Complementary Photocatalytic Toolbox: Control of Intramolecular endo- versus exo-trig Cyclizations of α-Phenyl Olefins to Oxa-heterocycic Products

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Organic Photoredox Catalysis in Synthesis – Honoring Prof. Shunichi Fukuzumi’s 70th Birthday

Abstract The regioselectivity of the intramolecular cyclization of bi-functional α-phenyl alkenes can be controlled simply by the choice of the organic chromophore as the photocatalyst. The central photocatalytic reaction in both cases is a nucleophilic addition of the hydroxy function to the olefin function of the substrates. N,N-(4-Diisobutylamino)phenothiazine catalyzes exo-trig cyclizations, whereas 1,7-dicyanopyrene-3,4,9,10-tetracarboxylic acid bisimides catalyze endo-trig additions to products with anti-Markovnikov regioselectivity. We preliminarily report the photocatalytic conversion of 11 representative substrates into 20 oxaheterocycles in order to demonstrate the similarity, but also the complementarity, of these two variants in this photocatalytic toolbox.

Key words photochemistry, photocatalysis, perylene bisimide, phenothiazine, nucleophilic addition, cyclization

Chemical photocatalysis uses light as an energy source for organic chemical reactions. In particular, photocatalysis of α-phenyl olefins is an important concept that applies UV or visible light to generate radical anions or cations as reactive intermediates. Photoredox catalysis either provides important alternatives to conventional thermal reactions or expands the repertoire of organic reactions. The current workhorses for photoredox catalysis are ruthenium and iridium complexes, due to their versatile photoredox properties and photochemical robustness. The advantage of these transition-metal photoredox catalysts is that they can be either oxidatively or reductively quenched, depending on the substrates. In contrast, organic photocatalysts cannot be similar applied to different types of organic reactions. The organic photocatalyst does not exist for a wide range of different reductive or oxidative reactions. Currently eosin Y, flavin, rhodamine 6G, mesityl- and aminoacridiniums, naphthochromenones, 4,6-dicyanobenzenes, pyrimidopiperidines, and thioxanthones have been used as organic photocatalysts and can be considered, taken together, as a photocatalytic toolbox.

Oxa heterocycles play an important role in medicinal chemistry; in particular, tetrahydropyrans and tetrahydrofurans are the most often used ring substructures. Tetrahydropyrans and chromanes are also important structural motifs in natural products. Tetrahydropyrans and chromanes are also important structural motifs in natural products. Due to their biological activity and effectiveness against a number of diseases, these substances are at the focus of organic syntheses. Recently, several groups have synthesized these compounds through cobalt-, indium-, and palladium-catalyzed reactions. Intramolecular cyclizations by photocatalysis complement this synthetic toolbox and provide experimentally very similar but more-sustainable alternatives based on metal-free photoredox catalysis. We have established 1-(N,N-di-methylamino)pyrene (APy), N-arylbenzothiazines, and 1,7-dicyanopyrene-3,4,9,10-tetracarboxylic acid bisimides as organic catalysts in the photocatalytic toolbox for the alkylation of α-phenyl and other alkenes. In particular, N,N-(4-diisobutylamino)phenothiazine (1) is one of the most strongly reducing photoredox catalysts reported in the literature, and yields products with Markovnikov orientation. On the other hand, 1,7-dicyanopyrene-3,4,9,10-tetracarboxylic acid bisimides photocatalyze additions to products with an anti-Markovnikov orientation. The latter reactions require thiophenol as an additive and hydrogen...
atom donor. Herein, we provide a preliminary report on the cyclization of bifunctional α-phenyl alkenes by intramolecular nucleophilic addition (Figure 1).

Figure 1 Two complementary, but experimentally very similar routes for photoredox-catalyzed cyclizations of α-phenylstyrenes 2–4 (n = 1–3) by intramolecular nucleophilic addition. The photoredox catalytic reduction of substrates 2–4 by the electron-rich N-arylphenothiazine Ptz, like 1, with irradiation at 365 nm yields the exo-trig cyclized products 5–7 (top), whereas the oxidation of substrates 2–4 by an electron-deficient perylene bisimide PBI, irradiated at 525 nm, gives the endo-trig cyclized products 8–10 (bottom). ET = electron transfer; PT = proton transfer.

Perylene bisimides are soluble in CH₂Cl₂ but generally have poor solubility or are even insoluble in MeCN, the preferred polar solvent for photocatalyzed reactions. To use 1,7-dicyanoperylene-3,4,9,10-tetracarboxylic acid bisimides as photocatalysts, we had to improve their solubility. We prepared the perylene bisimides 14a–j, differing in the substituents on the imide nitrogen (Figure 2, top). Their syntheses began from 1,7-dibromoperylene-3,4,9,10-tetracarboxylic acid dianhydride (11), which was modified with the various substituted imide functions. The two cyano substituents were introduced into 13a–j by treatment with zinc(II) cyanide and a Pd catalyst. The solubilities of the pure perylene bisimides 14a–j were determined by preparing their saturated solutions in pure MeCN. The absorbance was measured directly after filtration of the solution or after further dilution if the optical density in a cuvette with a 1 cm path length exceeded 1.29 The perylene bisimides with the lowest solubilities of <10 μmol/L are 14a and 14f (Figure 2, bottom). Obviously, the solubility was only enhanced for imides with secondary substituents, such as 14b, 14c, 14g, and 14h (~20 μmol/L), and was further enhanced for 14d, 14e, and 14i (~30 μmol/L). The perylene bisimide 14j had the best solubility (1.43 mmol/L) and was used in the subsequent photocatalytic experiments.

The N-arylphenothiazine 1 is a strongly reducing photocatalyst with an excited-state oxidation potential of approximately $E_{\text{ox}}(1^*/1^-) = -2.9$ V (vs. SCE). Accordingly, the intramolecular cyclization by 1 as photocatalyst starts with photoinduced reduction of the substrate, representatively shown for 2–4 (Figure 1). The reduction potentials of these substrates lie in the range between that of α-phenylstyrene, $E_{\text{red}}(S/S^-) = -2.3$ V, and that of styrene, $E_{\text{red}}(S/S^-) = -2.6$ V. The driving force $\Delta G$ for this initial electron-transfer process can be estimated from the Rehm–Weller equation $\Delta G = E_{\text{ox}} - E_{\text{red}} - E_0$ (omitting the Coulombic interaction energy...
The conversion was completed after 65 hours of irradiation, as representatively shown with substrate 3 (see Supporting Information (SI), Figure S1). The four-membered ring of product 5 is not formed from substrate 2. The photocatalysis gives good yields of 51–75% for the five- and six-membered rings in products 6 and 7 from substrates 3 and 4, and for the benzo-fused six-membered rings in products 10 and 14 from substrates 18 and 19, respectively, all according to Baldwin’s rules. Substrate 2 is converted into the benzo-fused seven-membered ring 23. To further broaden the scope, we used substrates 25–28 and 36 with variously modified phenyl groups. These were all converted into the expected exo-trig products in good yields. The occurrence of the byproducts 15–17 supports a photocatalytic mechanism, because these compounds are formed by simple deprotonation (elimination) from the cationic intermediates after back electron transfer.

The perylene bisimide 14 is a strongly oxidizing photocatalyst with an excited-state reduction potential of $E_{\text{red}}(14^{+}/14^{-}) = 2.1$ V. With the oxidation potential of α-phenylstyrene as a reference substrate, $E_{\text{ox}}(S^{+}/S) = 1.7$ V, the driving force is estimated to be $\Delta G = -0.4$ V. After this initial photoinduced electron transfer, an intramolecular nucleophilic attack occurs in the radical cations of the substrate, representatively shown for substrate 3 (Figure 1). Thereby, the anti-Markovnikov regioselectivity is controlled, which is equivalent to an endo-cyclization. Back electron transfer and proton transfer give the six- and seven-membered rings in products 9 and 10 in good yields (88% and 43%, respectively) from substrates 3 and 4. The yield of the five-membered ring in product 8 from substrate 2 is low (16%) and the reaction needs further optimization. Here also, the occurrence of the byproduct 18 supports a photocatalytic mechanism, because it is formed by cyclization after a 1,3-H shift in the intermediate to the higher substituted cation. Substrates 18 and 22, bearing an alkylhydroxy group in the position ortho to the vinyl substituent, are converted into the benzo-fused seven-membered ring 21 in 63% yield and into the benzo-fused eight-membered ring in 24, respectively. Substrates 25–28 and 36 were converted into the expected endo-trig products in good yields, except 29, which was a product of an exo-trig cyclization. Obviously, the methoxy substituent influences the stabilization of the intermediate radical cation formed after the initial photooxidation by 14 and which, of course, bears an unpaired spin and a charge. Normally, the unpaired spin is better stabilized at the benzylic position, which opens the way to an endo-trig cyclization. In this special case, the methoxy substituent stabilizes the cationic charge at the benzylic position leading to an exo-trig reaction. Product 41 was not obtained from substrate 39. Obviously, a phenolic hydroxy function cannot be used as a nucleophile in this photocatalytic method. This agrees with our previous studies with photocatalyst 14f and is probably due to the difference in the acidities of phe-
nols in comparison with alkyl alcohols, because the central cyclization step includes a proton transfer. Due to the long lifetime of the ground-state radical anions of biscyanosubstituted perylene bisimides,\textsuperscript{20} we were able to obtain evidence for the initial electron transfer in the proposed photocatalytic cycle by UV/vis absorption spectroscopy. When a reaction sample consisting of 14j together with substrate 3 was irradiated for five minutes at 525 nm, the radical anion 14j\textsuperscript{−} was observed through its characteristic bands at 686 and 770 nm (SI; Figure S2). Thiophenol was omitted in this experiment to block the back electron transfer. Finally, we checked the photocatalytic activity of 14i in comparison to the more soluble 14j by irradiating substrate 26 with the maximum soluble concentration of 14j (70 \(\mu\)M, 1.1 mol%). A conversion of 49% was achieved, whereas an experiment with 14j (1.24 mM, 2 mol%) generated a conversion of 67%, supporting the idea that the more soluble PBI is the more efficient photoredox catalyst.

In conclusion, the two presented variants are complementary parts of the photocatalytic toolbox with organic photoredox active chromophores. In the case of transition-metal complexes as photoredox catalysts, oxidative or reductive quenching is controlled by the choice of substrates and additional reagents. In our photocatalytic toolbox, the regioselectivity of the endo-trig versus exo-trig intramolecular cyclizations of bifunctional \(\alpha\)-phenyl alkenes is controlled by the choice of the organic photoredox catalyst and the appropriate irradiation wavelength. The central photoredox catalytic reaction in both variants is an intramolecular nucleophilic addition of the hydroxy function to the olefin function. The \(N\)-arylphenothiazine 1 photocatalyzes the exo-trig cyclization to form five- and six-membered oxaheterocycles, whereas the perylene bisimide 14j photocatalyzes the endo-trig cyclizations to give five-, six-, and seven-membered oxaheterocycles. The preliminary scope with 11 representative substrates presented here shows the complementarity and similarity of the two photocatalytic variants, together with the high potential of this photocatalytic toolbox as an important and more-sustainable alternative to transition-metal catalysis.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

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The appropriate amine RNH2 (5.46 mmol, 3.00 equiv) was added to a solution of dibromide 12 (1.82 mmol, 1.00 equiv) in DMF (13a–f) or propionic acid (13e–j), and the mixture heated to 80 °C (13a–f in DMF) or under reflux (13g–j in propionic acid) for 15 h. In the case of 13i and 13j, ZnOAc (0.87 mmol, 0.04 equiv) was added. The solution was then cooled to r.t. and poured into H2O. The resulting precipitate was collected by filtration and washed with H2O. The crude product was purified by column chromatography (silica gel, CH2Cl2) to give a red solid; yield: 0.32–0.65 mmol (18–36%).

Red solid; yield: 0.32–0.65 mmol (31%) Rf = 0.7. 1H NMR (500 MHz, CDCl3): δ = 9.57 (d, J = 8.1 Hz, 2 H), 9.03 (s, 2 H), 8.81 (d, J = 8.1 Hz, 2 H), 7.52 (t, J = 7.8 Hz, 2 H), 7.37 (d, J = 7.8 Hz, 6 H, 2.84–2.54 (m, 4 H), 1.19 (d, J = 6.8 Hz, 24 H). 13C NMR (126 MHz, CDCl3): δ = 163.14, 162.64, 145.73, 138.62, 133.58, 133.41, 130.26, 130.05, 129.77, 128.86, 124.86, 123.32, 122.99, 121.20, 29.43, 24.18. HRMS (ESI): m/z [M+H]+ calcd for C50H40N4O4: 760.3050; found: 760.3147 [MH+].

Red solid; yield: 0.32–0.65 mmol (31%) Rf = 0.7. 1H NMR (500 MHz, CDCl3): δ = 7.24 – 7.04 (m, 4 H), 5.19 (s, 1 H), 4.85 (s, 1 H), 3.67 (q, J = 6.1 Hz, 2 H), 2.76 – 2.67 (m, 2 H), 20.05 (s, 3 H), 1.92 – 1.80 (m, 2 H), 1.30 (t, J = 5.5 Hz, 1 H). 13C NMR (101 MHz, CDCl3): δ = 146.00, 143.87, 138.43, 129.23, 128.38, 127.14, 125.90, 115.03, 62.31, 49.29, 21.59. HRMS (ESI): m/z [M+H] calcld for C48H40Br2N2O4: 866.1355; found: 867.1431 [MH+].

Red solid; yield: 0.34–0.53 mmol (65%); Rf = 0.2. 1H NMR (500 MHz, CDCl3): δ = 9.75 (d, J = 7.9 Hz, 2 H), 9.08 (s, 2 H), 9.03 (d, J = 8.1 Hz, 2 H), 7.54 (t, J = 8.3 Hz, 2 H), 7.38 (d, J = 7.8 Hz, 2 H), 2.82–2.58 (m, 4 H), 1.19 (d, J = 6.9, 2.0 Hz, 24 H). 13C NMR (126 MHz, CDCl3): δ = 162.77, 162.37, 161.93, 145.63, 138.56, 136.66, 134.17, 132.65, 132.08, 130.33, 129.71, 129.17, 127.39, 124.96, 124.48, 124.02, 119.11, 108.94, 29.24, 24.16. HRMS (ESI): m/z [M+] calcd for C68H66Br2N2O2: 816.3050; found: 816.3147 [MH+].

Samples of 14a–i contained small amounts of the corresponding 1,6-regioisomers, detectable by NMR spectroscopy, which were separated by flash chromatography. Photosubstitution by 1,6-regioisomers, detectable by NMR spectroscopy, which were separated by flash chromatography.