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Azide/oxygen photocatalysis with homogeneous and heterogeneous photocatalysts for 1,2-aminohydroxylation of acyclic/cyclic alkenes and Michael acceptors

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Abstract Homogeneous as well as heterogeneous photocatalysts that are able to oxidize the azide anion with low competitive singlet oxygen quantum yields are used to generate azidyl radicals. These radicals add to electron-rich as well as electron-poor (Michael acceptors) alkenes, and carbon radicals are formed regioselectively. Trapping with triplet oxygen (type I photooxygenation) is diffusion controlled, and the initially formed peroxy radicals are reduced with regeneration of the photocatalyst. Fluorescence quenching studies reveal rapid photoinduced electron transfer in the first catalysis step. The lack of rearrangement products in the bicyclic terpene series (pinenes, limonene) accounts for rapid subsequent oxygen trapping and back electron transfer steps. The 1,2-azidohydroperoxidation enables synthesis of 1,2-azidoalcohols and 1,2-aminoalcohols by different reduction protocols. Substrate modification and combination of type II photooxygenation with electron transfer photocatalysis allows the synthesis of 1-amino-2,3-diols and 2-amino-1,3-diols.

Keywords Photochemistry · Photooxygenation · Azidyl radicals · Photoinduced electron transfer

Introduction

Oxygen transfer reactions are exceedingly important synthetic processes in organic synthesis and industrial chemistry of organic basic compounds [1]. With respect to atom economy [2], direct use of molecular oxygen appears as the most sustainable

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Dedicated to Professor Kazuhiko Mizuno on the occasion of his retirement from Osaka Prefecture University.

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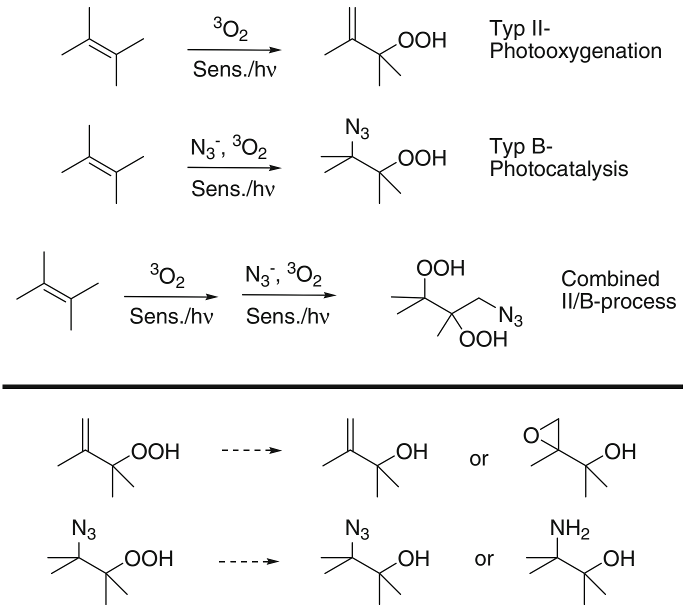
approach, encompassing activation of oxygen by specific oxygen transfer reagents or by transition-metal catalysts that activate oxygen transfer reagents. Triplet oxygen is however preferentially used in radical-type processes and not in polar reactions. Photochemical activation of triplet oxygen can occur by two initial processes: energy transfer and electron transfer, respectively, leading to singlet oxygen ($^1\Delta_g$–$^1O_2$) or to the superoxide radical anion [3]. Reactions of singlet oxygen with organic substrates that lead to oxygenated products ("chemical quenching") are termed type II reactions. These processes can be sensitized by numerous energy transfer photocatalysts, mostly triplet sensitizers with high intersystem crossing quantum yields and low-lying triplet states (1–2 eV). In these cases, the catalyst functions in a one-step process, initiating the spin inversion of oxygen from its triplet ground state with simultaneous formation of the catalyst in its electronic ground state. In the alternative electron transfer (ET) processes that are initiated by ET from or to a sensitizer molecule, a second electron transfer must occur in order to regenerate the ground state of the photocatalyst. If products are formed by concomitant combination, these processes are termed type A and type B for semiconductor photocatalysis [4]. In type A photocatalysis, from the light-generated electron–hole pair, two different products are formed, one resulting from substrate electron transfer to the semiconductor hole, and the other from substrate reduction by the semiconductor electron; in type B photocatalysis, combination products are formed.

Recently we described photocatalytic 1,2-aminohydroxylations via intermediate 1,2-azidohydroperoxides that make use of the azidyl radical as amino group precursor and molecular oxygen [5, 6]. This photochemical process is efficiently catalyzed by several photoinduced electron transfer (PET) sensitizers. Beside traditional fluorescent dyes, also nanosized semiconductor particles can be used [7]. It is crucial that these sensitizers do not (or hardly, e.g., Φ_Δ for fluorescein $= 0.03$) produce singlet oxygen by energy transfer from their excited triplet states, because most alkenes tend to react quickly under type II (singlet oxygen) conditions [8]. Thus, sensitizers with low triplet quantum yields and high singlet excited-state oxidation potential are most convenient. We have established rhodamine B and rhodamine 6G as efficient catalysts that are quenched by azide anions with rate constants of 1.6×10^9 and $3.3 \times 10^9\ M^{-1}\ s^{-1}$, respectively [5]. The well-studied PET catalyst 9,10-dicyanoanthracence (DCA) is quenched by azide in methanol/water with bimolecular rate constant of $6.4 \times 10^9\ M^{-1}\ s^{-1}$ [9]. The initial products of the complex reaction cascade are 1,2-azido-hydroperoxides that can be converted into azidoalcohols by mild reductants and into 1,2-aminoalcohols under stronger reduction conditions (Scheme 1). Even more appealing are processes that combine two photochemical steps, i.e., the type II photooxygenation that shifts the C=C double bond with concomitant allylic oxygenation and a subsequent type B photocatalysis that results in amino-1,2-diol structures.

The choice of sensitizer and solvent depends on the redox properties of the excited sensitizer and the solubility of the azide salt. Sodium and lithium azide can be used in water or in aqueous methanol, and trimethylsilyl azide is also applicable in acetonitrile in the presence of acetic acid [10]. The oxidation potential of azide anion in water has been reported as 1.32 V [11]. Thus, the limiting excited-state



Scheme 1 Reaction modes for the oxyfunctionalization and N,O-activation of alkenes

reduction potential is about 1.2 V, and most of the typical fluorescent dyes (e.g., fluoresceine, uranine, rhodamines, methylene blue) are applicable [12]. Rose Bengal with an excited-state reduction potential of 0.99 V [13] cannot oxidize azide exergonically and is used as a type II sensitizer for the generation of singlet oxygen.

Experimental

Photoreaction of substrates under homogeneous catalysis with sodium azide

A solution of 1 mmol of the alkene and 2.5 mmol (162 mg) sodium azide in 25 ml stock solution of methanol/water (95:5 vol %) containing 2×10^{-4} M sensitizer was irradiated under air for 24 h at 15 °C by means of a 70-W metal vapor lamp (Osram Vialux Super 44). The crude reaction solution was filtered and extracted with 3 × 15 ml methylene chloride. The organic phase was washed with 15 ml brine and dried over $MgSO_4$. After filtration, the crude reaction product was purified by column chromatography.

For 10 mmol reactions, 100 ml of solvent mixture and 5×10^{-3} M sensitizer concentration were applied.

Photoreaction of substrates under homogeneous catalysis with trimethylsilyl azide

A solution of 1 mmol mesitylol **12** (100 mg), 5 mmol (576 mg) trimethylsilyl azide, and 5 mmol (300 mg) acetic acid in 25 ml stock solution of methylene chloride containing 2 × 10^{-4} M rhodamine B (or 5 mg CdS) was irradiated under air for 12 h at 15 °C by means of a 70-W metal vapor lamp. Workup was as described above.

Photoreaction of substrates under heterogeneous semiconductor nanoparticle catalysis

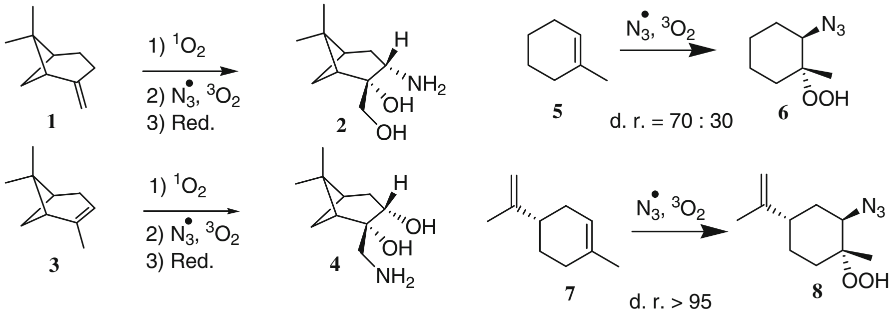
A solution of 1 mmol of the alkene and 2.5 mmol (162 mg) sodium azide in 25 ml stock solution of methanol/water (95:5 vol %) containing 5 mg CdS was irradiated under air for 12 h at 15 °C by means of a 70-W metal vapor lamp (Osram Vialux Super 44) under vigorous stirring. Workup was as described above.

Results and discussion

Substrates for the azidohydroperoxidation reaction

The rate constants of azidyl radical addition to alkenes were determined by Workentin and coworkers [11] and range from 10^{6} M^{-1} s^{-1} (for cyclohexene) to 1.3 × 10^{8} M^{-1} s^{-1} (for tetramethylethylene). No results for Michael acceptors are known. In Scheme 2, an overview on the azidohydroperoxidation of cyclic electron-rich alkenes is given. The pinenes **1**, **3** can be prior to the azidyl radical addition be converted to the corresponding allylic hydroperoxides by means of singlet oxygen reaction and eventually give the amino diols **2**, **4** in moderate overall yields [7]. Methylcyclohexene (**5**) and limonene (**7**) show moderate to high diastereoselectivity. In the case of limonene, the primary azidyl radical addition is *trans* selective with respect to the isobutenyl group and with high regioselectivity concerning the addition primarily to the higher-substituted double bond in Markovnikov fashion. The secondary oxygen addition is stereodirected in the case of limonene with much higher d.r. in comparison with the case of methylcyclohexene, possibly due to a steric combination effect of both isobutenyl and azide groups [5].

In the kinetic studies by Workentin et al. [11], styrene and α-methylstyrene are reported as azidyl acceptors with rate constants of 7 × 10^{6} M^{-1} s^{-1} and

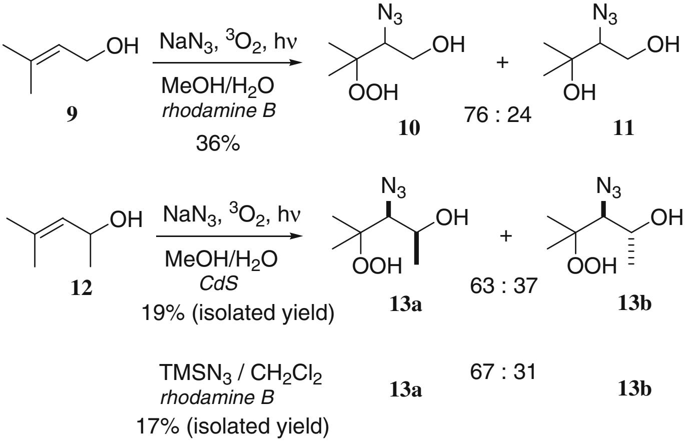


Scheme 2 Cycloalkenes as substrates under azidohydroperoxidation conditions

3×10^8 M^{-1} s^{-1}, respectively. We tested these substrates that are easily polymerizable under radical conditions and observed the corresponding azidohydroperoxides in moderate yields [5]. In all cases, the corresponding alcohols are formed as side products, and only for the styrene case as the major product.

As new substrates, which we currently use in singlet oxygen reactions as starting materials towards antimalarial peroxides [14], allylic alcohols were tested, among them prenol (**9**) and mesitylol (**12**). Allylic alcohol **9** could be reacted in methanol/water mixtures to give a mixture of azidohydroperoxide **10** and the azido 1,3-diol **11** with 36 % conversion and 30–40 % recovered substrate. In the case of the chiral substrate **12**, the solubility in protic media was low and only the heterogeneous CdS-catalyzed version resulted in products. A 2:1 mixture of *syn* and *anti* products, **13a** and **b**, respectively, was isolated. The relative configuration was determined by the characteristic $^3J_{HH}$-coupling constants. The major *syn* diastereoisomer has a $^3J_{HH}$ of 1 Hz whereas the minor *anti* diastereoisomer has a $^3J_{HH}$ of 8.2 Hz, which is in agreement with a preferred conformation with near-*anti* periplanar arrangement of the tertiary C–H bonds in the *anti* isomer. The direction of the stereodiscrimination effect parallels the result with singlet oxygen that also delivers preferentially the *syn* diastereoisomer [15]. This effect is slightly increased when changing the solvent to methylene chloride. Trimethylsilyl azide was used as azide ion source, and rhodamine B as photocatalyst (Scheme 3). This approach allows the synthesis of 2-amino-1,3-diols and enlarges the synthetic potential of the reaction.

A third class of substrates that was investigated for this communication were Michael acceptors. We used three α,β-unsaturated esters, the acrylate system **14** and two trisubstituted compounds, the methacrylate **17** and the tiglate **20**. In all cases, the substrate conversions were high but large amounts of polymeric materials were formed, especially from methylacrylate **14**. The major product was the β-azido propionate **15** beside the solvent incorporation product **16**. Whereas we have no convincing explanation for the Michael addition product **16** (which is not produced under thermal conditions), the azide **15** is the first example of a C-radical reduction



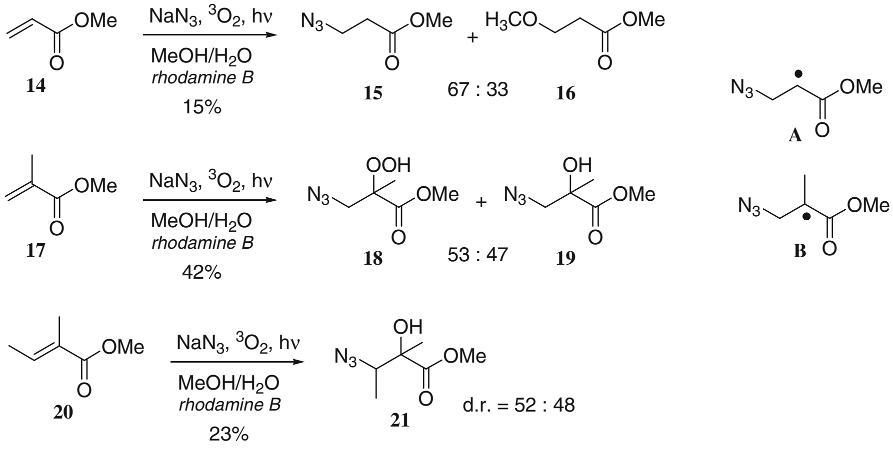
Scheme 3 Allylic alcohols **9** and **12** as substrates under azidohydroperoxidation conditions

by the sensitizer radical anion in the two-step electron transfer photocatalysis. This reaction is less preferred for α-methylated substrates, and thus was not observed for the compounds **17** and **20** (Scheme 4). Among all substrates investigated by us, the methacrylate **17** is the most efficient starting material, delivering a 1:1 mixture of azidohydroperoxide **18** and the corresponding alcohol **19** in good yields and with high substrate conversion. The difference in chemoselectivity (i.e., formation of an azide addition product **15** versus the regular trapping product **18**) appears due to the high tendency of C-radical **A** for back electron transfer by the sensitizer radical anion, whereas the C-radical **B** can be trapped by molecular (triplet) oxygen.

Sensitizers for the azidohydroperoxidation reaction

As already described in the "Introduction," the majority of the traditional fluorescent dyes are capable of exergonic electron transfer from azide anions to their electronically excited singlet states. The electron transfer rate can be determined by fluorescence quenching with a high degree of precision because accurate singlet lifetimes are available for all photocatalysts. The results for fluorescence quenching of four dyes that can be used in aqueous media or in acetonitrile (9,10-DCA) are summarized in Table 1. Typical fluorescence quenching and Stern–Volmer plots are shown in Fig. 1 for rhodamine 6G and coumain 151.

The efficiency of sensitizers as electron transfer photocatalysts were also studied by product analysis. In the azidohydroperoxidation of α-pinene (**3**), a highly reactive substrate with high regio- and stereocontrol, with total yields of 55–70 %, three products were formed, a 9:1 mixture of the azidohydroperoxide **22** and the azidoalcohol **23**, and an unknown side product, possibly a cyclobutane ring-opening derivative (Scheme 5). From the viewpoint of product chemoselectivity, uranine and coumarine 151 are the most effective photocatalysts, whereas the amount of azidoalcohol increases for rhodamine B and especially for CdS. This might be due



Scheme 4 Michael acceptors as substrates under azidohydroperoxidation conditions

Table 1 Fluorescence quenching in MeOH/H_2O (1:1) of dyes in the presence of azide anions: τ_S and k_q

Sensitizer	τ_S [ns]	k_q [10^9 l mol^{-1} s^{-1}]
9,10-DCA	14.8 [16]	6.4
Rhodamine B	6.2 [17]	1.6
Rhodamine 6G	3.7 [17]	3.3
Coumarin 151	6.7 [18]	2.3

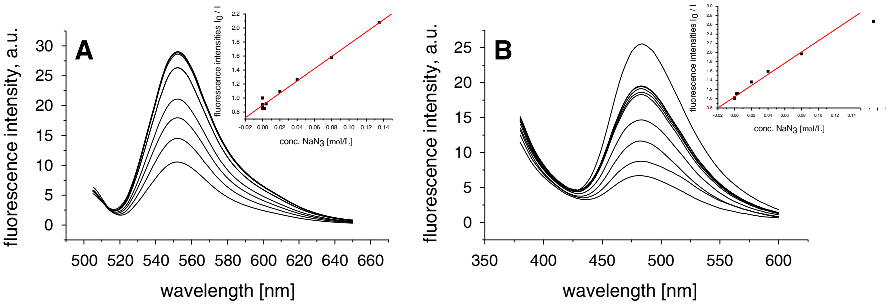
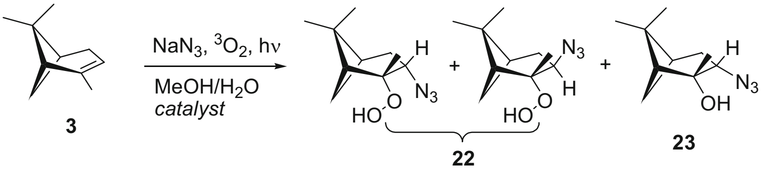


Fig. 1 Fluorescence quenching by azide anions (aqueous media) for rhodamine 6G (**a**) and coumarin 151 (**b**) in H_2O/MeOH (1:1); insets: Stern–Volmer plots

to less efficient electron back transfer from the photocatalyst radical anions (from uranine, coumarines, or 9,10-DCA) or radicals (from the cationic dyes rhodamine B and 6G). In competition with this electron back transfer to the rapidly formed peroxy radical, reductive pathways might exist that reduce the peroxy radical to the hydroxyl group with irreversible oxygenation of the catalyst. In the case of heterogeneous photocatalysis with semiconductor nanoparticles, this reaction leads to the formation of oxidized catalyst that precipitates out of the solution; rhodamine 6G shows rapid bleaching (Table 2).

Mechanism of the azidohydroperoxidation reaction

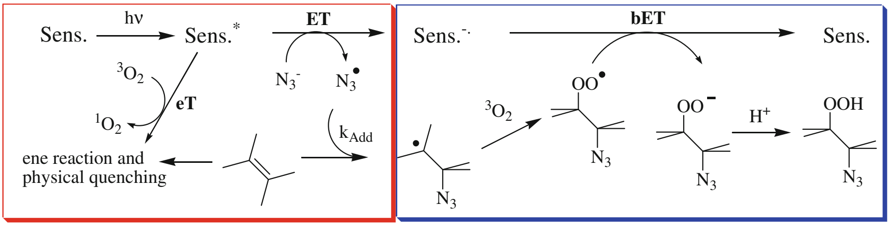
Describing a multistep catalytic process by kinetic data is obviously a challenging task that can only be achieved if the individual steps of the process can be investigated independently from the general process. Furthermore, molecular probes that report the feasibility of the postulated reaction steps in the global process are necessary. In the photocatalytic azidohydroperoxidation that we have developed,



Scheme 5 α-Pinene under azidohydroperoxidation conditions

Table 2 α-Pinene (**3**) under azidohydroperoxidation conditions: product pattern [rel. ratios by ^{1}H nuclear magnetic resonance (NMR)]

Sensitizer	Hydroperoxide (%) **22**	Alcohol (%) **23**	Byproduct (%)
Rhodamine B	79	20	1
Rhodamine 6G	82	7	11
9,10-Dicyanoanthracene	72	14	14
Uranine	87	2	11
Coumarine 151	88	4	8
CdS	62	25	10



Scheme 6 1,2-Azidohydroperoxidation: the overall mechanism

four reaction steps can be identified: primary electron transfer with formation of the azidyl radical, alkene addition of the azidyl radical, oxygen trapping of the carbon radical, and secondary electron transfer with formation of the peroxy anion and reformation of the photocatalyst.

In competition with step 1 (ET), triplet–triplet energy transfer (eT) can occur with formation of singlet oxygen. This process was evaluated by typical singlet oxygen acceptors and, under normal cases, cannot compete with ET in the case of highly fluorescent dyes with appropriate excited-state reduction potentials. The rate of azidyl radical addition to alkenes ($k_{\mathrm{add}} = 10^7$–$10^8\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$) was evaluated in the absence of oxygen [11], the formation of azidyl radicals ($k_q = 2$–$6 \times 10^9\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$) was evaluated by fluorescence quenching methods, and the rates of triplet oxygen addition to carbon-centered radicals are well known ($k_{\mathrm{add}} = 2$–$5 \times 10^9\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$ for benzylic radicals [19]). This is in excellent agreement with the low amounts of radical-induced ring-opening reactions that we have observed in the pinene series (vide supra) (Scheme 6).

Conclusions

Organic azides are highly useful substrates for numerous reactions in organic synthesis [20], including the fabulous "click" reaction [21]. Using the process developed by us, the azide group can be introduced into unsaturated substrates with high regio- and diastereoselectivity. The usefulness of the photocatalytic process is still limited concerning the azide source, the solvents, and especially the best possible photocatalyst. Promising photocatalysts are nanosized semiconductor particles such as CdS or TiO_2 [7] that are currently being studied.

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