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Acid promoted radical-chain difunctionalization of styrenes with stabilized radicals and (N,O)-nucleophiles†

Sensheng Liu and Martin Klussmann *

A difunctionalization of alkenes through sequential addition of a radical and a nucleophile has been developed, which is suggested to proceed by a radical chain mechanism not requiring a catalyst. An electron transfer step to the oxidant benzoyl peroxide is facilitated by protonation with a strong acid.

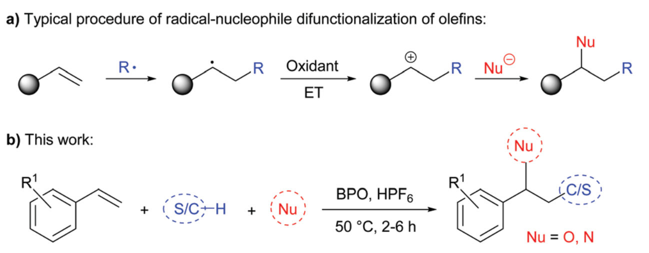
The difunctionalization of alkenes is a powerful transformation in synthetic organic chemistry. Besides transition-metal catalysed methods that proceed *via* organometallic intermediates,[1] such reactions can be efficiently conducted by addition of free radicals.[2] An interesting strategy amongst these is the consecutive addition of a radical and a nucleophile, which requires an electron transfer (ET) step after the radical addition, in order to generate a carbocation that could be trapped by a nucleophile (Scheme 1a).[2a,3] Such reactions would enable functionalizing olefins with a wide variety of reagents in a regioselective manner, given that radical precursors and nucleophiles mostly react complementarily. Although many synthetically interesting methods have been developed towards this goal, there is as of yet no method with a truly broad substrate scope of both radicals and nucleophiles.[4–6] Most of these methods require the presence of a transition metal catalyst or reagent to achieve the desired ET forming the carbocation intermediate, notable exceptions utilize an organic photocatalyst,[7] iodide as catalyst[8] or electrochemistry.[9]

We had previously worked on the activation of *tert*-butyl hydroperoxide by Brønsted acids, most notably in the presence of ketones.[10] We noticed the work by Zhang, Bao and co-workers, who reported a copper-catalysed difunctionalization of alkenes using benzoyl peroxide (BPO) in the presence of HPF_6.[11] Acetonitrile was both radical precursor and nucleophile and the role of the acid was not clear, thus it raised our interest for its combination of a peroxide and acid and its potential to add radicals and nucleophiles to olefins.

Here, we report mechanistic details of the effect of acid on benzoyl peroxide and a method for difunctionalization of styrene derivatives with stabilized C- and S-radicals and N- and O-nucleophiles. The reactions do not require a catalyst but the presence of a strong Brønsted acid, and they operate at only slightly elevated temperature (Scheme 1b).

We found that the combination of BPO with HPF_6 allowed for the addition of thioxanthene (**2a**) and acetonitrile to styrene (**1a**) without any additional catalyst within two hours at 50 °C (Table 1, entry 1). The product's structure (**3a**) suggested that a thioxanthenyl radical was added to styrene and subsequently acetonitrile attacked as a nucleophile in a Ritter reaction.[12] The C-radical of thioxanthene had apparently formed by H-atom transfer (HAT),[13] presumably to a benzoyloxyl radical generated from BPO.

The acid plays a crucial role for the reaction: with lower amounts, the yield drops significantly (entry 2) and without acid, no reaction occurs (entry 3; for further results under changed reaction conditions, see the ESI†). In the presence of other acids, the product was also formed, but apparently the yield is correlated with the acid strength. For example, trifluoroacetic acid gave only 11% of **3a**, while the stronger acids HBF_4 and $HClO_4$ gave 39% and 51% (entries 4–6). In the absence of BPO and with other peroxide oxidants, the product was not formed. Ambient temperature is sufficient for the reaction, but


a) Typical procedure of radical-nucleophile difunctionalization of olefins:

b) This work:

Scheme 1 Radical-nucleophile addition of olefins. BPO = Benzoyl peroxide.

Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, 45470 Mülheim an der Ruhr, Germany. E-mail: klusi@mpi-muelheim.mpg.de

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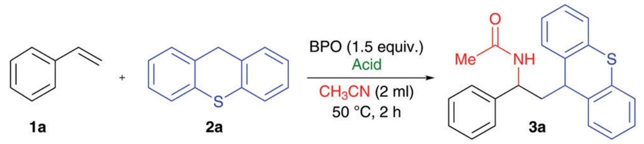
Table 1 Optimization of the reaction conditions[a]



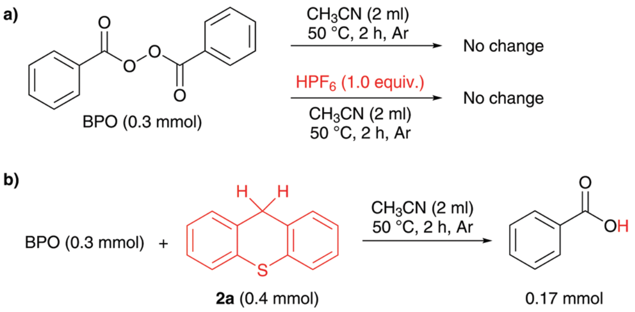
Entry	Acid	Acid equiv.	Yield[b] (%)
1	HPF_6 (aq., 55%)	1.0	88
2	HPF_6 (aq., 55%)[c]	0.1	20
3	—	—	0
4	CF_3CO_2H[c]	1.0	11
5	HBF_4 (aq., 48%)	1.0	39
6	$HClO_4$ (aq., 70%)	1.0	51
7[d]	HPF_6 (aq., 55%)	1.0	91 (88, 83[e])

[a] **1a** (0.2 mmol), **2a** (0.4 mmol, 2.0 equiv.), BPO (0.3 mmol, 1.5 equiv.), Acid (0.2 mmol, 1.0 equiv.) in CH_3CN (2 ml). [b] Yields determined by ^1H NMR spectroscopic analysis of the crude reaction mixture relative to internal standard CH_3NO_2, yield of isolated product in parentheses. [c] With addition of 1.0 equiv. of water. [d] Degassed, under argon. [e] Performed on a larger scale, isolating 1.5 g of **3a**.

the rate is significantly reduced. Performing the reaction under strict exclusion of oxygen increased the yield, and the reaction could also be performed on a larger scale, giving 1.5 g of **3a** with an isolated yield of 83% (entry 7).

The reaction is very likely proceeding *via* a radical mechanism, as the addition of radical inhibitors reduced the yield significantly (see the ESI† for details). The acid apparently does not affect the decomposition of BPO, which has a reported 10 hour half-life temperature of 73 °C.[14] As an NMR experiment revealed, BPO with or without acid did not change when heated in acetonitrile at 50 °C for two hours (Scheme 2a). However, in the presence of thioxanthene, benzoic acid was formed in significant amounts under these conditions, indicating that it accelerates the peroxide decomposition (Scheme 2b).

While the acid does not accelerate the homolytic cleavage of BPO, it does change its redox potential. We studied this effect by cyclic voltammetry (Fig. 1). The reduction of BPO alone was found to occur at −345 mV, which underwent a shift by +470 mV in the presence of 0.66 equiv. of HPF_6, the relative amount used under reaction conditions. Other acids also induced such a shift, but less strong, as is shown here for trifluoroacetic acid (for other acids, see the ESI†). The reduction was thus significantly eased by the strong acid HPF_6, possibly by protonation that turns the now cationic peroxide into a better electron acceptor.



Scheme 2 Experiments pointing to the reaction mechanism.

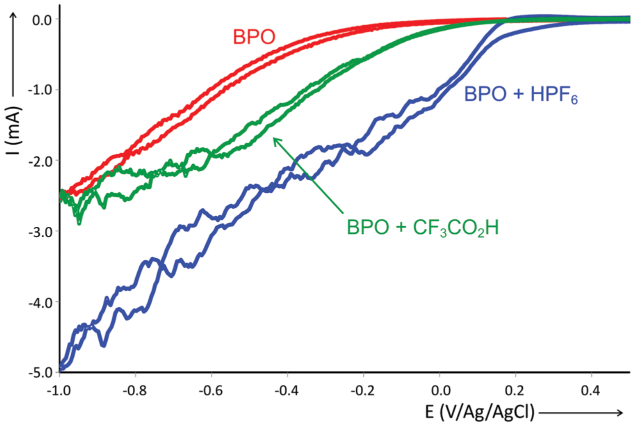
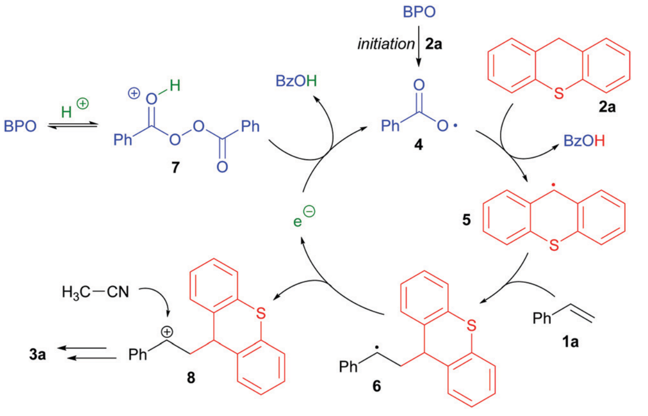


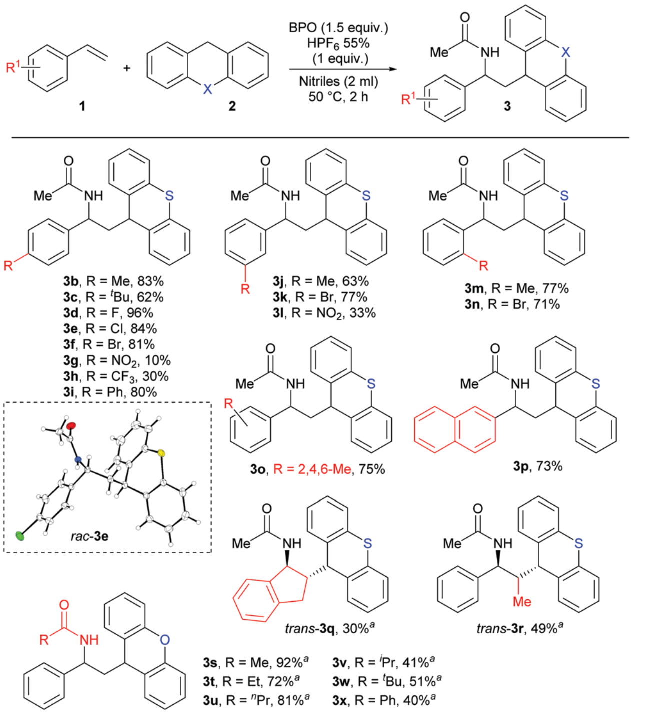
Fig. 1 Cyclic voltammograms showing the effect of acid addition on the reduction potential of BPO. Two platinized Pt wires as a counter and working electrode with a Ag/AgCl electrode as a reference were used. The cyclic voltammetry (CV) was conducted from −1.0 V to 2.0 V with a scan rate of 100 mV s^{-1}. BPO (0.3 mmol), acid (0.2 mmol), tetrabutylammonium hexafluorophosphate (0.1 M) in CH_3CN under Ar.

These results indicate a reaction mechanism that relies on electron transfer (ET) steps (Scheme 3). Initiating benzoyloxyl radicals (**4**) are formed from BPO in the presence of thioxanthene, possibly by ET to BPO that is facilitated by protonation. These induce HAT from thioxanthene, generating a new radical (**5**), which then adds to styrene, forming the benzylic radical **6**. This is oxidized by BPO in the presence of HPF_6, most likely by ET to the protonated peroxide (**7**), giving the intermediate carbocation **8**, benzoate and a new benzoyloxyl radical. The cation **8** can react as an electrophile with acetonitrile, generating the product **3a** in the fashion of a Ritter reaction. Thus, the reaction appears to run by a radical chain mechanism and can be seen as a case of "electron-catalysis".[15]

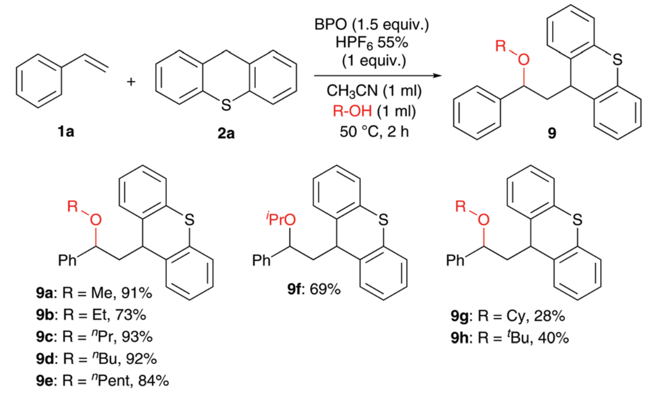
Based on this working model of the reaction's mechanism, other substrates that can initiate such a radical chain by interaction with BPO[16] and that easily form radicals by HAT to a benzoyloxyl radical should also be employable, as well as other olefins and alternative nucleophiles.



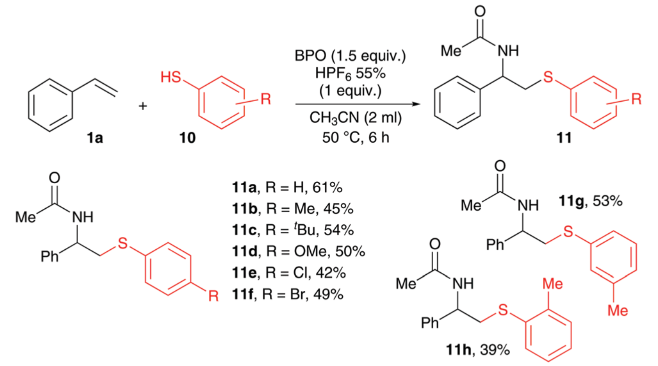
Scheme 3 Potential reaction mechanism, shown exemplary for **1a** and **2a**.



Scheme 4 Substrate scope for the reaction of styrenes and nitriles: **1** (0.2 mmol), **2** (0.4 mmol, 2.0 equiv.), BPO (0.3 mmol, 1.5 equiv.), HPF$_6$ (0.2 mmol, 1.0 equiv.) and nitriles (2 ml), Ar, isolated yield. ^{a}Reaction time: 6 hours. ORTEP diagram is drawn with displacement ellipsoids at the 50% probability level.



Scheme 5 Substrate scope for the reaction of alcohol nucleophiles: **1a** (0.2 mmol), **2a** (0.4 mmol, 2.0 equiv.), BPO (0.3 mmol, 1.5 equiv.), HPF$_6$ (0.2 mmol, 1.0 equiv.), alcohols (1 ml) and CH$_3$CN (1 ml), Ar, isolated yield.



Scheme 6 Substrate scope for thiylation: **1a** (0.2 mmol), **10** (0.4 mmol, 2.0 equiv.), BPO (0.3 mmol, 1.5 equiv.), HPF$_6$ (0.2 mmol, 1.0 equiv.) and CH$_3$CN (2 ml), Ar, isolated yield.

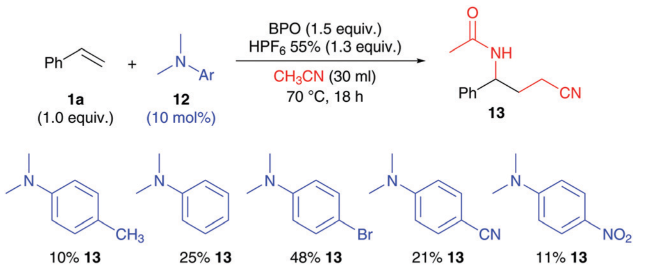
As shown in Scheme 4, styrenes with both weakly electron-donating (Me, ^{t}Bu) and withdrawing (F, Cl, Br) substituents on the aromatic ring, regardless of their positions, afforded the desired products in good yields 62–96% (**3b–3f, 3j–3k** and **3m–3o**), as did 4-vinylbiphenyl and vinylnaphthalene (**3i, 3p**). However, styrene bearing the strongly electron-donating methoxy substituent did not give the desired product, and the strongly electron-withdrawing NO_2 and CF_3 substituents led to low yields of **3g**, **3h** and **3l** in 10%, 30% and 33%. Using indene as olefin gave the product **3q** in 30% yield, but it is remarkable for its high trans-selectivity. A diastereomeric ratio of >21 : 1 was determined in the crude reaction mixture, but after purification, we received the pure trans-product **3q**. Similarly, only the trans-product **3r** was isolated from the reaction with *E*-β-methylstyrene. Strangely, other nitriles besides acetonitrile did not lead to the expected products with thioxanthene. However, when we used xanthene as HAT-donor, we could isolate different amide products by performing the reaction in different nitriles as solvent. Aliphatic and aromatic nitriles as well gave the products **3s–3x** with good yields after an extended reaction time of 6 hours. The general structure of these products was confirmed by X-ray crystallography of product **3e**.

Next, the scope with respect to nucleophiles was explored. Although we tried many substrates (see the ESI† for further details), only alcohols were successful, and only with thioxanthene but not with xanthene (Scheme 5). Reactions of styrene with various alcohols produced the expected products in good yields, with primary alcohols in generally higher yields (**9a–9e**, 73–93%) than secondary (**9f–9g**) and tertiary alcohols (**9h**).

Thiophenols (**10**) as HAT-donors with acetonitrile as nucleophile could also be employed successfully in this reaction with styrene (Scheme 6). While alkyl thiols did not react under those conditions, products **11** with various differently substituted thiophenols could be employed. Products of a thiol–ene reaction were not observed. Similar products like **11** had recently been reported, being synthesized by an iodide-catalysed radical reaction[8] or by ionic reactions also utilizing stoichiometric amounts of oxidants.[17]

Substrates not capable of initiating BPO decomposition obviously fail in this reaction. However, addition of extra initiators may overcome this limitation. We found that addition of *N*,*N*-dimethylanilines, well-known initiators for BPO,[18] enable the addition of two molecules of acetonitrile to styrene, furnishing **13** (Scheme 7). Although the yields are not as high as with Cu-catalysts,[11] 48% is reached with the use of 10 mol% of the *p*-bromo aniline. The product yield is obviously linked to the initiation rate and electronic properties of the anilines, as the comparison with more and less electron rich derivatives shows.

In conclusion, a method for the difunctionalization of styrenes with radicals derived from thioxanthene, xanthene



Scheme 7 Investigating dimethylaniline initiators: **1a** (0.5 mmol), BPO (0.75 mmol, 1.5 equiv.), HPF_6 (0.66 mmol, 1.3 equiv.), **12** (0.05 mmol) and CH_3CN (30 ml), isolated yield.

and thiophenols together with nitrile and alcohol nucleophiles was developed. The combination of benzoyl peroxide with HPF_6, a strong Brønsted acid, is a key element of the reaction that does not require transition-metal catalysts, high temperatures or prolonged reaction times. Mechanistic studies suggest that the acid can promote the electron transfer to the peroxide, and that the reaction proceeds by a radical chain that is initiated by interaction of the radical precursor with the peroxide. Addition of an extra radical initiator can overcome this limitation, which suggests a way to extend this synthetic strategy.

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Conflicts of interest

There are no conflicts to declare.

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