings, S.; Johansson, M. J.; Hayes, M. A.; Hyster, T. K. *J. Am. Chem. Soc.* **2024**. DOI: 10.1021/jacs.4c00482.