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Photoredox Catalytic Access to *N,O*-Acetals from Enamides by Means of Electron-Poor Perylene Bisimides

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N,O-acetals are found as structural motifs in natural products and are important synthetic precursors for N-acylimines as building blocks in organic synthesis for C–C-bond formation and amines. For the synthesis of *N,O*-acetals, an acid-, base- and metal-free catalytic method is reported applying *N,N*-di-(2,6-diisopropyl)-1,7-dicyano-perylen-3,4,9,10-tetracarboxylic acid imide and *N,N*-di-(2,6-diisopropyl)-1,6,7,12-tetrabromo-2,5,8,11-tetracyano-perylen-3,4,9,10-tetracarboxylic acid imide as extremely electron-deficient photocatalysts. The first perylene bisimide highly selectively photocatalyzes the formation of the *N,O*-acetals as products in high yields, and the second and more electron-deficient perylene bisimide allows these reactions without thiophenol as an H-atom transfer reagent. Calculated electron density maps support this. The reaction scope comprises different substituents at the nitrogen of the enamides and different alcohols as starting material. Dehydroalanines are converted to non-natural amino acids which shows the usefulness of this method for organic and medicinal chemistry.

Introduction

N-acylimines are often used as building blocks in organic synthesis for C–C-bond formation, the addition of nucleophiles gives amines.[1] However, *N*-acylimines are extremely reactive which is the key advantage for their use in synthesis, but is also the reason why they usually have to be formed *in situ* from stable precursors.[2] One of the most common precursors are *N,O*-acetals, which are relatively stable in both air and water, and can therefore be isolated before the actual use for synthetic activation into acylimines.[3] *N,O*-acetals act as reactive carbocations and form new C–C-bonds in reactions with C-nucleophiles. Reactions to α-functionalized amino acids or to β-amino aldehydes are of particular interest because they serve as key components in the synthesis of bioactive molecules, such as tolperison or oxyfedrin.[4] Besides being used as important synthetic precursors, *N,O*-acetals are also an important structural motif in a range of natural products with important bioactivity, including zampanolide, pymberine and pederine (Figure 1).[5] The synthesis of *N,O*-acetals is costly in terms of labor, because it requires several reaction steps. The established synthetic routes progress *via* Katritzky's benzotriazolylalkylamides or *via* amidosulphones.[6] While aromatic compounds are competent substrates for this transformation, alkylamides lead to the formation of enamides and not the desired products.[2a,7] Newer methods under mild conditions are mediated by titanium complexes.[8] A promising alternative is the application of photocatalysis that features a high level of sustainability by

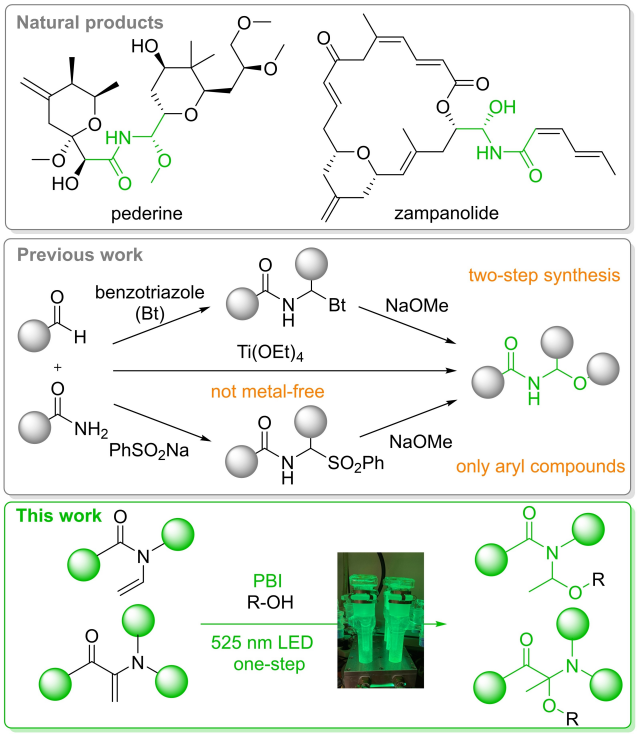

Figure 1. Natural products with *N,O*-acetals as structural motif (top), previous work on the synthesis of *N,O*-acetals via special amides (middle), and the photocatalytic preparation of N,O-acetals from enamides by means of PBIs in this work (bottom).

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the use of light as an energy source in combination with organophotoredox catalysts, as shown in particular for *N*-vinyl amides. *N,O*-acetals do not decompose when exposed to UV–A and visible light, which is a prerequisite for their preparation using photocatalysis. Herein, we report a novel, acid-, base- and metal-free method for the synthesis of *N,O*-acetals by photoredox catalysis using extremely electron-deficient perylene bisimides (PBIs, Figure 1).

Results and Discussion

Perylene Bisimides as Extremely Electron-Poor Organophotocatalysts

Perylene-3,4:9,10-tetracarboxylic acid bisimides belong to the rylene dyes and are broadly used for supramolecular dye aggregates,[10] but have only rarely been used in synthetic photocatalysis,[11] although they show unique photochemical properties and high photostability. They form stable radical anions and dianions which were used in photochemistry.[12] The chromophore was further improved for its photocatalytic use by the 2,6-di*iso*propylphenyl substituents at the imide nitrogens to enhance solubility in MeCN[13] and by the two cyano substituents at the core to make it even more electron-poor. *N,N*-di-(2,6-di*iso*propyl)-1,7-dicyano-perylen-3,4,9,10-tetracarboxylic acid imide (**PBI1**, Figure 2) has been successfully applied in the nucleophilic addition of alcohols to styrenes, turned out to give higher yields than the mesityl acridinium,[14] and the acid-free synthesis of acetals from silylenol ethers and aldehydes.[15] **PBI1** shows a reduction potential of E_{red}(**PBI1**/**PBI1**$^{\bullet-}$) = −0.15 V (vs. SCE); with E_{00} = 2.30 eV the reduction potential of **PBI1** in the excited state can be estimated to be E_{red}(**PBI1***/**PBI1**$^{\bullet-}$) = 2.15 V, showing that this chromophore is a strong photooxidant. Inefficient second electron transfer in photocatalytic cycles due to the early dissociation of the photocatalyst and the (pre)product radical ions is a known problem leading to low yields and to undesired byproducts, which can be solved by peptides with substrate binding sites.[16] In most cases, this problem is solved by additives, in particular thiophenol as an H-atom transfer reagent (an H-atom transfer comprises electron *and* proton transfer).[17] The second perylene bisimide, *N,N*-di-(2,6-di*iso*propyl)-1,6,7,12-tetrabromo-2,5,8,11-tetracyano-perylen-3,4,9,10-tetracarboxylic acid imide (**PBI2**), follows the idea that the strong electron-deficiency of the perylene core should increase the electrostatic interaction with the intermediate substrate/product radicals and radical ions and thus make additives dispensable. Accordingly, the **PBI2** was equipped with four bromo and four cyano substituents so that the perylene core is completely modified with electron-withdrawing substituents; both types of substituents are placed in ortho position to each other. **PBI2** shows a reduction potential of E_{red}(**PBI2**/**PBI2**$^{\bullet-}$) = −0.01 V (vs SCE) determined by cyclic voltammetry (Figure S97). With E_{00} = 2.20 eV, determined intersection between the normalized UV-visible absorption and emission spectra,[18] the reduction potential of **PBI2** in the excited state can be estimated to be E_{red}(**PBI2***/**PBI2**$^{\bullet-}$) = 2.20 V.

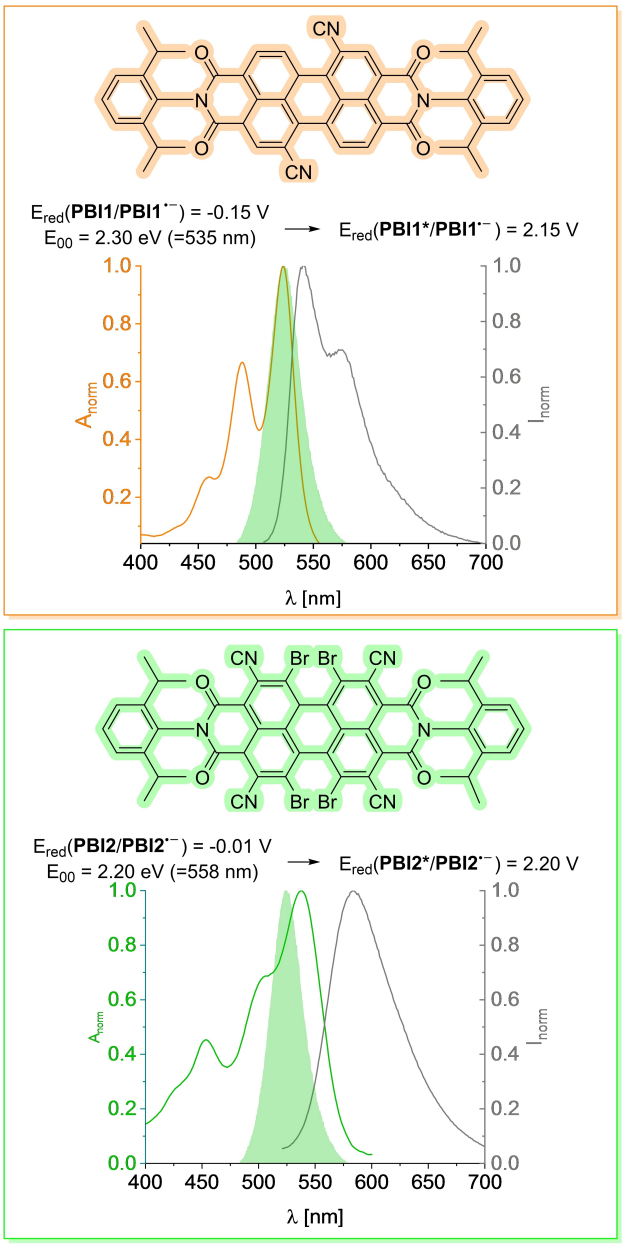

Figure 2. Optical (UV/Vis absorption and fluorescence, λ_{exc} = 390 nm) and redox properties of **PBI1** (top) and **PBI2** (bottom).

The excited state potential of this chromophore might probably be even higher, because the determination of E_{00} is generally not very accurate, if the 0–0 transition is not directly observed both in the UV/Vis absorption and fluorescence spectra, and thus should be able to activate substrates better than **PBI1**. The overlay of the emission of the 525 nm LED is optimal with the absorption of **PBI1** because it fits perfectly with the absorption maximum, but is also very good with the absorption of **PBI2**.

Photocatalytic Method to N,O-Acetals

The photocatalytic formation of *N,O*-acetals from enamides was worked out with substrate **1a** using both catalysts, **PBI1** and **PBI2**, in comparison (Table 1). Product **1b** in the photocatalysis with **PBI1** can only be yielded by the addition of thiophenol, a commonly applied and literature-known H-atom transfer reagent[17] that promotes the second electron transfer coupled to a proton transfer in the photocatalytic cycle. **PBI1** does not allow any conversion of **1a** without the addition of additives, whereas **PBI2** shows quantitative yields without additives. The yield of 65% is nevertheless below the quantitative yield achieved with **PBI2** without thiophenol. To further optimize this photocatalytic method, different solvent mixtures, light exposure times and temperatures were explored. For both catalysts, the best results were achieved using the following conditions: irradiation with the 525 nm LED at 25 °C for 65 h in a 1:3 mixture of methanol in acetonitrile. While **PBI1** requires 12 mol% thiophenol as an additive to achieve product at all, **PBI2** photocatalyzes the reaction without additives. Shorter irradiation times drop the yields drastically. After 24 h, only 68% of product **1b** are obtained, after 48 h 87%, and the quantitative yield after 65 h. Increasing the reaction temperatures to 40 °C produces progressively more byproducts, while decreasing the temperature to 15 °C results in lower conversion, and thus lower yields. Accordingly, quantitative yield of product **1b** is obtained at 25 °C, and lower yields of 93% at 40 °C, and 76% at 15 °C. Both the doubly substituted product **1c** and the corresponding amide **1d** are obtained as byproducts in low amounts (vide infra, see Figure 4).

The following mechanism was postulated for this photocatalysis (Figure 3). Firstly, a photoinduced electron transfer between **PBI2** and the enamide takes place to obtain the ion pair $\mathbf{1a}^{\bullet+}/\mathbf{PBI2}^{\bullet-}$. We measured the oxidation potential of enamides; they are found in the range of $E_{ox} = 0.9–2.0$ V (Figures S8–S12). It should be noted that these electron transfer processes were found to be irreversible by cyclovoltammetry. Based on the electrochemical potentials for **PBI2**, as discussed

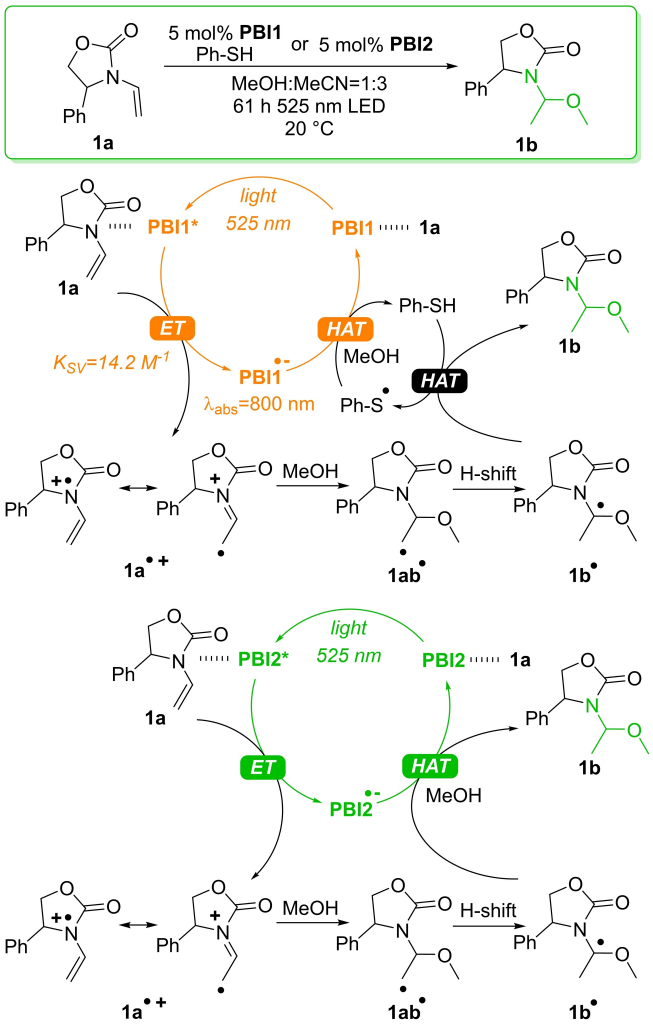

Figure 3. Photocatalytic model reaction from enamide **1a** to *N,O*-acetal **1b** and proposed photocatalytic cycle for **PBI1** with thiophenol as additive and H-atom transfer (HAT) reagent, and for **PBI2** without thiophenol; ET = electron transfer.

Table 1. Optimization of photocatalysis conditions for the conversion of enamide **1a** into *N,O*-acetal **1b**.

Catalyst	Solvent MeOH:MeCN	Additive	Temperature [°C]	Irradiation time [h]	Yield [%]	Conversion [%]
PBI1	1:3	–	25	65	–	–
PBI2	1:3	–	25	65	100	100
PBI1	1:3	PhSH	25	65	65	65
PBI1	1:3	PhSH	25	–	–	–
PBI1	0:1	PhSH	25	65	–	–
–	1:3	PhSH	25	65	–	–
PBI2	1:3	–	25	24	68	68
PBI2	1:3	–	25	48	87	87
PBI2	1:3	–	40	65	93	100
PBI2	1:3	–	15	65	76	76
PBI1	1:3	PhSH	40	65	51	87
PBI1	1:3	PhSH	15	65	35	35
PBI2	MeOH	–	25	65	87	100

above, the initial electron transfer is slightly exergonic even for the enamide **5a** with the strongest oxidation potential E_{ox}(**5a**$^{\bullet+}$/**5a**) = 2.0 V, according to $\Delta G = E_{ox} - E_{red} - E_{00} = (2.0 + 0.0 - 2.2)$ eV = 0.2 eV. Normally, a low Coulomb energy E_C of 100 meV is assumed for this initial electron transfer processes in polar solvents, like MeCN and MeOH. However, in case of **PBI2**, the Coulomb energy after the initial electron transfer might be higher due to the extreme electron-deficiency. Indeed, the enamide **1a** shows quenching of the **PBI2** fluorescence with a Stern-Volmer constant of $K_{SV} = 14.2\ M^{-1}$ (Figure S95). Furthermore, we are able to observe the radical anion **PBI2**$^{\bullet-}$ in the reaction mixture in the visible light range by its characteristic red-shifted absorption at approximately 800 nm (Figure S96). Both experimental results support the initial electron transfer in the photocatalytic cycle. Methanol reacts as a nucleophile with the radical cation **1a**$^{\bullet+}$ yielding the radical **1ab**$^{\bullet}$. According to the published reduction potential of a primary alkyl radical, E = ($MeCH_2/MeCH_2^{\bullet-}$) = 1.36 V,[19] it is not feasible that the radical **1b**$^{\bullet}$ can be reduced by the radical anion **PBI**$^{\bullet-}$ (E_{red}(**PBI2**/**PBI2**$^{\bullet-}$) = −0.01 V). Instead, it is more likely that the radical **1ab**$^{\bullet}$ undergoes a H shift to the more stable **1b**$^{\bullet}$ which shifts its reduction potential into the functional range.[20] The photocatalytic cycle is closed by the second electron and proton transfer (H atom transfer) of the electron from **PBI2**$^{\bullet-}$ to the resulting radical **1b**$^{\bullet}$, and the product **1b** is finally obtained.

Substrate Scope

In the next step, the substrate scope of the reaction was investigated (Figure 4). All photocatalytic experiments were repeated at least as triplicates. NMR yields are reported from the photocatalytic samples, and all products were then purified by column chromatography to characterize them by NMR spectroscopy. We could show that not only the cyclic product **1b** but also the acyclic **2b** was obtained in a very good yield of 85% with **PBI2** as a photocatalyst. **PBI1** leads also selectively to the Markovnikov products, but only in yields of 65% and 24%. The clear difference in yields between the two photocatalysts became evident. Furthermore, the substrates **3a**–**6a** were tested. Similar to the conversion of substrates **1a** and **2a**, **3b** was the single product from substrate **3a** in quantitative yield with **PBI2**. Due to the electron-withdrawing effect of the additional carbonyl group at the nitrogen of enamides **5a**–**6a**, these reactions do not only yield 12–50% of the desired *N*,*O*-acetals **5b**–**6b** but additionally form products **5c** and **6c** with opposite regioselectivity. With **PBI2** as a photocatalyst, **6c** is even the main product after the conversion of substrate **6a**. This is the result of the stronger electron-withdrawing effect of the Boc groups in substrate **6a** in comparison to the benzoyl groups in substrate **5a**. Obviously, the inverted radical cation can be stabilized better in this case than with the other substrates due to the strong electron-withdrawing effect of both Boc substituents at the nitrogen. Accordingly, the regioselectivity of the MeOH addition can be controlled by the choice of substituents at the nitrogen of the enamides. Alternatively, the different regioselectivity might be due to an

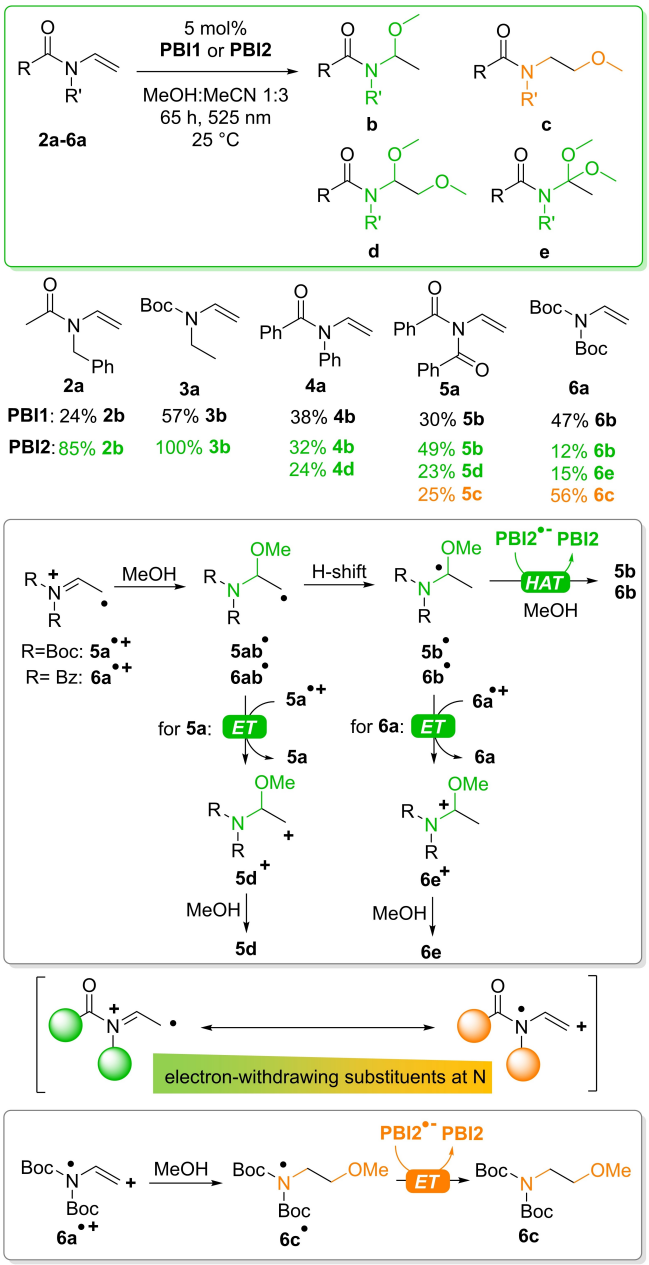

Figure 4. Substrates **2a**–**6a** and their conversion into products **2b**–**6e** with observed yields (top), and mechanisms representatively for the formation of products **5b**, **5d**, **6b** and **6e** from substrates **5a** and **6a** (middle), and the electron-withdrawing effect of the *N*-substituent for the formation of product **6c** from substrate **6a** in comparison (bottom).

N-acyl-aziridine radical cation as an intermediate, but we have no experimental evidence for this kind of intermediate. Furthermore, we identified products **4d** and **5d** as the double MeOH addition products by NMR and mass spectrometry. For substrate **6a**, the second MeOH addition is observed at the same position as the first addition which gave product **6e** in 15% yield. The twofold MeOH addition products **4d**–**6e** can only be explained by a second oxidative electron transfer step, for instance into the precursor cations **5d**$^{\bullet+}$ of product **5d** and **6e**$^{\bullet+}$ of product **6e**. It is not clear, which intermediates might act as oxidants here. Plausible oxidants are the substrate radical

cations $\mathbf{5a}^{\bullet+}$ and $\mathbf{6a}^{\bullet+}$ that are constantly produced by the initial photoinduced electron transfer in the photocatalytic cycle. The long irradiation times applied in this photocatalysis indicate such a pathway. Alternatively, hydrogen may evolve from the reaction mixture, but we have not found any evidence for that in the crude NMR samples. Neither the changed regioselectivity of products **5c** and **6c** nor the doubly methylated products **4d**, **5d** and **6e** were observed with **PBI1** as photocatalyst indicating that the intermediate radical ions and radicals are stronger and longer bound to **PBI2** due to its strong electron deficiency to allow further reactions into different products. The photocatalytic cycle for **PBI1** without an additive works very inefficiently probably due to the early dissociation of the photocatalyst and the (pre)product radicals rendering the second electron transfer inefficient. With thiophenol as an H-atom transfer reagent the photocatalytic cycle works also efficiently for **PBI1**.

In contrast to substrate **3a** which can be converted to the *N,O*-acetal **3b** using both photocatalysts, the other ethylated substrates **7a** and **8a** with benzoyl and benzylcarbonyl groups at the nitrogen were converted directly to the corresponding amides **7c** and **8c** (Figure 5). These compounds are the hydrolysis products of the intermediate *N,O*-acetals **7b** and **8b**, which can be explained by the insufficient stabilization of these products by the ethyl group that makes the nitrogen more basic. This effect is only observed with the benzoyl substituents in the ethylated substrates **7a** and **7b** which is less electron-withdrawing than the Boc group in the ethylated substrate **3a** for which the product **3b** could be isolated. Obviously, the non-bonding electron pair at the nitrogen of products **2b**–**6b** is less basic by mesomeric interactions with the carbonyl, benzyl or phenyl groups. Furthermore, the substrates **9a** and **10a** were used to check out if the catalysis works also intramolecularly (without the presence of MeOH). It was expected to obtain a 5-membered ring from **9a** and a six-membered ring from **10a** according to exo-trig cyclizations.[21] Indeed, product **9d** was obtained in a yield of 22%. However, the corresponding amide **9c** was also found as a product in a yield of 34%, which is not surprising due to the similarity to substrates **7a** and **8a**. Furthermore, the product **10d** with a morpholino 6-membered ring was obtained in 13% yield. A larger portion of 46% of the corresponding amide **10c** was formed. In both cases, the cyclic products **9d** and **10d** were not obtained with **PBI1** as a catalyst.

To further expand the scope of the reaction, different alcohols with different functional groups were added instead of simple methanol (Figure 6). For this purpose, substrate **1a** was used, which showed quantitative yields for the conversion with methanol. It should be noted that two different stereoisomers are formed in each of these reactions, which in the case of substrate **1a** and methanol are formed in a 1:1 mixture of products **1ba** and **1bb**. By using sterically more demanding alcohols, the yield decreases due to the increasing sterical hindrance from methanol over ethanol, isopropanol to tert-butanol. While an overall quantitative yield of products **11ba** and **11bb** is still obtained with ethanol, an overall yield of only 71% is observed for the products **13ba** and **13bb** with tert-butanol. Furthermore, it is noticeable that the isomer ratio shifts in favour of the *S,R*-diastereomer **13ba**. The conversion of **1a** with other alcohols bearing cyano-, allyl- or propargyl functionalities shows good overall yields for products **14ba**–**16bb** between 84% - 90%, again with a slight diastereomeric selectivity for the *S,R*-isomer. It was also possible to introduce a Boc functionality by the corresponding alcohol with an overall yield of 50% for products **17ba** and **17bb**. This reaction without the loss of the Boc groups shows that there are no significant amounts of photoacids or other intermediate acids are formed.

In addition to the substrates already mentioned, dehydroalanines can also be converted (Figure 7). These amino acids are potentially interesting for peptide chemistry. The single Boc-protected derivative **18a** can be converted into product **20b** in a moderate yield of 36%. In contrast, the corresponding *N*-methylated derivative **19a** gives a better yield of 52% for

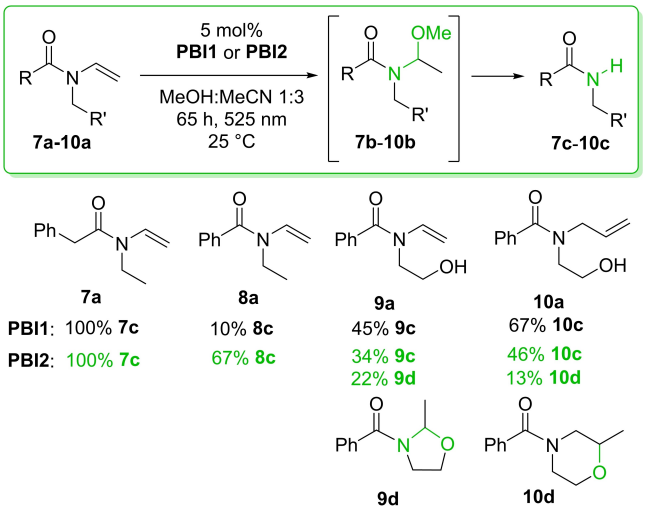

Figure 5. Substrates **7a**–**10a** and their conversion into products **7b**–**10d** with observed yields.

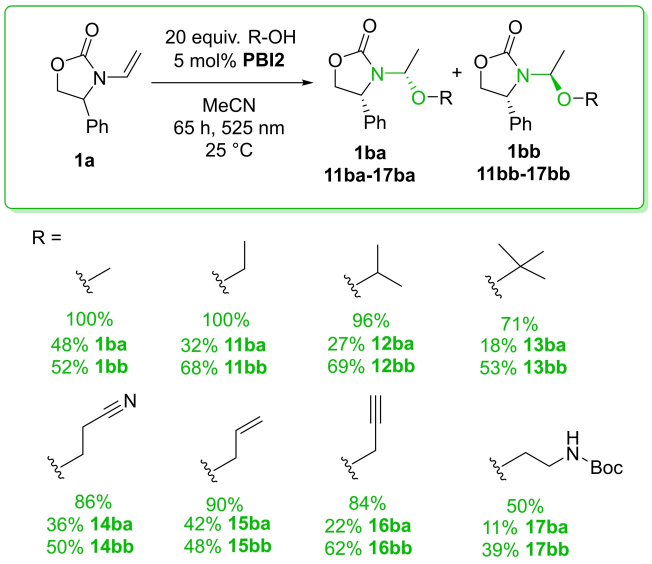

Figure 6. Substrate **1a** and its conversion into the diastereomeric products **1ba**–**19bb** and observed yields.

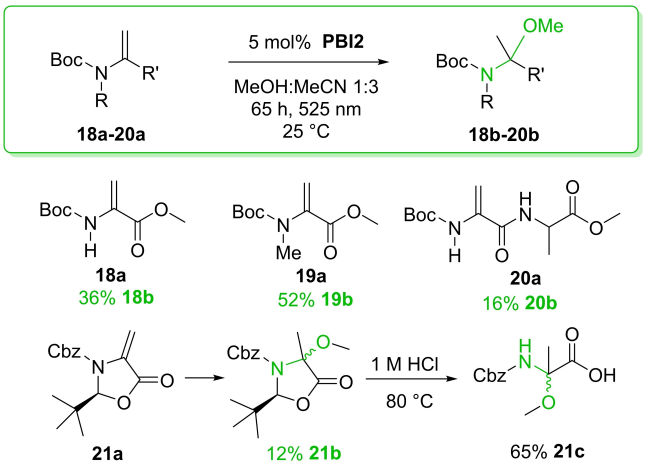

Figure 7. Substrates **18a**–**21a** and their conversion into products **18b**–**21b** and **21c**. Although the ^{1}H NMR spectrum indicates that **21b** is only one stereoisomer and the stereoselectivity for the MeOH addition is controlled by the *t*Bu group in **21a**, the structures of **21b** and **21c** are drawn with undefined stereochemistry.

product **19b**. The cyclic derivative **21a** was also tested. Although the obtained yield of 12% for product **21b** is very low, this is of particular interest, because it can be converted into an enantiomerically pure, derivatized amino acid **21c** by subsequent acidic work-up. After reaction with aq. HCl (1 M) at 80 °C, the methoxylated amino acid could be obtained in 67% yield. To realize the application of these methods for the modification of peptides, the peptide Boc–Ala–dAla–OMe **20a** was tested. The product **20b** was obtained in a yield of 16%, which shows the potential use for the synthesis of peptide therapeutics.

Theoretical Calculations of the Perylene Bisimide Surface

The photocatalytic experiments with substrates **1a**–**10a** elucidated that **PBI1** photocatalyzes the highly selective formation of the desired *N*,*O*-acetals as products in high yields only in the presence of thiophenol as H-atom transfer reagent whereas **PBI2** allows these reactions without the additive. This difference in reaction efficacy could be explained by the stabilizing effect of the electron-withdrawing substituents on the radical anion **PBI2**$^{\bullet-}$ rendering additives dispensable. This ensures sufficient time to enable the second electron transfer. To support this hypothesis the molecular electrostatic potentials of both chromophores were mapped on the van der Waals and analyzed (Figure 8). For the sake of clarity, the isopropyl groups at the N-phenyl substituents of **PBI1** and **PBI2** were replaced by methyl groups. Interestingly, **PBI2-Me** shows not only a much more electron-deficient perylene bisimide core ($V_{max} = +0.144$ a.u.) than **PBI1-Me** ($V_{max} = +0.082$) due to its very strongly electron-withdrawing substituent pattern as anticipated. Furthermore, it shows a highly significant twist of the aromatic basal plane due to distortion by four bromo and four cyano substituents. Thereby, an enzyme-like substrate binding pocket

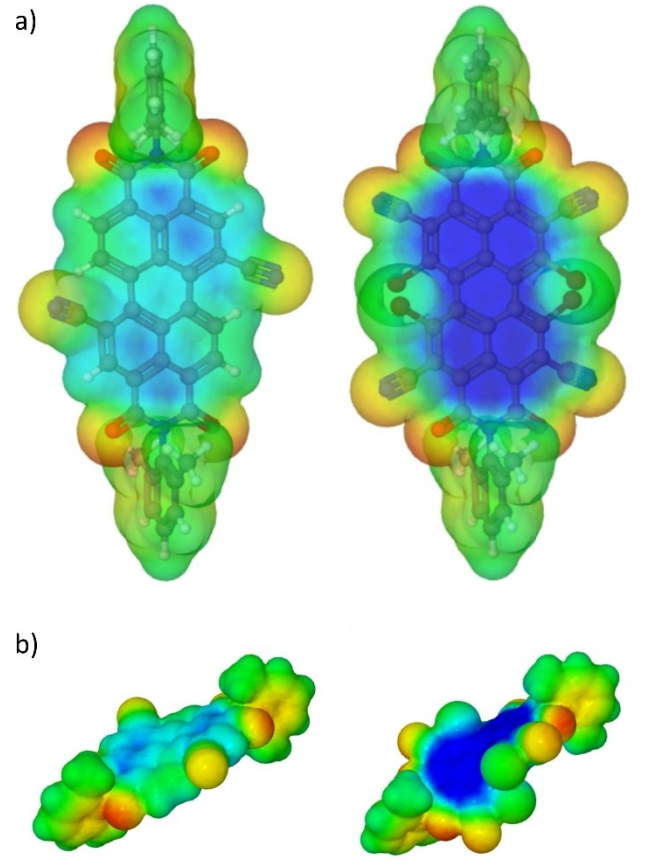

Figure 8. a) Molecular electrostatic potential (−0.1 a.u (red) to 0.1 a.u. (blue)) mapped on the van der Waals surface of **PBI1-Me** (left) and **PBI2-Me** (right). b) Perspective view on the surface shape of catalyst **PBI1-Me** and **PBI2-Me**. For the sake of clarity,the 2,6-dimethylaniline derivatives were subjected to analysis.

is formed that gives a good reason for the superior performance of **PBI2**, but not with **PBI1**.

Conclusions

We report a novel photoredox catalytic approach for the synthesis of *N*,*O*-acetals. The method works without acids, bases and metals. It uses the extremely electron-deficient perylene bismides **PBI1** and **PBI2**. **PBI1** gives selective photocatalytic reactions to the *N*,*O*-acetals, but requires thiophenol as an additive and H-atom transfer reagent, whereas **PBI2** allows the photocatalytic conversion of enamides without the addition of thiophenol. This was rationalized based on theoretical calculations by the more electron-deficient perylene bisimide core of **PBI2** due to its very strong electron-withdrawing and the significant twist of the aromatic basal plane due to distortion by four bromo and four cyano substituents. The substrate reactivity was explored concerning the substituents at the nitrogen of the enamides and the applied alcohol. The regioselectivity of the alcohol addition to the enamides is controlled by the electron-withdrawing substituents at the nitrogen. The stability of the

N,O-acetals is controlled by the mesomeric stabilization of the nitrogen substituents. If this stabilization is lacking, for instance in the case of an ethyl group, the *N,O*-acetals spontaneously hydrolyze to the amides. The photocatalyst **PBI2** enables the formation of additional products with altered regioselectivity or intramolecular cyclizations, and conversions not only of enamides but also of dehydroalanine derivatives leading to non-natural amino acids. Non-natural amino acids are key building blocks in therapeutically relevant peptides. Taken together, the substrate scope shows the significance of this photocatalytic method for application in synthetic and medicinal chemistry.

Supporting Information

The authors have cited additional references within the Supporting Information.[22–29]

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: photocatalysis · photochemistry · amide · chromophore · electron transfer

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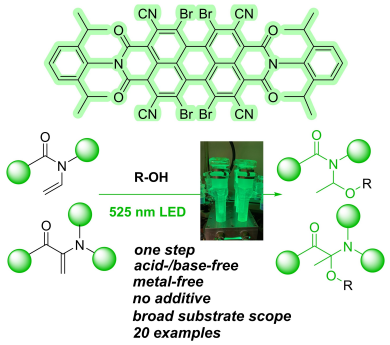
RESEARCH ARTICLE

Enamides can be converted into their *N,O*-acetals using just electron-poor perylene bisimides together with light, without the need for thiophenol as additive or strong acids as catalyst.



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