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Synthetic Methods

Acid-Catalyzed Oxidative Radical Addition of Ketones to Olefins**

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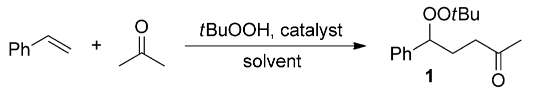
Dedicated to the MPI für Kohlenforschung on the occasion of its centenary

Abstract: *Based on a mechanistic study, we have discovered a Brønsted acid catalyzed formation of ketone radicals. This is believed to proceed via thermally labile alkenyl peroxides formed in situ from ketones and hydroperoxides. The discovery could be utilized to develop a multicomponent radical addition of unactivated ketones and tert-butyl hydroperoxide to olefins. The resulting γ-peroxyketones are synthetically useful intermediates that can be further transformed into 1,4-diketones, homoaldol products, and alkyl ketones. A one-pot reaction yielding a pharmaceutically active pyrrole is also described.*

During our mechanistic investigation of the autoxidative coupling of xanthene with ketones,[1] we discovered an intriguing formation of radicals from ketones and hydroperoxides, catalyzed by a strong Brønsted acid without involvement of a redox-active catalyst.[2] However, the mechanism of radical formation and their actual structure was not fully understood. Here we present results supporting the formation of ketone-derived radicals via intermediate alkenyl peroxides which enable a Brønsted acid catalyzed difunctionalization of styrenes.

Table 1: Initial discovery and optimization of reaction conditions.[a]



Entry	Solvent	T [°C]	Catalyst [mol %]	Equiv. tBuOOH	Yield [%][b]
1	acetone	40	MsOH (7)	2	43
2	acetone	60	MsOH (10)	4	55
3	acetone	60	TFA (10)	4	9
4	acetone	60	H_2SO_4 (10)	4	55
5	acetone	60	HNO_3 (10)	4	53
6	acetone	60	pTsOH (10)	4	57
7	CH_3CN	60	pTsOH (10)	4	58
8	CH_3CN	60	pTsOH (10)	3	48
9	CH_3CN	60	pTsOH (10)	5	58
10	CH_3CN	50	pTsOH (10)	4	74 (74)[c]
11	CH_3CN	50	pTsOH (2)	4	77 (76)[c]

[a] Styrene (0.5 mmol), acetone (2.5 mmol), tBuOOH (5.5 M solution in decane), acid (0.05 mmol), solvent (2 mL), reaction overnight (ca. 16 h). [b] Yield determined by NMR analysis using an internal standard, yield of isolated product in parentheses. [c] Degassed, under argon.

We chose the combination of acetone and *tert*-butyl hydroperoxide (in decane solution) together with catalytic amounts of methanesulfonic acid at 40 °C from our previous studies,[2] and added styrene in order to isolate potential trapping products. From this experiment, we could isolate compound **1** in 43 % yield (Table 1, entry 1). This strongly suggests the formation of a carbon-centered radical at the α-position of acetone, which added to the styrene double bond and subsequently formed **1**.

The carbofunctionalization of olefins represents an attractive strategy to rapidly build complex molecules from simple starting materials.[3] The addition of ketone-derived radicals to olefins has been reported by Kharasch using UV light[4] and was investigated with various other initiation methods since then, generally resulting in hydroalkylation products.[5,6] Cases of oxyalkylations as seen in product **1** can be achieved by using Mn compounds as catalyst and/or oxidant but are much less common.[6c,f,g,7] The direct formation of 1,4-diketones can be achieved by combined copper and organocatalysis using MnO_2 as an oxidant.[7] As an alternative to free ketones, ester enolates and enamines can be converted to the corresponding radicals by single-electron-transfer reagents.[8]

The related radical addition of 1,3-dicarbonyl compounds to olefins has been more thoroughly investigated,[5,9] as is also the case with alkylations[10] and acylations[11] using aldehydes. The concept of SOMO catalysis[12] enables the asymmetric carbofunctionalization of olefins with aldehydes.[10] Noteworthy and complementary reactions in this context are the metal-catalyzed formations of peroxides similar to **1** from 1,3-dicarbonyl compounds[9i] and aldehydes.[11d,g]

Since the formation of **1** is unique from a mechanistic as well as synthetic perspective and little is known about the synthetic utility of such compounds,[9i] we decided to investigate this reaction in more detail (see Table 1 and the Supporting Information for further details).

Because **1** was found to be stable under reaction conditions, all reactions were performed overnight to ensure complete conversion of tBuOOH. Increasing the amount of oxidant as well as increasing the temperature to 60 °C improved the yield (Table 1, entry 2). Different Brønsted acids were tested and we found that strong acids have to be used: trifluoroacetic acid (TFA) only gives 9 % yield (Table 1, entry 3), while nitric, sulfuric, and sulfonic acids all gave

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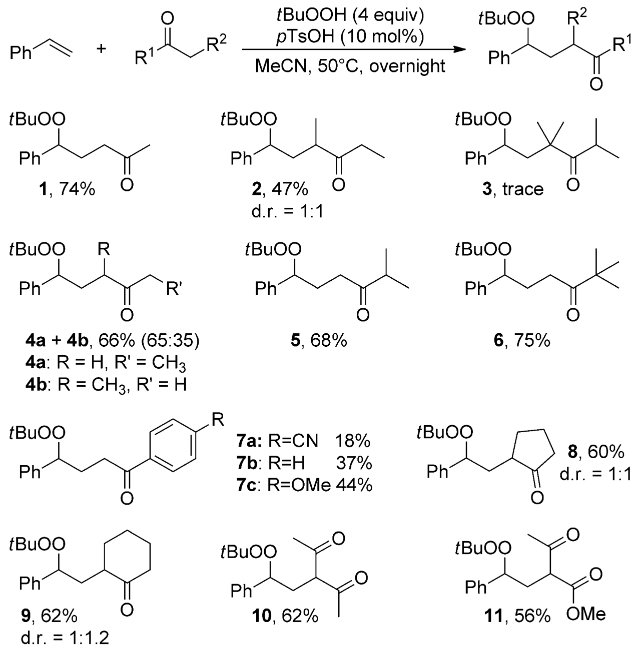
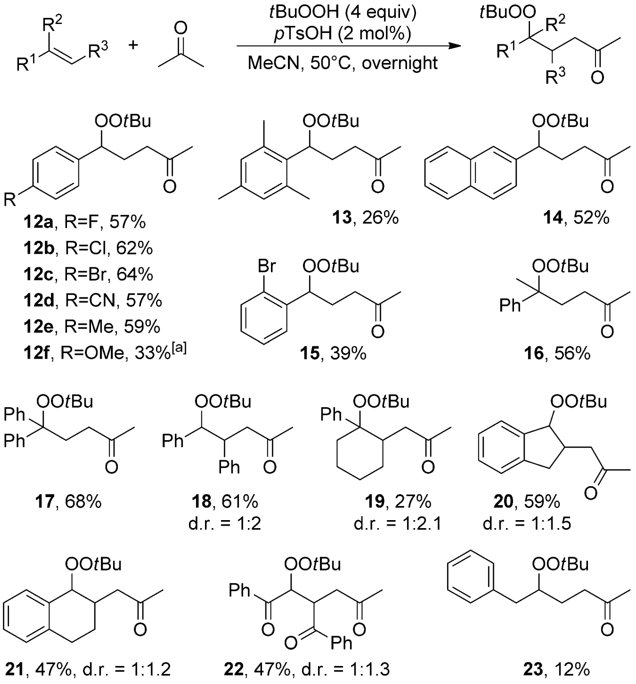
similar yields of 53–57 % (Table 1, entries 4–6), with *para*-toluenesulfonic acid (*p*TsOH) being the most effective (Table 1, entry 6, 57 %). In the absence of acid, **1** was not detected. Some Lewis acids were also found to be suitable catalysts, but Fe and Cu salts—common redox catalysts—failed completely. When acetonitrile was used as a cosolvent, the amount of ketone substrate could be reduced, with 5 equivalents being optimal (Table 1, entries 6 and 7). Similarly, an excess of 4 equivalents of *t*BuOOH gave the best product yields (Table 1, entries 7–9). Reducing the temperature to 50 °C proved to be beneficial, as well as performing the reactions with strict exclusion of oxygen (Table 1, entry 10). Reducing the acid loading from 10 to 2 mol % resulted in a longer reaction time but essentially unchanged yield (Table 1, entry 11). Since this was not general for all ketones, we used 10 mol % catalyst loading to study the ketone substrate scope (Scheme 1).



Scheme 1. Substrate scope for the reaction of ketones with styrene.

Going from primary over secondary to tertiary ketones, a major drop in reactivity is observed. Acetone gives a 74 % yield of product **1**, diethyl ketone afforded product **2** in 47 % yield, while diisopropyl ketone led to only traces of product **3**. This lack of reactivity could be due to steric effects. An asymmetric ketone like butanone showed a preference for radical formation at the primary carbon, giving 66 % yield of product **4** as a mixture with a ratio of about 2:1 in favor of the linear isomer **4a**. In the reaction of 3-methyl-2-butanone, in which both primary and tertiary carbons are available, **5** was isolated in 68 % yield as the only product, showing perfect selectivity for the primary carbon. Pinacolone gave a good 75 % yield of product **6**. Substituted acetophenones were used to probe electronic effects. An electron-withdrawing group reduced the yield (**7a**, 18 %) relative to that with unsubstituted acetophenone (**7b**, 37 %), and an electron-donating methoxy group was beneficial (**7c**, 44 %). Cyclopentanone and cyclohexanone gave good yields of products **8** and **9** (60 % and 62 %, respectively). Acetyl acetone selectively gave product **10** in 62 % yield as the only isomer. Similarly, methyl acetoacetate gave **11** in a yield of 56 %. Dimethyl malonate—a successful substrate type in metal-catalyzed reactions[5]—proved to be unreactive under these conditions.

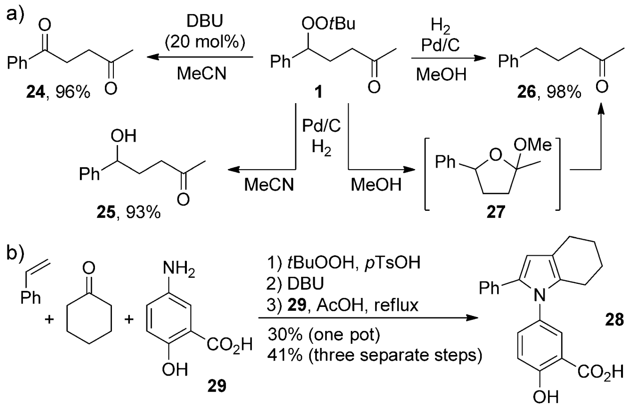
The olefin scope was explored using acetone as a standard coupling partner and an acid loading of 2 mol % (Scheme 2). Halogen-substituted styrenes were well tolerated and gave the corresponding products **12a–c** in good yields of 57 % to 64 %. Substrates with a strongly electron-withdrawing cyano substituent as well as with a methyl group showed similar reactivities and the corresponding products **12d** and **12e** were isolated in 57 % and 59 % yield, respectively. By contrast, a strongly electron-donating methoxy group led to a sharp reduction of yield and only traces of product **12f** could be isolated. This is mainly attributed to the instability of **12f** under the reaction conditions: when the reaction was performed in acetone at slightly lower temperature (40 °C), **12f** could be isolated in 33 % yield. 2,4,6-Trimethylstyrene, which combines electron-donating groups and steric hindrance, gave product **13** in a low yield of 26 %. Vinyl naphthalene gave a lower yield than styrene, providing **14** in 52 % yield. 2-Bromostyrene, having a bulky substituent close to the reactive site, similarly gave a moderate 39 % yield of **15**. Tertiary peroxides could also be accessed, as shown by the reactions of α-methylstyrene (product **16**, 56 %) and 1,1-diphenylethylene (product **17**, 68 %).



Scheme 2. Substrat scope for the reaction of acetone with various styrenes or other olefins. [a] Acetone as solvent, 40 °C, 10 % acid loading.

trans-Stilbene gave a 61% yield of product **18** as a 2:1 mixture of diastereomers. *cis*-Stilbene gave an identical mixture but in a much lower yield of 21%. Cyclic substrates such as 1-phenylcyclohexene (**19**, 27%), indene (**20**, 59%), and dihydronaphthalene (**21**, 47%) could be used successfully. Preliminary studies show that the reaction is not limited to styrenes: *trans*-dibenzoylethylene and allyl benzene provided the γ-peroxyketones **22** and **23** in 47% and 12% yield, respectively. The low yield of **23** suggests that a resonance-stabilizing group on the olefin is beneficial. Vinyl pyridines were completely unreactive, most likely because these basic substrates deactivate the acid catalyst.

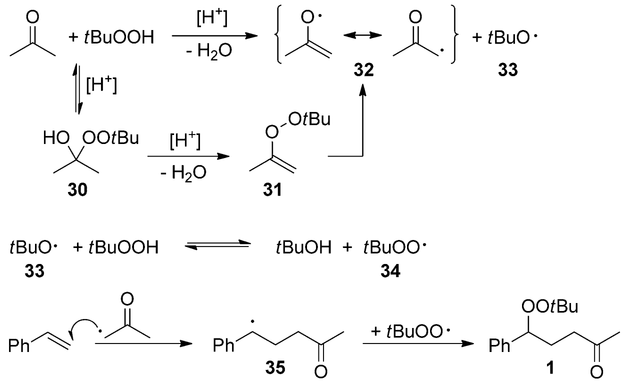
Further synthetic transformations of the γ-peroxyketone products were investigated with **1** as a model substrate (Scheme 3a). In the presence of a catalytic amount of base (Kornblum–DelaMare rearrangement[13]), **1** can be transformed into the corresponding 1,4-diketone **24**, an important class of intermediates in the synthesis of heterocycles such as pyrroles[14] and furans.[15] When **1** is hydrogenated using palladium on carbon in acetonitrile, the corresponding homoaldol product **25** is obtained. When the hydrogenation is performed in methanol, complete reduction of the benzylic position is observed, giving product **26**. The reaction proceeds via acetal **27**, which can be isolated if the reaction is not allowed to run to completion. The direct acid-catalyzed transformation of 1,3-diketo-γ-peroxides to furans has been reported.[9i]



Scheme 3. Further transformations of the γ-peroxyketone products.

Finally, a one-pot synthesis of pyrrole **28**, a nonsteroidal antiinflammatory agent,[16] was performed (Scheme 3b). The reaction of styrene and cyclohexanone as depicted in Scheme 1 resulted in the formation of peroxide **9**, which was directly converted to the corresponding diketone by adding one equivalent of DBU to the reaction mixture. After removing acetonitrile, we followed the reported procedure[16] and added aniline **29** together with acetic acid and heated the mixture at reflux. Pyrrole **28** was obtained in 30% yield over three steps using a single purification step and in 41% yield if each product was purified before the next step.

Consistent with these results and previous investigations,[2,17] a plausible mechanism is shown in Scheme 4. In the presence of a strong acid, *t*BuOOH adds to the ketone to form **30** and subsequently alkenylperoxide **31**. Such compounds are reported to undergo facile homolytic bond cleavage,[17c,d] which would generate the resonance-stabilized ketone radical **32** and a *tert*-butoxyl radical **33**. In the presence of *t*BuOOH, a fast equilibrium exists between **33** and the *tert*-butylperoxyl radical **34**, favoring the latter.[17a] Addition of **32** to the styrene double bond would form **35**, which reacts with the peroxy radical **34** to give the final product **1**. The selective cross-coupling of **35** with **34** can be explained by the "persistent radical" effect,[18] in that **34** is a persistent radical[18b] and **35** a transient radical.



Scheme 4. Suggested mechanism of product formation.

The observed selectivity for the linear versus branched product (**4a** vs. **4b**) could be explained by the rapid decomposition of alkenylperoxides like **31**, which gives the less substituted ketone radical rather than the thermodynamically preferred one owing to kinetic preferences. The observations that Fe and Cu salts fail as catalysts and that dimethyl malonate fails as a carbonyl component are both in agreement with the proposed mechanism. Fe and Cu salts are known catalysts for the decomposition of *t*BuOOH to radicals, which can mediate reactions by hydrogen-atom transfer (HAT) or by single-electron transfer (SET).[17a,19] Also, the radical addition of activated methylene compounds to olefins can be initiated by SET or HAT.[5,9] Accordingly, it appears that neither SET nor HAT is operative in the present system but rather the ketone radicals are formed directly. The presence of Fe and Cu salts could shut down the formation of **30** and **31** by fast decomposition of *t*BuOOH while a malonate could be too unreactive for the formation of ketene perketals analogous to **31** under reaction conditions.

In conclusion, we have developed a multicomponent alkylation–peroxidation reaction of styrene derivatives with ketones by Brønsted acid catalysis, based on a previous mechanistic study. The γ-peroxyketone products thus obtained can be further converted to synthetically useful 1,4-diketones, homoaldol products, and alkyl ketones. The reaction is thus a valuable addition to the mostly metal-mediated addition reactions employing activated methylene compounds, which are less effective with simple ketones. The mechanistic information gained by this study sheds further light on the autoxidative coupling reaction with xanthene[1,2] and could be useful for future developments.

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