Interplay of Method Development and Mechanistic Studies – From Aerobic Oxidative Coupling to Radical Reactions via Alkenyl Peroxides

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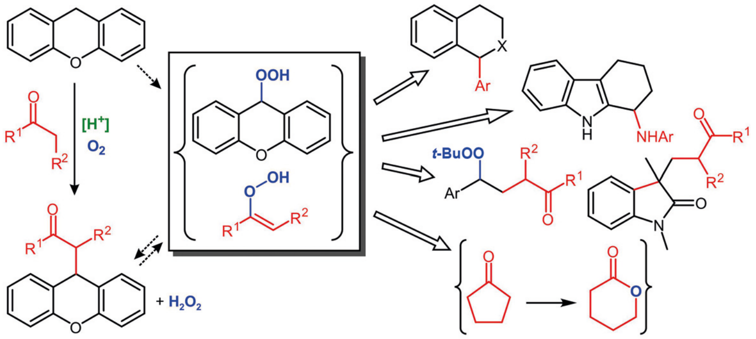

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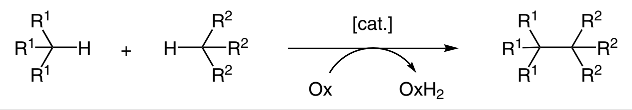
Abstract This account summarizes how scientific advances were made in the authors' research group by combining method development in organic synthesis with detailed mechanistic studies. The discovery of an unexpected autoxidative coupling reaction led, by virtue of an ever increased understanding of its mechanism, to a strategy for green C–H functionalization reactions, novel modes of radical generation, addition reactions of ketones to alkenes and new insights into an old reaction, the Baeyer–Villiger oxidation.

Key words homogeneous catalysis, green chemistry, oxygen, peroxides, radicals, reaction mechanisms, C–H functionalization

1 Introduction

Oxidative coupling reactions enable the formation of C–C bonds by functionalizing one or even two C–H bonds, which can obviously reduce the number of steps in a synthesis and allows simple starting materials to be utilized (Scheme 1).[2] Performing such reactions in a catalytic fashion is thus very attractive for green chemistry and explains the interest these reactions have received in recent years. However, many of the methods that have been developed require stoichiometric amounts of synthetic oxidants, additional additives and very high temperatures. It is thus desirable to develop reactions that can utilize simple and cheap oxidants such as elemental oxygen or air which produce benign waste products like water.[3]



Scheme 1 Catalytic oxidative coupling reactions forming new C–C bonds from two C–H bonds

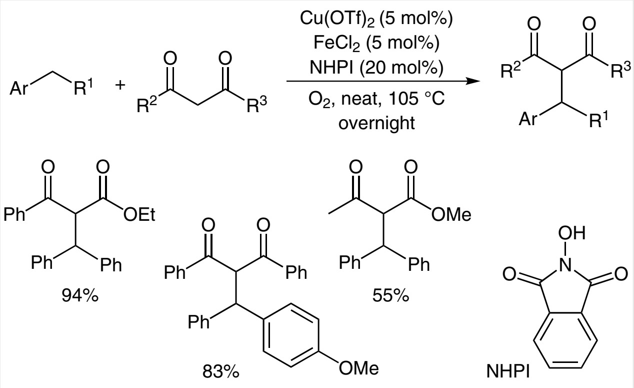
Our research group has committed itself to the development of oxidative coupling reactions that do not require extensive amounts of synthetic oxidants and additives. We are also intrigued by the mechanisms of these reactions, which are often not well understood. Our motivation to investigate oxidative coupling reactions is thus twofold: discovering synthetic methods and principles of chemical reactivity.

In this account, the development of a research project is outlined that illustrates the fruitful interplay of method development and mechanistic studies. It thus largely follows a chronological order and not a thematic one, and discusses results from our own group, but not without putting these into context with related topics.

2 Aerobic Oxidative Coupling Reactions with Benzylic C–H Bonds

In 2009, we started a project to develop a cross-coupling reaction that would functionalize benzylic C–H bonds by using oxygen as an oxidant. Several oxidative coupling reactions employing oxygen already existed at the time, for example with tertiary amines as substrates.[4] However, benzylic C–H bonds that are not stabilized by an adjacent nitrogen atom appeared to be significantly more difficult to cleave by oxidation.

In 2010 – and ahead of us – the Li group reported the first aerobic oxidative coupling method for benzylic compounds. It enabled the coupling of diarylmethanes and indane with various 1,3-dicarbonyl nucleophiles at 105 °C (Scheme 2).[5] They used a triple catalytic system of two transition-metal salts as well as *N*-hydroxyphthalimide (NHPI), an organic hydrogen atom transfer (HAT) mediator, as a variation of a system they had previously developed for the aerobic oxidative coupling of benzylic ethers.[6]



Scheme 2 Oxidative coupling reactions with benzylic C–H bonds using oxygen as the terminal oxidant

Conducting such transformations with oxygen remains a challenge even today. As one of the few developments besides this and the ones discussed below, Zhang et al. have developed a palladium-catalyzed method for benzyl ester formation using toluene.[7]

2.1 The Autoxidative Coupling with Xanthene

So, before the method shown in Scheme 2 had been published, we had set out to find substrates and conditions that would allow such an aerobic oxidative coupling reaction. Instead of high temperatures, we tried an approach of using elevated pressure, although the flammability of most organic solvents and substrates restricts such experiments to about 10 bar of oxygen, without more sophisticated equipment. The – perhaps somewhat naïve – rationale behind this approach was the assumption that if with oxygen as the oxidant the desired reactions would not run, more oxygen might help. After numerous screening experiments with various substrate and catalyst combinations, we found that xanthene (**1**) could be oxidatively coupled with simple ketones using transition-metal salts as catalysts together with a strong acid, and running the reactions at ambient temperature and at 10 bar partial pressure of oxygen. Some representative results are shown in Table 1. Commonly used redox-active metal chlorides were not very active (Table 1, entries 1–3), but palladium and nickel salts, for example, appeared as promising catalysts (Table 1, entries 4 and 5). Only later was a control experiment performed to study the reaction in the absence of a catalyst. Being very confi-

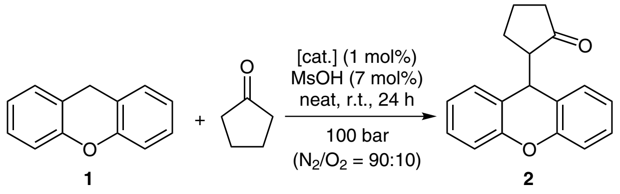
Biographical Sketches

Martin Klussmann leads a research group at the Max-Planck-Institut (MPI) für Kohlenforschung, Mülheim an der Ruhr, which develops synthetic methods with a focus on oxidative coupling reactions and green chemistry and investigates reaction mechanisms. He obtained his Ph.D. in the group of Professor M. Reggelin at the Technische Universität Darmstadt, Germany, and afterwards worked as a postdoctoral researcher with Professor D. G. Blackmond at Imperial College London, UK.

Bertrand Schweitzer-Chaput was born in Sèvres, France, in 1986. He received his bachelor's degree from Versailles-Saint-Quentin University, France, in 2008 and his master's degree from Paris XI University, France, in 2010. He then joined the Klussmann group at the MPI für Kohlenforschung for his doctoral studies. After staying there for an additional year as a postdoctoral researcher to reap (more of) the fruits of his discoveries, he moved to Tarragona, Spain, to take up a postdoctoral position with Paolo Melchiorre.

dent of the failure of this experiment, we were all the more surprised when the yield of the coupling product **2** actually improved (Table 1, entry 6).[8]

Table 1 Discovery of the Acid-Catalyzed Autoxidative Coupling

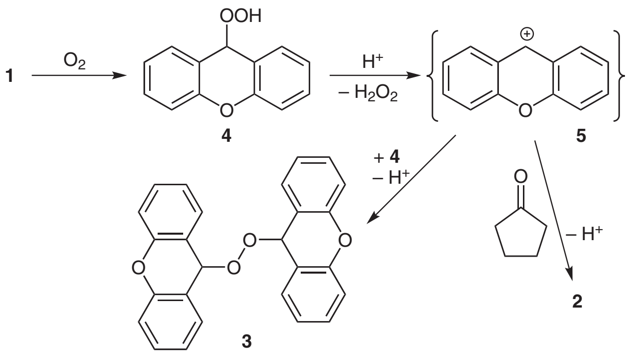


Entry	Catalyst	Yield (%)[a]
1	$CuCl_2$	0
2	$FeCl_2$	0
3	$MnCl_2$	18
4	$NiCl_2$	62
5	$PdCl_2$	78
6	–	85

[a] Determined by ^1H NMR spectroscopy

Obviously, this unexpected result was repeated and we wondered whether trace impurities of transition metals were responsible for the outcome. However, the experiment could be reliably reproduced and analysis by atomic adsorption spectroscopy indicated that the reagents were clean within the detection limit. Moreover, the addition of copper and iron salts actually inhibited the reaction (Table 1, entries 1 and 2) and so the seemingly positive effect of palladium and nickel salts obviously has to be attributed to their low activity as inhibitors. Accordingly, we believe that this reaction does not require any metal catalyst.

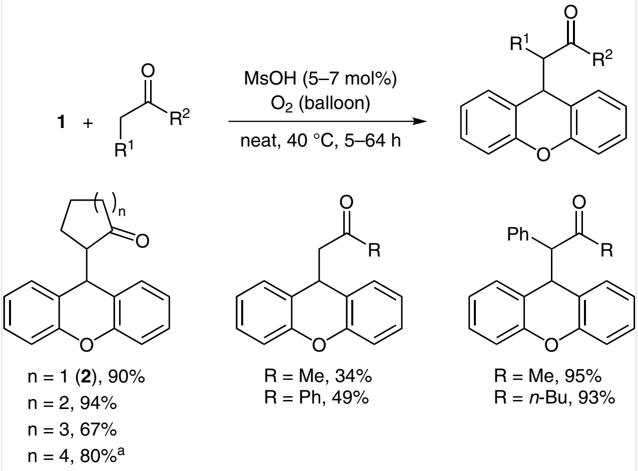
Under these circumstances, it was all the more intriguing to find out how the reaction worked, as it was undoubtedly an oxidative reaction that converted all of the starting material at ambient temperature within 24 hours, in the absence of any redox-active catalyst. During the screening of suitable acid catalysts, we observed the precipitation of xanthenyl peroxide **3** when using trifluoroacetic acid (TFA), an acid that was too weak to give high yields of the desired product. As a working model, we thus assumed that xanthene was activated by autoxidation, leading to a hydroperoxide **4**, which could be activated toward nucleophilic substitution by the acid catalyst, forming a stabilized xanthylium cation intermediate **5**. This could react with the enol form of a ketone to give **2** or with another hydroperoxide to yield **3** (Scheme 3).



Scheme 3 An initial working model of the autoxidative coupling reaction, including the formation of the observed by-product **3**

A hydroperoxide group is not usually regarded as a leaving group in nucleophilic substitution reactions, especially as organic hydroperoxides are known to undergo rearrangement reactions in the presence of strong acids, a process which is utilized in the industrial synthesis of phenol, for example.[9] However, it was also known from a few reports that hydroperoxides (including **4**) can be substituted under the right conditions, mediated by Brønsted or Lewis acids.[10]

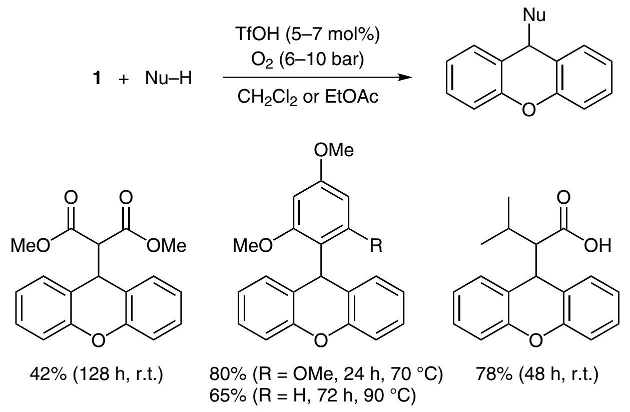
Obtaining a more refined model of the reaction mechanism turned out to take some time, but we will come back to that later. In the meantime, we turned our attention to exploring the synthetic possibilities of this discovery. We found that we could perform the reaction at ambient pressure under an atmosphere of oxygen, or even air, with only slightly reduced reaction rates, which could be improved by increasing the temperature a little to 40 °C. Under these conditions, the coupling product **2** was isolated in 90% yield and various other ketones could also be coupled with xanthene (Scheme 4).[8,11]



Scheme 4 Representative products from the autoxidative coupling reactions of ketones with xanthene at ambient pressure. [a] TfOH was used as the catalyst

Interestingly, acetone performed rather poorly, but in general, both acyclic and cyclic ketones could be coupled with xanthene under surprisingly simple conditions: stirring them neat in the presence of oxygen and a catalytic amount of a simple sulfonic acid.

At ambient pressure, only reactions with ketones gave reasonable product yields. Using other carbonyl derivatives was sometimes moderately successful, while all the other compounds tested did not show any reactivity. This indicates that high nucleophilicity[12] alone does not make a good substrate in this reaction. Again, by applying elevated pressure and temperature, we were able to broaden the product scope somewhat (Scheme 5).[8,11] Malonates, aldehydes and electron-rich benzenes could be used as nucleophiles. In the case of aldehydes, the isolated products turned out to be the over-oxidized carboxylic acids.

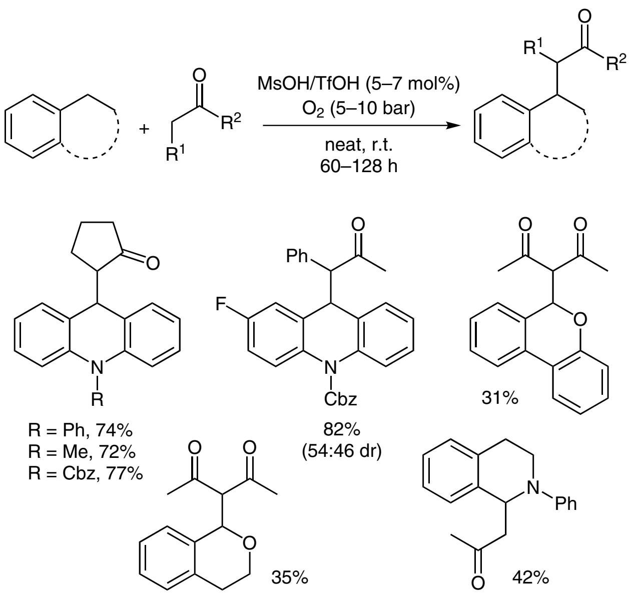


Scheme 5 Representative products with non-ketone nucleophiles using elevated pressure and temperature

Later studies revealed that the aerobic autoxidation of xanthene into peroxide **4** proceeds very well in ketones (and DMSO), but much less efficient in all the other solvents investigated.[13] This interesting solvent effect can explain the observed preference for ketone nucleophiles, but its nature remains unclear.

At ambient pressure of oxygen, xanthene was the only benzylic hydrocarbon substrate that we found to react with reasonable yields, with the exception of some acridanes. The latter, as well as a few other compounds with benzylic C–H bonds, reacted much better at elevated partial pressures of oxygen (Scheme 6).[8,11] As can be seen, the substrates are restricted to heterocycles. Diarylmethanes, however substituted, showed no reactivity under these conditions.

The observation of the isochromane-derived hydroperoxide **6** as an intermediate (Figure 1) supported the original working model of autoxidation and nucleophilic substitution.[11] However, it was also obvious from these results that any extension of the substrate and product scope would require to accelerate the autoxidation rate.



Scheme 6 Representative products from the autoxidative coupling reaction with other benzylic compounds at elevated pressure

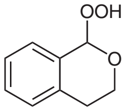


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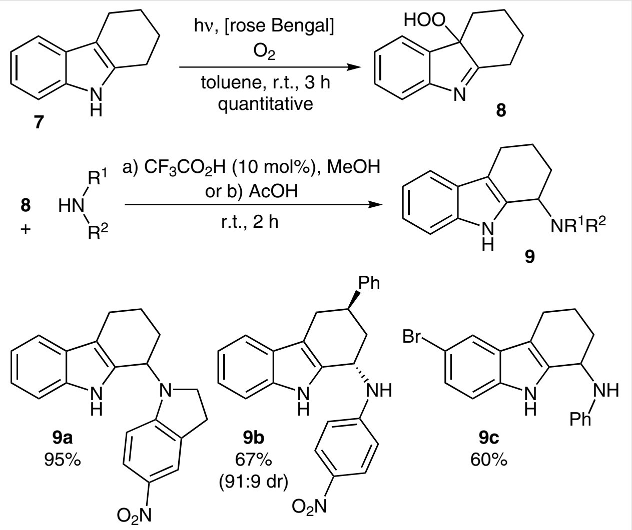
Figure 1 Isochromane-derived hydroperoxide **6**

2.2 With a Little Help from Light – CHIPS

The synthesis of hydroperoxides by reaction with singlet oxygen, generated by photochemical methods, is well-known.[14] We therefore investigated a strategy to combine their intentional synthesis with the acid-catalyzed substitution with nucleophiles, which would result in a two-step C–H functionalization via Intermediate PeroxideS (CHIPS), requiring only oxygen, visible light and catalysts and initiators, respectively. Related approaches had been investigated before but were generally limited to very few products.[15] We were able to achieve a proof-of-concept with tetrahydrocarbazoles **7** and N-nucleophiles (Scheme 7).[16]

The oxidation to the hydroperoxide **8** proceeds quantitatively by irradiation with visible light and rose Bengal as a sensitizer.[16a,17] Subjecting the isolated peroxide to acid in the presence of electron-poor anilines or related nucleophiles gave products **9** after short reaction times. Depending on the substrate, the reaction conditions of the second step can be varied to achieve optimum results.[16a] Some of the products, for example **9c**, have potent antiviral properties.[18]



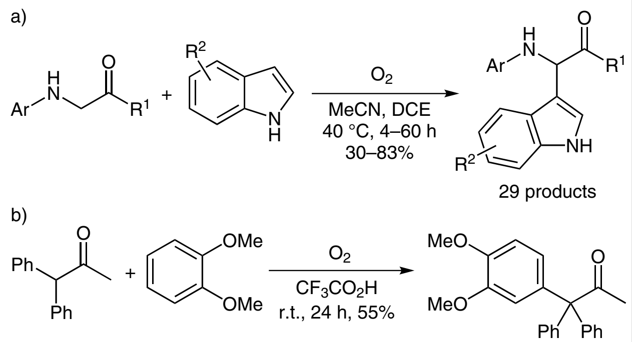
Scheme 7 Synthesis of substituted tetrahydrocarbazoles by CHIPS

The transformation of tetrahydrocarbazoles **7** into the products **9** can also be achieved in a one-pot reaction, but with reduced yields.[16a] The mechanism of this reaction including the remarkable shift of the hydroperoxide moiety at position 4a to the N-substituent at position 1 was found to proceed via an acid-mediated tautomerization of **8**.[19]

2.3 Related Autoxidative Coupling Reactions

The autoxidative coupling reaction with xanthenes also inspired research projects by other groups. For example, supported sulfonic acids were shown to be useful catalysts for the reaction and an asymmetric advancement was developed using a chiral organocatalyst for the coupling with aldehydes.[20]

Huo et al. reported the autoxidative coupling of *N*-arylglycine derivatives with indoles (Scheme 8a).[21] The reaction conditions simply involve stirring both substrates in 1,2-dichloroethane (DCE) under an atmosphere of oxygen at 40 °C. Freshly distilled DCE gave reduced yields in contrast to older batches, which supported the role of acidic decomposition products catalyzing the substitution of intermediate hydroperoxides.



Scheme 8 Related autoxidative coupling reactions

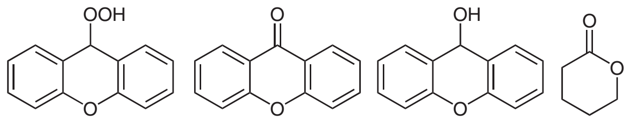
Jeganmohan and More reported the oxidative coupling of diarylmethylketones with electron-rich arenes, by simply stirring the substrates in air in the presence of an acid.[22] The addition of potassium persulfate ($K_2S_2O_8$) was found to be beneficial for the yield, but was not essential (Scheme 8b).

Possibly related reactions involving tetrahydrofuran, benzylic ethers and *N*-aryl tetrahydroisoquinolines have been reported, some of which required additives that could act as radical initiators to increase the rate of the autoxidation.[23] The concept of generating activated intermediates by autoxidation for the subsequent addition to double bonds is also interesting in this context, which shows that such a simple process can be utilized synthetically in many ways.[24]

3 How Does the Autoxidative Coupling Work?

As inspiring as the autoxidative coupling with xanthene is in the context of green chemistry, the accessible products have (so far) not been of any synthetic use. A much better understanding of the reaction mechanism became highly desirable to us to provide a foundation for further developments.

Thus, the reaction of xanthene with cyclopentanone was chosen as a model system for more detailed mechanistic studies.[13] Indeed, performing the reaction in the absence of acid resulted in an autoxidation, yielding hydroperoxide **4** as the major product, as well as xanthone **10** and xanthydrol **11** (Figure 2). The latter two only formed in larger amounts at higher conversions of xanthene, indicating that they are secondary products formed from **4**.



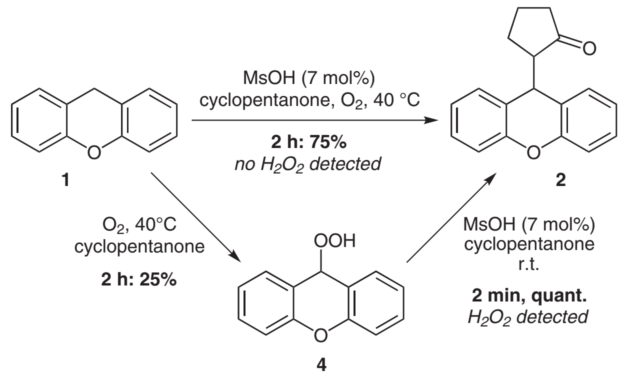
4 10 11 12

Figure 2 Oxidized compounds formed during the autoxidation of xanthene or during autoxidative coupling reactions

In reactions with cyclopentanone, δ-valerolactone (**12**) was also observed as a by-product in up to 25% yield, suggesting that a Baeyer–Villiger oxidation had taken place – we will discuss this later.

The working model for the reaction mechanism (Scheme 3) seemed to be fully in line with these observations, and that could have been the end of it, if we had not put it into our minds to also study the kinetics of the reaction a little bit. The autoxidation of **1** in the absence of acid proceeds with remarkable speed compared with most known autoxidation reactions (Scheme 9). At 40 °C, a 25%

yield of **4** is obtained after two hours, and nearly full conversion of **1** is achieved after 24 hours. If the hydroperoxide **4** is subjected to acid catalysis in cyclopentanone, it is quickly converted into product **2** in about two minutes. Thus, the autoxidation step seems to be rate-determining. But to our surprise, the coupling reaction itself actually proceeded faster than that! For example, after two hours, 75% of xanthene is converted into **2** compared with only 25% conversion in the autoxidation.

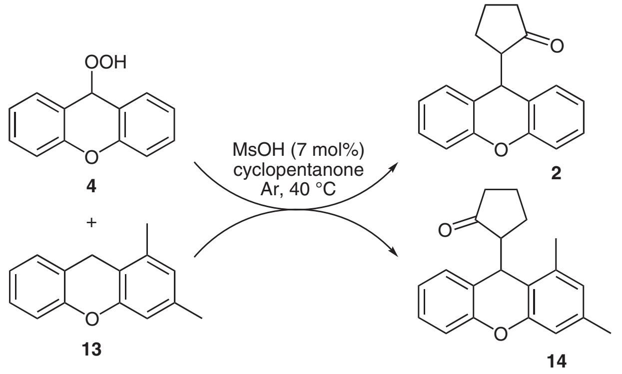


Scheme 9 Differences in the autoxidation versus the autoxidative coupling of xanthene

Obviously, the mechanism cannot be correct if the reaction proceeds faster than the proposed rate-controlling step. Since the evidence still pointed toward the involvement of an intermediate hydroperoxide, we wondered if the addition of the acid catalyst or the formation of the reaction product **2** were responsible for the increase in the reaction rate. The addition of **2** had been shown before to actually decrease the reaction rate.[8] Acids had been reported to influence autoxidation rates, but in systems not directly applicable to the reaction we studied.[25] When we investigated the addition of weaker acids on the autoxidation without significantly converting the hydroperoxide **4** into **2**, there was no effect, only acetic acid actually decreased the rate. The rate increase must therefore have another explanation.

Another difference between autoxidation and the autoxidative coupling concerns hydrogen peroxide. As expected, it was detected as a by-product by spectroscopic analysis of the reaction from isolated **4** to **2**, while it was not found in the reaction starting from **1** (Scheme 9).[13]

Attempts with aqueous solutions of hydrogen peroxide (H_2O_2) to study its effect on the reaction proved to be difficult due to solubility problems in presence of the relatively large amounts of water. A key experiment was performed with hydrogen peroxide formed in situ: an equimolar mixture of xanthenyl hydroperoxide (**4**) and the dimethyl xanthene **13** were dissolved under argon – in order to prevent aerobic autoxidation of **13** – and catalytic amounts of methanesulfonic acid (MsOH) were added. As expected, compound **4** readily formed the substitution product **2**. More slowly however, about 50% of **13** was converted into the coupling product **14** (Scheme 10).



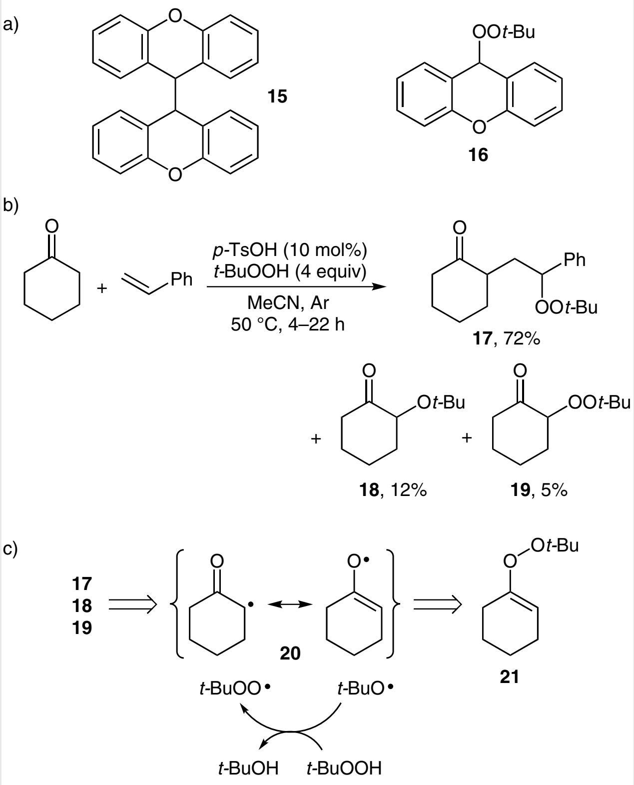
Scheme 10 Oxidative coupling of xanthene **13** with cyclopentanone by H_2O_2 formed in situ from the reaction with **4**

This clearly showed that the byproduct H_2O_2 is a competent oxidant under these reaction conditions mediating the oxidative coupling of xanthenes with ketones by acid catalysis, and explains why no H_2O_2 could be detected in the reaction mixtures of the autoxidative couplings. However, the mechanism of this transformation remained puzzling since the reaction still does not contain any redox-active catalysts.

To avoid the above-mentioned solubility problems associated with aqueous hydrogen peroxide, we instead used solutions of *tert*-butyl hydroperoxide (*t*-BuOOH) in decane, and found it to be a suitable substitute for further studies. It turned out that oxidative coupling reactions such as that forming **14** shown above displayed a remarkable solvent effect. Significant yields were achieved with the combination of acid catalysis, *t*-BuOOH or hydrogen peroxide and ketones, in contrast to all other solvents, regardless of their polarity.

There have been reports on the activation of hydrogen peroxide purely by acids, yet these concern superacidic media or gas-phase reactions, and propose ionic mechanisms triggered by full protonation of the peroxide.[26] In contrast, the C–H functionalization in the autoxidative coupling appears to be a radical process: the reaction as such does not proceed at all if catalytic amounts of 3,5-di-*tert*-4-butylhydroxytoluene (BHT), a common radical inhibitor, are added.[8] Additionally, in the experiment shown in Scheme 10, the formation of **14** is suppressed completely in the presence of BHT, while the formation of **2** is not.[13]

To gain more information regarding the nature of the radicals involved, we tried to carefully characterize all the products formed in the reactions of the hydroperoxides, ketones and acids. In the presence of xanthene, we discovered the dimer **15** as a by-product and *tert*-butyl peroxide **16** as a transient intermediate (Scheme 11a).[13] Both products suggest the involvement of xanthenyl and peroxyl radicals.

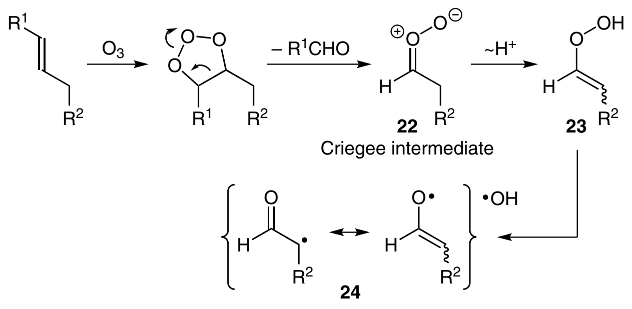


Scheme 11 (a) Oxidized by-products formed in reactions of xanthene with cyclopentanone, *t*-BuOOH and MsOH. (b) Products formed from reactions of styrene with cyclohexanone. (c) Retrosynthetic analysis leading to a putative intermediate

Particularly revealing were experiments in the presence of styrene as a trapping agent (Scheme 11b). We found high yields of γ-peroxyketones such as **17**,[27] and later, we also characterized the oxygenated ketones **18** and **19** as by-products.[28] In something like a retrosynthetic analysis, these products could be traced back to a ketone-radical **20**, a *tert*-butyl peroxyl and an oxyl radical (Scheme 11c). The *tert*-butyl peroxyl radical is well known to form in a very fast reaction by hydrogen atom transfer (HAT) between an oxyl radical and excess *t*-BuOOH.[29] Thus, it can probably be assumed that products **17**–**19** could arise from **20** and an oxyl radical alone. These, in turn, might have formed from a structure such as **21**, an alkenyl peroxide, by homolytic O–O bond cleavage. Not knowing about the properties of this putative intermediate, we looked for prior reports. However, we did not find such a structure in the synthetic chemistry literature, but instead did so in reports from an unexpected area.

3.1 An Excursion: Formation of Alkenyl Peroxides from Criegee Intermediates in the Atmosphere

Ozonolysis of alkenes leads to primary ozonides, which decompose into a carbonyl compound and a carbonyl oxide or Criegee intermediate **22**.[30] In contrast to ozonolysis in solution, these products rapidly dissociate in the gas phase and the reactions of the Criegee intermediate play an important role in atmospheric chemistry.[31] One reaction pathway is the intramolecular proton transfer to form an alkenyl hydroperoxide **23**, a highly unstable compound that rapidly decomposes via O–O bond homolysis into a hydroxyl and a carbonyl radical (**24**) (Scheme 12).



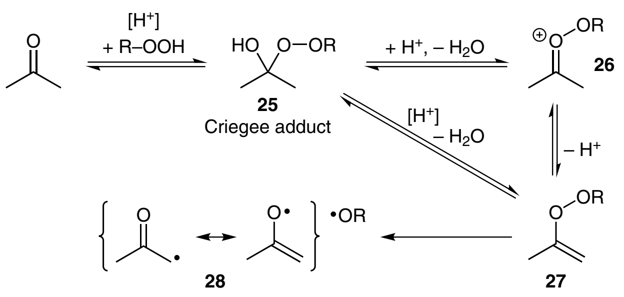
Scheme 12 Formation of alkenyl peroxides in the atmosphere by ozonolysis of alkenes

Since this reaction also proceeds in the dark, it is believed to be the major source of atmospheric hydroxyl radicals in the night time.[32]

Due to their instability, alkenyl peroxides have not been characterized directly. Instead, they have been the focus of many theoretical studies in the context of atmospheric chemistry.[33] Various substituted vinyl and alkenyl peroxides have been investigated and found to generally possess very labile O–O bonds, the ease of homolytic decomposition being rationalized by the resonance stabilization of the carbonyl radical **24**. It has been suggested that alkenyl, alkynyl and aryl peroxides in general do not exist as stable compounds under ambient conditions.[33b]

3.2 How do Alkenyl Peroxides Form in Solution? Meet Criegee Again

We rationalized that alkenyl peroxides could form in solution by a condensation reaction between ketones and hydrogen peroxide or hydroperoxides, catalyzed by acids (Scheme 13). While this mechanism is fundamentally different from the atmospheric one, it is interesting to note that it is once more connected with Rudolf Criegee: nucleophilic addition of a peroxide to the carbonyl group would first form a tetrahedral intermediate **25**, also known as a Criegee intermediate or adduct.[34] Under acidic conditions, this could form a peroxycarbenium ion[35] **26** by protonation and loss of water, followed by loss of a proton to generate the alkenyl peroxide **27**. Alternatively, acids might catalyze the concerted elimination of water. The alkenyl peroxide would in either case decay into a stabilized ketone radical **28** and an oxyl radical.



Scheme 13 Formation of alkenyl peroxides by acid-catalyzed condensation, shown with acetone as an example

Some observations support this proposal. If an aqueous solution of *t*-BuOOH is utilized in the addition reaction to styrene (Scheme 11b above), the reaction to afford **17** proceeds at a reduced rate. In contrast, in the presence of molecular sieves, the reaction does not take place and we observed the formation of geminal bisperoxide **29** instead (Figure 3), apparently resulting from condensation of cyclohexanone with two molecules of *t*-BuOOH.[28] These results are in agreement with a series of equilibria involving the peroxycarbenium ion: large amounts of water shift them toward the starting materials and thereby suppress the overall reaction rate, while its complete removal favors the condensation to give **29**.

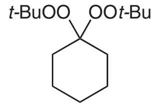


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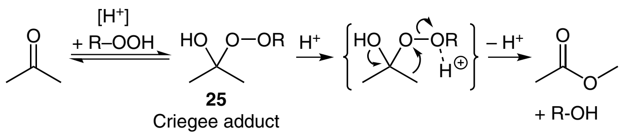
Figure 3 Geminal bisperoxide **29**

But that was not the end of this mechanistic investigation yet. Criegee adducts **25** are intermediates in the Baeyer–Villiger oxidation that transforms ketones into esters and lactones by reaction with a peroxide under acidic conditions, being in fact very similar conditions to the radical generation that we found.[34,36] For the Baeyer–Villiger oxidation, electron-poor peracids display the highest reactivities, but hydrogen peroxide is the reagent of choice with regard to atom economy. The generally accepted mechanism of the Baeyer–Villiger oxidation involves formation of the Criegee adduct **25** and subsequent rearrangement, both steps of which can be acid catalyzed (Scheme 14).[34]

So what factors decide the fate of the Criegee adduct? We asked a theoretical chemist for help and looked at the reaction pathways leading from three different Criegee adducts to alkenyl peroxides and esters, respectively.[28] We took peracetic acid as a model for peracids, preferred in the Baeyer–Villiger oxidation, hydrogen peroxide and *tert*-butyl hydroperoxide, preferred in our radical reactions, and methanesulfonic acid as a catalyst in all cases. The transition states **TS1** for the Baeyer–Villiger rearrangement were found to be quite close to each other, the barrier being lowest for peracetic acid, in line with the experimental preference. However, the barriers for the use of H_2O_2 and *t*-BuOOH were still easily accessible, indicating that both of these reagents should be suitable for the reaction per se (Figure 4).



Scheme 14 Baeyer–Villiger oxidation by acid-catalyzed reaction of ketones with peroxides, shown with acetone as an example

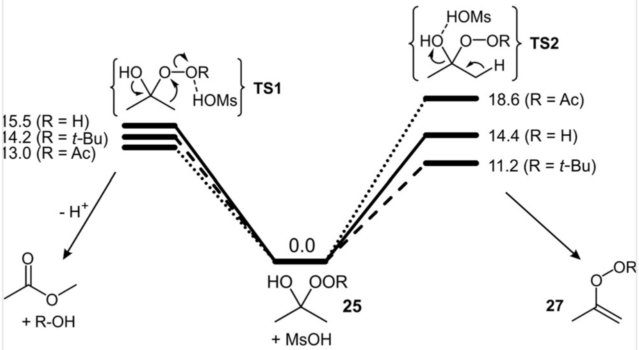


Figure 4 Energy diagram for the calculated reaction pathways of the Baeyer–Villiger oxidation and alkenyl peroxide formation from Criegee adducts **25**; enthalpy values are given in kcal/mol.[28] Calculated using the ωB97XD functional with the 6-31++G(d,p) basis set (geometries and frequencies), the aug-cc-pV(T+d)Z basis set (energies) and the IEF-PCM solvent model (acetone). The total enthalpies contain the enthalpy of one molecule of methanesulfonic acid and methanesulfonate, respectively.

For the alkenyl peroxide formation, the concerted pathway of water elimination via **TS2** (Figure 4) was found to be favorable compared with the stepwise mechanism via peroxycarbenium ions **26**. Now, the barrier was lowest for *t*-BuOOH and the three barriers differed more strongly in energy. Comparison of **TS1** and **TS2** for each peroxide can explain general trends for the two reactions. For peracetic acid, the Baeyer–Villiger rearrangement is favored over alkenyl peroxide formation by 5.6 kcal/mol, meaning that the latter will basically not be observed. For *t*-BuOOH, it is the other way around and alkenyl peroxide formation is favored by 3.0 kcal/mol. For H_2O_2, both barriers differ by only 1.1 kcal/mol in favor of the elimination. This provides an additional or alternative explanation for the choice of peracids in Baeyer–Villiger oxidations: these reagents have the lowest barriers for the rearrangement, but additionally disfavor the formation of alkenyl peroxides. For H_2O_2 and *t*-BuOOH, the Baeyer–Villiger oxidation is in principle also favorable, but they face strong competition from the elimination pathway. This, and not the often perceived leaving group ability of the peroxides could be the best rationalization for the performance of peroxides in Baeyer–Villiger oxidations.

Obviously, one should be able to influence these kinetic barriers by the choice of catalyst and ketone substrate. Indeed, it has been shown that an immobilized Sn–salen complex can utilize *t*-BuOOH for very selective Baeyer–Villiger oxidations with cyclohexanone, which gave no observable trace of the lactone with sulfonic acid catalysts.[28,37] Non-enolizable ketones will also not be able to form alkenyl peroxides. We found that under conditions that generate radicals from cyclohexanone (Scheme 11b above), adamantanone (**30**) (Figure 5) underwent cleanly the Baeyer–Villiger oxidation with *t*-BuOOH to give the corresponding lactone, and not much slower than when *m*-chloroperoxybenzoic acid was used.[28]

3.3 The Full Mechanism of the Autoxidative Coupling Reaction

Now we can outline the state-of-the-art mechanism of the autoxidative coupling reaction of xanthene with cyclopentanone (Scheme 15). Autoxidation proceeds according to the generally accepted mechanism[38] via the xanthenyl radical **31**, which in the presence of oxygen rapidly forms the peroxyl radical **32**. This in turn forms the observable hydroperoxide **4** after HAT, most likely from another molecule of xanthene (**1**) in a radical-chain reaction. In the presence of an acid of sufficient strength,[13] hydroperoxide **4** is protonated and liberates one molecule of hydrogen peroxide upon formation of the xanthenyl cation **5**. Reaction with cyclopentanone, for example via its enol form, then leads to the main product **2**. The observed by-products, xanthone **10**, xanthyl peroxide **3** and xanthydrol **11**, are formed from the hydroperoxide **4** and the cation **5**, respectively. Hydrogen peroxide can now react with cyclopentanone under acid catalysis forming the Criegee adduct **33**, which partially proceeds to the (observed) lactone **12** via Baeyer–Villiger rearrangement, and to the alkenyl hydroperoxide **34**. The latter will rapidly decompose into radicals, which accelerate the autoxidation of xanthene by forming additional amounts of radical **31** via HAT. If this reaction is run under argon, **31** dimerizes into **15**, which has sometimes been observed.

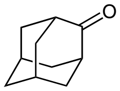
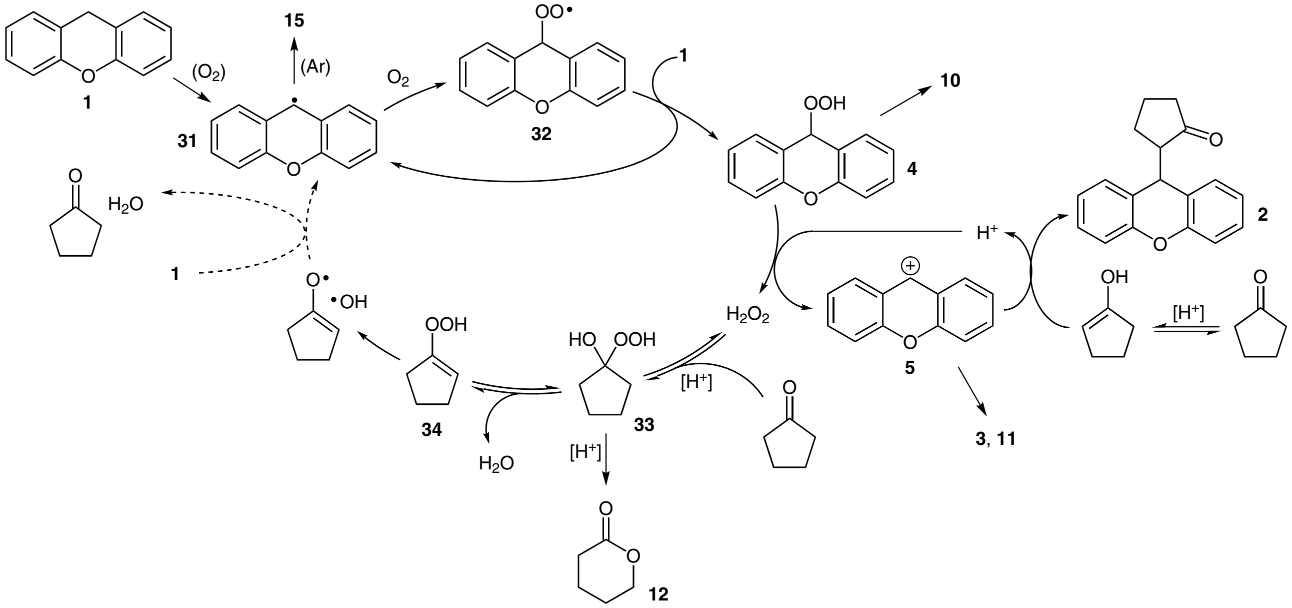

30

Figure 5 Structure of adamantanone (**30**)



Scheme 15 State-of-the-art reaction mechanism of the autoxidative coupling reaction of xanthene (**1**) with cyclopentanone

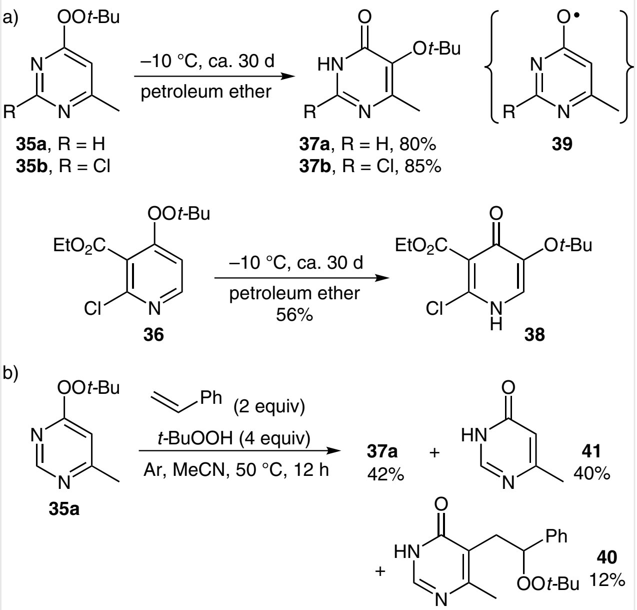
4 Previous Indications for Solution Chemistry of Alkenyl Peroxides

Although the chemistry of alkenyl peroxides was apparently only studied by atmospheric chemists in recent years, the fact that radical reactions start from the simple mixture of hydroperoxides, ketones and acids did not go entirely unnoticed. In addition, alkenyl peroxides have been discussed by synthetic chemists before, but these rare reports probably never received much attention.

A few groups had intentionally studied the synthesis of alkenyl peroxides, speculating about their instability due to the failure to observe them.[39] They suggested that the resulting decomposition products had formed by a sigmatropic rearrangement, while we consider homolytic decay and geminate recombination more likely.

Pavlinec and Lazar discovered that the radical polymerization of methyl methacrylate can be initiated at unusually low temperatures (40 °C) with *t*-BuOOH, if ketones and sulfuric acid are used as additives, but they did not consider the formation of alkenyl peroxides.[40] Solyanikov et al. have studied the decomposition of organic hydroperoxides in acidic media and found that the addition of ketones and aldehydes significantly accelerated the reaction.[41] A radical mechanism was proposed and suggested to proceed via O–O bond cleavage of Criegee adducts or related compounds.

Apparently the only known case of isolable alkenyl peroxides was reported by Kropf and Ball.[42] They synthesized the three heteroarene-peroxides **35a**,**b** and **36** by base-mediated nucleophilic aromatic substitution and noted their instability (Scheme 16a). At –10 °C, the compounds slowly decomposed to the *tert*-butyl ethers **37** and **38**. Indications from NMR studies led them to propose intermediate radicals such as **39**, which form the ethers by geminate recombination.

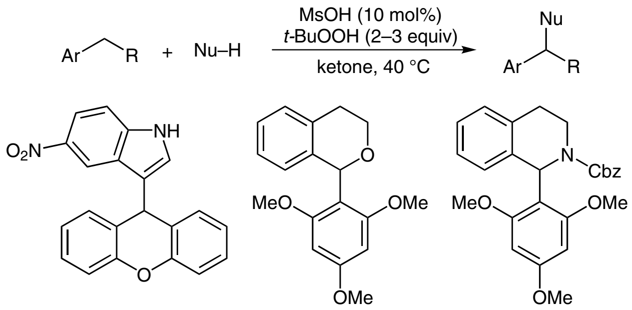


Scheme 16 Isolable heteroarene-peroxides and their decomposition reactions

When we stirred compound **35a** in the presence of styrene and *t*-BuOOH at 50 °C overnight, the addition product **40** was obtained in 12% yield along with **37a** and the reduced product **41** in 42% and 40% yields, respectively (Scheme 16b, see the Supporting Information). This further supports the assumption by Kropf and Ball, as reduction product **41** would have formed by HAT from *t*-BuOOH to the intermediate radical **39**, which also added to styrene forming **40** after subsequent reaction with a *tert*-butyl peroxyl radical. The analogous recombination product of a peroxyl radical and **39** was not observed, but this compound is once more an aryl peroxide and would thus not be stable under the reaction conditions.

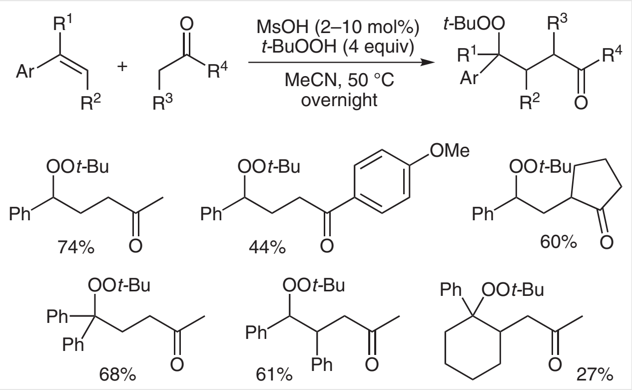
4.1 What Might Alkenyl Peroxides be Good for?

Intrigued by the mechanistic discoveries we had made, we also turned our eye to synthetic applications. As it has already been indicated above, the radicals formed by decay of alkenyl peroxides can mediate oxidative coupling reactions (Scheme 10) and add to styrene (Scheme 11b). In both cases, we could apply this chemistry to obtain a variety of products. Oxidative cross-coupling reactions between substrates bearing benzylic C–H bonds and nucleophiles worked more generally than just with xanthene, as shown by the products in Scheme 17.[13] Presumably, the radicals formed activate the benzylic substrate by HAT, ultimately generating cationic intermediates.



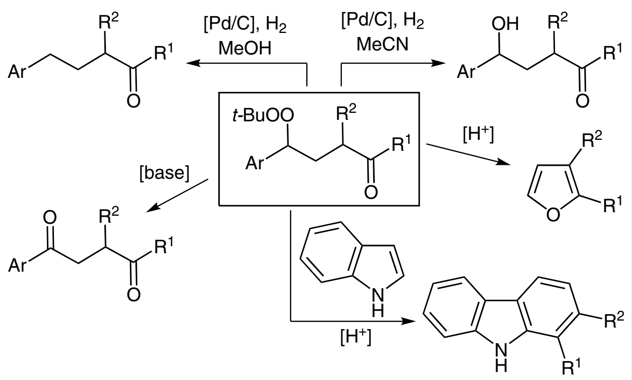
Scheme 17 Oxidative cross-coupling reactions mediated by ketones, *t*-BuOOH and acid-catalysis

Directly utilizing the ketone radicals derived from the alkenyl peroxides is synthetically interesting because efficient catalytic approaches to simple ketone radicals are limited.[43] We found the addition of ketones to styrenes to be more general and could utilize cyclic and open-chain ketones alike, as well as trisubstituted styrenes (Scheme 18).[27]



Scheme 18 Acid-catalyzed addition of ketones to styrenes

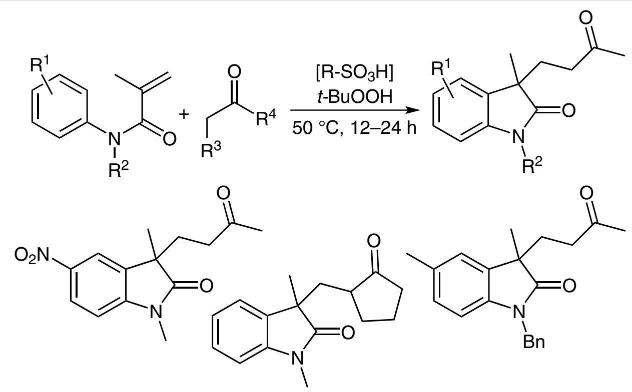
The resulting γ-peroxyketones were mostly unknown compounds, but turned out to be synthetically very useful, as the peroxide residue can easily be interconverted by Kornblum–DeLaMare rearrangement[44] or catalytic hydrogenation (Scheme 19). In this way, 1,4-diketones, homoaldol products or alkyl ketones are accessible.[27] The group of Zhiping Li has also recently developed direct, acid-catalyzed transformations of γ-peroxycarbonyl compounds into substituted furans or carbazoles.[45]



Scheme 19 Synthetic transformations of γ-peroxyketones

The addition of ketone radicals to *N*-aryl acrylamides generates oxindoles by a radical cascade reaction (Scheme 20). This reaction was developed simultaneously by the group of Xia and ours,[46] based on the aforementioned work with styrenes and on the known oxindole formation by radical cyclization.[47]

Further applications of alkenyl peroxides can be easily imagined, given that they can be used in various ways: as a form of activated carbonyl compounds (e.g., Schemes 18 and 20) and arenes (e.g., Scheme 16), or as mediators of reactions without becoming incorporated into the products (e.g., Scheme 17). In addition, different synthetic approaches to make them besides the acid-catalyzed procedure from ketones and hydroperoxides discussed here are possible, as has been shown previously.[39a,42a]



Scheme 20 Acid-catalyzed cascade reaction for the synthesis of oxindoles bearing ketone side chains

5 Concluding Remarks

The outlined progress of research in our group started with the unexpected discovery of an aerobic autoxidative coupling reaction that did not require any redox-active catalysts and ended with the discovery of the solution chemistry of alkenyl peroxides, which can be easily synthesized via the condensation of ketones and hydroperoxides, and which rapidly decompose into radicals. Along the way, new strategies for oxidative cross-coupling reactions were developed that utilize only acid catalysts as well as oxygen and hydroperoxides, respectively.

In retrospect, these discoveries could in principle have been predicted based on a very small number of less regarded reports from the last fifty years. As is so often the case, there is a lot of hidden wealth in old publications. Instead, they rely on dedicated mechanistic studies of the originally discovered autoxidative coupling reaction, including kinetic measurements, product studies, trapping experiments and theoretical calculations. The insight won this way allowed us to rationalize the old reports mentioned and gave us the inspiration for new research projects that we would not have devised otherwise. Without dedicated co-workers and an environment that supports the investigation of an obscure reaction for the sake of generating knowledge, this would not have been possible. Only the future will tell whether alkenyl peroxide chemistry can actually be considered useful, but we think so.

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Supporting Information

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