Tyrosine and Drug-like Late-stage Benzylic Functionalization via Photoredox Catalysis

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Article

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Abstract

Visible light mediated late-stage functionalization is a rising field in synthetic and medicinal chemistry, allowing the fast and diversified modification of valuable, potentially therapeutic compounds such as peptides. However, there are relatively few mild methodologies for the C(sp^3)-H functionalization of complex peptides. Herein, we report a visible light mediated photocatalytic protocol for the benzylic C-H modification of tyrosine and related C-H bonds. The embraced radical-cation/deprotonation strategy enables an incorporation of a wide range of valuable functional groups in high yields and chemoselectivity. The mild reaction conditions, site-selectivity and high functional group tolerance was highlighted by the functionalization of complex peptides, drugs and natural products, providing a promising synthetic platform in medicinal chemistry.

Introduction

Late-stage functionalization (LSF) of C-H bonds, which enables the incorporation of functional groups at the end of a synthesis sequence or in natural products, is an emerging field in organic synthesis and drug discovery.[1–3] The rapid access to structurally diverse chemical series has a significant impact on the time and cost consuming optimization of clinical candidates in drug discovery.[3] Nevertheless, due to the ubiquity of C-H bonds, the chemo- and site-selectivity are still major challenges in LSF.[4] Recently, LSF via photoredox catalysis has gained great attention.[5–8] In this regard, various selective photocatalyzed LSF methodologies, e.g. for the functionalization of C(sp^2)-H bonds,[9–10] α-heteroatom positions,[11–13] or decarboxylation reactions,[14–15] have been developed. However, benzylic photocatalyzed LSF is significantly underrepresented.[5] In particular, the benzylic functionalization of electron rich compounds such as in tyrosine or other phenolic drug-like derivatives is highly appealing, since this type benzylic C-H bonds are ubiquitous in biomolecules and pharmaceuticals (Fig. 1, a).[16]

A commonly used approach in photoredox C-H functionalization relies on hydrogen atom transfer (HAT),[17–25] in which a photocatalytically generated radical species is able to abstract a hydrogen atom from the substrate. However, C-H bond discrimination issues often lead to a poor site-selectivity for benzylic positions.[5] In fact, other C-H bonds like in tertiary or α-heteroatom positions are modified under similar HAT conditions, which compromises the potential for benzylic LSF.[23–26] Therefore, alternative methods to overcome the current reactivity and selectivity issues are highly demanded. On course of our research program on amino acid and peptide modification,[13,27–28] we imagined that a photocatalytic radical-cation/deprotonation strategy[29–33] could be employed as a more promising technique for the selective functionalization of tyrosine derivatives, as well as related phenolic drugs (Fig. 1, b). In this approach, a reactive radical cation is formed upon single electron transfer (SET) to the excited photocatalyst. Due to a significant increased acidity of the benzylic position in the radical cationic species (pk_A ~ − 13),[34] a deprotonation to form a benzylic radical is possible, which can then be further modified by reaction with a suitable acceptor. The selectivity of the method strongly depends on the

redox potentials of the photocatalyst and the substrate, and thus a predictable site activation can be achieved.

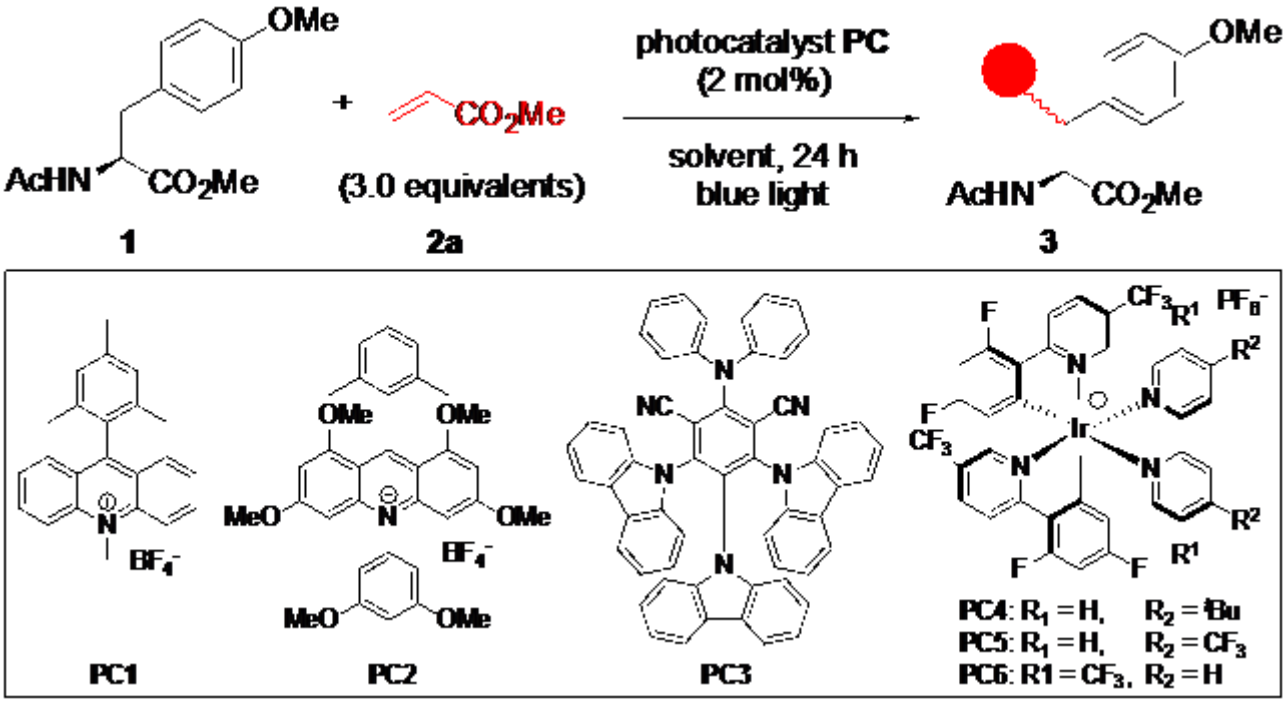
Although, this strategy has been efficiently employed in benzylic C(sp^3)-H modifications of simple substrates,[29–33] it has been long neglected for LSF.[35–37] Thus, a late-stage C-C coupling of electron-rich benzylic positions is unknown embracing this promising methodology. Taking all into account, the development of a novel site-selective LSF methodology of phenol-type structures is highly desirable as it would represent a powerful tool in synthetic and medicinal chemistry. Hence, we herein present a mild photocatalytic functionalization methodology of benzylic C-H bonds in tyrosine derivatives, which can be extended for LSF to other related C-H bonds in peptides and tyrosine-like phenolic drugs and natural products

Results

Reaction Optimization

In this regard, we started our studies with the examination of the reaction of *N*-acetyl tyrosine methyl ester (**1**, $E_{p/2}$ = + 1.58 V vs SCE in CH_3CN, see S.I.) as the model substrate with methyl acrylate (**2a**) as the radical acceptor in acetonitrile at room temperature upon irradiation with blue LEDs in a photoreactor (Table 1; see S.I. for full screening). As expected, the control experiments without catalyst and/or light were negative, illustrating the need of a photoredox catalyst (entry 1). Therefore, a preliminary screening of photocatalysts was made, showing that photosensitizers with a redox potential slightly above of the one of tyrosine were more effective. In particular, the iridium-based photocatalysts with the dCF_3bpy ligand ($E^*_{p/2}$ = +1.65 V[38] and +1.68 V[38] vs SCE for **PC5** and **PC6**, respectively) led to the best results (entries 6 and 7), while diminished conversions were obtained with the acridinium **PC2** ($E^*_{p/2}$ = +1.65 V vs SCE)[39] (entry 3). Photocatalysts with significant higher potentials like the Fukuzumi catalyst (**PC1**, +2.06 V vs SCE;[39] entry 2) or with potentials below of the tyrosine like 4-CzIPN (**PC3**, $E^*_{p/2}$ = +1.43 V vs SCE;[40] entry 4) or Ir-4,4´-dtbpy (**PC4,** $E^*_{p/2}$ = +1.21 V vs SCE;[41] entry 5) showed no conversion. Systematic reaction screening led to the identification of $[Ir(dFCF_3ppy)_2(4,4´\text{-}dCF_3bpy)]PF_6$ (**PC5**) (2 mol%) in CH_2Cl_2 (0.2 M) as the optimal system (entry 9). However, side product analysis revealed the dimerization of the tyrosine and oligomerization of methyl acrylate as major side-reactions. The observed oligomerization side reactions indicated an ineffective closing of catalytic cycle ($E_{p/2}$ = -0.79 V vs SCE).[38] Therefore, to hamper the dimerization reaction, the radical acceptor loading was increased to 5.0 equivalents (entry 10). Although only a slightly improvement in the yield (from 41 to 48%) was achieved, the formation of the dimerization product was drastically suppressed.

Table 1: Optimization studies for the benzylic C-H alkylation of tyrosine derivative 1.[a]



Entry	Photocatalyst (**PC**)	Solvent (M)	Conversion (%)[b]
1	No light or no **PC**	CH_3CN (0.1)	0
2	**PC1**	CH_3CN (0.1)	0
3	**PC2**	CH_3CN (0.1)	5
4	**PC3**	CH_3CN (0.1)	0
5	**PC4**	CH_3CN (0.1)	0
6	**PC5**	CH_3CN (0.1)	30
7	**PC6**	CH_3CN (0.1)	21
8	**PC5**	CH_2Cl_2 (0.1)	36
9	**PC5**	CH_2Cl_2 (0.2)	41
10	**PC5**	CH_2Cl_2 (0.2)	48[c]

[a] Reactions conducted using 0.05 mmol of **1** in degassed solvents and irradiated for 24 h in a HepatoChem PhotoRedOx Box. [b] Conversion determined by LC-MS. [c] 5.0 equivalents of **2a** were used.

Functionalization of tyrosine derivatives.

With the optimized conditions in hand (2 mol% **PC5** and 5.0 equiv. radical acceptor in 0.2 M CH_2Cl_2 under blue light irradiation at 20 °C), different radical acceptors were next explored with **1** as substrate (Fig. 2,

a). Aiming at further improving the conversion of this process, the more reactive radical acceptor 1,1-bis(phenylsulfonyl)ethylene (**2b**) was first explored. Pleasantly, the desired product was afforded in an excellent yield of 96% and a good diastereomeric ratio (d.r. 3:1). Moreover, no oligomerization was observed and only low amounts of difunctionalized product was formed after elongated reaction time. The configuration of the major diastereoisomer of product **3b** was determined as (2*S*,3*S*) by NOESY experiments (see S.I.). Similarly, other activated alkenes like benzylidene malonitrile (**2c**) or electron acceptors with aryl sulfonyl leaving groups **2d-f** [42-44] could be efficiently enrolled in the reaction. As a result, valuable cyano, allyl and alkynyl groups could be selectively introduced in excellent yields (up to 96%) and good diastereoselectivities (up to 6:1 d.r).

Considering the importance of orthogonal protecting group strategies in peptide chemistry,[45] the influence of different protecting groups often used in medicinal chemistry and drug-target discovery was studied next (Fig. 2, b). Alkylic *O*-protecting groups, such as methyl, *tert*-butyl or benzyl afforded the benzylic substitution products in excellent yields (**3**-**5**, up to 96%). In case of the *O*-silyl protection (TBS), a synthetically useful yield of 69% (**6b**), was observed. *N*-acyl protecting groups like acetyl or carbamates such as Boc, Fmoc or Cbz were well tolerated, leading to the desired products **7**-**9** in good yields. Additional to methyl esters, *tert*-butyl and benzyl esters were also accepted, providing the products in excellent yields (**10b** and **11b**, 87 and 91%, respectively).

The synthetic utility of the methodology was subsequently illustrated with synthesis of novel tyrosine amino acids by derivatization of the bissulfonyl product **3b** (Fig. 2, c). Tyrosine **12** was obtained in an excellent 93% yield after deprotection of the methyl ether upon addition of TMSI. Moreover, the reductive desulfonylation by the Mg/MeOH system afforded the ethyl tyrosine analogue **15** in 84% yield and with no change in the diastereomeric ratio. By fluorination of **3b** with selectfluor prior to the reduction, valuable mono-fluorinated ethyl tyrosine **16** was obtained in a good yield. The bisphenylsulfonyl group could be also converted to an ester moiety by oxidation with *m*CBPA, which cyclizes to the lactame **14**.

Functionalization of tyrosine-containing peptides

Next, the methodology was investigated for the functionalization of complex tyrosine-containing peptides (Fig. 3). In this regard, a selective tyrosine functionalization in benzylic position was obtained in good to excellent yields in peptides with up to 8 amino acid units. Other possible reactive sites like tertiary C-H bonds (Val, Ile, Leu), other benzylic positions (Phe), α-to heteroatom positions (Pro, Lys, Thr) or αC-H glycine bonds remained untouched under the applied conditions, which provides a complementary strategy to previous reported HAT functionalization approaches.[13,23,26] Noteworthy, the configuration analysis on dipeptides revealed an opposite configuration at the newly formed stereocenter compared to the single amino acid **3b**. Hence, the major isomer of the dipeptide **17b** was determined as the (2*S*, 3*R*) (see S.I.). Moreover, other alkyl and alkynyl functional groups could also be introduced in moderate to very good yields.

Late-stage benzylic functionalization of drugs

Considering that tyrosine is an important metabolic precursor,[46-48] especially in the synthesis of neurotransmitters (dopamine, adrenaline, etc.) or other secondary metabolites, we were interested in applying our methodology directly to this type of substrates (Fig. 4). To our delight, dopamine and the Parkinson drug *L*-Dopa were converted to the corresponding products **22** and **23** in excellent yields. Moreover, due to a higher observed reactivity, the amount of radical acceptor could be decreased to 3.0 equivalents.

Additionally, unnatural α-aryl substituted derivatives can also participate in this reaction upon elongated reaction times (≥72 h). Consequently, α-quaternary carbon containing compounds such as **24b** could be obtained in good yield. Furthermore, natural products like the opium alkaloid papaverine or the secondary metabolite catechin were successfully modified under these conditions, providing the alkylated products **25c** and **26b** in good to very good yields. Interestingly, the catechin analogue was obtained as a single diastereomer with exclusive functionalization of the secondary benzylic center. Aiming at a broader applicability, we further focused our attention to additional phenol moieties, which are encountered in many dugs. In this regard, blockbuster drugs, like gemfibrozil or indomethacin, and the insecticide etofenprox were transformed to the corresponding products **27**-**29** in good to excellent yields. In case of the functionalization of primary benzylic positions (gemfibrozil and indomethacin), the amount of radical acceptor was decreased to 1.1 or 1.5 equivalents in order to prevent dialkylation. Moreover, a selectivity control was also observed from the used radical acceptor. Consequently, the reaction of the sterically hindered benzyliden malonitrile (**2c**) with indomethacin showed exclusive mono-functionalization of the primary, electronically richer position (product **28c**). A similar observation was made in the modification of gemfibrozil presenting two primary benzylic positions. A favored functionalization of the more activated *ortho* over the *meta* methyl group was observed with **2c** (product **27c**). However, a small amount of the less favored *meta*-benzylic alkylation was observed with the more reactive bissulfonyl alkene **2b** (**27b**, r.r. >18:1).

Mechanistic investigation

Finally, aiming at shedding some light into the photoredox catalytic process of this reaction, mechanistic investigations were carried out. Stern-Volmer quenching experiments showed a strong interaction of the excited photocatalyst with the tyrosine derivative **1** and no quenching with the alkene **2b** (Fig. 5). Interestingly, the product **3b** was found to be a good quencher too, though no difunctionalized products could be detected. Presumably, the possible di-functionalization is suppressed due to steric effects. Additionally, a low quantum yield (F) of 0.03 was measured (see S.I.), which might most likely exclude a radical chain reaction.

Taking all the previous observations into account, a proposed mechanism for the photocatalytic oxidative C-H functionalization of tyrosine with alkenes as radical acceptors is outlined in Fig. 6. Upon light excitation of the photoredox catalyst, tyrosine is oxidized to the corresponding radical cation **II** by single electron transfer to the excited photocatalyst [Ir*], following a reductive quenching cycle. Next, deprotonation of **II** to form the benzylic radical **III**, followed by radical addition to the alkene lead to the

radical intermediate **IV**. The catalytic cycle is closed by electron transfer from the reduced photocatalyst species [$Ir^{\bullet -}$] to the radical **IV**, forming the anionic species **V**. Then, the final product **VI** is obtained after protonation. In order to determine the source of protons for this last step, the reaction was performed in deuterated dichloromethane. However, no deuterium incorporation in the product was observed, indicating the tyrosine substrate as the proton source.

Discussion

In summary, we have developed a novel visible light-mediated functionalization strategy of electron-rich benzylic C-H bonds in tyrosine containing peptides and drug-like compounds. In this photoredox catalyzed radical-cation/deprotonation approach, a broad range of valuable functional groups could be selectively introduced into the tyrosine backbone. The combination of mild reaction conditions, chemoselectivity and functional group tolerance was highlighted by the late-stage functionalization of complex peptides, drugs and natural products. Hence, the demonstrated mild and selective generation of benzyl radicals in complex molecule scaffolds provides a powerful strategy with broad applicability in synthetic and medicinal chemistry.

Methods

General procedure for the photocatalytic reaction

In an oven-dried screw-cap vial, [Ir(dF(CF_3)ppy)(4,4´-dCF_3bpy)]PF_6 (**PC5**) (2.3 mg, 0.002 mmol, 2 mol%), the substrate (0.1 mmol, 1.0 equiv.) and the radical acceptor (1.1–5.0 equiv.) were dissolved in 0.5 mL dry CH_2Cl_2 (0.2 M). The mixture was degassed by bubbling argon for several minutes and the vial was sealed. The reaction mixture was irradiated by blue LEDs (max. 415 nm) for 18–72 h (the reaction progress was monitored by LC-MS or TLC). The crude was purified by flash column chromatography.

Data Availability

The authors declare that the data supporting the findings of this study are available within the article and Supplementary Information file, and also are available from the corresponding author upon reasonable request.

Declarations

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Ethics declarations

Competing interests

The authors declare no competing financial interest.

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Figures

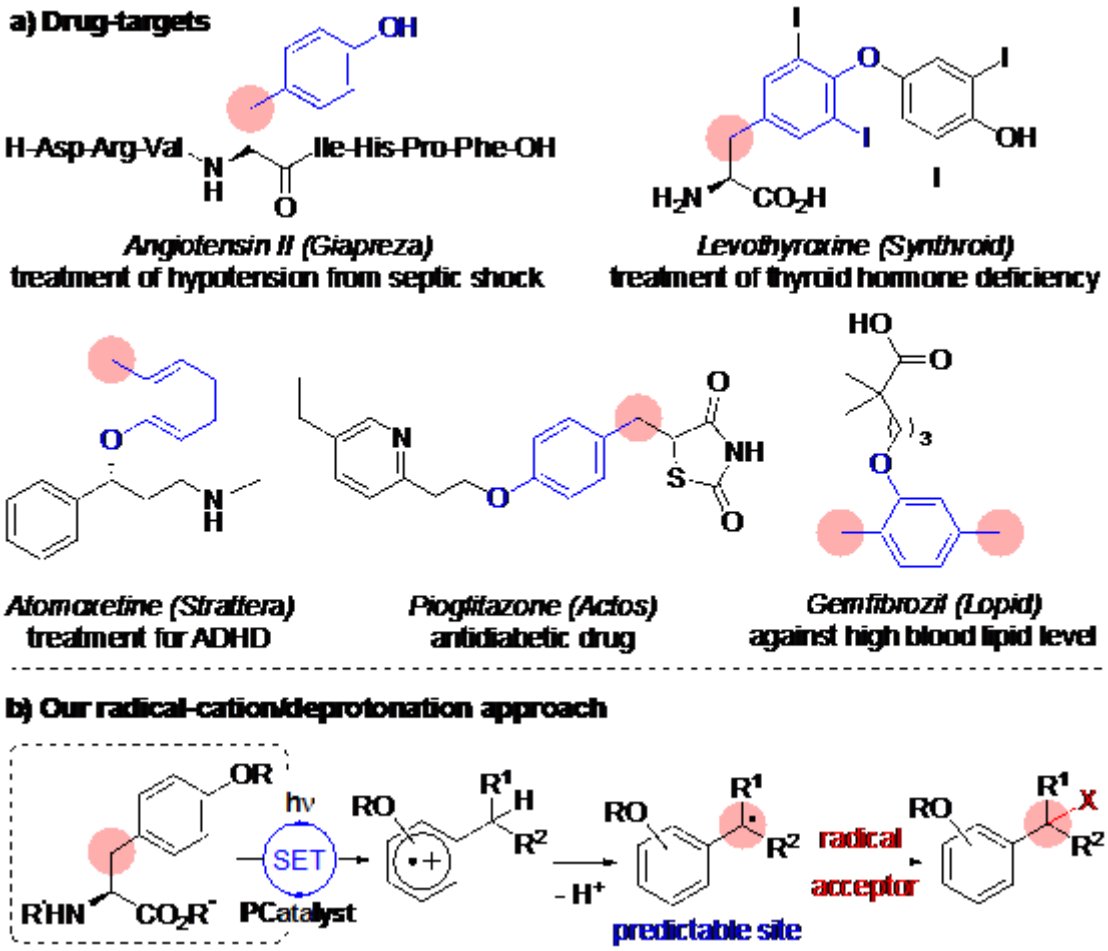

Figure 1

Selected phenolic-drug targets for benzylic LSF (a), and photocatalytic radical-cation/deprotonation strategy (b).

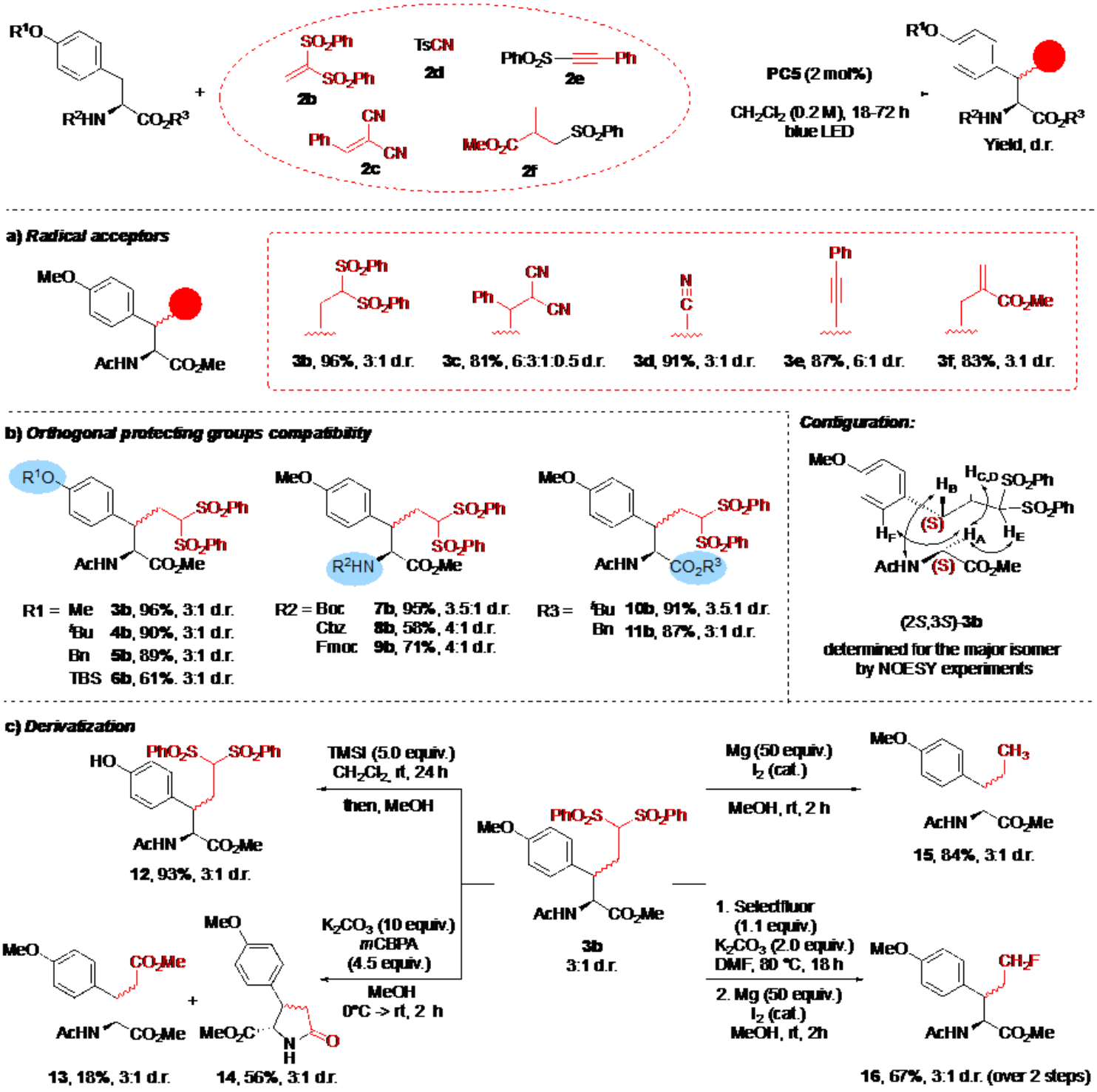

Figure 2

Benzylic functionalization of tyrosine-amino acid derivatives. a Conditions: PC5 (2 mol%), amino acid (1 equiv.) and radical acceptor (5 equiv.) in degassed CH2Cl2 (0.2 M) under blue LED irradiation.

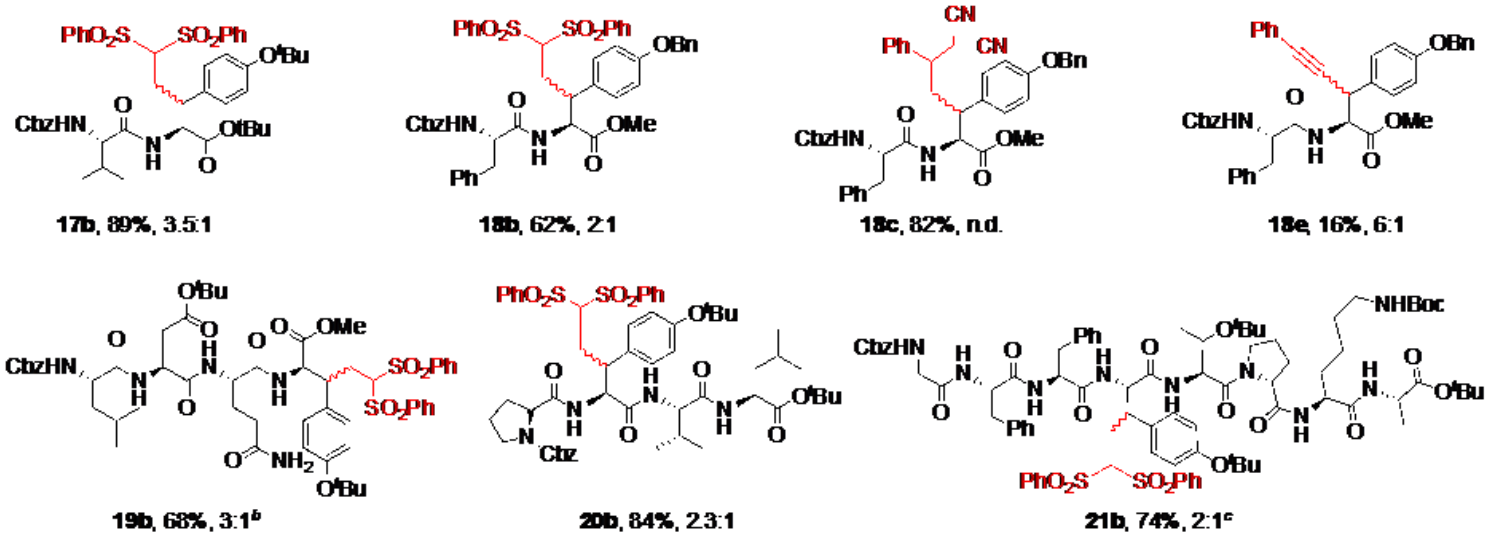

Figure 3

Benzylic functionalization of tyrosine-containing peptides. a Standard conditions: PC5 (2 mol%), peptide (1 equiv.) and radical acceptor (5 equiv.) in degassed CH2Cl2 (0.2 M) under blue LED irradiation. b Gln(Mbh) was deprotected under the photocatalytic conditions. c 0.08 M concentration.

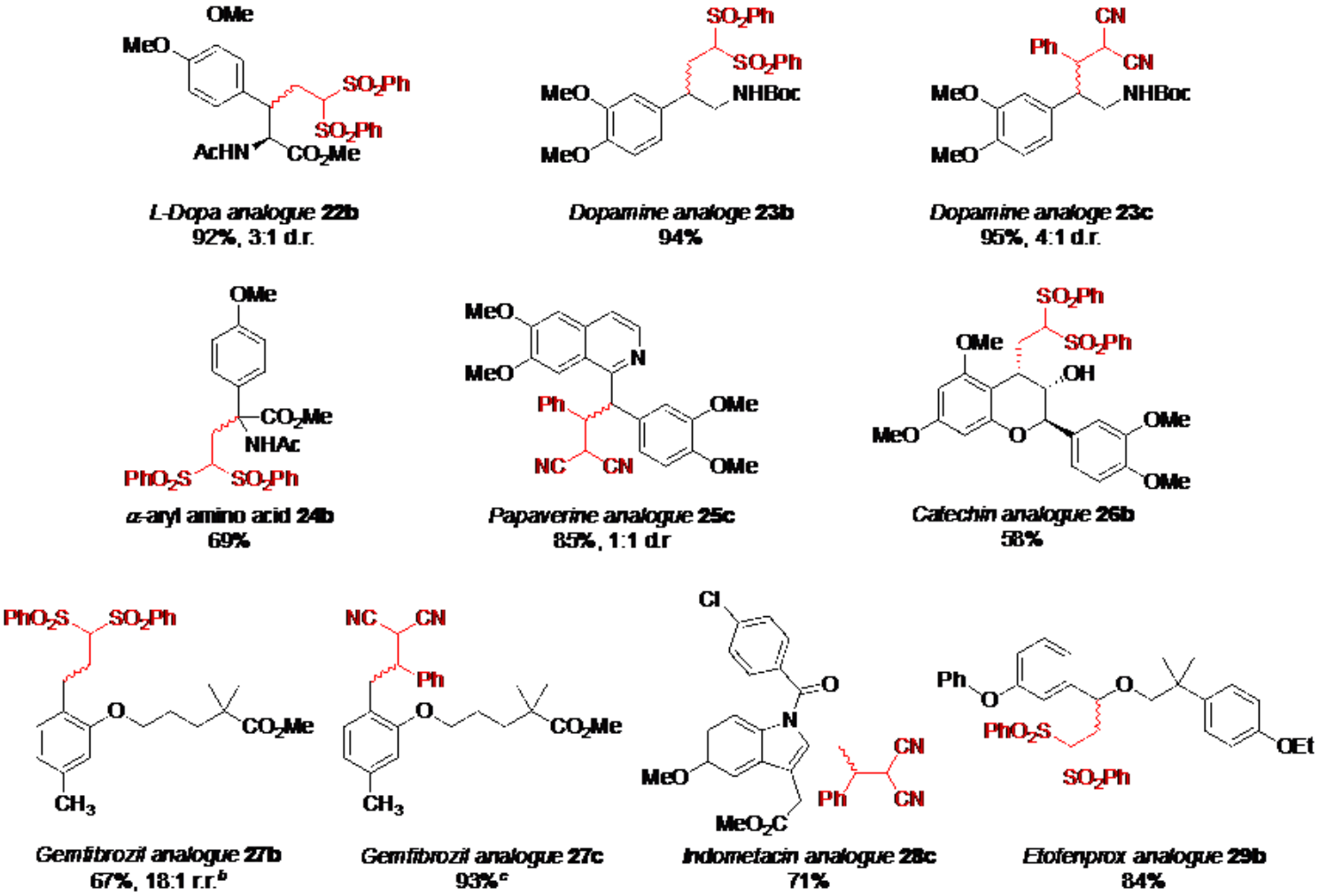

Figure 4

Late-stage functionalization of natural products and drugs. a Standard conditions: PC5 (2 mol%), substrate (1.0 equiv.) and radical acceptor (3.0 equiv.) in degassed CH2Cl2 under blue LED irradiation. b 1.1 equiv. of radical acceptor. c 1.5 equiv. of radical acceptor.

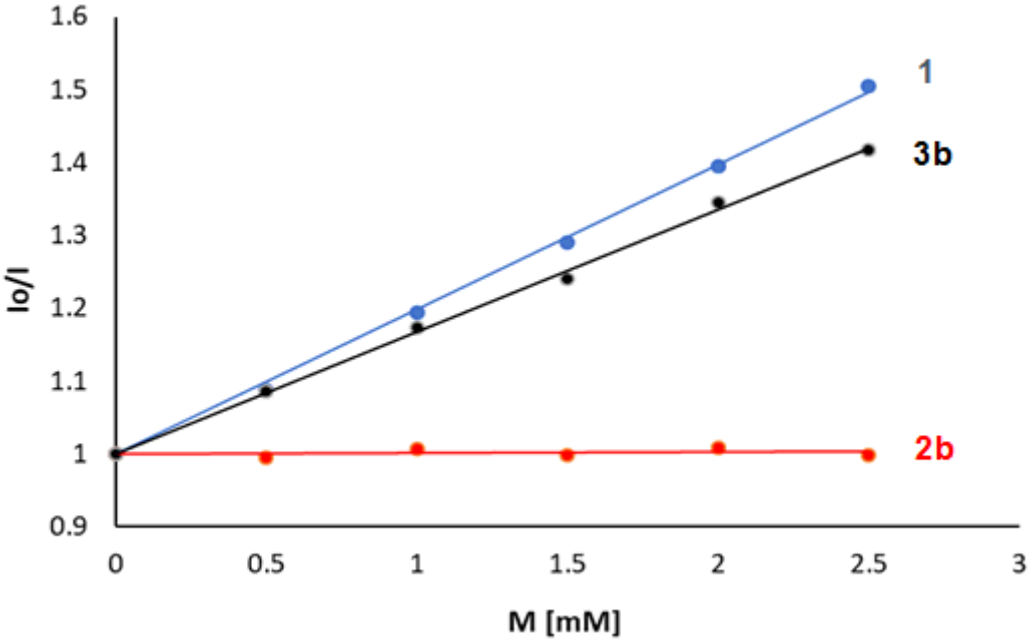

Figure 5

Stern Volmer Quenching Studies.

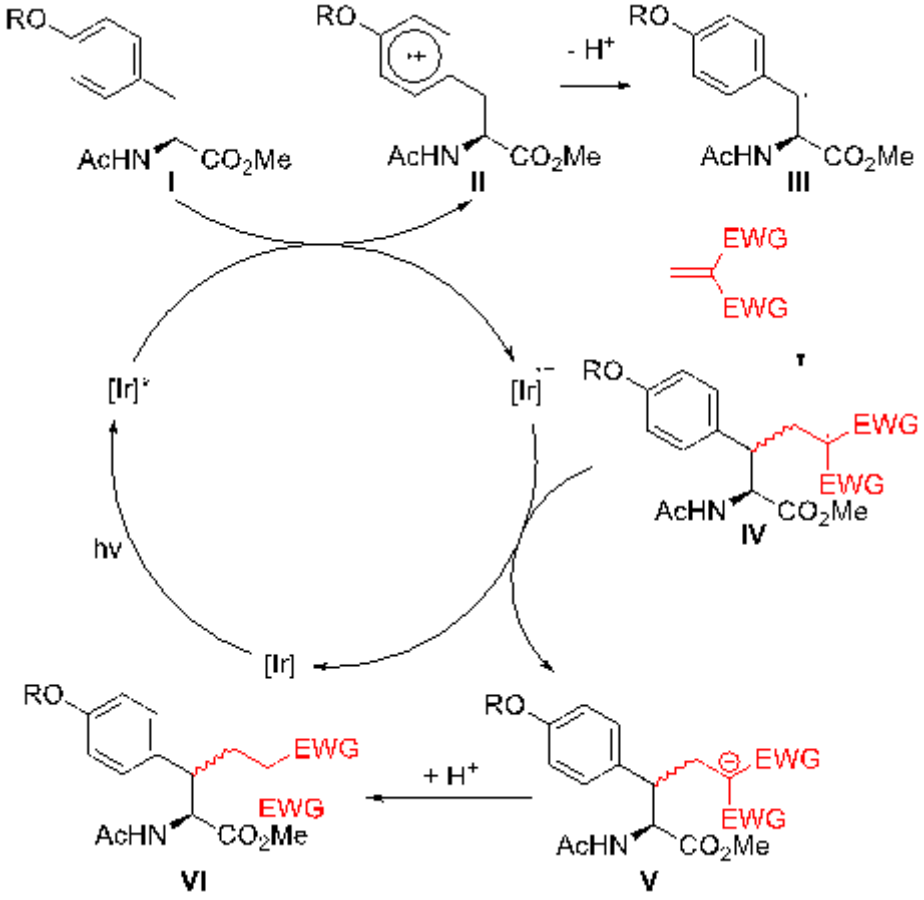

Figure 6

Proposed mechanism.

Supplementary Files

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- SupportingInformation.pdf