EurJOC
European Journal of Organic Chemistry

Communications
doi.org/10.1002/ejoc.202001533

Chemistry Europe
European Chemical Societies Publishing

Nucleophilic Alkoxylations of Unactivated Alkyl Olefins and α-Methyl Styrene by Photoredox Catalysis

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N,N-diisobutylaminophenyl-phenothiazine is a strongly reducing catalyst that allows – for the first time – the photoredox catalytic addition of alcohols to alkyl olefins as non-activated substrates to products with Markovnikov orientation. The irradiation at 365 nm does not require any additional reagent. Using α-methyl styrene as activated substrate we additionally show that this photoredox catalytic method tolerates other functional groups, including allyl, alkynyl, cyanide, and even acid-labile Boc groups within the substrate scope.

Photoredox catalysis is a recently established method of synthetic organic chemistry that uses light, from the UV to the visible range, to run reactions by alternative paths that are not trodden by conventional thermal reactions.[1] As a result, photoredox catalysis expands the current repertoire of organic reactions.[2] Transition metal complexes, in particular with ruthenium, are typically used as photoredox catalysts. With respect to the limited availability and the rate of rare earth metals, organic chromophores provide important alternatives, as recently demonstrated with e.g. eosin Y,[3] rhodamine 6G,[4] mesityl[5] and aminoacridinium,[6] naphthochromenones,[7] 4,6-dicyanobenzenes,[8] and thioxanthones.[9] In contrast to transition metal complexes, the versatility of organic chromophore is much more restricted; there is not one single organic photoredox catalyst for diverse photoredox catalytic transformations. It is therefore important that organic chromophores can be modified to adjust the photoredox properties to the given synthetic problems.[9,10] *N*-phenylphenothiazines (PPT)[11] fulfill this requirement because they can be modified by electron-donating or -withdrawing groups either at the core or at the phenyl substituent to vary the optoelectronic properties.[12] Other groups used PPT for dehalogenations[13] and for ATRA (atom transfer radical addition) polymerization.[14] We were able to activate inert SF_6 by PPT to yield pentafluorosulfanylated organic compounds.[15] PPT can also be used for nucleophilic Markovnikov-type addition of simple alcohols to activated olefins, such as α-phenyl and α-methyl styrene (**3** and **4**).[16] The non-photochemical version of this reaction is a key step in organic chemistry; conventional methods are the two-step procedure consisting of iodoalkoxylation using NIS and subsequent reduction of the alkyl iodide in moderate yields[17] or the direct acid-catalyzed addition, e.g. by heated ion exchange resin.[18] Accordingly, these methods are not suited for the alkoxylation of acid-labile olefins as substrates or with acid-labile alcohols. We present herein the photoredox catalytic addition of alcohols to unactivated alkyl olefins by the use of alkylated PPTs **1** and **2** (Figure 1). We demonstrate a broad substrate scope with respect to the non-activated olefins **5**–**9** as substrates for methanol addition. Using α-methyl styrene (**4**) as activated substrate we additionally show that this photoredox catalytic method tolerates other functional groups in the alcohols that are added.

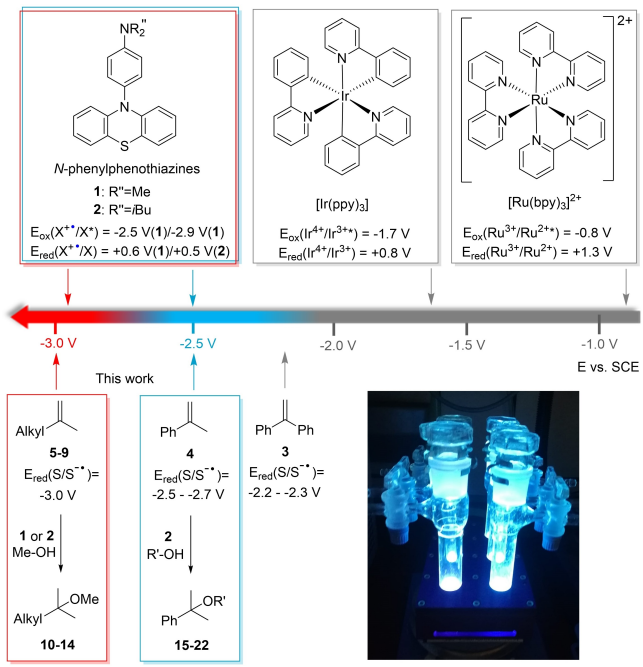

Figure 1. *N*-phenylphenothiazines **1** and **2** and transition metal complexes as photoredox catalysts, their redox potentials in relation to the redox potentials of differently substituted olefin substrates, like activated α-phenyl and α-methyl styrene (blue, **3** and **4**) and unactivated alkyl olefins **5**–**9** (red), for nucleophilic alkoxylation (R"–OH) to products with Markovnikov selectivity **10**–**22**, for R' see Figure 4. The image illustrates the photochemistry reactors.

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Supporting information for this article is available on the WWW under https://doi.org/10.1002/ejoc.202001533

The oxidation potentials $E_{ox}(X^{+\bullet}/X) = 0.49\ V - 0.57\ V$ (vs. SCE) together with the singlet excited state energies $E_{00} = 3.1–3.5$ eV give estimated excited state oxidation potentials $E_{ox}(X^{+\bullet}/X^*)$ between −2.5 V (for **1**) and −2.9 V (for **2**). α-methyl styrene (**4**) is an activated substrate due to the phenyl group whereas 2-methylhept-1-ene (**5**), 2-methylhex-1-ene (**6**), methylenecyclopentane (**7**), 1-methylcyclopent-1-ene (**8**) and 1-methylcyclohex-1-ene (**9**) are only alkylated and therefore considered as non-activated substrates. This difference is documented by their reduction potentials; the potential of **4** lies in the range between that of α-phenyl styrene (**3**), $E_{red}(S/S^{-\bullet}) = -2.3$ V, and that of styrene, $E_{red}(S/S^{-\bullet}) = -2.6$ V,[19] whereas the potential of alkyl olefins, like **5**–**9**, is found at approximately $E_{red}(S/S^{-\bullet}) = -3.0$ V.[20] After excitation of **1** or **2** as photoredox catalyst, an electron is transferred onto the substrate (**5** representatively shown as substrate in Figure 2) if the oxidation potential in the excited state is sufficiently high. The driving force ΔG of this critical electron transfer process can be estimated according to Rehm-Weller $\Delta G = E_{ox} - E_{red} - E_{00}$ (lacking the Coulomb interaction energy E_c). For the photoredox catalysts **1** and **2** the ΔG values lie in the range between −0.5 eV and ±0.0 eV, predicting an exergonic electron transfer with substrate **4**, but borderline cases for the less activated substrates **5**–**9**. The radical anion $\mathbf{5}^{-\bullet}$ that is formed after the photoinduced electron transfer gets instantaneously protonated to the neutral radical **5**˙. Back electron transfer to the photoredox catalysts converts the substrate into an electrophile which subsequently reacts with alcohols (R′–OH, like MeOH) as nucleophiles to the final addition product **10**. We studied this mechanism in our previous publications.[15,16] Additionally, the steric hindrance of the alcohols strongly influences yields (*vide infra*) and thereby supports the nucleophilic attack onto the cation $\mathbf{5}^+$.

In control experiments without the addition of a catalyst or without irradiation no products could be isolated. The substrates **5**–**9** were irradiated at 365 nm in the presence of methanol and the respective photoredox catalyst **1** or **2** (10 or 5 mol%). In general, the use of photoredox catalyst **2** gives higher yields of products **10**–**14** than catalyst **1**, also with higher catalyst loadings of 10 mol% (Figure 3). This difference can be attributed to the much stronger excited state redox potential of **2**, $E_{ox}(X^{+\bullet}/X^*) = -2.9$ V, in comparison to $E_{ox}(X^{+\bullet}/X^*) = -2.5$ V for **1**. Using a catalyst loading of 5 mol% **2**, the products **10**–**14** were formed in yields of 12–68% (Table 1). The yields could not be simply increased by a higher catalyst loading of 10 mol% **2**. The best yields of 46% and 68% were obtained for products **10** and **11**, respectively, after an extended irradiation time of 185 h. These are extremely long irradiation times, but these examples should be considered as proof-of-principle since is very remarkable that terminal alkyl olefins can indeed be converted by such simple photoredox catalysis.

Furthermore, there is no need for any additive, in particular, no trimethylamine as an electron shuttle for efficient back electron transfer.[21] This is an important feature of our photoredox catalytic method. Thus, a broad variety of different functional groups should be tolerated that are typically not stable during conventional reaction conditions for alcohol additions to olefins.[17,18] To widen the substrate scope not only with respect to the olefins but also with respect to the alcohols we applied the activated substrate **4** for the photoredox

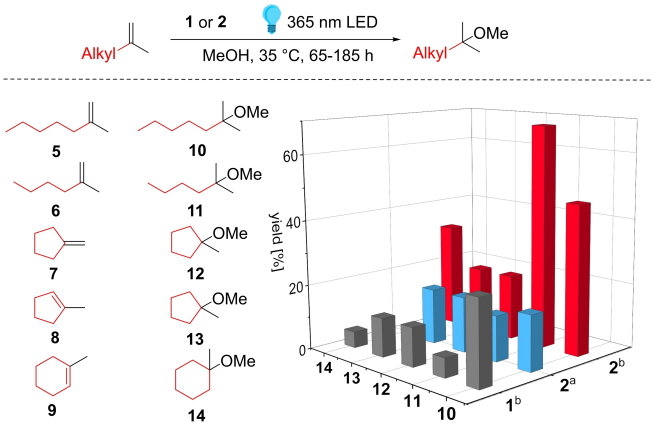

Figure 3. Substrate scope **5**–**9** and yields of products **10**–**14** after photoredox catalytic methoxylation by *N*-phenylphenothiazines **1** and **2**; [a]10 mol%; [b]5 mol%. For irradiation times, see Table 1. The yields were determined by GC.

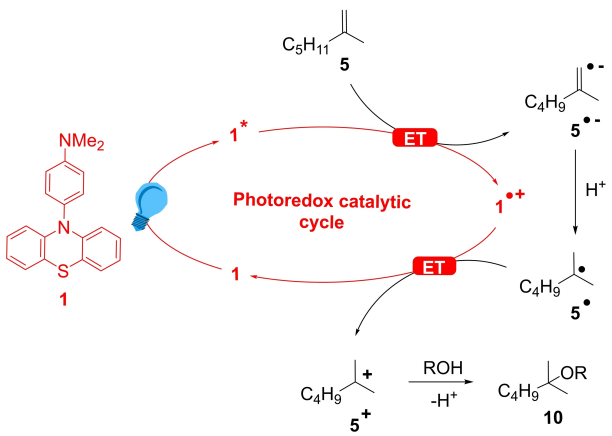

Figure 2. Proposed mechanism for photoredox catalyzed addition of alcohols (ROH) to alkenes, like the non-activated alkene **5**, ET = electron transfer, irradiation by 365 nm LED.

Table 1. Screening of reaction conditions for methoxylation of alkenes **5**–**9** to products **10**–**24**, 35 °C, MeOH, 365 nm LEDs. The yields were determined via GC.

Catalyst	[mol %]	Substrate	T [h]	Product	Yield [%]
1	5	**5**	65	**10**	26
2	5	**5**	185	**10**	46
2	2	**5**	185	**10**	24
1	5	**6**	65	**11**	6
2	10	**6**	65	**11**	14
2	5	**6**	185	**11**	68
1	5	**7**	65	**12**	12
2	10	**7**	65	**12**	12
2	10	**7**	185	**12**	20
1	5	**8**	65	**13**	12
2	10	**8**	65	**13**	17
2	5	**8**	185	**13**	20
1	5	**9**	65	**14**	5
2	5	**9**	185	**14**	32

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catalytic alkoxylation with a broad range of different alcohols (Figure 4). Remarkably, alcohols with allyl, alkynyl, and cyanide groups are converted to products **18**, **20**, and **21** in excellent yields of 66–98%. Even the Boc protecting group is tolerated, both as part of the alcohol yielding product **22** or as part of the olefin substrate **23**. The photoredox catalyzed conversion of **4** with 3-(Boc-amino)1-propanol gives product **22** in 85% yield. The methoxylation of the Boc-protected substrate **23** gives product **24** in 80% yield. These results show that this type of photocatalysis is also well suited for alkoxylation of acid-labile substrates and peptide chemistry based on Boc-protected building blocks.

In conclusion, we showed that the photoredox catalytic addition of alcohols to non-activated terminal alkyl olefins is obtained by the use of *N*,*N*-di*iso*butylamino-phenylphenothiazine **2**. Its excited state redox potential is sufficiently high to promote the photoreduction of non-activated alkyl olefins and the subsequent nucleophilic addition of MeOH. Despite the long irradiation times and the moderate yields, this is -to the best of our knowledge- the first time that alkyl olefins have been at all converted by photoredox catalysis. In particular, this will offer new synthetic routes in polymer chemistry. We demonstrate a broad substrate scope not only with respect to the non-activated olefins as substrates but also with respect to a variety of alcohols with additional functional groups. In particular, allyl, alkynyl, and cyanide groups are tolerated. Even the very acid-labile Boc protecting group is tolerated, both as part of olefin and as part of the alcohol as substrates. In general, this photoredox catalysis complements conventional thermal addition reactions with alcohols to products with Markovnikov-type regioselectivity, and in particular for Boc-protected amino acid building blocks in peptide chemistry. Since no additives are needed, the reaction conditions are extremely mild and simple. Furthermore, a high level of sustainability is achieved by the use of light and the use of an organic chromophore as a photoredox catalyst.

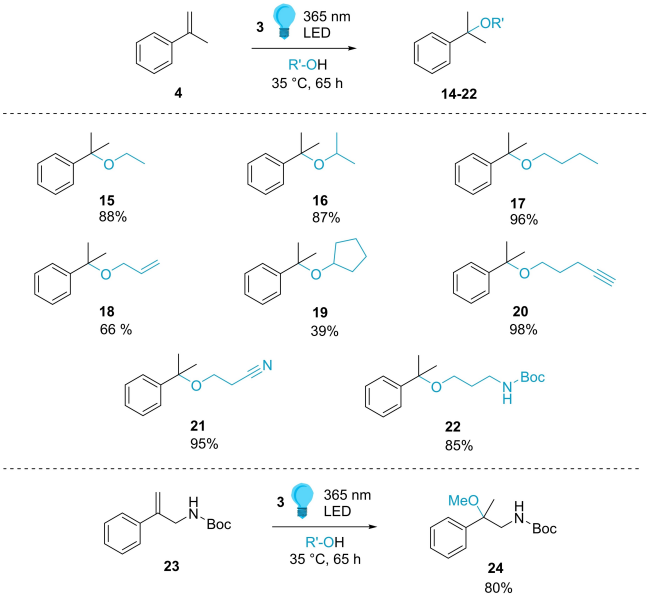

Figure 4. Substrate scope for the reaction of α-methyl styrene (**4**) with respect to different types of alcohols R'–OH to products **15**–**22**. Additionally, the Boc-protected substrate **23** was methoxylated to product **24**. General reaction conditions: 0.17 mmol **4**, alcohol (R'–OH) as solvent, 10 mol% **2**, 35 °C, 65 h, 365 nm LEDs. The yields were determined by ^{1}H NMR by using an internal standard (CH_2Cl_2).

Acknowledgements

This work was financially supported by the Deutsche Forschungsgemeinschaft (DFG, grant Wa 1386/16-2) and the Karlsruhe Institute of Technology (KIT). Open access funding enabled and organized by Projekt DEAL.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Chromophores · Energy transfer · Phenothiazine · Photocatalysis · Radicals

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Manuscript received: November 24, 2020
Revised manuscript received: December 4, 2020
Accepted manuscript online: December 8, 2020

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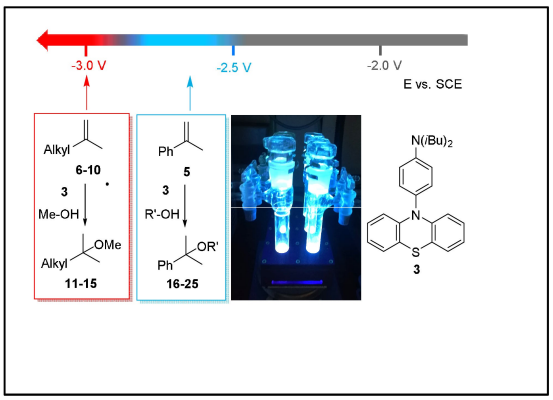

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The photoredox catalytic addition of alcohols to non-activated terminal alkyl olefins is obtained by the use of *N*,*N*-di*iso*butylamino-phenylphenothiazine. Its excited state redox potential is sufficiently high to promote the photoreduction.