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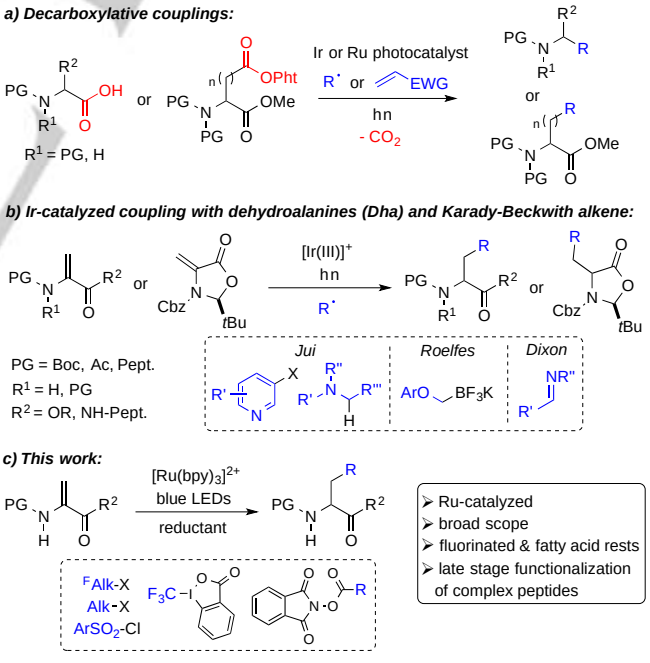
# Versatile Ru-Photoredox-Catalyzed Functionalization of Dehydro-Amino Acids and Peptides

Tobias Brandhofer, [a],[b] and Olga García Mancheño*[a]

**Abstract:** A versatile photoredox-catalyzed synthesis of unnatural amino acids and peptides is presented. Commercially available $Ru(bpy)_3(PF_6)_2$ was efficiently used as visible light photocatalyst in combination with a broad number of different types of radical precursors in the coupling with several dehydrogenated amino acid residues. This method provides new entries to the mild, selective and direct modification of both simple and complex peptide-like compounds towards novel structures with improved or unusual properties. Hence, (fluorinated)alkyl halides, arylsulfonyl chlorides or various *N*-(acyloxy)phthalimides (NHPI esters) were effectively reacted with a series of natural and unnatural α,β-dehydroamino acids and dipeptides. Moreover, the applicability of the process was also proved by the late stage functionalization of the naturally occurring peptide thiostrepton.

Amino acids and peptides play a key role in chemistry and biology, being important chiral building blocks for the construction of biomolecules, as well as synthetic catalysts and drugs.[1] Moreover, they present an unlimited potential for the discovery of new bioactive targets with extremely diverse activities upon chemical alteration of their structures. However, there are still substantial challenges in peptide drug design,[2] for which the straightforward modification of naturally occurring amino acid residues would overcome some of these constraints. As a consequence, catalytic site-selective functionalization methods of amino acids and peptides under mild, biocompatible conditions towards novel drug candidates and therapeutics are of current growing demand.

In this regard, visible-light photoredox catalysis has recently emerged as a powerful strategy for the activation of organic molecules under mild conditions, while enabling unprecedented transformations.[3] Indeed, due to its mildness, photocatalysis presents an intrinsic large functional group tolerance, being compatible with highly functionalized compounds such as amino acids or peptides.[4] Based on this, several procedures for the photocatalytic modification of amino acid derivatives have been recently developed. Besides the derivatization of functional groups of amino acid residues such as sulfur-containing cysteine[5] and methionine[6] or aromatic rests such as in tyrosine[7] and tryptophan,[8] an interesting alternative approach is based on decarboxylative couplings (Figure 1a).[9] In this case, the amino acid structure is lost[9b,c] or aspartic or glutamic acid units suffer the decarboxylation/functionalization at the side-chain,[9d] which limit their general application. More recently, the photoredox catalyzed cross-coupling of α,β-dehydroamino acid derivatives, such as dehydroalanine (Dha), have attracted a great attention (Figure 1b).[10] α,β-Dehydroamino acids are naturally occurring non-coded amino acids present in a large number of peptides.[11] They are very useful synthetic building blocks for the synthesis of unnatural amino acids and peptides, since they allow the coupling with different radicals at their olefinic moieties. Thus, pioneer work employing iridium(III) photoredox catalysis has been made in this field in the past few years. However, these methods are restricted to the Karady-Beckwith alkene[10a,b] or, for the more valuable acyclic α,β-dehydroamino acids, to the use of halopyridines,[10a] *N*-alkyl tertiary amines,[10b] potassium phenoxymethyl trifluoroborates[10c] and imines[10d] as radical precursors and/or coupling partners. Aiming at a more general and less costly method, we herein present a ruthenium(II) photoredox-catalyzed functionalization of dehydroamino acids and peptides with a broad variety of alkyl radical precursors, which allows to easily introduce fluorinated and fatty acid-derived chain groups, as well as carrying on late stage peptide functionalization (Figure 1c).




**Scheme 1.** Visible Light photocatalytic functionalization of amino acid derivatives.

We started our study by optimizing the reaction of dehydroaniline **1a** as model substrate with $CBrCl_3$ as radical precursor using 2 mol% of commercially available $Ru(bpy)_3(PF_6)_2$ as photoredox catalyst in a blue LED's photoreactor at room temperature (Table 1, see S.I. for the complete screening). Several common reducing agents such as diisopropylethylamine

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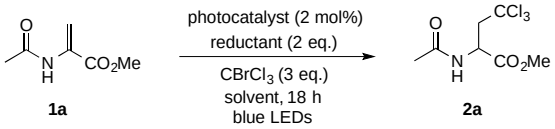
(DIPEA), 1-benzyl-1,4-dihydronicotinamide (BNAH) or the Hantzsch ester (HE) were initially tested in acetonitrile as solvent (entries 1-3). Among them, the Hantzsch ester showed the best performance, providing the desired coupling product **2a** in a good 59% yield (entry 3). This result could be enhanced when using $H_2O$ as co-solvent (65%, entry 4). Under these conditions, a similar good 64% yield was obtained with the N-methyl HE (entry 5), which facilitated in this case the purification of the product. Instead, the absence of the Ru-catalyst or use of the organophotocatalyst Eosin Y[12] provided lower conversions (entries 6 and 7). Moreover, other solvent mixtures (entries 8-9), as well as by carrying out the reaction under air atmosphere (entry 10) or without reductant and/or light irradiation (entry 11), led to low amounts of **2a** or no reaction.

**Table 1.** Screening of the reaction conditions with **1a** as model substrate.[a]

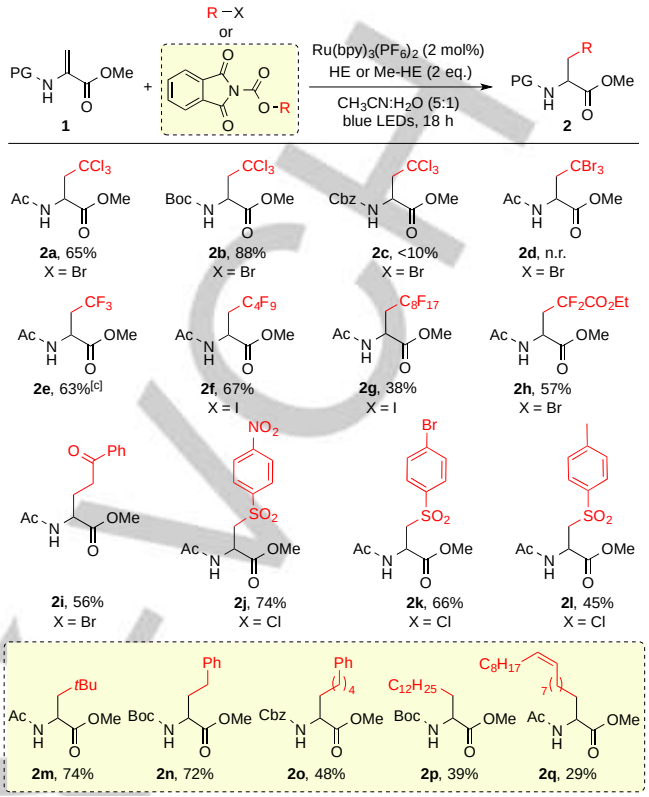



| Entry | Catalyst | Red. | Solvent | Yield (%)[b] |
|---|---|---|---|---|
| 1 | $Ru(bpy)_3(PF_6)_2$ | DIPEA | MeCN | 37 |
| 2 | $Ru(bpy)_3(PF_6)_2$ | BNAH | MeCN | 55 |
| 3 | $Ru(bpy)_3(PF_6)_2$ | HE | MeCN | 59 |
| 4 | $Ru(bpy)_3(PF_6)_2$ | HE | MeCN/$H_2O$ (5:1) | 65 |
| 5 | $Ru(bpy)_3(PF_6)_2$ | Me-HE | MeCN/$H_2O$ (5:1) | 64 |
| 6 | -- | HE | MeCN/$H_2O$ (5:1) | 4 |
| 7 | Eosin Y | HE | MeCN/$H_2O$ (5:1) | 17 |
| 8 | $Ru(bpy)_3(PF_6)_2$ | HE | MeOH/$H_2O$ (5:1) | 35 |
| 9 | $Ru(bpy)_3(PF_6)_2$ | HE | DMSO/$H_2O$ (5:1) | 57 |
| 10 | $Ru(bpy)_3(PF_6)_2$ | HE | MeCN/$H_2O$ (5:1) | 16[c] |
| 11 | $Ru(bpy)_3(PF_6)_2$ | -- | MeCN/$H_2O$ (5:1) | --[d] |

[a] Conditions: Photocatalyst (2 mol%), **1a** (0.2 mmol, 1 eq.), HE or Me-HE (0.4 mmol, 2 eq.) and $CBrCl_3$ (0.6 mmol, 3 eq.) were reacted at r.t. for 18 h. [b] Isolated yield. [c] Reaction under air. [d] Reaction without reductant or without light irradiation led to no reaction or traces of **2a**.

Having identified the optimal reaction conditions ($Ru(bpy)_3(PF_6)_2$ as catalyst and HE or Me-HE as reductant in MeCN:$H_2O$ (5:1) at room temperature for 18 h), the scope of the reaction with various alkyl radical precursors was investigated (Table 2). First, different N-protected Dha derivatives were explored in the reaction with $Cl_3CBr$. Whereas the N-Boc protected Dha led to the product **2b** in an excellent 88% yield, other protecting groups such as Cbz proved less effective. Choosing **1a** as model substrate for next studies, analogous trihalogenated C1-precursors were reacted. Under these conditions, $CBr_4$ did not participate in the reaction, while Togni's reagent (1-trifluormethyl-1,2-benziodoxol-3(1*H*)-on)[13] delivered

**Table 2.** Reaction scope with dehydroamino acids **1**.[a],[b]




[a] Conditions: $Ru(bpy)_3(PF_6)_2$ (2 mol%), **1** (0.2 mmol, 1 eq.), HE or Me-HE (0.4 mmol, 2 eq.) and the coupling partner (0.6 mmol, 3 eq.) were reacted in MeCN/$H_2O$ (5:1) at r.t. for 18 h. [b] Isolated yield. [c] Togni's reagent was used.

the corresponding trifluoromethylated product **2e** in a good 63% yield. Fluorinated alkylhalides with various chain lengths were effectively enrolled under the standard reaction conditions. The desired coupling products **2f-h** were obtained in moderate to good yields (38-67%), depending on the introduced chain (i.e. longer chains led to lower conversions).[14] Other alkylhalides bearing carbonyl groups, as well as arylsulfonyl chlorides, were employed as radical precursors, leading to the corresponding alkylated and sulfonylated products **2i** and **2j-l**, respectively. Finally, a series of *N*-(acyloxy)phthalimides (NHPI esters)[15] with branched (*t*Bu, product **2m**) and linear rests (products **2n-q**) were also efficiently coupled, including the more challenging reaction with derivatives from fatty acids and olefin-containing moieties.

This method was then extended to other natural and unnatural amino acids such as dehydro-2-methyl-β-alanine, dehydrophenylalanine and dehydrobutyrine derivatives (Scheme 2, top). In all these cases presenting a substituted olefin group, we could observe an important steric effect, which notable hindered the reaction with $CBrCl_3$ (e.g. **3a**, 15%). Therefore, to overcome this issue, the reactions were performed with $EtO_2CCF_2$-Br as coupling partner, leading then to the desired products **3b**, **4** and **5** in good yields (up to 91%). Furthermore, an itaconic acid derivate and dipeptides with dissimilar substitution pattern and protecting groups were also effectively alkylated to the corresponding products **6** and **7a-b** with moderate to good diastereomeric ratios. Finally, this method was also employed for the late stage

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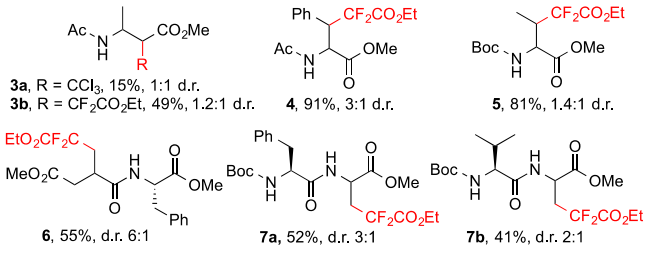
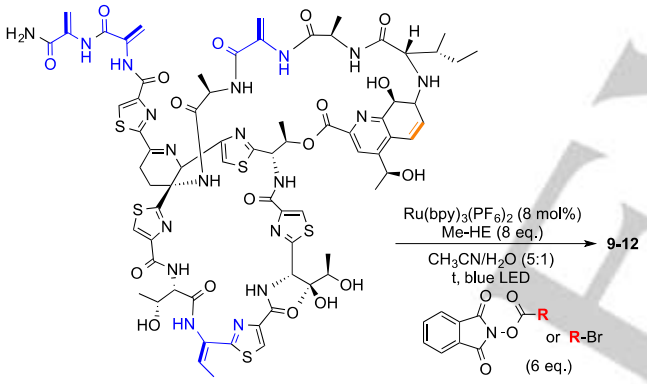
functionalization of a naturally occurring peptide such as the natural cyclic oligopeptide antibiotic thiostrepton (**8**),[16] which present four dehydroamino acid residues (in blue) and a further unreactive cyclic olefin in its structure (orange) (Scheme 2, bottom). In this case, a different product distribution could be obtained by varying the stoichiometries of the reactants and, especially, the reaction time. Thus, in the reaction with the *tert*-butyl NHPI ester we could observe a low conversion of **8** into the mono to tri-alkylated derivatives **9-12** (entry 1), while by increasing the reaction time to 18 or 36 h favored the formation of the tri- (**11**) and tetra-substituted (**12**) products, respectively (entries 2 and 3). Similarly, the 18 h reaction with $EtO_2CCF_2$-Br (entry 4) led to a product distribution in favor of the tri-substituted products **11** (43%).



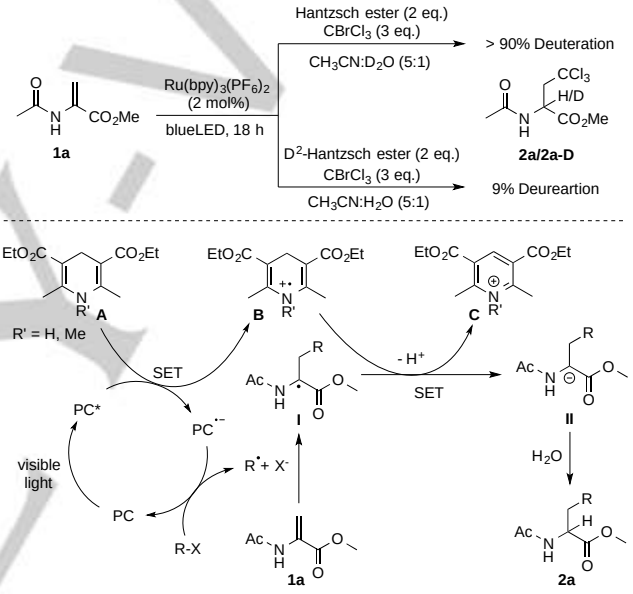

*Product Distribution*[b]

| Entry[a] | R | time (h) | SM (**8**) | mono (**9**) | di (**10**) | tri (**11**) | tetra (**12**) |
|---|---|---|---|---|---|---|---|
| 1 | *t*Bu | 8 | 75 | 4 | 6 | 15 | 0 |
| 2 | *t*Bu | 18 | 14 | 13 | 18 | 40 | 15 |
| 3 | *t*Bu | 36 | 7 | 17 | 12 | 19 | 45 |
| 4 | $CF_2CO_2Et$ | 18 | 41 | 4 | 10 | 43 | 2 |

[a] Conditions: Ru-catalyst (8 mol%), **8** (0,02 mmol, 1 eq.), Me-HE (0.16 mmol, 8 eq.) and *t*Bu-NHPI ester or $EtO_2CCF_2$-Br (0.12 mmol, 6 eq.) were reacted in MeCN/$H_2O$ (5:1) at r.t. [b] Product distribution analyzed by MS (MALDI-TOF).

**Scheme 2.** Functionalization of different dehydroamino acids and peptides.

Lastly, in order to get some insights into the mechanism of this transformation, deuteration and quenching studies were carried out. Hence, whereas the use of $D_2O$ as co-solvent led to a >90% of deuteration, the deuterated labelled Hantzsch ester provided the product within a low 9% of deuteration level (Scheme 3, top). Furthermore, a notable fluorescence quenching of the catalyst was observed with the Hantzsch ester (Figure 1), not being significant for the α,β-dehydroamino acid **1a** (see S.I. for the complete quenching study).[17,18] Moreover, the quantum yield was determined as 0.4 (see S.I.), which suggests that the main pathway does not involve a radical chain propagation process (Φ ≤1). Based on these observations and previous reports in the literature,[19] a plausible reaction mechanism implying a catalyst reductive quenching with the HE is outlined in Scheme 3 (bottom).[20] Accordingly, the excitation of the catalyst in its ground state $Ru(bpy)_3^{+2}$ (PC) by absorption of visible light generates the photoexcited state PC*. The PC* is able to oxidize the Hantzsch ester (**A**) by a single electron transfer (SET) to form the HE-radical cation (**B**) and the reduced catalyst $PC^{-\bullet}$. The $PC^{-\bullet}$ species reacts then with the reagent partner R-X, forming the radical intermediate R• and regenerating the photocatalyst PC in its ground state. The generated carbon radical adds to the double bond of the α,β-dehydroamino acid **1a** to form the radical **I**. Then, a SET from the HE-radical cation to **I** led to the anionic intermediate **II** and the pyridine/pyridinium species **C**. Finally, the co-solvent $H_2O$ protonates **II** to form the product **2a**.




**Scheme 3.** Deuteration studies and proposed mechanism.

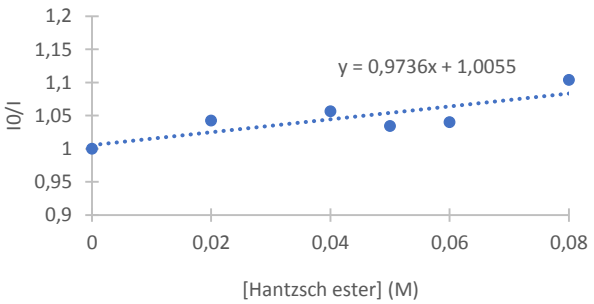



**Figure 1.** Stern-Volmer Plot: Fluorescence quenching of $Ru(bpy)_3(PF_6)_2$ ($4 \cdot 10^{-4}$ M in MeCN) with HE. $k_q = 1.09 \cdot 10^6$ $M^{-1}$ $s^{-1}$.

In conclusion, we have developed a versatile photoredox-catalyzed synthesis of unnatural amino acids and peptides by coupling of α,β-dehydroamino amino acids and peptides with a broad number of different types of radical precursors using

commercially available $Ru(bpy)_3(PF_6)_2$ as visible light photocatalyst. Accordingly, (fluorinated)alkyl halides, arylsulfonyl chlorides or various N-(acyloxy)phthalimides (NHPI esters) were effectively reacted. Moreover, the applicability of the process was also proved by the late stage functionalization of the naturally occurring peptide thiostrepton. In addition, the determination of the quantum yield, quenching and deuterium experiments were performed to enlighten the reaction mechanism. Moreover, we found that the co-solvent $H_2O$ is more prompt than the HE to participate in the final protonation step.

## Experimental Section

***General catalytic procedure:*** In a screw cap vial, $Ru(bpy)_3(PF_6)_2$ (3.4 mg, 0.004 mmol, 2 mol%), dehydroamino acid **1** or peptide (0.2 mmol, 1 eq.), HE or Me-HE (0.4 mmol, 2 eq.) and the coupling partner **2** (0.6 mmol, 3 eq.) were added and the vial was degassed three times by evacuating and refilling with Argon. 2 mL of a 5:1 mixture of $MeCN/H_2O$ was added and the vial was degassed by three freeze-pump-thaw cycles. The reaction mixture was stirred at room temperature for 18 h under irradiation of blue light. Then, the mixture was transferred in a separation funnel and 5mL DCM and 5 mL water was added. The phases were separated and the aqueous phase was extracted three times with DCM. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography.

## Acknowledgements

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**Keywords:** Photoredox catalysis • Dehydroamino acids • Peptides • Visible light • Ruthenium

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[18] Due to solubility issues, higher concentrations as 0.08M for the HE quencher loading could not be used.

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[20] Though presenting a lower $K_q$, a fluorescence quenching of the Ru-catalyst with $Cl_3CBr$ could also be observed (see S.I.). Therefore, an alternative mechanism implying an oxidative quenching by the coupling reagent could not be excluded.

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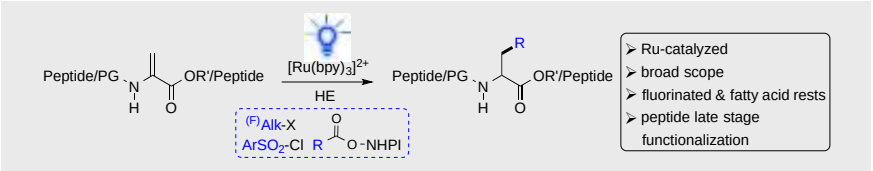
# COMMUNICATION




A versatile photoredox-catalyzed synthesis of unnatural amino acids and peptides by coupling of α,β-dehydroamino amino acids and peptides with a broad number of different types of radical precursors using commercially available $Ru(bpy)_3(PF_6)_2$ as visible light photocatalyst is presented.

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**Versatile Ru-Photoredox-Catalyzed Functionalization of Dehydro-Amino Acids and Peptides**