Oxidative Coupling

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Synergistic Effect of Ketone and Hydroperoxide in Brønsted Acid Catalyzed Oxidative Coupling Reactions**

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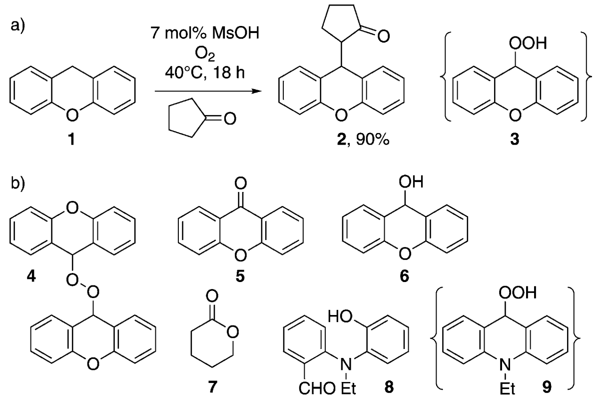
The functionalization of C–H bonds by oxidative coupling has attracted a lot of attention in recent years.[1] These reactions offer several advantages, in particular the direct use of unfunctionalized starting materials which can help to streamline synthesis. Often transition metal catalysts are used together with peroxides, but metal-free and organocatalytic examples of oxidative coupling reactions are known as well.[2–4]

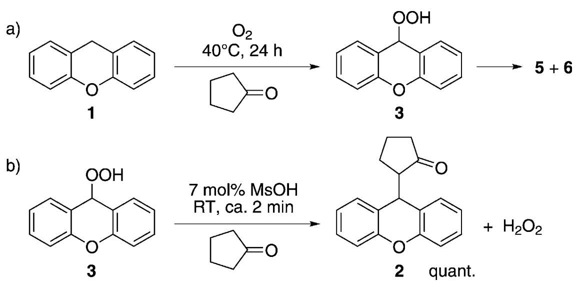
We reported an oxidative coupling reaction of xanthene (**1**) and related compounds with C-nucleophiles which only requires a simple Brønsted acid as the catalyst and elemental oxygen as the oxidant.[5] A representative example is the coupling of xanthene with cyclopentanone using methanesulfonic acid (MsOH), which forms product **2** (Scheme 1 a). The reaction proceeds at ambient temperature, but was usually performed at 40 °C for faster conversion. The lack of a redox-active catalyst is remarkable and it was presumed that the reaction proceeded via hydroperoxide **3** formed by autoxidation, hence the term "autoxidative coupling".[6] Here, we present results from a mechanistic study.

Even though we did not detect peroxides under standard reaction conditions, we could characterize byproducts **4**–**8** in some reaction mixtures, which indicate autoxidation processes (Scheme 1 b). For example, peroxide **4** (CF_3CO_2H served as the catalyst)[5a] and xanthone **5**—which was seen in almost all reactions using xanthene—are most likely secondary products of **3**. Up to a 25 % yield of valerolactone **7** (based on **1**) could be observed, which is obviously formed from cyclopentanone and a hydroperoxide by Baeyer–Villiger oxidation. When we used acridanes, we could isolate **8**, indicating rearrangement[7] of the corresponding hydroperoxide **9**. An involvement of catalytic transition metal impurities was discounted as unlikely based on trace element analysis.[5a]

For further investigations into the reaction mechanism, we chose the coupling of xanthene (**1**) and cyclopentanone at 40 °C as a model reaction (Scheme 1 a). When we subjected **1** to the reaction conditions but without acid we observed full conversion to oxygenated products within 24 h (Scheme 2 a).



Scheme 1. a) Autoxidative coupling reaction of xanthene and cyclopentanone, the model reaction of the present study. b) Byproducts **4**–**8** isolated in this or related reactions.



Scheme 2. a) Autoxidation of xanthene in cyclopentanone. b) Conversion of hydroperoxide **3** to coupling product **2**.

Initially, hydroperoxide **3** is the major product, which over time decomposes to the secondary products xanthone (**5**) and xanthydrol (**6**) (see the Supporting Information, chapter S2.4).

When hydroperoxide **3** was subjected to the reaction conditions, coupling product **2** was formed in essentially quantitative yield in a short time (Scheme 2 b). As expected, hydrogen peroxide was formed as well, as detected by UV/Vis spectroscopy immediately after the reaction (see chapter S2.14). Under the same conditions, xanthydrol **6** did not form **2** but equal amounts of **1** and **5** by disproportionation,[8] discounting it as key intermediate (see chapter S2.8). During autoxidation as well as the oxidative coupling reaction, one mole of oxygen was consumed per mole of converted xanthene (see chapter S2.9).

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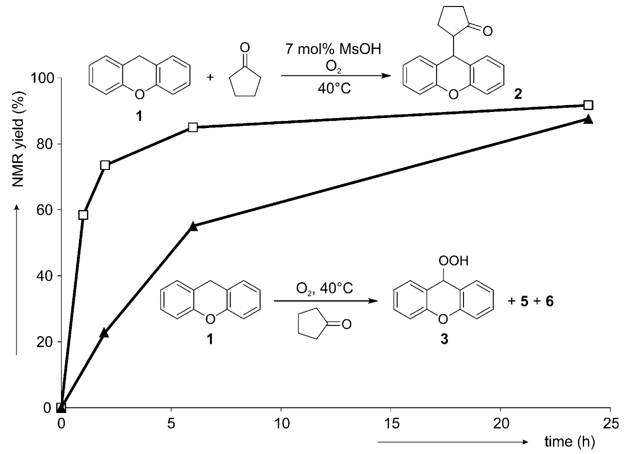
It seemed that all these experiments adequately explained the mechanism: rate-limiting aerobic autoxidation of xanthene generates hydroperoxide **3**, which forms **2** and H_2O_2 by a fast acid-catalyzed nucleophilic substitution of the hydroperoxide group with cyclopentanone. However, we could not detect hydrogen peroxide during and at the end of the reaction. Additionally, when we took a closer look at the reaction rates, we were surprised to see that the autoxidation is actually slower than the overall reaction (Scheme 3). This result suggested either that another factor influences the kinetics of the autoxidation process, that we overlooked a secondary pathway or that a completely different mechanism is in effect.

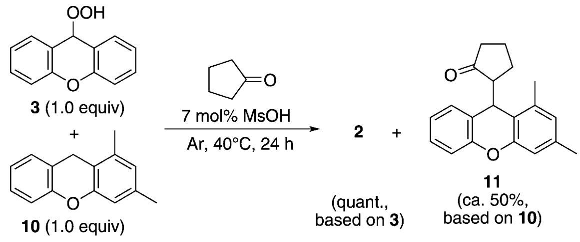


Scheme 3. Representative conversion profile of the coupling reaction (squares) and of the autoxidation (triangles, sum of oxygenated products **3**, **5**, and **6**).

We first studied the autoxidation of **1** separately and realized its strong solvent dependence. The fastest rates and highest yields were obtained in ketones, with cyclopentanone being one of the most efficient solvents. Low or moderate yields and rates of autoxidation were observed for reactions in all other solvents tested (see chapter S2.10). This explains our difficulties in achieving high yields with nucleophiles other than ketones[5] and the solvent effects seen in a related reaction.[6a] The autoxidation of organic compounds is obviously a known phenomenon[9] and acceleration by ketones has been reported for cyclohexane at 145 °C,[10] but the rate at which **1** is fully converted by autoxidation in cyclopentanone at ambient temperature is still remarkable.

There are only a few reports of acid effects on the rate of autoxidation reactions.[11] To investigate whether the autoxidation of Scheme 2a is accelerated by the Brønsted acid catalyst, we employed weaker acids that do not or only barely promote the nucleophilic substitution of the hydroperoxide, because the effect of strong acids on the autoxidation cannot be deconvoluted from the coupling step of Scheme 2b. These experiments gave no indication that catalytic amounts of acid accelerate the autoxidation of **1** under our conditions (see chapters S2.7, S2.11, and S2.12). Moreover, the question of why no H_2O_2 is detectable remains unexplained.

Although hydrogen peroxide usually requires transition metal catalysis for oxidative coupling reactions,[3] we wondered whether it could enter another reaction pathway. Using aqueous or anhydrous H_2O_2 was unsuccessful due to problems with solubility and reproducibility, respectively. To stay as close as possible to our reaction conditions, we studied the effect of H_2O_2 generated in situ. Hydroperoxide **3**, substituted xanthene **10**,[12] and MsOH were mixed in cyclopentanone under argon to exclude aerobic autoxidation. After several hours, roughly 50 % of **10** was converted to **11** (Scheme 4).

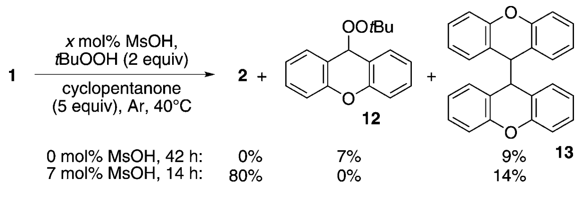


Scheme 4. Oxidative coupling of **10** by hydrogen peroxide generated in situ as a byproduct in the reaction of **3** with cyclopentanone.

While the general outcome of this experiment was reproducible, the yield of the oxidatively formed product varied between 15 and 46 % after three to five hours. In the presence of 2,6-di-*tert*-butyl-4-methylphenol (BHT) as a radical inhibitor, substitution of the hydroperoxide in **3** by cyclopentanone occurred, but oxidative coupling of xanthene did not. These experiments clearly demonstrate that the byproduct H_2O_2 induces an alternative radical pathway, which could explain the accelerated rate of the reaction compared with the autoxidation (see chapter S2.13, for details). While it has been shown that the oxidative power of H_2O_2 can be enhanced under acidic conditions, the suggested mechanisms were ionic.[13]

For further experiments, we chose *tert*-butylhydroperoxide in decane as an easily available and safe source of a nonaqueous hydroperoxide. Stirring xanthene, cyclopentanone, and two equivalents of *t*BuOOH under an atmosphere of argon resulted in low conversion of xanthene. Product **2** was not formed but small amounts of mixed peroxide **12** as well as the dimer **13** arose instead (Scheme 5). In the presence of 7 mol % of MsOH, full conversion of xanthene was achieved, giving 80 % yield of the coupling product **2** and 14 % yield of **13**.

The presence of **13** suggests the intermediate formation of a xanthenyl radical, once more indicating the radical nature of the hydro(gen)peroxide-mediated oxidation pathway. Interestingly, we could see the mixed peroxide **12** as a transient

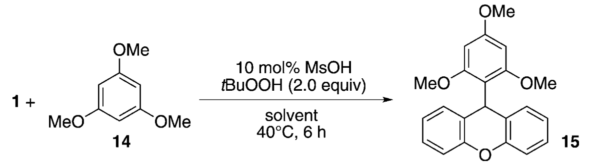


Scheme 5. Anaerobic reaction of **1** with *t*BuOOH in cyclopentanone.

intermediate when this reaction was monitored by ^{1}H NMR spectroscopy, unlike the more reactive hydroperoxide **3**, and full conversion of *t*BuOOH to *tert*-butanol. If instead of cyclopentanone, dichloromethane was used as a solvent, hardly any conversion of xanthene was observed. In other solvents, mostly low conversion to unidentified products occurred (see chapter S2.16).

To separate the aspects of the solvent and the nucleophile, we used **14** as a nucleophilic additive (Table 1). The reactions were performed for six hours in closed vials but without strict exclusion of oxygen. When we stirred xanthene, *t*BuOOH, **14**, and catalytic amounts of MsOH in acetone in a closed vial, nearly full conversion to the coupling product **15** was achieved (Table 1, entry 1). In cyclopentanone, the reactivity was decreased and **15** was formed in about 50 % yield (Table 1, entry 2). For comparison, the aerobic formation of **15** can only be performed under more forcing conditions (70 °C, 10 bar partial pressure of oxygen, 24 h).[5b] In all other solvents investigated, yields reached 5–27 % only (Table 1, entries 3–10). While some conversion could be observed in all cases, the solvent effects cannot be rationalized based on polarity; for example, both DMSO and toluene give very low conversions (Table 1, entries 8 and 9).

Table 1: Investigating the solvent effect.[a]



Entry	Solvent	**1** [%][b]	**15** [%][b]	**13** [%][b]
1	acetone	7	92	< 1
2	cyclopentanone	52	48	< 1
3	CH_3CN	73	27	< 1
4	MeOH	78	21	1
5	EtOAc	79	17	1
6	$CHCl_3$	81	18	1
7	CH_3NO_2	84	15	1
8	DMSO	90	7	0
9	toluene	90	8	1
10	MTBE	93	5	1

[a] **1** (0.25 mmol), **14** (0.25 mmol) solvent (0.25 mL), *t*BuOOH (0.5 mmol, in decane), MsOH (0.025 mmol). [b] Analysis by ^{1}H NMR spectroscopy.

Instead, the results of Scheme 5 and Table 1 indicate that the combination of acid, hydroperoxide, and ketone as a solvent are optimal to achieve high conversion of xanthene to the coupling products **2** and **15**. Potentially, peroxy hemiketals, perketals, or related compounds like **16**–**19** (Figure 1) form by Brønsted acid catalysis in the presence of hydrogen peroxide or *tert*-butylhydroperoxide and undergo homolytic O–O bond cleavage. This is further supported by the lack of reactivity with di-*tert*-butyl peroxide, which cannot form such compounds, while aqueous *t*BuOOH or cumyl hydroperoxide are effective (see chapter S2.18).

Cyclohexanone is suggested to assist the O–O bond cleavage of cyclohexylhydroperoxide by H-atom transfer at 145 °C, but no acid was present in this study.[10] Perketals or perhemiketals are said to be labile compounds which decompose into radicals.[14] Solyanikov and co-workers actually investigated the synergistic effect of ketone and strong acid in the radical decomposition of hydroperoxides.[15] They suggested the involvement of peroxy hemiketals, but the mechanism was not further investigated and their results were not utilized for any application in synthesis.

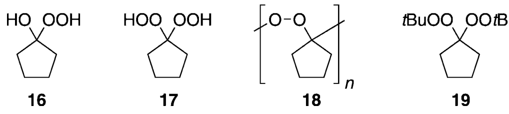


Figure 1. Potential radical initiators formed in situ.

To further evaluate the potential occurrence of such compounds, we synthesized **17** and **19** from cyclopentanone by acid catalysis.[16] No reaction occurred when xanthene and cyclopentanone were stirred with these under strict exclusion of oxygen (Table 2, entries 1 and 2). In the presence of MsOH, however, conversion to coupling product **2** and dimer **13** was observed within hours, with **19** being more efficient than **17** (Table 2, entries 3 and 4). Once more, stronger acids are required: nitric acid was only effective with **17** and trifluoroacetic acid was ineffective with both **17** and **19** (see chapters S2.19 and S2.20).

Table 2: Evaluating **17** and **19** as oxidants.[a]

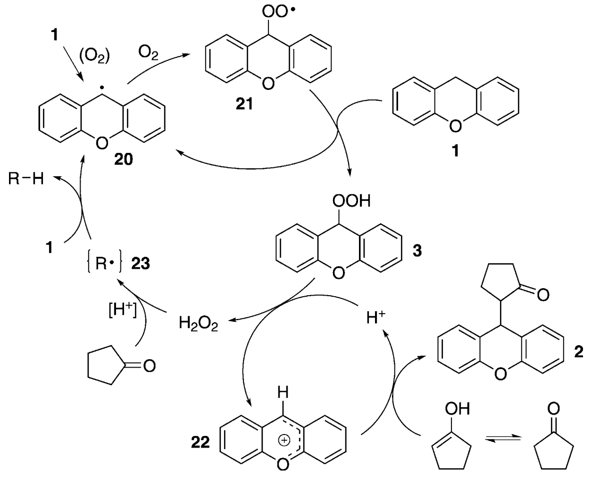
$$\mathbf{1} \xrightarrow[\text{cyclopentanone, Ar, 40°C}]{x\text{ mol\% MsOH, } \mathbf{17/19}\text{ (1.0 equiv)}} \mathbf{2} + \mathbf{13}$$

Entry	mol % MsOH	*t* [h]	oxidant	**2** [%][b]	**13** [%][b]
1	0	12	**17**	0	0
2	0	12	**19**	0	0
3	7	1	**17**	4	5
4	7	1	**19**	25	35

[a] **1** (0.5 mmol), **17**/**19** (0. 5 mmol) cyclopentanone (2.0 mmol), MsOH (0.035 mmol), under Ar. [b] Yields determined by ^{1}H NMR spectroscopy.

While these experiments do not unequivocally determine whether **17** and **19** are truly intermediates in the reactions studied, they support the suggested role of acid, ketone, and hydroperoxide. The role of the acid is twofold, catalyzing the formation of perketals or related compounds *and* their decomposition to radicals. Further studies are needed to elucidate the exact mechanism of this Brønsted acid catalyzed radical formation and the structure of the radicals involved.

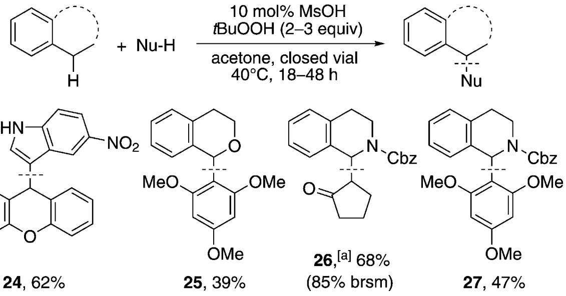
Consistent with the results discussed above, we propose a mechanism for the autoxidative coupling as shown in Scheme 6. In the presence of oxygen, autoxidation of **1** is initiated and proceeds via radicals **20** and **21** to hydroperoxide **3**, which under strong Brønsted acid catalysis generates H_2O_2 and a stabilized carbocation **22**. Reaction with the nucleophilic enol form of the ketone forms reaction product **2**. A second pathway is opened by the release of H_2O_2: in the presence of ketone and Brønsted acid, radicals of a yet unknown structure ("**23**") are formed, probably via inter-



Scheme 6. Mechanistic proposal for the autoxidative coupling of xanthene **1** with cyclopentanone to **2**, showing the autoinductive effect of waste product H_2O_2 on the formation of hydroperoxide **3**.

mediates like **16** or **17**. These abstract a hydrogen atom from xanthene to give radical **20**, which is quickly trapped by oxygen, channeling into the same reaction path as in the aerobic autoxidation. This autoinductive effect of the byproduct hydrogen peroxide explains why the conversion of xanthene under reaction conditions is accelerated compared to the autoxidation alone and the disappearance of H_2O_2. In the absence of oxygen, the lifetime of radical **20** is sufficient to allow for dimerization to dimer **13**, which is not observed under standard reaction conditions.

Inspired by this Brønsted acid catalyzed radical formation, we investigated whether it has a broader synthetic utility (Scheme 7). Compounds **24**–**27** were formed by the oxidative coupling of xanthene, isochromane, and carbamate-protected tetrahydroisoquinoline, respectively, with an added nucleophile (see chapters S3.10–S3.13). These products had previously been synthesized by oxidative coupling at temperatures above 100 °C or using transition metal catalysis.[17]



Scheme 7. Application of the Brønsted acid catalyzed radical formation. New bonds are indicated by a dashed line. brsm: based on recovered starting material. [a] Cyclopentanone as solvent/nucleophile.

In summary, the investigation of the aerobic oxidative coupling of xanthene with cyclopentanone catalyzed by methanesulfonic acid supported the originally proposed mechanism via autoxidation, but also uncovered a second pathway. The byproduct of the reaction, hydrogen peroxide, shows an autoinductive effect, inducing its own re-formation and accelerating the formation of the final product. This radical-forming process is mediated by the presence of ketones and strong Brønsted acids and presumably proceeds via perketals or related compounds. Inspired by this, we could facilitate the Brønsted acid catalyzed oxidative coupling of other substrates using *tert*-butyl hydroperoxide. These discoveries indicate the potential to develop further acid-catalyzed oxidative radical reactions and could have implications for other mechanisms.[18]

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[1] a) W.-J. Yoo, C.-J. Li, *Top. Curr. Chem.* **2010**, *292*, 281–302; b) C. J. Scheuermann, *Chem. Asian J.* **2010**, *5*, 436–451; c) M. Klussmann, D. Sureshkumar, *Synthesis* **2011**, 353–369; d) C. Liu, H. Zhang, W. Shi, A. Lei, *Chem. Rev.* **2011**, *111*, 1780–1824; e) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215–1292.

[2] For examples using transition metal catalysis and organic peroxides: a) M. S. Kharasch, A. Fono, *J. Org. Chem.* **1959**, *24*, 72–78; b) D. H. R. Barton, T.-L. Wang, *Tetrahedron* **1994**, *50*, 1011–1032; c) F. Minisci, F. Fontana, *Tetrahedron Lett.* **1994**, *35*, 1427–1430; d) Z. Li, D. S. Bohle, C.-J. Li, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 8928–8933; e) H. A. Wegner, S. Ahles, M. Neuburger, *Chem. Eur. J.* **2008**, *14*, 11310–11313.

[3] For examples using transition metal catalysis and H_2O_2: a) S. Sharma, N. Barooah, J. B. Baruah, *J. Mol. Catal. A* **2005**, *229*, 171–176; b) S.-I. Murahashi, N. Komiya, H. Terai, *Angew. Chem.* **2005**, *117*, 7091–7093; *Angew. Chem. Int. Ed.* **2005**, *44*, 6931–6933; c) Y. Shen, Z. Tan, D. Chen, X. Feng, M. Li, C.-C. Guo, C. Zhu, *Tetrahedron* **2009**, *65*, 158–163; d) X.-F. Wu, C. Darcel, *Eur. J. Org. Chem.* **2009**, 1144–1147; e) B. Guo, Q. Zhang, G. Li, J. Yao, C. Hu, *Green Chem.* **2012**, *14*, 1880–1883.

[4] For metal-free reactions, see: a) R. Rohlmann, O. G. Mancheño, *Synlett* **2013**, *24*, 6–10; b) M. Uyanik, K. Ishihara, *ChemCatChem* **2012**, *4*, 177–185; c) J. Santamaria, D. Herlem, F. Khuong-Huu, *Tetrahedron* **1977**, *33*, 2389–2392; d) T. Dohi, A. Maruyama, M. Yoshimura, K. Morimoto, H. Tohma, Y. Kita, *Angew. Chem.* **2005**, *117*, 6349–6352; *Angew. Chem. Int. Ed.* **2005**, *44*, 6193–6196; e) M. Ochiai, Y. Takeuchi, T. Katayama, T. Sueda, K. Miyamoto, *J. Am. Chem. Soc.* **2005**, *127*, 12244–12245; f) K. R. Reddy, C. U. Maheswari, M. Venkateshwar, M. L. Kantam, *Eur. J. Org. Chem.* **2008**, 3619–3622; g) M. Uyanik, H. Okamoto, T. Yasui, K. Ishihara, *Science* **2010**, *328*, 1376–1379; h) A. P. Antonchick, R. Samanta, K. Kulikov, J. Lategahn, *Angew. Chem.* **2011**, *123*, 8764–8767; *Angew. Chem. Int. Ed.* **2011**, *50*, 8605–8608; i) D. P. Hari, B. König, *Org. Lett.* **2011**, *13*, 3852–3855; j) Y. Pan, C. W. Kee, L. Chen, C.-H. Tan, *Green Chem.* **2011**, *13*, 2682–2685; k) T. Froehr, C. P. Sindlinger, U. Kloeckner, P. Finkbeiner, B. J. Nachtsheim, *Org. Lett.* **2011**, *13*, 3754–3757.

[5] a) Á. Pintér, A. Sud, D. Sureshkumar, M. Klussmann, *Angew. Chem.* **2010**, *122*, 5124–5128; *Angew. Chem. Int. Ed.* **2010**, *49*, 5004–5007; b) Á. Pintér, M. Klussmann, *Adv. Synth. Catal.* **2012**, *354*, 701–711.

[6] For related cases, see: a) B. Zhang, S.-K. Xiang, L. H. Zhang, Y. Cui, N. Jiao, *Org. Lett.* **2011**, *13*, 5212–5215; b) M. Brasse, J. A. Ellman, R. G. Bergman, *Chem. Commun.* **2011**, *47*, 5019–5021; c) Y.-C. Wong, M.-T. Hsieh, P. K. Amancha, C.-L. Chin, C.-F.

Liao, C.-W. Kuo, K.-S. Shia, *Org. Lett.* **2011**, *13*, 896 – 899; d) C. G. Piscopo, S. Buhler, G. Sartori, R. Maggi, *Catal. Sci. Technol.* **2012**, *2*, 2449 – 2452; e) N. Jiao, B. Zhang, Y. Cui, *Chem. Commun.* **2012**, *48*, 4498 – 4500; f) H. Gunduz, V. Kumbaraci, N. Talinli, *Synlett* **2012**, *23*, 2473 – 2476; g) L. Liu, Z. Wang, X. Fu, C.-H. Yan, *Org. Lett.* **2012**, *14*, 5692 – 5695; h) Q. Lu, J. Zhang, G. Zhao, Y. Qi, H. Wang, A. Lei, *J. Am. Chem. Soc.* **2013**, *135*, 11481 – 11484.

[7] H. Hock, S. Lang, *Berichte* **1944**, *77*, 257 – 264.

[8] F. G. Kny-Jones, A. M. Ward, *J. Chem. Soc.* **1930**, 535 – 542.

[9] a) N. A. Milas, *Chem. Rev.* **1932**, *10*, 295 – 364; b) I. Hermans, J. Peeters, P. A. Jacobs, *Top. Catal.* **2008**, *50*, 124 – 132.

[10] I. Hermans, P. A. Jacobs, J. Peeters, *Chem. Eur. J.* **2006**, *12*, 4229 – 4240.

[11] a) L. Valgimigli, R. Amorati, S. Petrucci, G. F. Pedulli, D. Hu, J. J. Hanthorn, D. A. Pratt, *Angew. Chem.* **2009**, *121*, 8498 – 8501; *Angew. Chem. Int. Ed.* **2009**, *48*, 8348 – 8351; b) L. Dulog, K. Tsobanidis, *Makromol. Chem. Rapid Commun.* **1981**, *2*, 407 – 410; c) A. P. ter Borg, R. van Helden, A. F. Bickel, *Recl. Trav. Chim. Pays-Bas* **1962**, *81*, 164 – 176; d) A. P. ter Borg, H. R. Gersmann, A. F. Bickel, *Recl. Trav. Chim. Pays-Bas* **1966**, *85*, 899 – 918.

[12] E. Böß, T. Hillringhaus, J. Nitsch, M. Klussmann, *Org. Biomol. Chem.* **2011**, *9*, 1744 – 1748.

[13] a) Å. M. Leere Øiestad, A. C. Petersen, V. Bakken, J. Vedde, E. Uggerud, *Angew. Chem.* **2001**, *113*, 1345 – 1349; *Angew. Chem. Int. Ed.* **2001**, *40*, 1305 – 1309; b) G. A. Olah, D. G. Parker, N. Yoneda, *Angew. Chem.* **1978**, *90*, 962 – 984; *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 909 – 931.

[14] “Oxidation: G. Franz, R. A. Sheldon in *Ullmann’s Encyclopedia of Industrial Chemistry*, Wiley-VCH, Weinheim, **2000**.

[15] a) L. V. Petrov, T. I. Drozdova, L. Y. Lyuta, V. M. Solyanikov, *Russ. Chem. Bull.* **1990**, *39*, 226 – 232; b) L. V. Petrov, V. M. Solyanikov, *Russ. Chem. Bull.* **1996**, *45*, 340 – 345.

[16] a) A. O. Terent′ev, A. V. Kutkin, N. A. Troizky, Y. N. Ogibin, G. I. Nikishin, *Synthesis* **2005**, 2215 – 2219; b) D. Azarifar, K. Khosravi, F. Soleimanei, *Molecules* **2010**, *15*, 1433 – 1441.

[17] a) W. Hanefeld, I. Hunz, *Arch. Pharm.* **1993**, *326*, 323 – 329; b) M. Ghobrial, M. Schnürch, M. D. Mihovilovic, *J. Org. Chem.* **2011**, *76*, 8781 – 8793; c) B. Schweitzer-Chaput, M. Klussmann, *Eur. J. Org. Chem.* **2013**, 666 – 671.

[18] a) Y. He, C. R. Goldsmith, *Synlett* **2010**, 1377 – 1380; b) Y. Fujiwara, J. A. Dixon, R. A. Rodriguez, R. D. Baxter, D. D. Dixon, M. R. Collins, D. G. Blackmond, P. S. Baran, *J. Am. Chem. Soc.* **2012**, *134*, 1494 – 1497; c) A. Khazaei, M. A. Zolfigol, M. Mokhlesi, F. D. Panah, S. Sajjadifar, *Helv. Chim. Acta* **2012**, *95*, 106 – 114.