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Flavin Metallaphotoredox Catalysis: Synergistic Synthesis in Water

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Abstract

Combining a transition metal with a photocatalyst can drive modern synthetic chemistry. For transformations performed in water, this concept has been largely unexplored. We report the successful merger of a biocompatible flavin photocatalyst with a palladium catalyst to build isotopically enriched peptidomimetics, to mediate conjugate addition and $C{-}H$ functionalization reactions, and to assemble unprotected proteinogenic and nonproteinogenic peptides, in water. We detail the important role of the ligand and the palladium oxidation state for controlling product selectivity when constructing synthetic peptides.

Graphical Abstract

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.2c00773.

Experimental optimizations, general considerations, computational data, experimental procedures, and characterization data for all compounds including NMR spectra and LC-MS/MS spectra (PDF)

Complete contact information is available at: https://pubs.acs.org/10.1021/acscatal.2c00773

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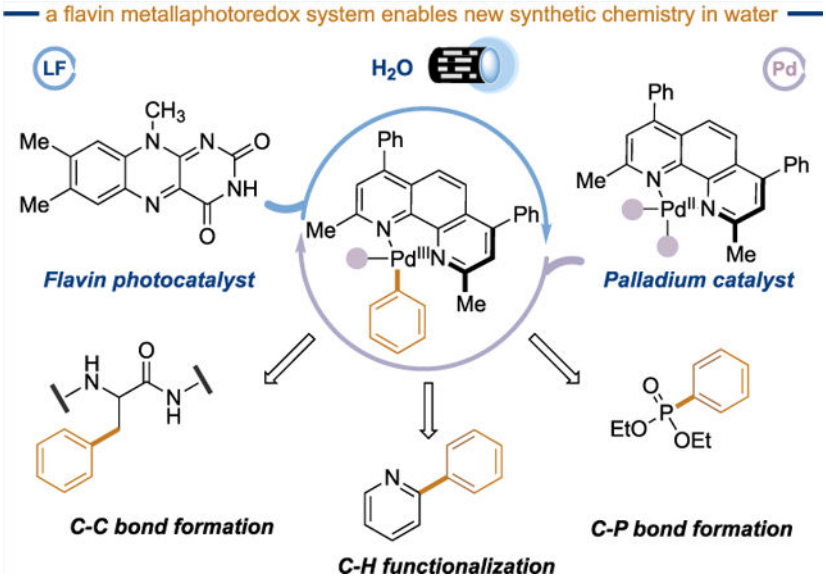

Keywords

metallaphotoredox; flavin; boronic acids; biocompatible; isotopes; peptidomimetics

Marrying a transition metal with a photocatalyst, termed *metallaphotoredox catalysis*, is a powerful tool for accessing new chemical space and revolutionizing modern organic synthesis. Examples include driving fundamentally new cross-coupling reactions, biasing stereochemical outcomes in open-shell protocols, and guiding atypical regio- and/or chemo-selective *C*−*X* and *C*−*C* bond forming events.[1–5] However, the utility of metallaphotoredox catalysis for biocompatible synthesis (i.e., reactions performed under mild, aqueous conditions) remains largely unexplored.[6–10] The main reasons are the chemical lability (prone to protodematallation, disproportionation, and oxidative insertion of water) of organometallic complexes in aqueous media[11–14] and the poor water solubility of standard photocatalysts, admixed with their propensity to oxidize and to reduce water molecules.[15–18] Identifying synergistic pairs of aqueous-compatible photocatalysts and transition-metal complexes could greatly expand the application of metallaphotoredox catalysis to work on biomolecules (like peptides and proteins) and to access new medicinal agents without the need for organic solvents.

Previous results from our lab showed that a biocompatible lumiflavin (LF) photocatalyst can convert boronic acids into *C*-centered radicals in water.[19] Later, we showed that many of these radicals (sp^3 and sp^2) could add to a dehydroalanine (Dha) residue in a peptide, forging synthetic amino acid side chains by open-shell conjugate addition.[20] However, very nucleophilic aryl radicals (like phenyl radical) barely engage Dha residues in a peptide.[21,22] The addition of a phenyl radical to Dha is highly endergonic (SOMO-LUMO gap of 122 $kcalmol^{-1}$ at B3LYP/6–311+G**). We postulated that if we could capture the “free” aryl radical with an appropriate transition metal, the resulting organometallic species would minimize the energy required for phenyl group transfer to Dha, delivering the desired phenylalanine product. If successful, this one proof-of-principle reaction

would provide convincing evidence that (1) radicals generated by a flavin photoredox catalyst can form aqueous organometallic intermediates and (2) these intermediates can facilitate new synthetic chemistry that cannot be achieved by either catalyst independently, thus establishing the *first ever* flavin metallaphotoredox catalysis platform with general applications for biocompatible synthesis (Figure 1).

To test our mechanistic hypothesis, we set out to identify a metal that could work synergistically with lumiflavin to accomplish side chain addition, that is, to merge a nucleophilic sp^2 *C*-centered radical generated by lumiflavin and an aryl boronic acid with a Dha residue in a peptide under 440 nm irradiation after 6 h. We selected phenylboronic acid (5 equiv), a notoriously difficult substrate for open-shell conjugate addition to Dha, as a prototypical substrate for reaction discovery.[21,22] We selected Ac-G-P-**Dha**-F-NH_2 (1 equiv) as a standard peptide, and pH 7.0 phosphate buffered water as solvent (10 mM). We first surveyed a variety of base metals and transition metals as cocatalysts (10 mol %) for our standard reaction. (Note: Photoexcited flavin catalysts have been shown to act on or alongside various metal salts to mediate different processes, including prodrug activation (Pt^{IV}), detoxification of heavy metals (Hg^{II}), and *C*−*O* bond formation ($Fe^{II/III}$, Sc^{III}, Yb^{II}, and Mg^{II}). Heretofore, no examples of *C*−*C* bond formation have been reported.[23–26]) We found that palladium trifluoroacetate $Pd(TFA)_2$ afforded a mixture of the desired phenylalanine-containing conjugate addition product Ac-G-P-F-F-NH_2 as a 60:40 (*D*/*L*)-mixture of diastereomers, and a Heck byproduct (dehydrophenylalanine side chain) in 10% combined conversion (3:2 conjugate addition-to-Heck product). All other metal salts (e.g., In^{III}, Zn^{II}, $Cu^{I/II}$, Fe^{II}, Ni^{II}, Co^{II}, Mn^{III}, Cr^{II}, and Pt^{II}) were ineffective. Increasing both the amount of $Pd(TFA)_2$ and lumiflavin to 50 mol % enhanced the conversion of the conjugate addition product to 12%. The larger amount of Pd presumably helps to sequester the phenyl radical generated under our very dilute conditions. Lower loadings of Pd gave decreased yields. Importantly, a control reaction with $Pd(TFA)_2$ and no photocatalyst gave only the Heck product in 2% conversion. Removing $Pd(TFA)_2$ and using only lumiflavin in the reaction gave a 1% conversion to the desired conjugate addition product. The improved efficiency of the reaction (12% conversion to the conjugate addition product) obtained by combining $Pd(TFA)_2$ and lumiflavin suggests a cooperative effect between these two catalysts. We next examined a series of cosolvents for the reaction, which is heterogeneous in water. The use of 5% v:v 2,2,2-trifluoroethanol (TFE) greatly diminished the amount of the Heck side-product in our standard reaction (8:1 conjugate addition-to-Heck product; 9% overall conversion). Hence, we examined other palladium catalysts in aqueous TFE solvent. We found that tetrakis(acetonitrile)palladium tetrafluoroborate $[MeCN]_4Pd(BF_4)_2$ gave a marked improvement in conversion (28%) and retained product selectivity. Adding bathocuproine (BC) ligand and extending the reaction time to 16 h gave an optimal 73% conversion (38:<1 selectivity) to the desired phenylalanine conjugate addition product. (Other ligands were examined, and their results will be discussed later as part of our complete mechanistic studies.) Our finding demonstrates the *first* example of a flavin photocatalyst cooperatively working with a metal catalyst to achieve *C*−*C* bond formation.

We explored the scope of our aqueous metallaphotoredox platform for building synthetic peptides. It is important to point out that we limited our scope to aromatic boronic acids

that do not readily engage Dha residues through direct palladium catalysis or lumiflavin-mediated open-shell conjugate addition (see control reactions for compounds **1–5**, Table 1). The electrophilicity of the corresponding *C*-centered radicals from each boronic acid were calculated at the B3LYP/6–311+G** level of theory and are listed next to their structures in Table 1. While the use of a simple phenylboronic acid (**1**) enables a phenylalanine residue to be incorporated into our Dha-peptide, deprotection of the *p*-acetoxy side chain of **2** under basic conditions facilitates rapid access to a tyrosine-containing peptide. Thus, our method is a useful strategy for incorporating two endogenous amino acids (Phe and Tyr) into Dha-peptides. The use of d5- and 13C6-phenylboronic acid (**4** and **5**, Table 1) are also noteworthy as they form side chains that are valuable mechanistic probes (Phe mimics) for exploring the chemical biology of endogenous peptides.[27,28] Isotopic-enrichment at the α-position of peptide amides can also enhance the plasma and metabolic stability of ordinary peptides.[29–31] We were delighted to find that performing our standard reaction in D_2O solvent formed the α-deuterophenylalanine containing peptide (**6**) exclusively. When combined with d5- or 13C6-phenylboronic acid, our method for α-deuteration will enable highly isotopically enriched amino acids—up to 7.0 isotopic atoms over seven different carbon centers—to be readily assembled. This is significant because molecules with higher equivalents of isotopically enriched atoms are preferable for mechanistic studies (mass- and NMR-based) and as internal standards (ideally more than 4.0 deuterium atoms per molecule for pharmaceutical studies).[32,33] Finally, *p*-fluorophenylalanine (made from **3**) is one of the most common nonproteinogenic amino acids found in peptide drugs, being a biomimetic replacement for a Tyr residue. The lone fluorine atom of *p*-fluorophenylalanine also makes it a valuable tool for deciphering the three-dimensional structure of proteins and for exploring protein-to-protein interactions by ^{19}F NMR.[34–36] In all, our results highlight the practical utility of our aqueous metallaphotoredox system to furnish endogenous peptide side chains, isotopically enriched peptidomimetics, and peptides with biomimetic side chains.

To test whether our metallaphotoredox platform could generate small molecule therapeutics, we examined a series of electrophiles where open-shell conjugate addition of phenylboronic acid is not favored when lumiflavin or BC(Pd)^{II} are omitted from the reaction. We assessed tetraisopropylvinyli-denediphosphonate (7), acrylic acid, and methylvinyl ketone (MVK), Table 1. From these electrophiles, we successfully prepared an antiresorptive bisphosphonate (**13**, 31%),[37,38] the antioxidant phloretic acid (**16**, 35%)[39] and the NSAID nabumetone (**19**, 48%),[40,41] respectively. We also assessed an eneimido acid (**9**). The phthalimide (Phth) group of **9** can be cleaved with hydrazine to reveal the free amino acid. Reacting 9 with phenylboronic acid (**1**) under our standard metallaphotoredox conditions afforded (±)-phenylalanine after treatment with hydrazine (18%). Despite its low yield, our synthesis of phenylalanine is significant as organic radicals (sp^2 or sp^3) do not readily couple to Dha residues having a free carboxylic acid group. A free carboxylic acid group hinders radical addition to the Dha residue, and the *C*-terminus of the Dha is protected in most cases.[42] We surmise that the free carboxylic acid in our reaction may guide the delivery of an organopalladium intermediate to forge the desired phenylalanine product. (Carboxylic acids are known to be weak directing groups for organopalladium chemistry,[43–45] and we could not recapitulate the conjugate addition reaction when standard Lewis acid such as $Sc(OTf)_3$, $In(OAc)_3$, or $Zn(OAc)_2$ were used in place of palladium.) We leveraged the

unique ability of our metallaphotoredox reaction to mediate the arylation of **9** to prepare 3,4,5-trioxygenated phenylalanine (**14**, 24% yield), a privileged structural fragment in many natural products that have antitumor and antimicrobial activity.[46]

We imagined that other coordinating functional groups might also direct arylation. To test this idea, we examined simple pyridine (**11**). Coordination of palladium to the basic pyridine nitrogen atom would position an organopalladium intermediate next to the C_2 carbon(s) of the pyridine ring, and this could result in selective $C_2{-}H$ arylation. As expected, we obtained the C_2-arylated pyridine (**12**, 42%) in high regioselectivty (8:1, C_2 vs C_4) using phenylboronic acid. We capitalized on the ability of the pyridine nitrogen to direct C_2−H arylation to prepare cinchophen methylester (**15**, 28%) in one step. Surveying additional substrate classes, we found that acetylacetone and allyl acetate, two substrates which can also function as suitable ligands for palladium,[47,48] underwent successful arylation (by comparison to known ^{1}H NMR spectra). Taken together, our results show that coordinating substrates and functional groups can assist arylation in our metallaphotoredox reaction and, in some cases, help drive regioselective outcomes. Aside the examples highlighted above, we also found that our system could facilitate $C{-}X$ bond formation, including the deborylative-phosphorylation (**18**, 65%) of phenylboronic acid. These reactions serve to highlight the untapped potential of our new platform for synthetic organic chemistry and for the late-stage diversification of small organic molecules in water.

In our optimization studies, we found that the choice of ligand for the palladium catalyst dramatically affected the ratio between the conjugate addition and the Heck products (Figure 2A). We found that palladium complexes with more electropositive metal centers (i.e., stronger oxidants) such as (DAF)Pd^{II}L$_2$ ($E_{Pd(II)/Pd(0)}$ ~ 98 mV vs Fc$^{+/0}$)[49] favored the Heck product. This product was formed in the absence of lumiflavin or light, suggesting its formation comes from direct transmetalation of the boronic acid to palladium.[50] Palladium complexes with more electronegative metal centers (i.e., stronger reductants) such as our optimal (BC)Pd^{II}L$_2$ ($E_{Pd(II)/Pd(0)}$ ~ −4 mV vs Fc$^{+/0}$) favored the conjugate addition product and did not form Heck products. Aside from deterring background transmetalation, electron-rich palladium complexes like (BC)Pd^{II} can stabilize transitory Pd^{III} intermediates. Bathocuproine and methyl-substituted phenanthroline ligands destabilize inactive dimeric resting states of palladium catalysts, particularly those formed in water and favor palladium complexes with a distorted square planar geometry.[51,52] A distorted coordination sphere can stabilize Pd^{III}.[53] The role of the BC ligand in our reaction is, therefore, multifarious as it can promote and stabilize the formation of a Pd^{III}–Ph intermediate in water, which is poised to engage our Dha peptide through conjugate addition.

To probe for the formation of a Pd^{III}–Ph intermediate, we obtained a crude high resolution mass spectrum of our metallaphotoredox reaction performed with phenylboronic acid and our Dha peptide (Figure 2B). We identified the formation of desolvated (BC)Pd^{II} [**A**; 468 m/z] and two arylated palladium complexes, (BC)Pd−Ph [**B**; 543 m/z] and [MeCN](BC)Pd−Ph [**C**; 584 m/z], and an adduct between our expected phenylalanine conjugate addition product and (BC)Pd, [**D**; 973 m/z] (Figure S2). Together, these masses suggest that the phenyl ring that becomes the new phenylalanine residue in our Dha peptide is delivered by a (BC)Pd−Ph intermediate. To probe what oxidation state of palladium might

be responsible for aryl group transfer, we prepared (BC)Pd^{II}−Ph.[54,55] No conjugate addition was observed when this complex was reacted with our standard peptide. This suggests that delivery of the aryl group from (BC)Pd−Ph may require the metal center to be in an odd electron state, such as Pd^{III}. A Pd^{III}−Ph is a widely accepted intermediate in palladium-photoredox reactions that make arylated products.[56–58] We propose that (BC)Pd^{III}−Ph could mediate aryl group transfer to our Dha peptide, affording a Pd^{III} enolate. Lumiflavin semiquinone radical (HLF•; formed by initial oxidation of the boronic acid) reduces the Pd^{III} enolate to a Pd^{II} enolate. The $Pd^{III/II}$ redox couple is ~0.5 V vs SCE,[59] and this is within the range of HLF• which is reported to be ~ −0.46 V vs SCE.[60] Protonation of the Pd^{II} enolate by solvent gives the final phenylalanine conjugate addition product. The results from our investigations are summarized in a proposed mechanism depicted in Figure 2C.

In conclusion, we report the first example of flavin metallaphotoredox catalysis for *C*−*C* and *C*−*X* bond formation in water. We highlight the utility of our system to (1) construct endogenous peptides and isotopically enriched peptidomimetics, (2) generate medicinally relevant small molecules, and (3) mediate the late stage arylation of *C*−*H* bonds. We expect that our mechanistic studies will help to guide the design of other aqueous metallaphotoredox reactions in the future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

(1). Chan AY; Perry IB; Bissonnette NB; Buksh BF; Edwards GA; Frye LI; Garry OL; Lavagnino MN; Li BX; Liang Y.; Mao E.; Millet A.; Oakley JV; Reed NL; Sakai HA; Seath CP; MacMillan DWC Metallaphotoredox: The Merger of Photoredox and Transition Metal Catalysis. Chem. Rev 2022, 122, 1485–1542. [PubMed: 34793128]

(2). Gualandi A.; Anselmi M.; Calogero F.; Potenti S.; Bassan E.; Ceroni P.; Cozzi PG Metallaphotoredox catalysis with organic dyes. Org. Biomol. Chem 2021, 19, 3527–3550. [PubMed: 33908565]

(3). Zhang H-H; Chen H.; Zhu C.; Yu S. A review of enantioselective dual transition metal/photoredox catalysis. Science China Chemistry 2020, 63, 637–647.

(4). Lipp A.; Badir SO; Molander GA Stereoinduction in Metallaphotoredox Catalysis. Angew. Chem., Int. Ed 2021, 60, 1714–1726.

(5). Guillemard L.; Wencel-Delord J. When metal-catalyzed C-H functionalization meets visible-light photocatalysis. Beilsten. J. Org. Chem 2020, 16, 1754–1804.

(6). Zhong J-J; Meng Q-Y; Liu B.; Li X-B; Gao X-W; Lei T.; Wu C-J; Li Z-J; Tung C-H; Wu L-Z Cross-Coupling Hydrogen Evolution Reaction in Homogeneous Solution without Noble Metals. Org. Lett 2014, 16, 1988–1991. [PubMed: 24628016]

(7). Call A.; Casadevall C.; Acuna-Pares F.; Casitas A.; Lloret-Fillol J. Dual cobalt-copper light-driven catalytic reduction of aldehydes and aromatic ketones in aqueous media. Chem. Sci 2017, 8, 4739–4749. [PubMed: 30155221]

(8). Kolmel DK; Meng J.; Tsai M-H; Que J.; Loach RP; Knauber T.; Wan J.; Flanagan ME On-DNA Decarboxylative Arylation: Merging Photoredox with Nickel Catalysis in Water. ACS Comb. Sci 2019, 21, 588–597. [PubMed: 31283168]

(9). Kolmel DK; Ratnayake AS; Flanagan ME Photoredox cross-electrophile coupling in DNA-encoded chemistry. Biochem. Biophys. Res. Commun 2020, 533, 201–208. [PubMed: 32414574]

(10). Sahoo MK; Balaraman E. Room temperature catalytic dehydrogenation of cyclic amines with the liberation of H2 using water as a solvent. Green Chem. 2019, 21, 2119–2128.

(11). Ozerov OV Oxidative addition of water to transition metal complexes. Chem. Soc. Rev 2009, 38, 83–88. [PubMed: 19088967]

(12). Sather AC; Lee HG; Colombe JR; Zhang A.; Buchwald SL Dosage delivery of sensitive reagents enables glove-box-free synthesis. Nature 2015, 524, 208–211. [PubMed: 26268191]

(13). Zhou F.; Li C-J En route to metal-mediated and metalcatalysed reactions in water. Chem. Sci 2019, 10, 34–46. [PubMed: 30746071]

(14). Roesky HW; Walawalkar MG; Murugavel R. Is Water a Friend or Foe in Organometallic Chemistry? The Case of Group 13 Organometallic Compounds. Acc. Chem. Res 2001, 34, 201–211. [PubMed: 11263878]

(15). Jespersen D.; Keen B.; Day JI; Singh A.; Briles J.; Mullins D.; Weaver JD III Solubility of Iridium and Ruthenium Organometallic Photoredox Catalysts. Org. Process Res. Dev 2019, 23, 1087–1095. [PubMed: 31396008]

(16). Graetzel M. Artificial photosynthesis: water cleavage into hydrogen and oxygen by visible light. Acc. Chem. Res 1981, 14, 376–384.

(17). Meyer TJ Chemical approaches to artificial photosynthesis. Acc. Chem. Res 1989, 22, 163–170.

(18). Bard AJ; Fox MA Artificial Photosynthesis: Solar Splitting of Water to Hydrogen and Oxygen. Acc. Chem. Res 1995, 28, 141–145.

(19). Chilamari M.; Immel JR; Bloom S. General Access to C-Centered Radicals: Combining a Bioinspired Photocatalyst with Boronic Acids in Aqueous Media. ACS Catal. 2020, 10, 12727–12737.

(20). Immel JR; Chilamari M.; Bloom S. Combining flavin photocatalysis with parallel synthesis: a general platform to optimize peptides with non-proteinogenic amino acids. Chem. Sci 2021, 12, 10083–10091. [PubMed: 34377401]

(21). de Bruijn AD; Roelfes G. Chemical Modification of Dehydrated Amino Acids in Natural Antimicrobial Peptides by Photoredox Catalysis. Chem.—Eur. J 2018, 24, 11314–11318. [PubMed: 29939448]

(22). Josephson B.; Fehl C.; Isenegger PG; Nadal S.; Wright TH; Poh AWJ; Bower BJ; Giltrap AM; Chen L.; Batchelor-McAuley C.; Roper G.; Arisa O.; Sap JBI; Kawamura A.; Baldwin AJ; Mohammed S.; Compton RG; Gouverneur V.; Davis BG Light-driven post-translational installation of reactive protein side chains. Nature 2020, 585, 530–537. [PubMed: 32968259]

(23). Alonso-de Castro S.; Cortajarena AL; López-Gallego F.; Salassa L. Bioorthogonal Catalytic Activation of Platinum and Ruthenium Anticancer Complexes by FAD and Flavoproteins. Agnew. Chem. Int. Ed 2018, 57, 3143–3147.

(24). Mühldorf B.; Wolf R. Photocatalytic benzylic C-H bond oxidation with a flavin scandium complex. Chem. Commun 2015, 51, 8425–8428.

(25). Fox B.; Walsh CT Purification and characterization of a transposon-encoded flavoprotein containing an oxidation-reduction-active disulfide. J. Biol. Chem 1982, 257, 2498–2503. [PubMed: 6277900]

(26). Muhldorf B.; Lennert U.; Wolf R. Coupling photoredox and biomimetic catalysis for the visible-light-driven oxygenation of organic compounds. Phys. Sci. Rev 2019, 4, 20180030.

(27). Young BM; Rossi P.; Slavish PJ; Cui Y.; Sowaileh M.; Das J.; Kalodimos CG; Rankovic Z. Synthesis of Isotopically Labeled, Spin-Isolated Tyrosine and Phenylalanine for Protein NMR Applications. Org. Lett 2021, 23, 6288–6292. [PubMed: 34379431]

(28). Vuister GW; Kim S-J; Wu C.; Bax A. 2D and 3D NMR Study of Phenylalanine Residues in Proteins by Reverse Isotopic Labeling. J. Am. Chem. Soc 1994, 116, 9206–9210.

(29). Galan SGG; Wickens JR; Dadova J.; Ng W-L; Zhang X.; Simion RA; Quinlan R.; Pires E.; Paton RF; Caddick S.; Chudasama V.; Davis BG Post-translational site-selective protein back bone α-dueteration. Nat. Chem. Biol 2018, 14, 955–963. [PubMed: 30224694]

(30). Claydon AJ; Thom MD; Hurst JL; Beynon RJ Protein turnover: Measurement of proteome dynamics by whole animal metabolic labelling with stable isotope labelled amino acids. Proteomics 2012, 12, 1194–1206. [PubMed: 22577021]

(31). Atzrodt J.; Derdau V.; Kerr WJ; Reid M. Deuterium- and Tritium-Labelled Compounds: Applications in the Life Sciences. Agnew. Chem. Int. Ed 2018, 57, 1758–1784.

(32). Loh YY; Nagao K.; Hoover AJ; Hesk D.; Rivera NR; Colletti SL; Davies IW; MacMillan DWC Photoredox-catalyzed deuteration and tritiation of pharmaceutical compounds. Science 2017, 358, 1182–1187. [PubMed: 29123019]

(33). Derdau V.; Atzrodt J.; Zimmermann J.; Kroll C.; Bruckner F. Chem. A. Eur. J 2009, 15, 10397–10404.

(34). Awad LF; Ayoup MS Fluorinated phenylalanines: synthesis and pharmaceutical applications. Beilsten J. Org. Chem 2020, 16, 1022–1050.

(35). Marsh ENG; Suzuki Y. Using 19F NMR to Probe Biological Interactions of Proteins and Peptides. ACS Chem. Biol 2014, 9, 1242–1250. [PubMed: 24762032]

(36). Mei H.; Han J.; Klika KD; Izawa K.; Sato T.; Meanwell NA; Soloshonok VA Applications of fluorine-containing amino acids for drug design. Eur. J. Med. Chem 2020, 186, 111826. [PubMed: 31740056]

(37). Mong NLE; Niesor E.; Bentzen CL gem-Diphosphonate and gem-phosphonate-phosphate compounds with specific high density lipoprotein inducing activity. J. Med. Chem 1987, 30, 1426–1433. [PubMed: 3612689]

(38). Nguyen LM; Niesor EJ; Bentzen CL; Phan HT Inhibition of Cholesterol Synthesis and Antiproliferative Activity of a Series of Novel Phenol-Substituted 1,1-Bisphosphonate Esters. Current Medicinal Chemistry: Immunology, Endocrine & Metabolic Agents 2002, 2, 205–217.

(39). Owen RW; Haubner R.; Mier W.; Giacosa A.; Hull WE; Spiegelhalder B.; Bartsch H. Isolation, structure elucidation and antioxidant potential of the major phenolic and flavonoid compounds in brined olive drupes. Food Chem. Toxicol 2003, 41, 703–717. [PubMed: 12659724]

(40). Hedner T.; Samulesson O.; Währborg P.; Wadenvik H.; Ung K-A; Ekbom A. Nabumetone: therapeutic use and safety profile in the management of osteoarthritis and rheumatoid arthritis. Drugs 2004, 64, 2315–2343. [PubMed: 15456329]

(41). Dahl SL Nabumetone: a “nonacidic” nonsteroidal anti-inflammatory drug. Ann. Pharmacother 1993, 27, 456–463. [PubMed: 8477124]

(42). Larionov VA; Stoletova NV; Maleev VI Advances in Asymmetric Amino Acid Synthesis Enabled by Radical Chemistry. Adv. Synth. Catal 2020, 362, 4325–4367.

(43). Uttry A.; Mal S.; van Gemmeren M. Late-Stage β-C(sp3)-H Deuteration of Carboxylic Acids. J. Am. Chem. Soc 2021, 143, 10895–10901. [PubMed: 34279928]

(44). Zhu Y.; Chen X.; Yuan C.; Li G.; Zhang J.; Zhao Y. Pd-catalysed ligand-enabled carboxylate-directed highly regioselective arylation of aliphatic acids. Nat. Commun 2017, 8, 14904. [PubMed: 28383026]

(45). Sambiagio C.; Schonbauer D.; Blieck R.; Dao-Huy T.; Pototschnig G.; Schaaf P.; Wiesinger T.; Zia MF; Wencel-Delord J.; Besset T.; Maes BUW; Schnurch M. A comprehensive overview of directing groups applied in metal-catalysed C-H functionalisation chemistry. Chem. Soc. Rev 2018, 47, 6603–6743. [PubMed: 30033454]

(46). Chen R.; Liu H.; Liu X.; Chen X. An efficient synthesis of l-3,4,5-trioxygenated phenylalanine compounds from l-tyrosine. Tetrahedron 2013, 69, 3565–3570.

(47). Churchill MR; Mason R. Molecular Structure of pi-allyl-palladium Acetate. Nature 1964, 204, 777.

(48). Lyons TW; Sanford MS Palladium-Catalyzed Ligand-Directed C-H Functionalization Reactions. Chem. Rev 2010, 110, 1147–1169. [PubMed: 20078038]

(49). Bruns DL; Musaev DG; Stahl SS Can Donar Ligands Make Pd(OAc)2 a Stonger Oxidant? Access to Elusive Palladium(II) Reduction Potentials and Effects of Ancillary Ligands via

Palladium(II)/Hydroquinone Redox Equilibria. J. Am. Chem. Soc 2020, 142, 19678–19688. [PubMed: 33167610]

(50). de Bruijn AD; Roelfes G. Catalytic Modification of Dehydroalanine in Peptides and Proteins by Palladium-Mediated Cross-Coupling. Chemistry 2018, 24, 12728–12733. [PubMed: 29923249]

(51). Wang D.; Weinstein AB; White PB; Stahl SS Ligand-promoted palladium-catalyzed aerobic oxidation reactions. Chem. Rev 2018, 118, 2636–2679. [PubMed: 28975795]

(52). Milani B.; Alessio E.; Mestroni G.; Sommazzi A.; Garbassi F.; Zangrando E.; Bresciani-Pahor N.; Randaccio L. Synthesis and characterization of monochelated carboxylatopalladium (II) complexes with nitrogen-donor chelating ligands. Crystal structure of Diacetato(1,10-phenanthroline)- and Diacetato(2,9-dimethyl-1,10-phenanthroline)-palladium (II). J. Chem. Soc., Dalton Trans 1994, 13, 1903–1911.

(53). Powers DC; Ritter T. Palladium (III) in synthesis and catalysis. Top. Organomet. Chem 2011, 35, 129–156.

(54). Ingram AJ; Walker KL; Zare RN; Waymouth RM Catalytic Role of Multinuclear Palladium-Oxygen Intermediates in Aerobic Oxidation Followed by Hydrogen Peroxide Disproportionation. J. Am. Chem. Soc 2015, 137, 13632–13646. [PubMed: 26444100]

(55). Enquist P-A; Nilsson P.; Sjoberg P.; Larhed M. ESI_MS Detection of Proposed Reaction Intermediates in the Air-Promoted and Ligand-Modulated Oxidative Heck Reaction. J. Org. Chem 2006, 71, 8779–8786. [PubMed: 17081006]

(56). Shee M.; Singh NDP Cooperative photoredox and palladium catalysis: recent advances in various functionalization reactions. Catal. Sci. Technol 2021, 11, 742–767.

(57). Babu SS; Shahid M.; Gopinath P. Dual palladium-photoredox catalyzed chemoselective C-H arylation of phenylureas. Chem. Commun 2020, 56, 5985–5988.

(58). Jiang J.; Zhang W-M; Dai J-J; Xu J.; Xu H-J Visible-Light-Promoted C-H Arylation by Merging Palladium Catalysis with Organic Photoredox Catalysis. J. Org. Chem 2017, 82, 3622–3630. [PubMed: 28303717]

(59). Budnikova YH; Dudkina YB; Khrizanforov MN Redox-Induced Aromatic C-H Bond Functionalization in Metal Complex Catalysis from the Electrochemical Point of View. Inorganics 2017, 5, 70.

(60). Ksenzhek OS; Petrova SA Electrochemical properties of flavins in aqueous solutions. Bioelectrochem. Bioenerg 1983, 11, 105–127.

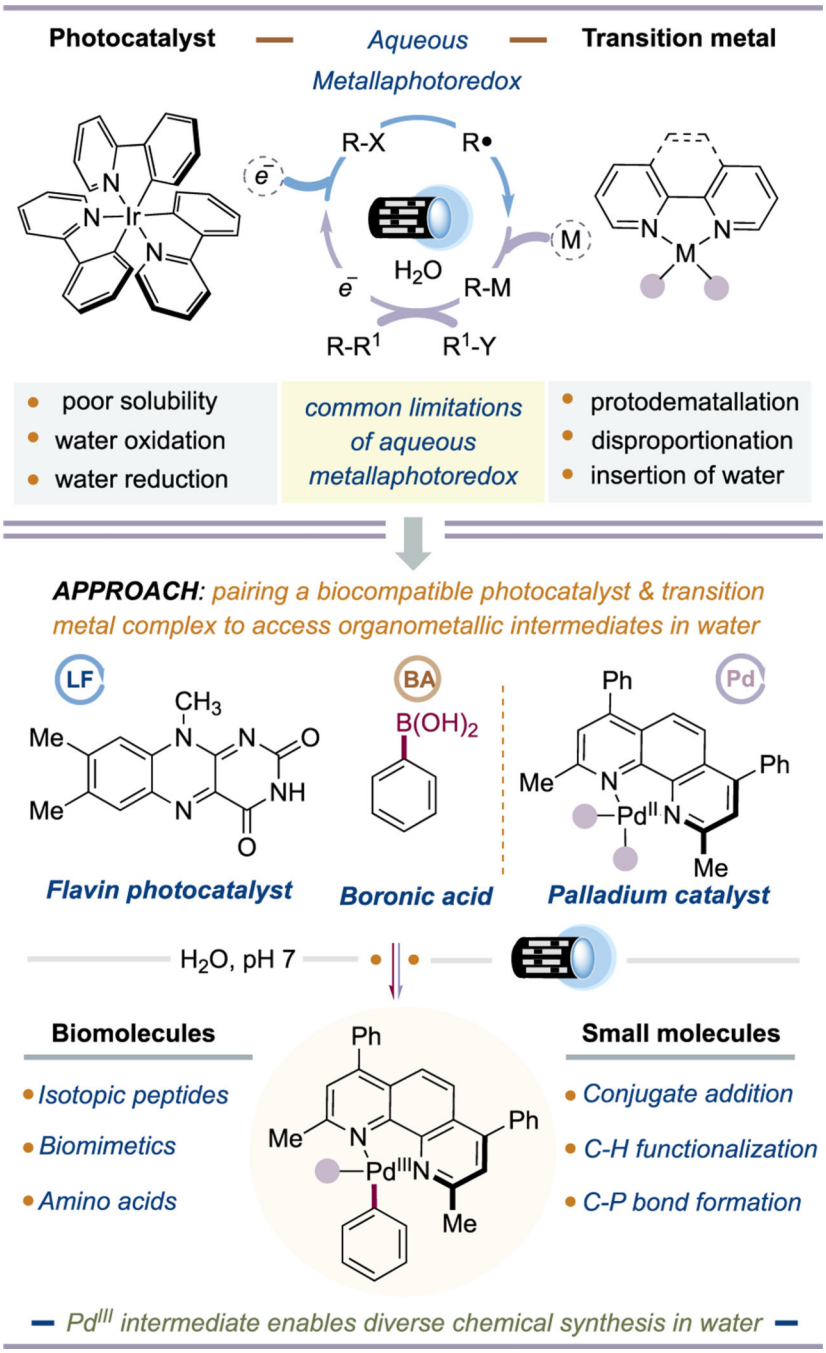


Figure 1.
Hypothesis for the flavin metallaphotoredox reaction.

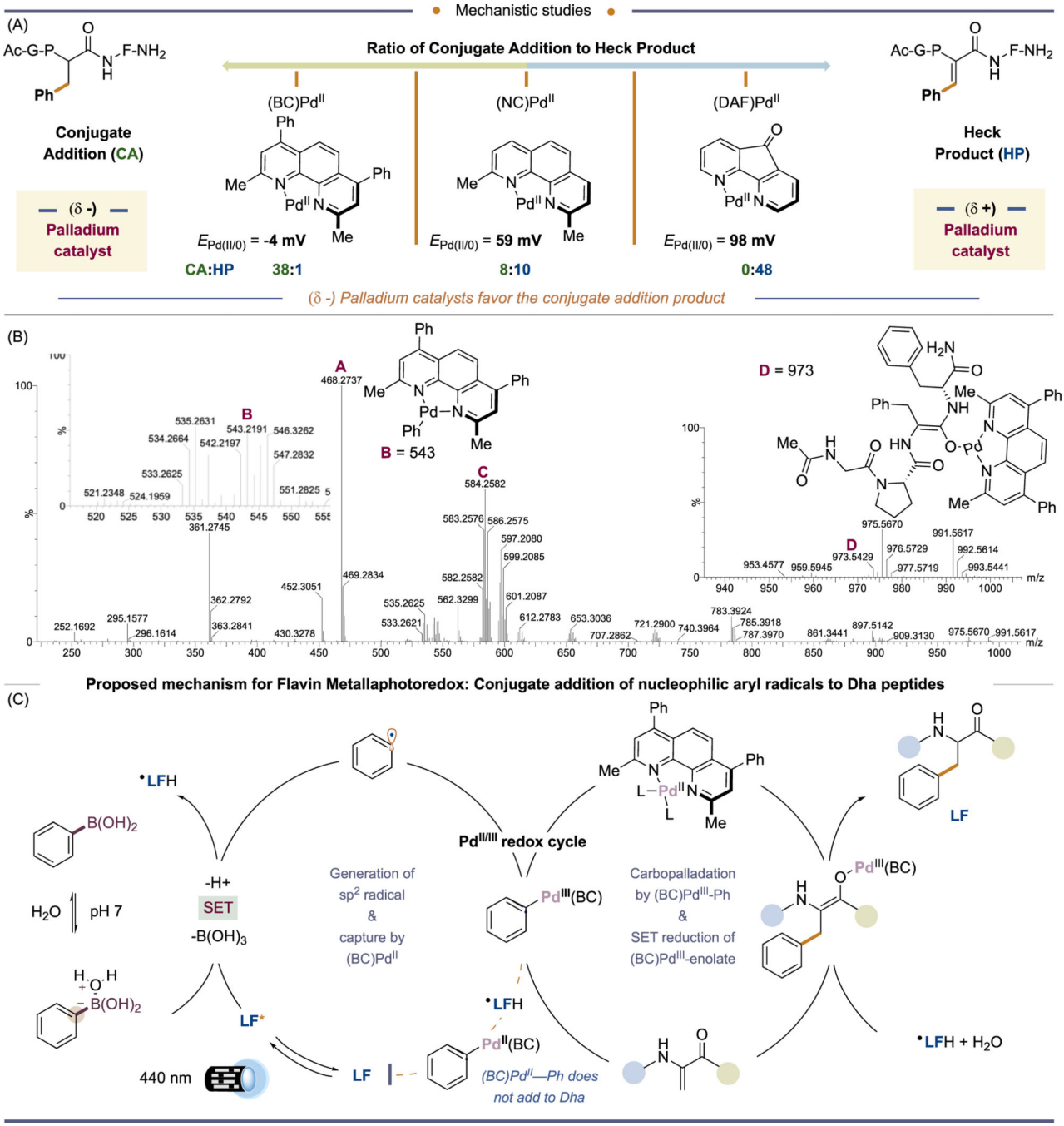
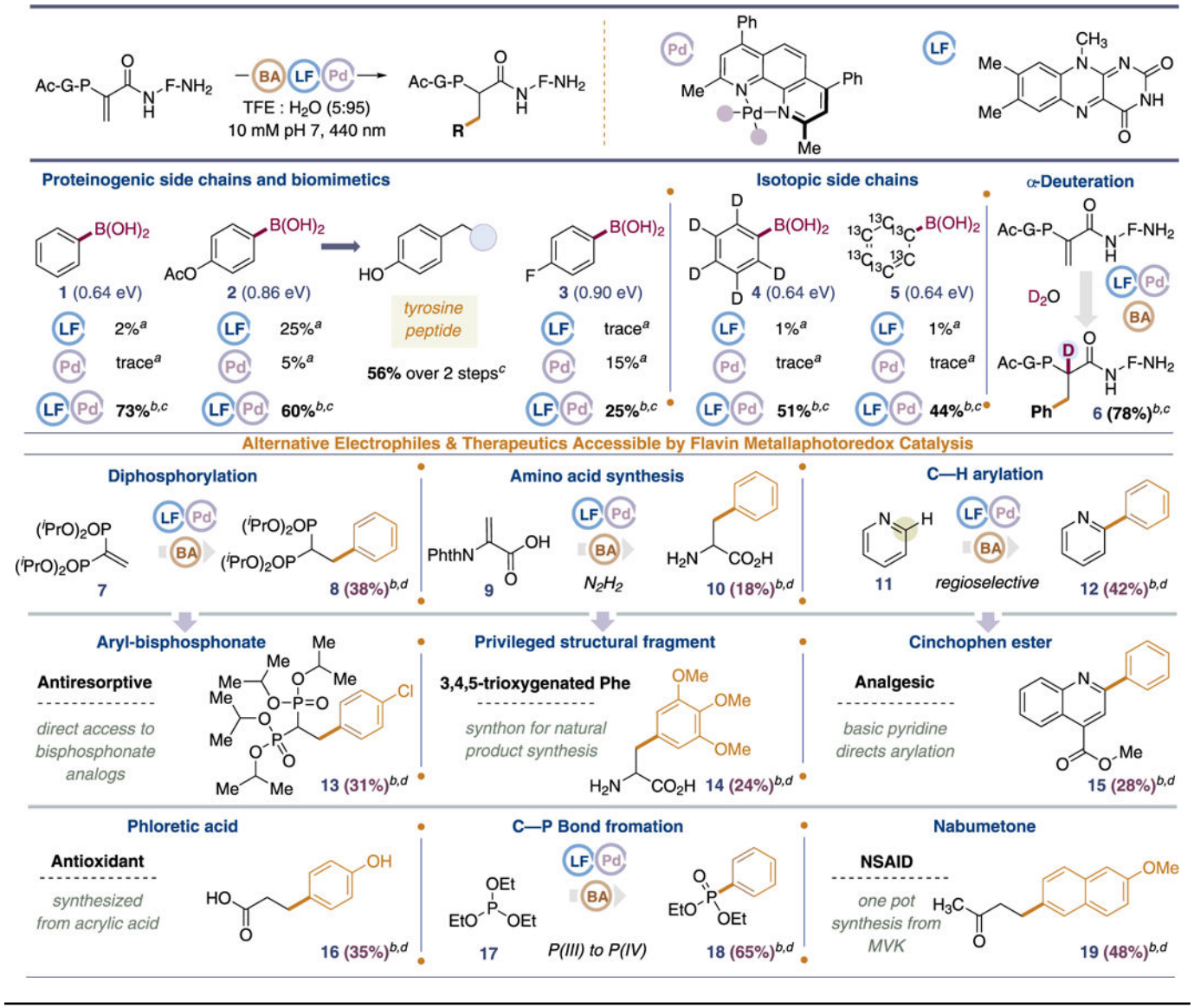


Figure 2.

(a) Effect of ligand coordination to palladium on the selective conjugate addition vs Heck product. (b) ESI-MS spectra of crude reaction mixture. (c) Proposed mechanism for the flavin metallaphotoredox reaction.

Table 1.

Scope of the Flavin Metallaphotoredox Platform[†]



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[†]All products are made from the respective boronic acids shown either as R-B(OH)$_2$ or highlighed in orange above.

[a]Reactions were performed with 0.0023 mmol peptide (1 mg), 5 equiv of phenylboronic acid, 50 mol % lumiflavin, 50 mol % Pd catalyst, 50 mol % ligand, and 10 mM phosphate buffer at overall concentration 3 mM.

[b]Reactions were performed with 0.023 mmol peptide (10 mg) or coupling partner, 5 equiv of phenylboronic acid, 50 mol % lumiflavin, 50 mol % Pd catalyst, 50 mol % ligand, and 10 mM phosphate buffer at overall concentration 3 mM.

[c]% Conversions reported.

[d]Isolated yield. Tyrosine containing peptide and compound **16** were synthesized using 4-acetoxyphenylboronic acid (**2**), followed by base hydrolysis. Compound **13**, **14**, and **19** were synthesized using their respective boronic acids, 4-chlorophenylboronic acid, 3,4,5-trismethoxyphenylboronic acid, and 6-methoxy-2-napthaleneboronic acid.