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# Desyl and Phenacyl as Versatile, Photocatalytically Cleavable Protecting Groups – A Classic Approach in a Different (Visible) Light

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# Desyl and Phenacyl as Versatile, Photocatalytically Cleavable Protecting Groups – A Classic Approach in a Different (Visible) Light

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**ABSTRACT:** A highly efficient, catalytic strategy for the deprotection of classical phenacyl (Pac) as well as desyl (Dsy) protection groups has been developed using visible light photoredox catalysis. The deliberate use of a neutral two-phase acetonitrile/water mixture with $K_3PO_4$ applying catalytic amounts of $[Ru(bpy)_3](PF_6)_2$ in combination with ascorbic acid is key to this truly catalytic deprotection of Pac and Dsy-protected carboxylic acids. Our mild, yet robust protocol allows for fast and selective liberation of the free carboxylic acids in very good to quantitative yields while only low catalysts loadings (1 mol %) are required. Both Pac and Dsy, easily introduced from commercially available precursors, can be applied for the direct protection of carboxylic acids and amino acids offering orthogonality to a great variety of other common protecting groups. We further demonstrate the general applicability and versatility of these formerly underrated protecting groups in combination with our catalytic cleavage conditions as underscored by the gained high functional group tolerance. Moreover, this method could successfully be adapted to the requirements of solid phase synthesis. As a proof-of-principle for an efficient visible light, photocatalytic linker cleavage a Boc-protected tripeptide was split off from commercially available Brominated Wang resin.

***KEYWORDS*** *photoredox catalysis, protecting groups, orthogonality, acids, photocleavable linker, peptide synthesis*

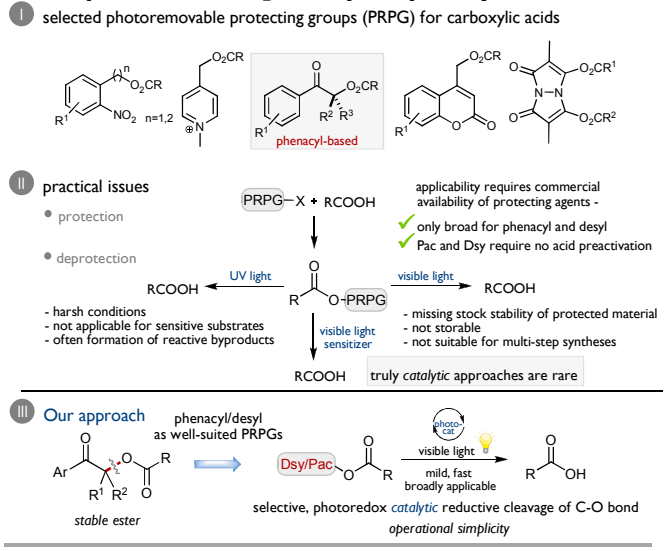
## INTRODUCTION

In organic synthesis[1] the selective control over reactivity within challenging, multifunctional complex molecular settings is of essential importance. Here, visible light photo(redox) catalysis[2] has emerged as one of the most powerful tools to selectively address single bonds by virtue of their redox properties and bond dissociation energies (BDEs). The broad compatibility to most polar groups and the intrinsic selectivity of photoredox catalytic methodology, albeit perfectly suited to offer orthogonality, has only rarely been applied for protection/deprotection manipulations,[3,4,5] for which orthogonal transformations are of crucial importance.

Despite their obvious advantages by avoiding the formation of reactive by-products[6] and the use of excess reagents and thereby meeting requirements for biological systems or cells (bioorthogonality)),[7] catalytic protecting group removals have only received limited reports.[3ac,8] The use of sensitizers (*photocatalysts*) can also shift the photochemical initiation of the deprotection to the *visible region*, e.g. by photoinduced electron transfer (PET),[9] hence offering alternative cleavage conditions to highly valuable photoremovable protecting groups (PRPG)[3bd] while bypassing the common use of UV light, that is often recognized as a typical drawback (Figure 1).[10] This approach has been advanced during the last years, but the required large excess of the corresponding sensitizers has curtailed broader applications; truly catalytic examples are only very rare.[4,5]

Falvey and co-workers initiated studies for PET-mediated photodeprotection for the cleavage of Pac-groups with a 400 W Xe- or Hg lamp in the presence of *superstoichiometric* amounts of a photosensitizer.[11] Later, they also studied *N*-alkyl-picolinium (NAP) protecting groups for carboxylic acids, albeit again with excess of sensitizer (50 to 100 mol %) and donors.[12] The Boncella group then developed a first catalytic protocol for NAP-carbamate release.[4a]

**Figure 1. General strategies for the deprotection of photoremovable protection groups (PRPGs) for carboxylic acids (Pac =phenacyl, Dsy = *desyl*).**




Thus, further improvements towards efficient, mild and operationally simple means of orthogonal, visible light *catalytic* deprotection are greatly desirable.

Herein, we report the deliberate development of a highly selective, photoredox catalytic cleavage protocol for facilely introduced, established protecting groups for ubiquitous carboxylic acids,[13] tolerating a great variety of functional groups. We initially decided to focus on arylcarbonylmethyl-based protecting groups for carboxylic acids for our catalytic studies; both benzoin-derived desyl (Dsy) as well as the phenacyl group (Pac) and their derivatives[14] have been employed in biological studies and synthesis since more than 50 years.[3b,d,15] Furthermore, their halogenated precursors are inex-

pensive and commercially available and yield the protected acids as stable, mostly solid material, which are soluble in all common organic solvents. Together with their identified stability against stronger acids, which offers orthogonality to a great variety of other protecting groups, we thought to develop catalytic cleavage conditions to increase the applicability of this protecting group family that has been impeded by typical deprotection protocols' harsh character.[3,16]

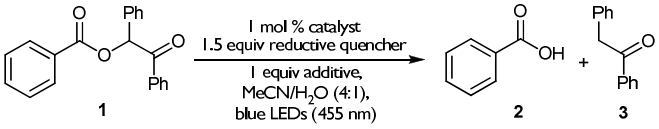
Building on our expertise in photocatalytic reductive C-O-bond cleavage,[17] we recently questioned whether a visible light, photoredox catalytic protocol could provide a novel facile deprotection alternative, tolerant to a great variety of functional groups. As a critical design element, we focused on fast and mild aqueous conditions to ensure broad applicability. Though conceptually straightforward a suitable cleavage protocol was only realized after considerable experimentation. Table 1 provides a shortened, simplified, yet instructive picture of the optimization process for Dsy-protected benzoic acid **1**.[18] We commenced our studies with $[Ru(bpy)_3]^{2+}$ as photocatalyst, starting with DIPEA as tertiary amine reductive quencher[17] (entries 1-3) affording deprotection in aqueous solvent mixtures with good yields as judged by formation of deoxybenzoin (**3**). In view of the intended broad applicability and orthogonality (potentially also for reactions in biological systems), we then turned our attention to ascorbic acid (vit. C.) as a mild and inexpensive reductant substituting rather harsh DIPEA.

While water proved essential to enable product formation (entry 4 vs. 5) the usage of $CH_3CN/H_2O$ mixtures improves the solubility of ascorbic acid, but is also related to the improved efficiency of other radical processes in aqueous solvents[19] supporting the mesolytic cleavage to the carboxylate and the corresponding α-carbonyl radical. Throughout the course of this study we observed the unique efficiency of $K_3PO_4$ as an additive (entry 6 and entries 7, 9&13). This may relate to its multiple functions within this transformation: buffering the reaction mixture leads to a rather neutral pH, the deprotonation of the ascorbic acid results in an acceleration of the reductive quench[20] and $K_3PO_4$ also effects the phase separation of the otherwise homogenous $CH_3CN/H_2O$ mixture.[21]

While the reaction itself takes place in the organic phase,[22] the two-phase-system promotes the cleavage by transfer of the deprotected acid as carboxylate into the water phase and allows for quantitative deprotection in 1 hour (entry 6). Diminished yield for $Na_2SO_4$ as phase-separating, non-basic additive (entry 9) supports the hypothesized multifunctional role of $K_3PO_4$. We also tested other common photocatalysts, such as eosin Y,[23] often used as organic dye surrogate for $[Ru(bpy)_3]^{2+}$ in reductive processes, as well as $[Ir(dtbbpy)(ppy)_2]PF_6$.

While the Ir photocatalyst performed well with both reductive quenchers (entries 3 and 7), eosin Y failed to promote this transformation (entry 8).[23c] Furthermore, control experiments demonstrated that the reaction requires photocatalyst, visible light and ascorbic acid (entries 10-12), albeit revealing a weak background reaction without catalyst after *24 h of irradiation*.

**Table 1. Optimization of reaction conditions.**



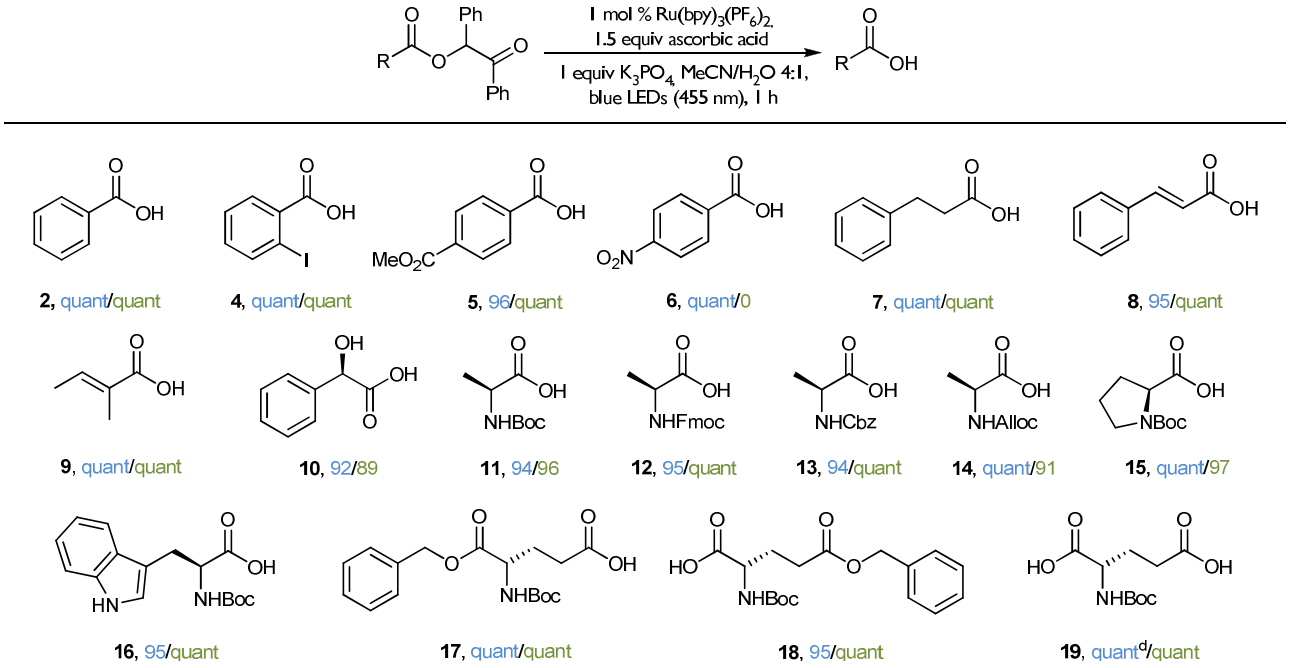

| entry[a] | photocatalyst | reductive quencher | additive | yield[b] of **3** |
|---|---|---|---|---|
| 1 | $Ru(bpy)_3(PF_6)_2$ | DIPEA | – | 78% |
| 2[c] | $Ru(bpy)_3(PF_6)_2$ | DIPEA | – | 77% |
| 3[c] | $[Ir(dtbbpy)(ppy)_2]PF_6$ | DIPEA | – | 91% |
| 4[d] | $Ru(bpy)_3(PF_6)_2$ | vit. C. | – | 0% |
| 5 | $Ru(bpy)_3(PF_6)_2$ | vit. C. | – | 9% |
| 6 | $Ru(bpy)_3(PF_6)_2$ | vit. C. | $K_3PO_4$ | 100% |
| 7 | $[Ir(dtbbpy)(ppy)_2]PF_6$ | vit. C. | $K_3PO_4$ | 91% |
| 8[e] | eosin Y | vit. C. | $K_3PO_4$ | 2% |
| 9 | $Ru(bpy)_3(PF_6)_2$ | vit. C. | $Na_2SO_4$ | 39% |
| 10[f] | – | vit. C. | $K_3PO_4$ | 17% |
| 11[g] | $Ru(bpy)_3(PF_6)_2$ | vit. C. | $K_3PO_4$ | 0% |
| 12[f,h] | $Ru(bpy)_3(PF_6)_2$ | — | $K_3PO_4$ | 2% |
| 13[i] | $Ru(bpy)_3(PF_6)_2$ | vit. C. | $K_3PO_4$ | 95% |

[a] conditions: 0.5 mmol 1, 1 mol % $Ru(bpy)_3(PF_6)2$, 0.75 mmol ascorbic acid, 0.5 mmol $K_3PO_4$ in 3 ml $MeCN/H_2O$ 4:1, irradiated with blue LEDs (455 nm), 1 h, rt; [b] yields determined by GC-FID with mesitylene as internal standard; [c] DMF/$H_2O$ 10:1 was used as solvent; [d] acetonitrile as solvent without water; [e] irradiated with green LEDs (530 nm); [f] 24 h of irradiation; [g] reaction without light, 24 h; [h] reaction without ascorbic acid (vit. C), 24 h; [i] irradiated with a 23 W CFL household lamp for 5 h.

To assess the general feasibility of the catalytic deprotection we also tested alternative light sources: the reaction performs equally well if irradiated with a normal CFL household lamp providing excellent yields after an increased reaction time of 5 h (entry 13). Notably, the optimal combination of catalyst and additives does not require any special experimental precautions. Our optimization results to allow for both fast and complete bond cleavage with a minimal amount of catalyst (1 mol %) showcase the often underrated importance of conditions for the outcome of photoredox catalytic transformations.[24]

With this optimized conditions in hand we investigated the scope of a protection/deprotection sequence for both our target Dsy and Pac protecting groups starting with different desyl caged carboxylic acids (Scheme 1). A great variety of aliphatic, aromatic and amino acids can be successfully employed, illustrating mildness and functional group tolerance likewise.

**Scheme 1 Substrate Scope for the protection[a] and catalytic deprotection[b] with desyl (Dsy) as protecting group.[c]**



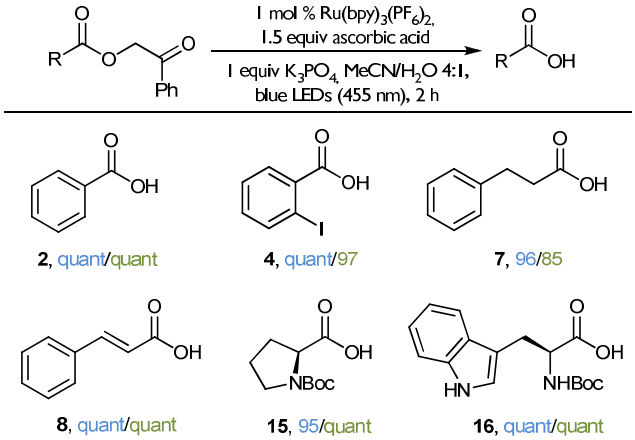

[a] Conditions: for carboxylic acid protection: 1.0 mmol carboxylic acid, 1.1 mmol desyl bromide, 5.0 mmol DIPEA in 4 mL acetone; [b] standard deprotection conditions: 0.5 mmol Dsy-protected carboxylic acid, 1 mol % $Ru(bpy)_3(PF_6)_2$, 0.75 mmol ascorbic acid, 0.5 mmol $K_3PO_4$ in 3 ml $MeCN/H_2O$ 4:1, irradiated with blue LEDs, rt, 1 h; [c] yield of isolated protected acid and deprotection product; [d] 2.2 mmol desyl bromide and 10 mmol DIPEA were used.

Protection with desyl bromide furnishes all tested Dsy-derivatives in excellent to quantitative yield as easy to isolate, stable solids with great stock stability that are readily detected with simple TLC, GC or HPLC experiments. The catalytic deprotection tolerates ester groups (entry#: **5**) and free alcohols (entry#: **10**) as well as conjugated and isolated double bonds (entry#: **8**, **9** and **14**) without any isomerization or problems of competitive reduction during the photoreductive process, as e. g. described by Falvey[11a] for **Pac-9**. Notably, the efficiency of the reaction sequence was not impeded by large *ortho* substituents on the aryl ring (entry#: **4**), demonstrating the great applicability despite the size of the Dsy protection group. Additionally, the Ru-catalyzed cleavage is selective for the targeted C–O bond fission leaving the $C_{Ar}$–I bond (entry#: **4**) untouched.[25]

Furthermore, amino acids including rather sensitive exemplars such as tryptophan **16** can be readily protected/deprotected using our standard protocol. Importantly, in view of the sought orthogonality, commonly used protecting groups, such as Boc (entry#: **11**, **15-19**), Fmoc (entry#: **12**), Cbz (entry#: **13**) and Alloc (entry#: **14**) were left unaffected during both our protection and deprotection procedure. As shown for L-Cbz-Ala-OH (**13**) the stereocenter of the amino acid also remains unscathed during the sequence.[26] Interestingly, the double deprotection of bis-Dsy-glutamate **Dsy$_2$-19** to **19** could also be effected in quantitative yields employing the same amount of catalyst and additives as used per single deprotections of the monobenzyl esters **Dsy-17** and **Dsy-18**. Due to competing electron transfer with $Ru(bpy)_3^{2+}$ easily reducible aryl nitro groups[11a] (entry#: **6**, no product within 1 h) are one of the few current limitations for our conditions.

We next examined the generality of our protection and deprotection protocol for the phenacyl (Pac) group (Scheme 2).

**Scheme 2 Protection[a] and catalytic deprotection[b] with Phenacyl (Pac).[c]**

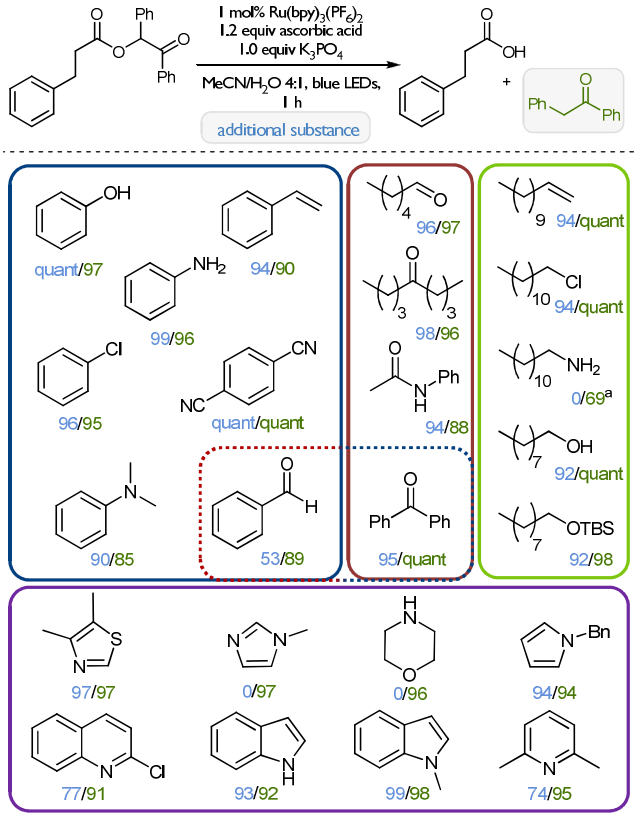



[a] Conditions: for carboxylic acid protection: 1.0 mmol carboxylic acid, 1.1 mmol phenacyl bromide, 5.0 mmol DIPEA in 4 mL acetone; [b] standard deprotection conditions: 0.5 mmol Pac-protected carboxylic acid, 1 mol % $Ru(bpy)_3(PF_6)_2$, 0.75 mmol ascorbic acid, 0.5 mmol $K_3PO_4$ in 3 ml $MeCN/H_2O$ 4:1, irradiated with blue LEDs, rt, 2 h; [c] yield of isolated protected product and deprotected product.

Catalytic conditions as established for desyl derivatives could conveniently be transferred without any conditional changes, except for an increased reaction time of 2 h instead of 1 h, hence again illustrating the broad applicability. Yields obtained for protection as well as deprotection were uniformly excellent to quantitative showing no considerable performance difference as compared to the corresponding Dsy-derivatives.

To further prove the orthogonality and mildness of our optimal deprotection conditions beyond the demonstrated substrate scope we carried out a diversified screening to assess the functional group tolerance[27] of the protocol using desyl protected hydrocinnamoic acid as substrate (Scheme 3).[28] Therefore, we tested our standard conditions against a broadly designed matrix of 24 different substances, including aromatic compounds of varying electronic nature, heterocycles (including such with basic and nucleophilic character), carbonyl derivatives and functionalized alkyls bearing typically reactive functional groups potentially being present in natural product synthesis (Scheme 3).

**Scheme 3 Functional group tolerance survey for desyl as a protecting group checking for arenes, carbonyl compounds, functionalized alkyls and heterocycles.**

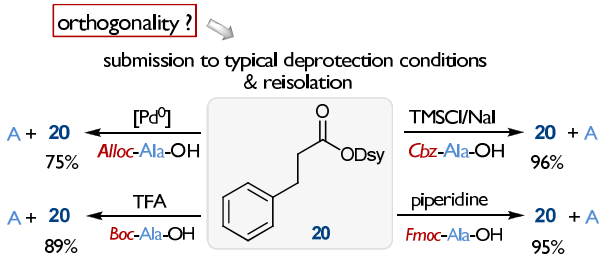



Conditions: 0.25 mmol desyl-protected hydrocinnamic acid, 0.25 mmol additional substrate, 1 mol % $Ru(bpy)_3(PF_6)_2$, 0.38 mmol ascorbic acid, 0.25 mmol $K_3PO_4$ in 1.5 ml $MeCN/H_2O$ 4:1, irradiated with blue LEDs, RT, 1 h; yields of remaining additional substrate/deoxybenzoin determined by GC-FID with mesitylene as internal standard. [a] Yields could be higher; reaction mixture builds slurry suspension upon addition of alkylamine.

For a reliable quantification of the products by GC-FID deoxybenzoin (**3**) was used as detection target instead of the free hydrocinnamoic acid. Notably, as shown in scheme 3, none of the examined additive substrates had a considerable influence on the deprotection reaction. Deoxybenzoin (**3**) could be detected in excellent to quantitative yield in all examples. The concurrent identification of the remaining additive substrates also emphasize that the catalytic cleavage conditions are extremely mild and selective. Apart from benzaldehyde every tested aromatic and carbonyl additive withstand the reaction in excellent to quantitative yields and the functionalized alkanes could be redetected in excellent yields as well, which further testifies to the robustness of the cleavage reaction. Notably, the mildness and selectivity of our aqueous conditions allow for the presence of both competitive electron acceptors (dicyano benzene) and electron donors (dimethyl aniline), which persist during successful Dsy and Pac[28] deprotection. Only basic amines, such as alkylamines and heterocycles like morpholine and imidazole, proved to be more challenging: their considerable solubility in water as well as potential salt formation prevents proper GC-based detection in the used two-phase system. Chloroquinoline and 2,6-lutidine were also present in both phases and hence could not be detected properly, accounting for the lower amount of detected additive.

Furthermore, we performed orthogonal deprotections for the most common protecting groups Alloc, Cbz, Boc and Fmoc in the presence of Dsy-protected hydrocinnamoic acid (**20**) to assess its stability under these conditions (Scheme 4).[29] With yields from 75% to 96% of reisolated desyl ester **20**, we were able to demonstrate the stability of typical desyl esters against TFA (Boc deprotection);[3a] piperidine (Fmoc deprotection)[3a] TMSCl/NaI (Cbz deprotection)[30] and $Pd(PPh_3)_4$/$TMSNEt_2$ (Alloc deprotection).[31]

**Scheme 4: Verification of orthogonality towards commonly used protection group families (Alloc, Cbz, Boc and Fmoc; A = H-Ala-OH).**[32]

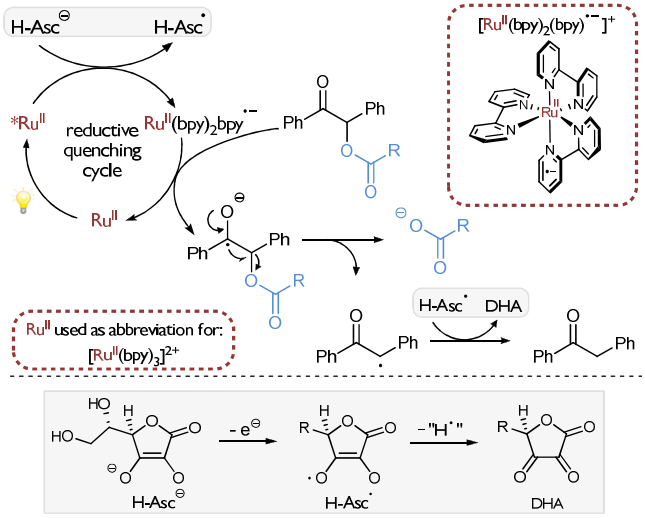



[a] Conditions: for carboxylic acid protection: 1.0 mmol carboxylic acid, 1.1 mmol phenacyl bromide, 5.0 mmol DIPEA in 4 mL acetone; [b] standard deprotection conditions: 0.5 mmol Pac-protected carboxylic acid, 1 mol % $Ru(bpy)_3(PF_6)_2$, 0.75 mmol ascorbic acid, 0.5 mmol $K_3PO_4$ in 3 ml MeCN/H2O 4:1, irradiated with blue LEDs, rt, 2 h; [c] yield of isolated protected product and deprotected product.

The proposed catalytic cycle for the photocatalytic deprotection based on a mesolytic C-O bond cleavage is outlined in Scheme 5.[17] The reductive quenching of

photoexcited $Ru(bpy)_3^{2+*}$ is effected with ascorbate ($H\text{-}Asc^-$) as reductive quencher. Upon single electron reduction (SET) of the carbonyl group the photocatalyst is regenerated; the generated ketyl radical anion undergoes mesolytic C-O bond cleavage to release the protected carboxylic acid as carboxylate into the aqueous phase. Both the two-phase system as well as supported by the CV data of phenacyl acetate ($E_{1/2}$ = -1.74 V vs SCE)[33] predicting an endergonic SET step from Ru(I) (≙ $[Ru(II)bpy_2bpy^{\bullet-}]$; $E_{1/2}$ = -1.33 V vs SCE)[2b] suggest a more complex mechanism, where ascorbic acid may play a dual role as both reductive quencher and LUMO-lowering, respectively PCET[34] activator of the carbonyl group. Hydrogen atom abstraction (HAT) from radical $H\text{-}Asc^{\bullet}$ finally yields deoxybenzoin and dehydroascorbic acid (DHA).

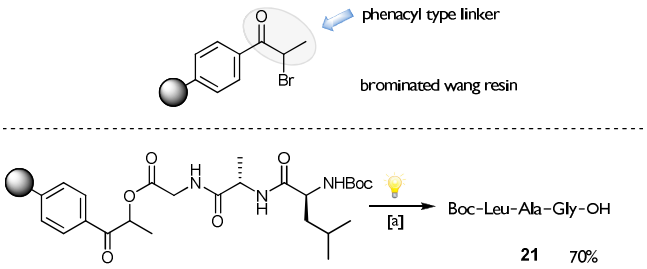
**Scheme 5: Proposed mechanism.**




Based on the consideration of linkers[35] as "immobilized protecting groups" and the increasing interest of carbohydrate chemistry, nucleotide and peptide synthesis in practical photocleavable linker strategies, we decided to further exemplify the versatility of our photocatalytic deprotection protocol. Using well-known and commercially available polystyrene-based Brominated Wang resin[36a] with its structural analogy to Pac protecting groups as test system, we sought to expand our cleavage conditions to typical requirements of solid phase synthesis. Apart from changing the solvent to a DMF/$H_2O$ mixture offering improved swelling properties, employment of $[Ir(dtbbpy)(ppy)_2]PF_6$ together with DIPEA as reductive quencher (see table 1, entry 3) led to improved stability of the catalytic system.

The practicability of these adjusted cleavage conditions was examined using tripeptide Boc-Leu-Ala-Gly-OH **21** which was synthesized on Brominated Wang resin following a Boc-strategy.[33] Unlike to the known UV cleavage protocol[36a] complete cleavage from the resin could be achieved after only 6 h of irradiation under mild conditions; the Boc-protected tripeptide **21** was isolated with a good yield of 70% (Scheme 6).[33]

**Scheme 6: Photocatalytic cleavage protocol for Brominated Wang resin.**




[a] Conditions: Cleavage conditions: 0.25 mmol loaded resin, 0.75 mmol DIPEA, 2 mol % $[Ir(dtbbpy)(ppy)_2]PF_6$ in 3 mL DMF/$H_2O$ 10:1, irradiation with blue LEDs, rt, 6 h.

In summary, we have developed a mild and highly selective catalytic deprotection protocol for desyl and phenacyl protected carboxylic acids tolerating a great variety of functional groups. Visible light, photoredox catalytic reductive C–O bond scission has enabled versatile, orthogonal deprotection as well as linker cleavage on solid phase support as exemplified with Brominated Wang resin. These operationally simple catalytic cleavage protocols circumvent long-lasting shortcomings of classical deprotection chemistry, avoiding harsh conditions and UV irradiation. The simple reagents, low catalyst loading and the protocol's robustness should make these methods amenable for further synthetic applications in various areas as illustrated by a tripeptide synthesis with terminal photocatalytic linker cleavage.

## EXPERIMENTAL SECTION

*General procedure for carboxylic acid deprotection*:

$[Ru(bpy)_3](PF_6)_2$ (1.0 mol %), ascorbic acid (1.5 equiv), $K_3PO_4$ (1.0 equiv) and the protected carboxylic acid (1.0 equiv) were dissolved in an $CH_3CN$ / $H_2O$ mixture (4:1 v/v; 0.17 m). The mixture was irradiated with blue LEDs at room temperature under vigorous stirring for the time indicated (Dsy: 1 h; Pac: 2 h) and was then poured into water and extracted with EtOAc (1×). The aqueous layer was acidified with aq. $KHSO_4$ (1 m) to pH 2-3 and extracted again with EtOAc (3×). The organic layers were combined and dried over $Na_2SO_4$. Following filtration the solvent was removed under reduced pressure; the residue was purified by column chromatography.

## ASSOCIATED CONTENT

**Supporting Information**. Experimental procedures and characterization data for all compounds, including copies of $^1H$ NMR, $^{13}C$ NMR (PDF).

This material is available free of charge via the Internet at http://pubs.acs.org.

## AUTHOR INFORMATION

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### Funding Sources

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