Synergistic Photoenzymatic Anti-Markovnikov Hydroarylation of Olefins via Heteroaryl Radical Intermediates

Prasun Mukherjee, Zayed Alassad, Todd K. Hyster*

Department of Chemistry, Princeton University, Princeton, New Jersey 08544, United States

*Corresponding author Email: thyster@princeton.edu.

Supporting Information Placeholder

ABSTRACT: Heteroaromatic alkylations are indispensable reactions for synthesizing biologically active molecules. The anti-Markovnikov hydroarylation of olefins using heteroaryl halides furnishes the product as a single regioisomer, however, catalytic variants are ineffective in controlling the stereochemical outcome of these reactions. Here, we report a synergistic photoenzymatic hydroarylation of olefins using flavin-dependent 'ene'-reductases with ruthenium photoredox catalysts. Enzyme homologs were identified, which provide access to both product enantiomers in greater than 80% yield with up to 99:1 er. This method is effective for styrenyl and unactivated alkenes, highlighting the generality of this approach. Binding assay study revealed strong binding of the photocatalyst with the enzyme for superior catalytic activity. Mechanistic studies suggest efficient intermolecular coupling is possible because alkene binding accelerates the consumption of the aryl halide.

Heteroaromatics are essential structural components of small-molecule pharmaceutical and agrochemical compounds (Figure 1a).[1] As the percentage of sp^3 hybridized atoms in drugs increases, there is an increased need for pyridyl structures with adjacent stereocenters.[2,3] Benzylic and homobenzylic stereocenters are traditionally set via asymmetric reduction of the corresponding alkene.[4,5] While these methods offer unparalleled levels of enantioselectivity, they do not build molecular complexity. Transition metal and Brønsted acid catalyzed cross-couplings and conjugate additions to vinyl pyridines also provide access to alkylated heterocycles, however, there remains a need for alternative asymmetric reactions that use readily available starting materials.[6–14]

Olefin hydroarylations are attractive for preparing structurally complex alkyl-substituted pyridines with benzylic and homobenzylic stereocenters. This general coupling reaction can be achieved using a few distinct catalytic strategies, including aromatic C–H activation,[15–17] reductive Heck reactions,[18] metal-catalyzed hydrogen atom transfer to olefins,[19–21] and reductive radical couplings using photoredox catalysts.[22–25] Despite the bevy of synthetic methods, none of these reactions have been rendered asymmetric.

Enzymes are ideal scaffolds for asymmetric synthesis because they can use numerous non-covalent interactions to control the reaction trajectories of highly reactive intermediates.[26] Over the past decade, our group has pioneered the area of photoenzymatic catalysis, where photonic energy is used to drive biocatalytic transformations.[27] Our group and others demonstrated that flavin-dependent 'ene'-reductases (EREDs) could generate alkyl and nitrogen-centered radicals for olefin hydroalkylation and hydroamination reactions.[28–43] Reactions occur with high levels of enantioselectivity because the protein can preferentially deliver a hydrogen atom to one prochiral face of the alkyl radical formed after C–C or C–N bond formation. Hydrogen atom transfer remains a challenging mechanistic step to render asymmetric, with reports only recently demonstrating the ability of small molecule thiols to achieve this feat.[44,45]

Based on the ability of EREDs to control HAT, we questioned whether they could catalyze asymmetric hydroarylations using aryl radicals (Figure 1b). Based on pioneered studies by Jui, we hypothesized that aryl halides could be photochemically reduced to generate an aryl radical.[22–25] This ambiphilic intermediate can react with electronically diverse alkenes to afford an alkyl radical which is reductively quenched via HAT from the flavin cofactor.[46]

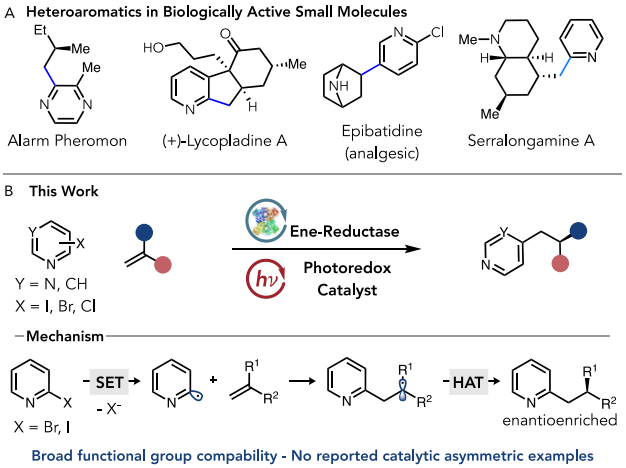
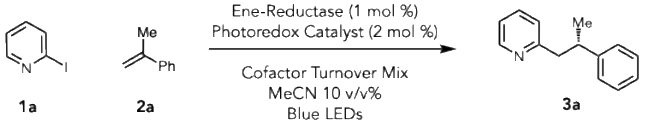


Figure 1. Synthesis of Heteroaromatics with Stereocenters. A) examples of heteroaromatics in biologically active molecules. B) Olefin hydroarylation using aryl radicals. C) Synergistic photoenzymatic strategy for asymmetric hydroarylation.

We began by exploring the coupling of 2-iodopyridine with α-methylstyrene using a series of ERED homologs in the presence of a cofactor turnover system to reduce the enzyme to the hydroquinone (FMN_{hq}) oxidation state while irradiating with blue LEDs (Table 1). While electron-deficient aryl halides are known to form charge transfer complexes with electron donors (amines, thiolates),[47–50] no product was formed under these conditions

(Supplemental Table 24, entry 2). We hypothesized that the lack of product formation was due to back electron transfer from the aryl radical anion to the flavin semiquinone (FMN_{sq}) being fast compared to mesolytic cleavage of the C–I bond.[51,52] To slow back electron transfer rates, we explore using exogenous photocatalysts for radical initiation. Previous studies found that exogenous photocatalysts could generate radicals when the biological cofactor alone was ineffective.[28,32,35,53,54] When catalytic quantities of $Ru(bpy)_3Cl_2$ were added to a reaction containing old yellow enzyme 3 (OYE3), the hydroarylated product was formed in 25% yield with 96:4 e.r. favoring the (*S*)-enantiomer (Table 1, entry 2). We hypothesized that superior yields could be achieved by modifying the photocatalyst structure. Adding two carboxylates to the 4,4′ positions of one of the bipyridine ligands increased the yield to 54% with no change in enantioselectivity (Table 1, entry 3). The (*R*)-enantiomer of the product can be formed in 29% yield using a previously identified variant of the ERED from *Gluconobacter oxydans* (GluER-T36A-Y177F) (Table 1, entry 4).



Entry	ERED	Photocatalyst	Yield (%)	Enantiomeric Ratio (e.r.)
1[a]	OYE3	-	1	98:2
2	OYE3	$Ru(bpy)_3Cl_2$	25	96:4
3	OYE3	$Ru(bpy)_2$(4,4′-CO_2Hbpy)	54	96:4
4[b]	GluER-T36A-Y177F	$Ru(bpy)_2$(4-CO_2Hbpy)	25	3:97
5[c]	OYE3	$Ru(bpy)_2$(4-CO_2Hbpy)	81	98:2
6[d]	OYE3	$Ru(bpy)_2$(4-CO_2Hbpy)	59	96:4
7[e]	OYE3	$Ru(bpy)_2$(4-CO_2Hbpy)	29	91:9
8[f]	OYE3	$Ru(bpy)_2$(4-CO_2Hbpy)	41	97:3
9[g]	OYE3	$Ru(bpy)_2$(4-CO_2Hbpy)	36	97:3

Table 2. Reaction Optimization. Reaction conditions: 2-iodopyridine **1a** (20 µmol), **2a** (5 equiv.), $NADP^+$ (1 mol%), GDH-105 (1.5 mg), Glucose (1 equiv.), MES buffer (pH 6, 100 mM, 750 µL), acetonitrile (250 µL), Blue LEDs, 17 h. [a] **2a** (3 equiv.), GDH-105 (0.1 mg), Glucose (1 equiv.). [b] glucose (2 equiv.), acetonitrile (180 mL, 18% v/v). [c] 4-iodopyridine **1b** (20 µmol), **2a** (3 equiv.), GDH-105 (0.1 mg), Glucose (1 equiv.). [d] OYE3 (0.5 mol%), 4-iodopyridine **1b** (20 µmol), [e] OYE3 (0.1 mol%), 4-iodopyridine **1b** (20 µmol). [f] 4-bromopyridine was used instead of **1a**, [g] 4-chloropyridine used as a substrate instead of **1a**.

When exploring other iodopyridine isomers, we found that 4-iodopyridine was more reactive, affording the coupled product in 81% yield with 98:2 e.r. when using $Ru(bpy)_2$(4-CO_2Hbpy) as the photocatalyst (Table 1, entry 5). Lowering the enzyme loading to 0.5 mol % and 0.1 mol % resulted in lower yields with a modest decrease in enantioselectivity (Table 1, entries 6 and 7). We were pleased that 4-bromo and 4-chloropyridines were effective radical precursors, producing 41% and 36% yield, respectively (Table 1, entries 8 and 9). Reactions can be run on a preparative scale using crude enzyme lysate, affording product in 30% yield with 97:3 er while reactions with purified enzyme formed the product in 60% yield with 97:3 e.r. (Supplemental Figure S2 and S3), With either 2-iodopyridine or 4-iodopyridine, control experiments confirmed that each reaction component was necessary for product formation (Supplemental Table 17 and 24).

We explored the alkene scope and limitations of the reaction using 4-iodopyridines as a radical precursor (Figure 2, 3b-3v). We tested different substituted α-methylstyrenes and found that the enzyme tolerates varying electron-donating groups on the arene (Figure 2, **3b-3f**). Halogen substituents are also tolerated on the alkene, affording the product a good yield with high levels of enantioselectivity (Figure 2, **3g-3l**). While *ortho*-substitution affords product in diminished yield, the high enantioselectivity indicates that these substituents impact the C–C bond formation more than the radical termination event (Figure 2, **3c,** and **3f**). The enzyme tolerates unprotected allylic alcohols, highlighting the functional group tolerance of the reaction (Figure 2, **3m**). Vinyl pyridines were efficient coupling partners for this reaction, providing the product with up to 98% yield with excellent enantioselectivity (Figure 2, **3n-p**). Importantly, this reaction also accepts non-styrenyl substrates, significantly expanding the types of products that can be accessed using this method. Protected piperidines bearing exocyclic methylenes were reactive. Spirocyclic cyclobutanes were also reactive but afforded products with lower yields. Finally, unprotected allylic alcohols are tolerated, producing products in good yield but low levels of enantioselectivity.

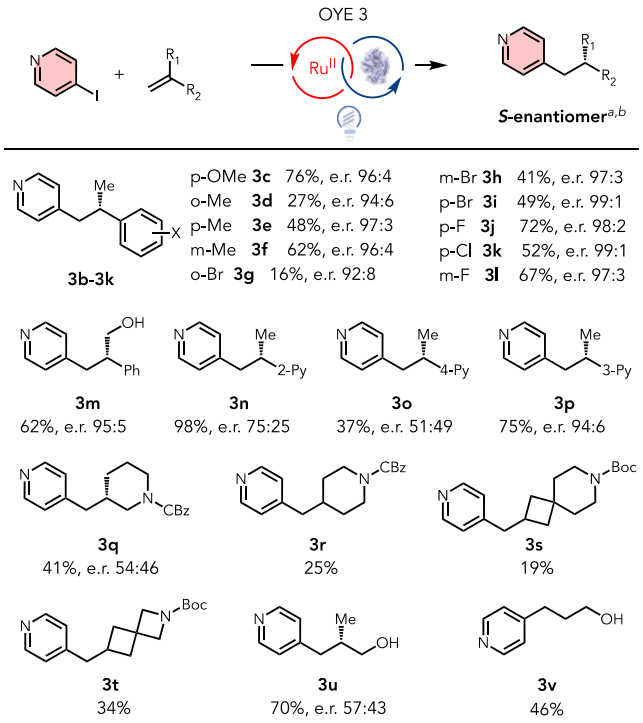


Figure 2. Scope of olefins: Reaction conditions for the *S* enantiomers: Aryl iodide (20 µmol, 1 equiv.), olefins (60 µmol, 3 equiv.), purified OYE 3 aliquot (200 nmol, 1 mol%), photocatalyst (2 mol%), NADP+ (1 mol%), GDH-105 (0.1 mg), glucose (1 equiv.), acetonitrile (250 µL, 25% v/v), MES buffer (pH 6, 100 mM, 750 µL). The reaction mixture was stirred at 360 rpm and irradiated,

Next, we explore the scope and limitations of heteroaromatic halides (Figure 3, **3aa-ar**). This reaction accepts a diverse range of substituted iodopyridine decorated with electron-donating and withdrawing groups on the pyridine ring (Figure 3, **3aa-aj**). Notably, the reaction accepts 2-, 3-, and 4- iodopyridines, forming the product in good yield and selectivity, suggesting that the locations of the basic nitrogen relative to the radical do not

significantly impact the reaction. Beyond pyridines, the reaction also accommodates various iodoquinolines. While the yields are more modest, the enantioselectivity remains high (Figure 3, **3ak-an**). 2-bromoquinoline can also afford the corresponding product in modest yield and selectivity (Figure 3, 3am). 2-iodopyrazine and 2-bromopyrimidine are also reactive and provided the corresponding products in good yields and excellent enantioselectivity (Table 3, 3ao and 3ap). Finally, electron-deficient non-heteroaromatic aryl iodoide provided the products in moderate yield but with high enantioselectivity (Table 3, 3aq and 3ar). As halopyridines have a similar reduction potential (between -1.85 and -2.29 V vs SCE) to 4-iodoacetophenone (-1.85 V vs SCE),[22] these results suggest that reduction potential is a better predictor of reactivity than the presence of a basic nitrogen.

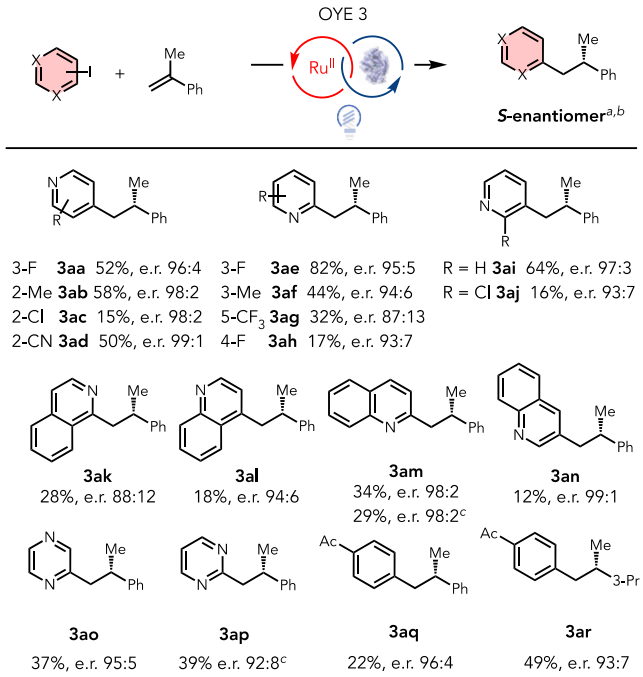
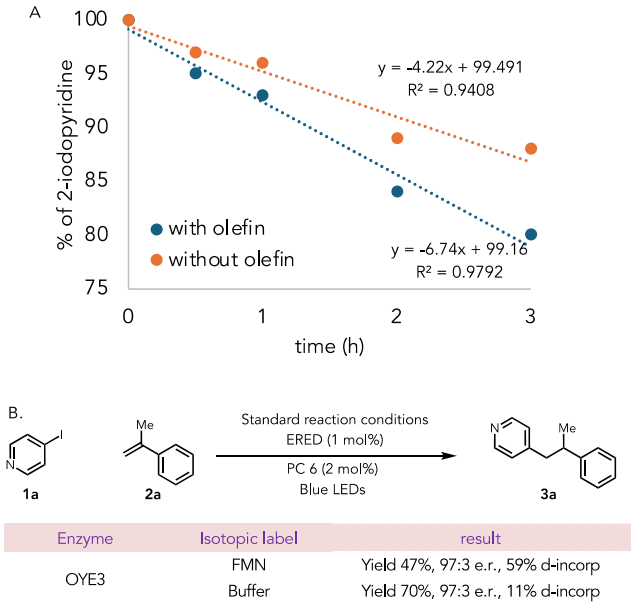


Figure 3. Scope of heterocycles: Reaction conditions for the *S* enantiomers: Aryl iodide (20 µmol, 1 equiv.), olefins (60 µmol, 3 equiv.), purified OYE 3 aliquot (200 nmol, 1 mol%), photocatalyst (2 mol%), NADP+ (1 mol%), GDH-105 (0.1 mg), glucose (1 equiv.), acetonitrile (250 µL, 25% v/v), MES buffer (pH 6, 100 mM, 750 µL). The reaction mixture was stirred at 360 rpm and irradiated with blue LEDs for 17 h. Reaction conditions for the *R* enantiomers: Aryl iodide (20 µmol, 1 equiv.), olefins (60 µmol, 3 equiv.), purified GluER T36A Y177F aliquot (200 nmol, 1 mol%), photocatalyst (2 mol%), NADP+ (1 mol%), GDH-105 (0.1 mg), glucose (2 equiv.), acetonitrile (200 µL, 20% v/v), MES buffer (pH 6, 100 mM, 800 µL). The reaction mixture was stirred at 360 rpm and irradiated with blue LEDs for 17 h. [a] Yield (average of three runs) determined using LCMS relative to an internal standard 1,3,5-tribromobenzene. [b]e.r. was determined using HPLC on a chiral stationary phase. [c] 2-bromoquinoline used as a radical precursor.

Next, we investigated the improved performance of the carboxylated photocatalysts compared to Ru(bpy)$_3$. We initially hypothesized that the difference was due to enhanced binding of the photocatalyst to the protein. We began by conducting steady-state and time-resolved fluorescence quenching experiments and observed static quenching, indicating a binding interaction between the photocatalyst and OYE3. From binding assay experiments (Supplemental Figures 12-15) we found that dissociation constant of Ru(bpy)$_2$(4,4′-CO$_2$Hbpy) for OYE 3 to be K_d = 6.7 nM, indicating that the carboxylated photocatalyst is a strong protein binding than Ru(bpy)$_3$.[28] This result suggests that enhanced photocatalyst binding accounts, in part, for the reactivity differences between the two photocatalysts. Next, we questioned whether there was a difference in the reduction potential of the photocatalyst. Indeed, we found that Ru(bpy)$_3$ was less reducing ($Ru^{II/I}$ = -1.175 V vs Ag/AgCl in acetonitrile) than Ru(bpy)$_2$(4,4′-CO$_2$Hbpy) ($Ru^{II/I}$ = -1.25 V vs. Ag/AgCl in acetonitrile) (Supplemental Figures 10 and 11), potentially accounting for its improved performance with 2-iodopyridine.

Another striking observation was the correlation between the conversion of 2-iodopyridine and product yield, indicating that the aryl halide was not unproductively consumed throughout the reaction. This observation suggests that the alkene and aryl halide are bound within the protein active site prior to radical formation. To determine whether the presence of alkene accelerates the consumption of aryl halides, we explore the kinetics of the reaction with and without alkene. During the initial rate of the reaction, we found that 2-iodopyridine is consumed 1.6 times faster in the presence of alkene than in its absence. This observation suggests that the alkene either attenuates the reduction potential of the aryl halide or helps to facilitate mesolytic cleavage of the aryl radical anion. This observation is consistent with our observations with α-bromoketones and alkenes.[55] As the magnitude of this effect is relatively small with aryl halides, we hypothesize that the alkene must bind to the hydrophobic ERED active site with higher affinity than the aryl halide.



Enzyme	Isotopic label	result
OYE3	FMN	Yield 47%, 97:3 e.r., 59% d-incorp
	Buffer	Yield 70%, 97:3 e.r., 11% d-incorp

Figure 4. A) Kinetics of 2-iodopyridine consumption with and without alkene. B) Deuterium incorporation study

Finally, we conducted isotope incorporation experiments to determine the mechanism of radical termination. When using 4-iodopyridine with D-Glucose-1-d$_1$ to isotopically label the N5-position of the flavin cofactor, the product is isolated with 59% deuterium incorporation. In contrast, when using a buffer made with D_2O to isotopically label the O–H bonds of tyrosine phenols, we observe 11% deuterium incorporation. These results suggest that flavin is terminating the reaction via hydrogen atom transfer from flavin.

In conclusion, we have developed a photoenzymatic system to catalyze an asymmetric hydroarylation of alkenes using aryl halides as radical precursors. This work expands the types of reactive intermediates that EREDs can use for alkene

functionalization. We expect this reactivity mode to be compatible with other photoenzymes for other non-natural catalytic functions.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, NMR spectra, and HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

Todd K. Hyster – *Department of Chemistry, Princeton University, Princeton, New Jersey 08544, United States; orcid.org/0000-0003-3560-355X; Email: thyster@princeton.edu.*

Authors

Prasun Mukherjee – *Department of Chemistry, Princeton University, Princeton, New Jersey 08544, United States;*

Zayed Alassad – *Department of Chemistry, Princeton University, Princeton, New Jersey 08544, United States*

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

The research reported here was supported by the National Science Foundation (CHE-2135973). The authors would like to acknowledge Venu Vandavasi for assistance running Fluorescence quenching experiments.

REFERENCES

(1) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals. *J. Med. Chem.* **2014**, *57* (24), 10257–10274. https://doi.org/10.1021/jm501100b.

(2) Lovering, F.; Bikker, J.; Humblet, C. Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. *J. Med. Chem.* **2009**, *52* (21), 6752–6756. https://doi.org/10.1021/jm901241e.

(3) Krzyzanowski, A.; Pahl, A.; Grigalunas, M.; Waldmann, H. Spacial Score—A Comprehensive Topological Indicator for Small-Molecule Complexity. *J. Med. Chem.* **2023**. https://doi.org/10.1021/acs.jmedchem.3c00689.

(4) Verendel, J. J.; Pàmies, O.; Diéguez, M.; Andersson, P. G. Asymmetric Hydrogenation of Olefins Using Chiral Crabtree-Type Catalysts: Scope and Limitations. *Chem. Rev.* **2014**, *114* (4), 2130–2169. https://doi.org/10.1021/cr400037u.

(5) Roseblade, S. J.; Pfaltz, A. Iridium-Catalyzed Asymmetric Hydrogenation of Olefins. *Acc. Chem. Res.* **2007**, *40* (12), 1402–1411. https://doi.org/10.1021/ar700113g.

(6) Pattison, G.; Piraux, G.; Lam, H. W. Enantioselective Rhodium-Catalyzed Addition of Arylboronic Acids to Alkenylheteroarenes. *J. Am. Chem. Soc.* **2010**, *132* (41), 14373–14375. https://doi.org/10.1021/ja106809p.

(7) Jumde, R. P.; Lanza, F.; Pellegrini, T.; Harutyunyan, S. R. Highly Enantioselective Catalytic Synthesis of Chiral Pyridines. *Nat. Commun.* **2017**, *8* (1), 2058. https://doi.org/10.1038/s41467-017-01966-7.

(8) Jumde, R. P.; Lanza, F.; Veenstra, M. J.; Harutyunyan, S. R. Catalytic Asymmetric Addition of Grignard Reagents to Alkenyl-Substituted Aromatic N-Heterocycles. *Science* **2016**, *352* (6284), 433–437. https://doi.org/10.1126/science.aaf1983.

(9) Yang, J.-S.; Lu, K.; Li, C.-X.; Zhao, Z.-H.; Zhang, F.-M.; Zhang, X.-M.; Tu, Y.-Q. NiH-Catalyzed Regio- and Enantioselective Hydroalkylation for the Synthesis of β- or Γ-Branched Chiral Aromatic N-Heterocycles. *J. Am. Chem. Soc.* **2023**, *145* (40), 22122–22134. https://doi.org/10.1021/jacs.3c07919.

(10) Appella, D. H.; Moritani, Y.; Shintani, R.; Ferreira, E. M.; Buchwald, S. L. Asymmetric Conjugate Reduction of α,β-Unsaturated Esters Using a Chiral Phosphine−Copper Catalyst. *J. Am. Chem. Soc.* **1999**, *121* (40), 9473–9474. https://doi.org/10.1021/ja992366l.

(11) Kong, M.; Tan, Y.; Zhao, X.; Qiao, B.; Tan, C.-H.; Cao, S.; Jiang, Z. Catalytic Reductive Cross Coupling and Enantioselective Protonation of Olefins to Construct Remote Stereocenters for Azaarenes. *J. Am. Chem. Soc.* **2021**, *143* (10), 4024–4031. https://doi.org/10.1021/jacs.1c01073.

(12) Fu, Q.; Cao, S.; Wang, J.; Lv, X.; Wang, H.; Zhao, X.; Jiang, Z. Enantioselective [2π + 2σ] Cycloadditions of Bicyclo[1.1.0]Butanes with Vinylazaarenes through Asymmetric Photoredox Catalysis. *J. Am. Chem. Soc.* **2024**, *146* (12), 8372–8380. https://doi.org/10.1021/jacs.3c14077.

(13) Li, Y.; Han, C.; Wang, Y.; Huang, X.; Zhao, X.; Qiao, B.; Jiang, Z. Catalytic Asymmetric Reductive Azaarylation of Olefins via Enantioselective Radical Coupling. *J. Am. Chem. Soc.* **2022**, *144* (17), 7805–7814. https://doi.org/10.1021/jacs.2c01458.

(14) Guo, J.; Xie, Y.; Lai, Z.-M.; Weng, J.; Chan, A. S. C.; Lu, G. Enantioselective Hydroalkylation of Alkenylpyridines Enabled by Merging Photoactive Electron Donor–Acceptor Complexes with Chiral Bifunctional Organocatalysis. *ACS Catal.* **2022**, *12* (20), 13065–13074. https://doi.org/10.1021/acscatal.2c03902.

(15) Zhang, W.-B.; Yang, X.-T.; Ma, J.-B.; Su, Z.-M.; Shi, S.-L. Regio- and Enantioselective C–H Cyclization of Pyridines with Alkenes Enabled by a Nickel/N-Heterocyclic Carbene Catalysis. *J. Am. Chem. Soc.* **2019**, *141* (14), 5628–5634. https://doi.org/10.1021/jacs.9b00931.

(16) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. Rh(I)-Catalyzed Alkylation of Quinolines and Pyridines via C−H Bond Activation. *J. Am. Chem. Soc.* **2007**, *129* (17), 5332–5333. https://doi.org/10.1021/ja070388z.

(17) Nakao, Y.; Yamada, Y.; Kashihara, N.; Hiyama, T. Selective C-4 Alkylation of Pyridine by Nickel/Lewis Acid Catalysis. *J. Am. Chem. Soc.* **2010**, *132* (39), 13666–13668. https://doi.org/10.1021/ja106514b.

(18) Gurak, J. A.; Engle, K. M. Practical Intermolecular Hydroarylation of Diverse Alkenes via Reductive Heck Coupling. *ACS Catal.* **2018**, *8* (10), 8987–8992. https://doi.org/10.1021/acscatal.8b02717.

(19) Liu, H.-C.; Xu, X.-Y.; Tang, S.; Bao, J.; Wang, Y.-Z.; Chen, Y.; Han, X.; Liang, Y.-M.; Zhang, K. Photoinduced Co/Ni-Cocatalyzed Markovnikov Hydroarylation of Unactivated Olefins with Aryl Bromides. *Chem. Sci.* **2024**, *15* (36), 14865–14871. https://doi.org/10.1039/d4sc03355h.

(20) Green, S. A.; Vásquez-Céspedes, S.; Shenvi, R. A. Iron–Nickel Dual-Catalysis: A New Engine for Olefin Functionalization and the Formation of Quaternary Centers. *J. Am. Chem. Soc.* **2018**, *140* (36), 11317–11324. https://doi.org/10.1021/jacs.8b05868.

(21) Green, S. A.; Matos, J. L. M.; Yagi, A.; Shenvi, R. A. Branch-Selective Hydroarylation: Iodoarene-Olefin Cross-Coupling. *J. Am. Chem. Soc.* **2016**, *138* (39), 12779–12782. https://doi.org/10.1021/jacs.6b08507.

(22) Boyington, A. J.; Seath, C. P.; Zearfoss, A. M.; Xu, Z.; Jui, N. T. Catalytic Strategy for Regioselective Arylethylamine Synthesis. *J. Am. Chem. Soc.* **2019**, *141* (9), 4147–4153. https://doi.org/10.1021/jacs.9b01077.

(23) Seath, C. P.; Vogt, D. B.; Xu, Z.; Boyington, A. J.; Jui, N. T. Radical Hydroarylation of Functionalized Olefins and Mechanistic Investigation of Photocatalytic Pyridyl Radical Reactions. *J. Am. Chem. Soc.* **2018**, *140* (45), 15525–15534. https://doi.org/10.1021/jacs.8b10238.

(24) Maust, M. C.; Hendy, C. M.; Jui, N. T.; Blakey, S. B. Switchable Regioselective 6-Endo or 5-Exo Radical Cyclization via Photoredox Catalysis. *J. Am. Chem. Soc.* **2022**, *144* (9), 3776–3781. https://doi.org/10.1021/jacs.2c00192.

(25) Boyington, A. J.; Riu, M.-L. Y.; Jui, N. T. Anti-Markovnikov Hydroarylation of Unactivated Olefins via Pyridyl Radical Intermediates. *J. Am. Chem. Soc.* **2017**, *139* (19), 6582–6585. https://doi.org/10.1021/jacs.7b03262.

(26) Cossy, J. Biocatalyts: Catalysts of the Future for Organic Synthesis and Beyond? *Tetrahedron* **2022**, *123*, 132966. https://doi.org/10.1016/j.tet.2022.132966.

(27) Fu, H.; Hyster, T. K. From Ground-State to Excited-State Activation Modes: Flavin-Dependent "Ene"-Reductases Catalyzed Non-Natural Radical Reactions. *Acc. Chem. Res.* **2024**, *57* (9), 1446–1457. https://doi.org/10.1021/acs.accounts.4c00129.

(28) Sun, S.-Z.; Nicholls, B. T.; Bain, D.; Qiao, T.; Page, C. G.; Musser, A. J.; Hyster, T. K. Enantioselective Decarboxylative Alkylation Using

Synergistic Photoenzymatic Catalysis. *Nat. Catal.* **2024**, *7* (1), 35–42. https://doi.org/10.1038/s41929-023-01065-5.

(29) Bender, S. G.; Hyster, T. K. Pyridylmethyl Radicals for Enantioselective Alkene Hydroalkylation Using "Ene"-Reductases. *ACS Catal.* **2023**, *13* (22), 14680–14684. https://doi.org/10.1021/acscatal.3c03771.

(30) Fu, H.; Lam, H.; Emmanuel, M. A.; Kim, J. H.; Sandoval, B. A.; Hyster, T. K. Ground-State Electron Transfer as an Initiation Mechanism for Biocatalytic C–C Bond Forming Reactions. *J. Am. Chem. Soc.* **2021**, *143* (25), 9622–9629. https://doi.org/10.1021/jacs.1c04334.

(31) Laguerre, N.; Riehl, P. S.; Oblinsky, D. G.; Emmanuel, M. A.; Black, M. J.; Scholes, G. D.; Hyster, T. K. Radical Termination via B-Scission Enables Photoenzymatic Allylic Alkylation Using "Ene"-Reductases. *ACS Catal.* **2022**, *12* (15), 9801–9805. https://doi.org/10.1021/acscatal.2c02294.

(32) Nakano, Y.; Black, M. J.; Meichan, A. J.; Sandoval, B. A.; Chung, M. M.; Biegasiewicz, K. F.; Zhu, T.; Hyster, T. K. Photoenzymatic Hydrogenation of Heteroaromatic Olefins Using 'Ene'-Reductases with Photoredox Catalysts. *Angew. Chem. Int. Ed.* **2020**, *59* (26), 10484–10488. https://doi.org/10.1002/anie.202003125.

(33) Biegasiewicz, K. F.; Cooper, S. J.; Gao, X.; Oblinsky, D. G.; Kim, J. H.; Garfinkle, S. E.; Joyce, L. A.; Sandoval, B. A.; Scholes, G. D.; Hyster, T. K. Photoexcitation of Flavoenzymes Enables a Stereoselective Radical Cyclization. *Science* **2019**, *364* (6446), 1166–1169. https://doi.org/10.1126/science.aaw1143.

(34) Page, C. G.; Cooper, S. J.; DeHovitz, J. S.; Oblinsky, D. G.; Biegasiewicz, K. F.; Antropow, A. H.; Armbrust, K. W.; Ellis, J. M.; Hamann, L. G.; Horn, E. J.; Oberg, K. M.; Scholes, G. D.; Hyster, T. K. Quaternary Charge-Transfer Complex Enables Photoenzymatic Intermolecular Hydroalkylation of Olefins. *J. Am. Chem. Soc.* **2020**, *143* (1), 97–102. https://doi.org/10.1021/jacs.0c11462.

(35) Ye, Y.; Cao, J.; Oblinsky, D. G.; Verma, D.; Prier, C. K.; Scholes, G. D.; Hyster, T. K. Using Enzymes to Tame Nitrogen-Centred Radicals for Enantioselective Hydroamination. *Nat. Chem.* **2023**, *15* (2), 206–212. https://doi.org/10.1038/s41557-022-01083-z.

(36) Fu, H.; Cao, J.; Qiao, T.; Qi, Y.; Charnock, S. J.; Garfinkle, S.; Hyster, T. K. An Asymmetric Sp3-Sp3 Cross-Electrophile Coupling Using 'Ene'-Reductases. *Nature* **2022**, *610* (7931), 302–307. https://doi.org/10.1038/s41586-022-05167-1.

(37) Huang, X.; Wang, B.; Wang, Y.; Jiang, G.; Feng, J.; Zhao, H. Photoenzymatic Enantioselective Intermolecular Radical Hydroalkylation. *Nature* **2020**, *584* (7819), 69–74. https://doi.org/10.1038/s41586-020-2406-6.

(38) Zhang, Z.; Feng, J.; Yang, C.; Cui, H.; Harrison, W.; Zhong, D.; Wang, B.; Zhao, H. Photoenzymatic Enantioselective Intermolecular Radical Hydroamination. *Nat. Catal.* **2023**, *6* (8), 687–694. https://doi.org/10.1038/s41929-023-00994-5.

(39) Harrison, W.; Jiang, G.; Zhang, Z.; Li, M.; Chen, H.; Zhao, H. Photoenzymatic Asymmetric Hydroamination for Chiral Alkyl Amine Synthesis. *J. Am. Chem. Soc.* **2024**, *146* (15), 10716–10722. https://doi.org/10.1021/jacs.4c00620.

(40) Li, M.; Yuan, Y.; Harrison, W.; Zhang, Z.; Zhao, H. Asymmetric Photoenzymatic Incorporation of Fluorinated Motifs into Olefins. *Science* **2024**, *385* (6707), 416–421. https://doi.org/10.1126/science.adk8464.

(41) Shi, Q.; Kang, X.-W.; Liu, Z.; Sakthivel, P.; Aman, H.; Chang, R.; Yan, X.; Pang, Y.; Dai, S.; Ding, B.; Ye, J. Single-Electron Oxidation-Initiated Enantioselective Hydrosulfonylation of Olefins Enabled by Photoenzymatic Catalysis. *J. Am. Chem. Soc.* **2024**, *146* (4), 2748–2756. https://doi.org/10.1021/jacs.3c12513.

(42) Zhao, B.; Feng, J.; Yu, L.; Xing, Z.; Chen, B.; Liu, A.; Liu, F.; Shi, F.; Zhao, Y.; Tian, C.; Wang, B.; Huang, X. Direct Visible-Light-Excited Flavoproteins for Redox-Neutral Asymmetric Radical Hydroarylation. *Nat. Catal.* **2023**, *6* (11), 996–1004. https://doi.org/10.1038/s41929-023-01024-0.

(43) Xing, Z.; Liu, F.; Feng, J.; Yu, L.; Wu, Z.; Zhao, B.; Chen, B.; Ping, H.; Xu, Y.; Liu, A.; Zhao, Y.; Wang, C.; Wang, B.; Huang, X. Synergistic Photobiocatalysis for Enantioselective Triple Radical Sorting. *Nature* **2024**, 1–3. https://doi.org/10.1038/s41586-024-08399-5.

(44) Shin, N. Y.; Ryss, J. M.; Zhang, X.; Miller, S. J.; Knowles, R. R. Light - Driven Deracemization Enabled by Excited - State Electron Transfer. *Science* **2019**, *366* (6463), 364–369. https://doi.org/10.1126/science.aay2204.

(45) Hejna, B. G.; Ganley, J. M.; Shao, H.; Tian, H.; Ellefsen, J. D.; Fastuca, N. J.; Houk, K. N.; Miller, S. J.; Knowles, R. R. Catalytic Asymmetric Hydrogen Atom Transfer: Enantioselective Hydroamination of Alkenes. *J. Am. Chem. Soc.* **2023**, *145* (29), 16118–16129. https://doi.org/10.1021/jacs.3c04591.

(46) Parsaee, F.; Senarathna, M. C.; Kannangara, P. B.; Alexander, S. N.; Arche, P. D. E.; Welin, E. R. Radical Philicity and Its Role in Selective Organic Transformations. *Nat. Rev. Chem.* **2021**, *5* (7), 486–499. https://doi.org/10.1038/s41570-021-00284-3.

(47) Pan, P.; Liu, S.; Lan, Y.; Zeng, H.; Li, C.-J. Visible-Light-Induced Cross-Coupling of Aryl Iodides with Hydrazones via an EDA-Complex. *Chem. Sci.* **2022**, *13* (24), 7165–7171. https://doi.org/10.1039/d2sc01909d.

(48) Zhao, H.; Cuomo, V. D.; Rossi-Ashton, J. A.; Procter, D. J. Aryl Sulfonium Salt Electron Donor-Acceptor Complexes for Halogen Atom Transfer: Isocyanides as Tunable Coupling Partners. *Chem* **2024**, *10* (4), 1240–1251. https://doi.org/10.1016/j.chempr.2024.01.020.

(49) Liang, K.; Li, N.; Zhang, Y.; Li, T.; Xia, C. Transition-Metal-Free α-Arylation of Oxindoles vi a Visible-Light-Promoted Electron Transfer. *Chem. Sci.* **2019**, *10* (10), 3049–3053. https://doi.org/10.1039/c8sc05170d.

(50) Liu, B.; Lim, C.-H.; Miyake, G. M. Visible-Light-Promoted C–S Cross-Coupling via Intermolecular Charge Transfer. *J. Am. Chem. Soc.* **2017**, *139* (39), 13616–13619. https://doi.org/10.1021/jacs.7b07390.

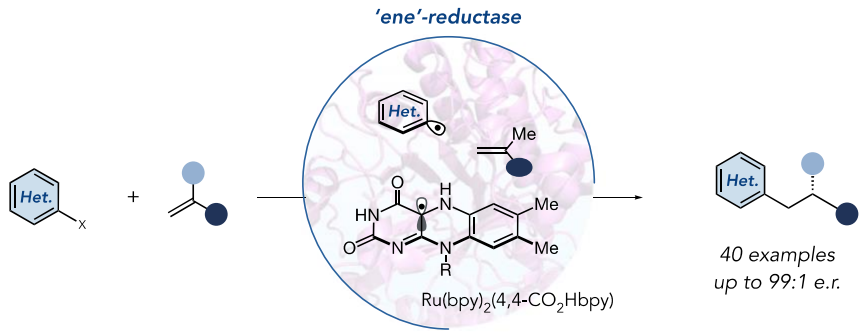
(51) Andrieux, C. P.; Savéant, J.-M.; Tallec, A.; Tardivel, R.; Tardy, C. Concerted and Stepwise Dissociative Electron Transfers. Oxidability of the Leaving Group and Strength of the Breaking Bond as Mechanism and Reactivity Governing Factors Illustrated by the Electrochemical Reduction of α-Substituted Acetophenones. *J. Am. Chem. Soc.* **1997**, *119* (10), 2420–2429. https://doi.org/10.1021/ja963674b.

(52) Costentin, C.; Robert, M.; Savéant, J.-M. Fragmentation of Aryl Halide π Anion Radicals. Bending of the Cleaving Bond and Activation vs Driving Force Relationships. *J. Am. Chem. Soc.* **2004**, *126* (49), 16051–16057. https://doi.org/10.1021/ja045989u.

(53) Sandoval, B. A.; Kurtoic, S. I.; Chung, M. M.; Biegasiewicz, K. F.; Hyster, T. K. Photoenzymatic Catalysis Enables Radical-Mediated Ketone Reduction in Ene-Reductases. *Angew. Chem. Int. Ed.* **2019**, *58* (26), 8714–8718. https://doi.org/10.1002/anie.201902005.

(54) Biegasiewicz, K. F.; Cooper, S. J.; Emmanuel, M. A.; Miller, D. C.; Hyster, T. K. Catalytic Promiscuity Enabled by Photoredox Catalysis in Nicotinamide-Dependent Oxidoreductases. *Nat Chem* **2018**, *10* (7), 770–775. https://doi.org/10.1038/s41557-018-0059-y.

(55) Fu, H.; Lam, H.; Emmanuel, M.; Kim, J. H.; Sandoval, B.; Hyster, T. K. Ground-State Electron Transfer as an Initiation Mechanism for Asymmetric Hydroalkylations in Radical Biocatalysis. **2021**. https://doi.org/10.26434/chemrxiv.14128685.v1.



Synergistic Merger of Enzymes with Photoredox Catalysts