JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Article
pubs.acs.org/JACS

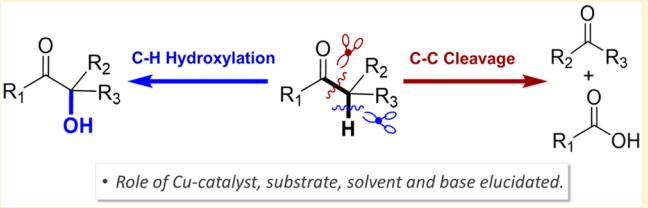
Factors That Control C−C Cleavage versus C−H Bond Hydroxylation in Copper-Catalyzed Oxidations of Ketones with O_2

Althea S.-K. Tsang,[§] Ajoy Kapat,[§] and Franziska Schoenebeck*

Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, 52074 Aachen, Germany

Supporting Information

ABSTRACT: The Cu-catalyzed oxidation of ketones with O_2 has recently been extensively utilized to cleave the α-C−C bond. This report examines the selective aerobic hydroxylation of tertiary α-C−H bonds in ketones without C−C cleavage. We set out to understand the underlying mechanisms of these two possible reactivity modes. Using experimental, *in situ* IR spectroscopic, and computational studies, we investigated several mechanisms. Our data suggest that both C−C cleavage and C−H hydroxylation pathways proceed via a common key intermediate, i.e., an α-peroxo ketone. The fate of this peroxide dictates the ultimate product selectivity. Specifically, we uncovered the role of hppH [= 1,3,4,6,7,8-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidine] to act not only as a base in the transformation but also as *a reductant* of the peroxide to the corresponding α-hydroxy ketone. This reduction may also be accomplished through exogenous phosphine additives, therefore allowing the tuning of reduction efficiency toward higher driving forces, if required (e.g., for more-activated substrates). The likely competitive pathway is the cleavage of peroxide to the α-oxy radical (likely catalyzed by Cu), which is computationally predicted to spontaneously trigger C−C bond cleavage. Increasing the susceptibility of this deperoxidation step via (i) the removal of reductant (use of different base, e.g., DBU) or the modulation of (ii) the substitution pattern toward greater activation (substrate control) and (iii) the nature of Cu catalyst (counterion and solvent dependence) will favor the C−C cleavage product.



INTRODUCTION

Selective oxidations are of critical importance to industrial and academic research, being a key challenge in large-scale industrial processes that convert hydrocarbon feedstock into commodity and fine chemicals,[1] in energy-related developments (e.g., lignin biomass conversion),[2] and in synthesis.[3] While impressive progress has been made to date, there is an increasing demand to move away from precious transition metal catalysts and stoichiometric oxidants toward more environmentally benign approaches, ideally using molecular oxygen as a waste-free and abundant oxidant.[4] Nature achieves selective aerobic oxidations with the use of tailored metalloenzymes that frequently contain copper in the active site.[5] These feature either "oxidase" reactivity, in which substrates are oxidized under concurrent reduction of O_2 to water/H_2O_2, or "oxygenase" reactivity that leads to oxygen-atom incorporation into C−H bonds.

While biomimetic approaches are a popular means to achieve selective oxidation also with synthetic Cu catalysts,[6] there have recently been numerous reports of homogeneous Cu catalysis protocols that selectively triggered formal oxidase[7,9] or also oxygenase reactivity,[8,9] even in the absence of the beneficial reactivity elements of the enzyme pocket or its mimic.

In this context, homogeneous aerobic copper catalysis has been shown to give selective cleavage of the α-C−C bond of ketones (Figure 1).[10] Utilizing this reactivity mode, ketones were recently converted to aldehydes,[11] amides,[12] or esters.[13] The underlying mechanism of C−C cleavage is unclear but has been proposed to be a result of (i) overoxidation,[11,14] (ii) Baeyer−Villiger/Criegee-type rearrangements of peroxide intermediates,[15] (iii) base-induced fragmentations,[13,16,33] (iv) free-radical pathways,[9a] or (v) more-complex sequences consisting of hydration and hydride-shift-induced C−C fragmentation[11] (see Results and Discussion).

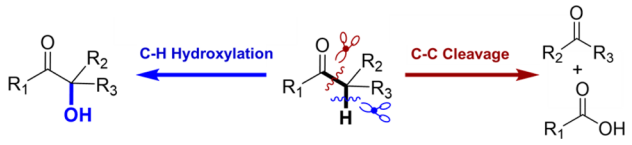


Figure 1. C−H hydroxylation versus C−C cleavage.

On the other hand, the selective α-hydroxylation of ketones without C−C cleavage constitutes an equally important alternative reactivity mode, as the α-hydroxy ketone moiety is a central motif in a wide range of natural products and biologically active molecules (e.g., the antitumoral pirarubicin and the antibiotics daunorubicin and doxycycline) (Figure 1).[17] Consequently, the preparation of this building block has received considerable attention.[18] While it can, in principle, be achieved via the oxidation of enolates or silyl enol ethers with stoichiometric oxidants [e.g., *N*-sulfonyl oxaziridines, DMDO (dimethyldioxirane), *m*-CPBA],[19] the direct catalytic hydroxylation of ketones with O_2 is more challenging. Commonly

Received: August 7, 2015
Published: December 16, 2015

DOI: 10.1021/jacs.5b08347
J. Am. Chem. Soc. 2016, 138, 518−526

encountered complications include a limited substrate scope and/or low selectivities, with byproducts resulting from C−C cleavage frequently observed.[20,14] However, recently there have been two significant advances that allowed a general and selective hydroxylation of ketones with O_2, employing either (i) transition metal (Pd dimer) catalysis[21] or (ii) proposed base catalysis along with multiple equivalents of phosphine additive.[22] In terms of Cu catalysis, intriguingly, selective α-hydroxylation has also been accomplished, albeit *heterogeneously*, using $\{[Cu(bpy)(BF_4)_2(H_2O)_2](bpy)\}_n$.[23] The origins of selectivity for formal C−H hydroxylation in these transformations and the precise mechanism that ultimately leads to the alcohol product are unknown.

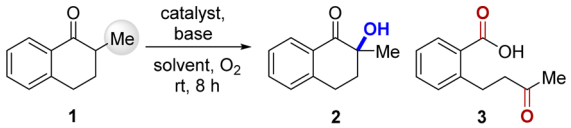
We herein report our combined experimental and computational study to elucidate the factors that control formal C−H hydroxylation versus C−C cleavage in the Cu-catalyzed homogeneous oxidation of ketones with O_2. The crucial roles of substrate, catalyst, solvent, and additives are explored and rationalized. As a stringent test of mechanism, the switchability between selective α-hydroxylation versus C−C cleavage is demonstrated.

RESULTS AND DISCUSSION

We started our investigations with the cyclic ketone **1** (see Table 1). We initially explored various conditions, investigating the effects of base, Cu catalyst, and solvent under aerobic reaction conditions. This revealed that the use of hppH (1,3,4,6,7,8-hexahydro-2*H*-pyrimido[1,2-*a*]pyrimidine, see Scheme 1) as base and DMSO as solvent along with copper(I) oxide as catalyst converted **1** selectively to the C−H hydroxylated product **2** within 8 h at room temperature (entry 1). Modification of either base (entries 9−15) or solvent (entries 16−18) lowered the conversion and/or selectivity, giving rise also to product **3**, resulting from formal C−C cleavage in a mixture with α-hydroxylated ketone **2**. All non-oxide Cu sources explored (i.e., CuX_n with X = Br, Cl, I, OAc, OTf, entries 2−8), with the exception of CuF_2 (entry 6), resulted in a mixture of products **2** and **3** (see Table 1). Control experiments in the absence of base (entry 19) or oxygen (entries 20, 21) revealed that, for conversion to take place, these components were required.

The ability to selectively hydroxylate the C−H bond in ketone **1** under Cu_2O/DMSO/hppH conditions (entry 1, Table 1) was intriguing, and we therefore set out to explore the generality of these conditions. Our investigations revealed that there is a pronounced substrate dependence as to whether the C−H hydroxylated or C−C cleaved product is formed. For α-methyl ketones, only the hydroxylated products were formed under these conditions, tolerating different ring sizes, heteroatoms, and substituents at the aromatic ring (see Scheme 1). Also a non-aromatic example (**6**, Scheme 1) was successfully converted to the single C−H hydroxylated product.

Table 1. Investigation of the Effect of Cu Source, Solvent, and Base on the Selectivity of the Cu-Catalyzed Reaction of 1 with O_2[a,24]

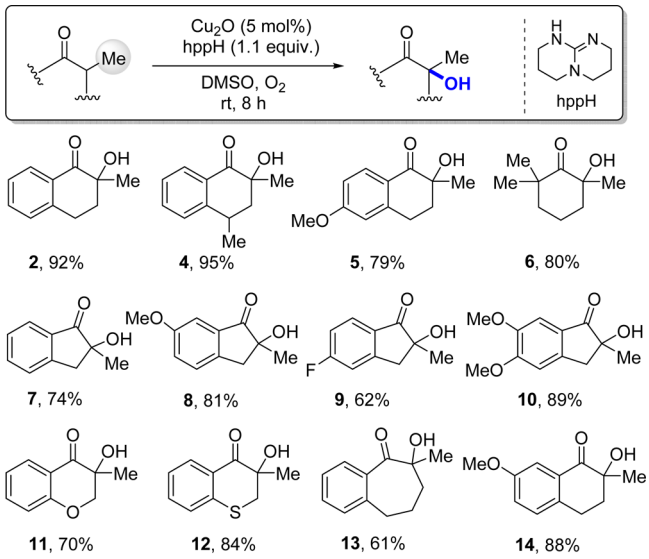


1 2 3

				yield (%)		
entry	catalyst	base	solvent	2	3	1
1	Cu_2O	hppH	DMSO	94	0	0
2	$CuBr_2$	hppH	DMSO	16	10	0
3	CuI	hppH	DMSO	23	26	10
4	CuCl	hppH	DMSO	22	12	0
5	$CuCl_2$	hppH	DMSO	32	27	0
6	CuF_2	hppH	DMSO	72	0	0
7	$Cu(OAc)_2$	hppH	DMSO	21	20	0
8	$Cu(OTf)_2$	hppH	DMSO	20	23	0
9	Cu_2O	DBU	DMSO	20	10	70
10	Cu_2O	K_2CO_3	DMSO	5	5	90
11	Cu_2O	Cs_2CO_3	DMSO	50	30	0
12	Cu_2O	*i*Pr_2EtN	DMSO			quant.
13	Cu_2O	Et_2NH	DMSO			quant.
14	Cu_2O	DMAP	DMSO			quant.
15	Cu_2O	C_5H_5N	DMSO			quant.
16	Cu_2O	hppH	DMF	55	22	4
17	Cu_2O	hppH	THF	25	4	71
18	Cu_2O	hppH	MeCN	40	25	30
19	Cu_2O		DMSO	0	0	quant.
20[b]	Cu_2O	hppH	DMSO	0	0	quant.
21[c]	Cu_2O	hppH	DMSO	0	0	quant.

[a]Conditions: **1** (0.3 mmol), catalyst (5 mol%), base (1.1 equiv), solvent (1 mL), O_2, rt, 8 h. [b]Under N_2. [c]1.0 equiv of Cu_2O, N_2.

Scheme 1. Scope of Cu_2O-Catalyzed Hydroxylation of α-Methyl Ketones[a]



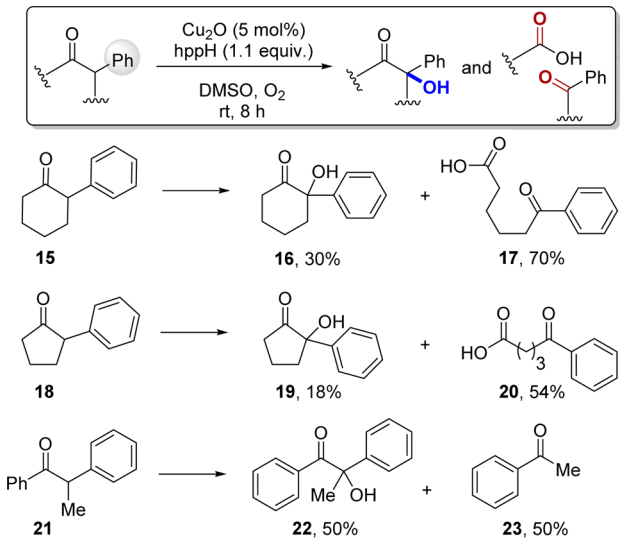
[a]Hydroxylated products were formed exclusively.[24]

However, when a slightly more "activating" substituent was present in the α-position of the ketone, such as a phenyl group, then the reactions were unselective under the Cu_2O/DMSO/hppH conditions, and we observed the formation of the C−C cleavage product along with that resulting from C−H hydroxylation (see Scheme 2). This reactivity was observed for cyclic (**15**, **18**) and acyclic (**21**) α-phenyl ketones (Scheme 2).[24,25]

These results indicate that the product selectivity, C−H hydroxylation versus C−C cleavage, depends on the substrate, oxidant, base, and solvent. To gain deeper insights, we next set out to explore the origins of the two products.

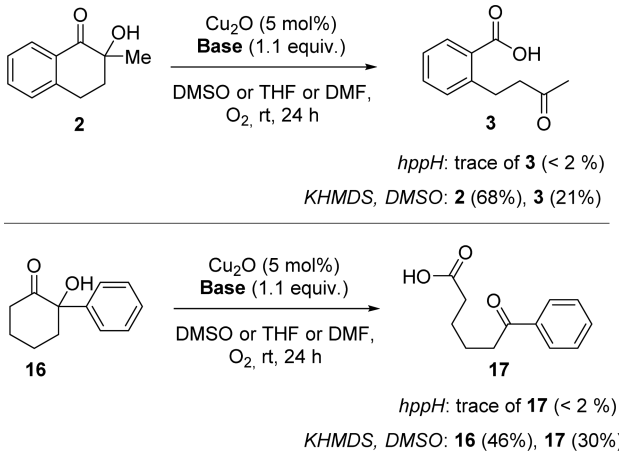
DOI: 10.1021/jacs.5b08347
J. Am. Chem. Soc. 2016, 138, 518−526

Scheme 2. Substrate-Controlled Selectivity: α-Phenyl Ketones Give Mixtures of Hydroxylation (Left) and C−C Scission (Right) Products



Does the C−C Cleavage Product Form Independently or from the α-Hydroxy Ketone? Previous reports proposed that the α-hydroxy ketone may potentially be oxidized further to the formally C−C activated product.[11,14] To test whether this is indeed the origin of the C−C cleaved products **3** or **17**, we subjected the α-hydroxy ketones **2** and **16** to the general catalytic reaction conditions, i.e., involving Cu_2O/hppH in the solvents DMSO, DMF, and THF. The results are shown in Scheme 3. For both substrates only trace conversions (<2%) to the C−C cleaved products were seen after 24 h at room temperature (Scheme 3). When using the stronger base KHMDS, slow conversion to the C−C cleaved products were observed for both substrates. Thus, very strong base is needed to enable oxidative C−C cleavage from **2** or **16**, suggesting that this reaction is not the main pathway responsible for the C−C activated product observed under the oxidation conditions in Table 1.

Scheme 3. Examination of the Origin of C−C Cleavage Products 3 and 17: Oxidation of α-Hydroxy Ketones Is Not the Origin of C−C Cleaved Product



To gain additional insight, we performed *in situ* IR studies (using ReactIR) and followed the conversion of α-phenyl ketone **15** under Cu-catalyzed reaction with O_2 in the presence of hppH in DMSO. Figure 2 presents an overlay of spectra of the study over the course of 2 h. The reaction was rapid and essentially complete after 1 h. Furthermore, two products clearly evolved over time. Through comparison of the IR signals with those of the separately prepared compounds, these could be unambiguously assigned as α-hydroxy ketone **16** and C−C cleaved product **17** (see Figure 2). These data suggest that the two products (**16**, **17**) form in parallel, reinforcing that the C−C cleaved product **17** does not result from further oxidation of **16**. Instead, it appears more likely that the hydroxylated and C−C cleaved products form in parallel from a common precursor (see also discussion below).

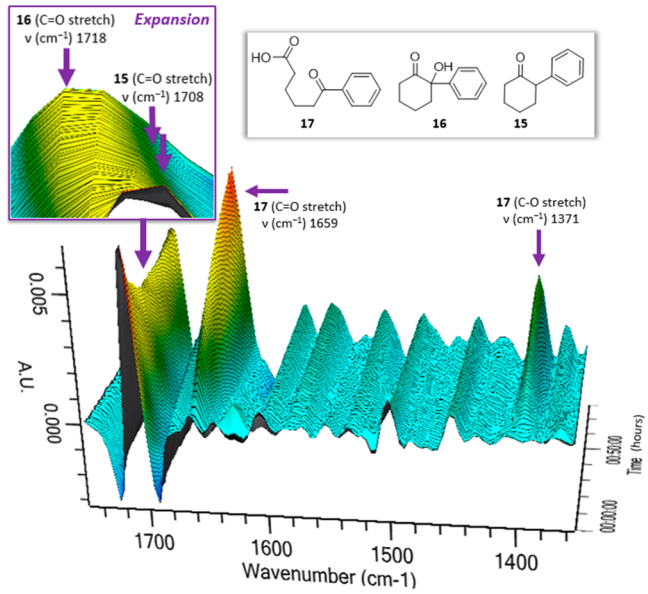


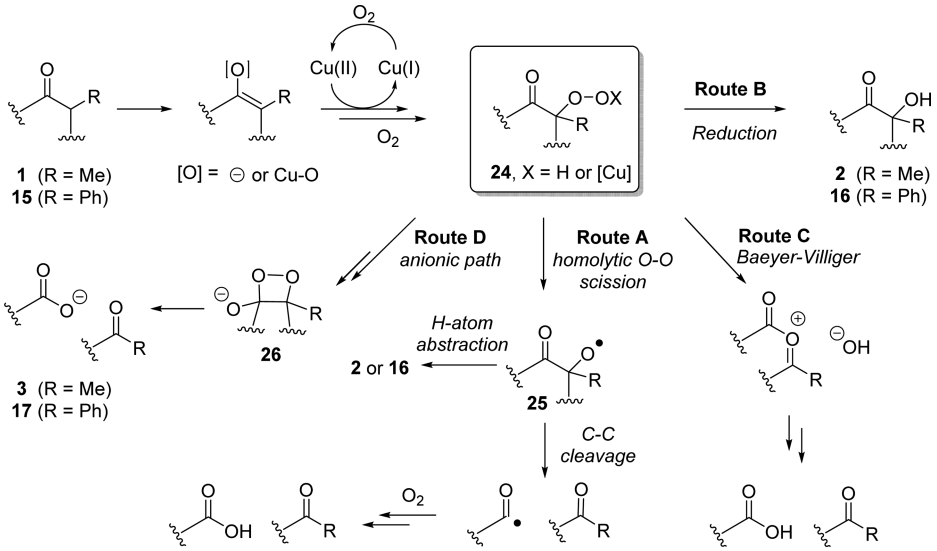
Figure 2. React IR study of Cu_2O/hppH/DMSO reaction of **15** with O_2. Signals of **15** and **16** are close, see expansion.

Mechanism of C−C Cleavage versus C−H Hydroxylation. Given the need for base in this transformation, a reasonable mechanistic scenario starts with the deprotonation of the ketone to give the corresponding enolate (see Scheme 4). This is likely subsequently oxygenated, either aerobically involving a Cu-induced single electron transfer (SET) pathway or alternatively through reaction with an electrophilic copper−dioxygen adduct. Cu(II) superoxo complexes have been implicated as key oxidants in enzymatic tranformations.[26,6c] On the other hand, Cu(I) salts are also readily oxidized to Cu(II) salts in the presence of oxygen, and Cu(II) in turn is an effective single-electron oxidant. Given that both Cu(I) and Cu(II) salts had triggered the conversion of ketone **1** to **2** and **3** (see Table 1, e.g., entries 1 and 2), the primary role of the Cu salt in the early stages of the mechanism might therefore be to oxidize the enolate to the corresponding radical, which in turn reacts with oxygen to a peroxide intermediate **24** or Cu-bound derivative thereof (Scheme 4).

Such peroxide intermediates have frequently been implicated in aerobic oxygenations.[9,27] For example, Rudler and Denise isolated a peroxide intermediate upon Cu(II)-catalyzed aerobic oxidation of indanes,[28] and Chiba and co-workers generated stable peroxides in Cu(II)-catalyzed benzylic C−H oxygenation with O_2.[29] Moreover, the Cu-catalyzed oxidation of cumene to cumyl hydroperoxide is an important industrial process.[30]

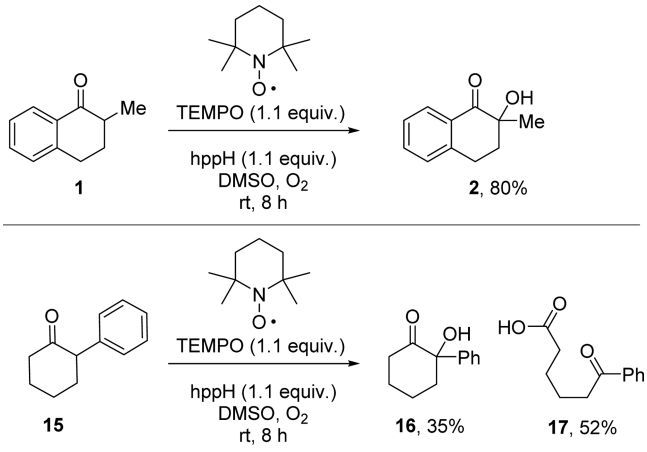
DOI: 10.1021/jacs.5b08347
J. Am. Chem. Soc. 2016, 138, 518−526

Scheme 4. Potential Mechanisms Leading to Either C−C Cleaved or C−H Hydroxylated Products



Our additional investigations with substrate **1**, in the absence of exogenously added Cu salt (but not fully copper-free, according to our trace metal analysis) also gave rise to **2**, albeit more slowly, which indicates that the Cu salt may primarily act as initiator (see also later discussion, "On the Role of Copper"). To find additional support, we also subjected ketones **1** and **15** to oxidations with O_2 in DMSO at room temperature in the presence of TEMPO (without added Cu). TEMPO has previously been employed in the oxidation of enolates, ultimately leading to α-TEMPO-bound carbonyl species upon trapping of the generated radical.[31] This gave rise to the analogous reaction outcome as we had previously obtained, furnishing exclusive hydroxylation of ketone **1** to **2** (80%). For α-phenyl ketone **15** a mixture of C−C cleaved (52%) and C−H hydroxylated (35%) products was again generated (Scheme 5). No TEMPO-trapped intermediate was observed. These data indicate that the key mechanistic intermediate that leads to either products resulting from C−H or C−C activation may not necessarily contain copper. The proposed hydroperoxide intermediate **24** (Scheme 3) would be fully consistent with these observations.

Scheme 5. Reactions of 1 and 15 in the Presence of TEMPO[a]



[a]The selectivity parallels those results obtained under Cu catalysis.

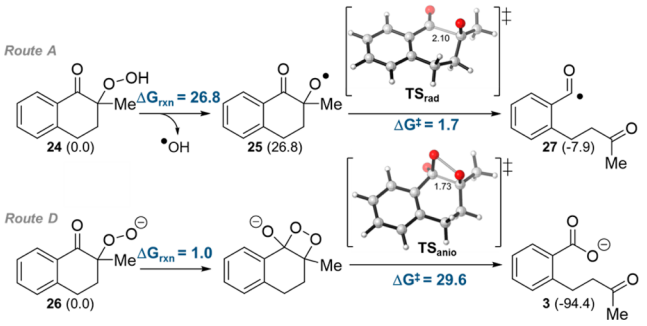
Hydroperoxide **24** might then homolytically cleave to the corresponding oxygen-centered radical (Scheme 4, Route A), which may abstract a hydrogen atom to give the α-hydroxy ketone. This possibility has frequently been proposed in Cu-catalyzed oxygenations of aliphatic and aromatic C−H bonds.[32]

Depending on the relative kinetics of H-atom abstraction, the oxygen-centered radical **25** might alternatively undergo C−C cleavage to yield the C−C activated products (such as **3** or **17**). Peroxide **24** might alternatively also be reduced directly to the corresponding α-hydroxy ketone (Route B) or undergo a Baeyer−Villiger/Criegee-type rearrangement to result in the C−C cleaved intermediate(s) (Route C). Finally, C−C fragmentation could potentially also arise upon deprotonation of the peroxide, followed by formation of dioxetane **26** and subsequent fragmentation (Route D).[12b,33]

Computational Investigations. To gain further insight into the likely mechanism(s), we subsequently undertook computational studies[34] and calculated the various mechanistic routes (Routes A−D) for the peroxide intermediate **24** (X = H) derived from ketones **1** and **15**. We employed the M06-2X/6-311++G(d,p)//B3LYP/6-31G(d) method of theory and accounted for DMSO solvation with the CPCM solvation model.[35] The homolytic bond cleavage of the peroxide intermediate RO−OH to RO radical **25** was calculated to be 26.8 kcal/mol for the peroxide derived from ketone **1** (see Scheme 6). The subsequent C−C cleavage from the corresponding oxygen-centered radical **25** was calculated to be very facile, requiring less than 2 kcal/mol activation free energy. For the peroxide derived from α-phenyl ketone **15** (not shown, see Supporting Information, Figure S8), the homolytic peroxide scission was calculated to be slightly more favored (ΔG_{rxn} = 25.6 kcal/mol). The subsequent radical-induced C−C fragmentation was similarly facile as for substrate **1** ($\Delta G^{\ddagger} \approx 1$ kcal/mol). Differences in overall product selectivities of hydroxylation versus C−C fragmentation for substrate **1** versus **15** would in this pathway (Route A) only result, if the rates of H-atom abstraction by the oxygen-centered radical **25** were very different for the two substrates. This seems a rather unlikely scenario. Given the extremely low barriers to C−C

DOI: 10.1021/jacs.5b08347
J. Am. Chem. Soc. 2016, 138, 518−526

Scheme 6. CPCM (DMSO) M06-2X/6-311++G(d,p)//B3LYP/6-31G(d) Computational Study of Routes A and D for Substrate 1[a]



[a]Free energies are shown in kcal/mol.

cleavage, any oxygen-centered radical produced should spontaneously fragment to the corresponding C−C cleavage product.

In competition with homolytic peroxide cleavage, deprotonation of peroxide could potentially take place under the basic conditions employed, leading to the formation of dioxetane **26** (see Scheme 6, Route D), followed by fragmentation to the C−C cleaved product. This pathway is higher in energy than the radical pathway for substrate **1** (see Scheme 6), but could be competitive for the activated substrate **15**, for which the barrier to anionic C−C fragmentation was calculated to be $\Delta G^{\ddagger}$ = 19.4 kcal/mol (see Supporting Information, Figure S8, for an illustration or Figure 3). While the homolytic peroxide bond scission is higher in energy for substrate **15** (ΔG_{rxn} = 25.6 kcal/mol), Cu salts are known to catalyze this homolytic bond scission,[36,37] so that the radical pathway under Cu-catalyzed conditions is likely more favorable than calculated. In any case, the base-induced peroxide cleavage via Route D does not account for the different C−H versus C−C product selectivities observed for substrate **1** in the presence of different copper catalysts or solvents (see Table 1).[38]

The alternative Baeyer−Villiger pathway (Scheme 4, Route C, or see Figure 3) was calculated to be significantly higher in energy and was only marginally different for the peroxides derived from **1** vs. **15** ($\Delta G^{\ddagger}$ = 48.8 kcal/mol for **1** and 43.4 kcal/mol for **15**). It should therefore not be competitive with the mechanistic alternatives presented in Scheme 4.

Overall, the comparative computational study of the peroxides derived from substrates **1** and **15** revealed that homolytic peroxide cleavage to the oxygen-centered radical (**25**) should spontaneously give rise to C−C fragmentation. As opposed to literature proposals,[9a] H-atom abstraction by this radical to the corresponding alcohol (here, α-hydroxy ketone **2** or **15**) is unlikely. The origin of the α-hydroxy ketone therefore remained unclear and was subsequently examined experimentally in greater detail.

Preparation and Study of the Putative Peroxide Intermediate 24. While the above calculations suggest that the predominant mechanism to the C−C cleaved product is the radical pathway (Route A), it is not clear how the α-hydroxy ketone would form. It has been suggested that the hydroxylation occurs via H-atom transfer to the oxygen-centered radical **25** (Scheme 4).[9a,39] However, as discussed above, this seems to be an unlikely mechanistic scenario as any oxygen-centered radical should undergo rapid C−C cleavage as soon as it is formed (and there are no obvious sources of better H-atom donors in the reactions presented in Table 1, e.g., entry 1 versus entry 3). Moreover, it is also not clear why there is a dependence on Cu salt, solvent, and base in the distribution of C−C versus C−H activated products. In order to answer these questions, we set out to prepare the putative peroxide intermediate **24**.

Peroxide **24** was synthesized by autoxidation of the corresponding ketoacid **28**, which in turn was synthesized in three steps from 1-tetralone.[40] Stirring the acid **28** for 3 days under oxygen in CD_3CN gave the peroxide **24** in a mixture with 1-tetralone. Various reagents were then added to the peroxide intermediate, and the effect of each addition was studied. For every set of experiments, the peroxide was synthesized *in situ* and its formation verified by ^{1}H NMR spectroscopic analysis.

We initially added PPh_3 to **24**, which gave rise to the quantitative formation of α-hydroxy ketone **2** under concomitant formation of $Ph_3P{=}O$ in 5 min at room temperature.[41]

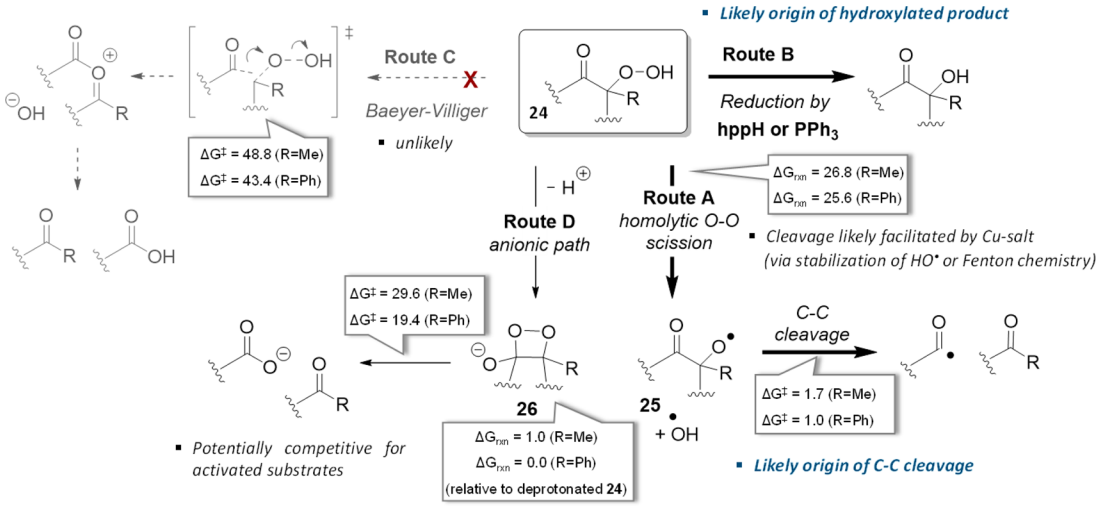
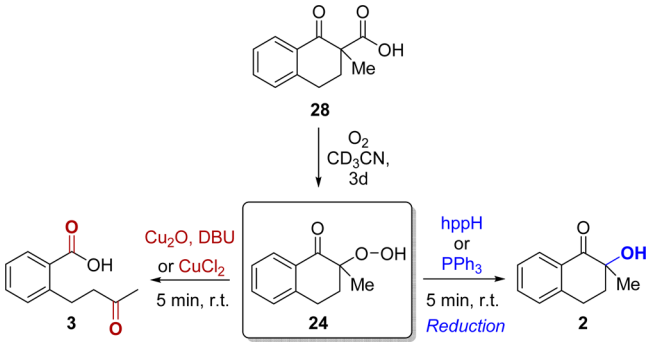


Figure 3. Overview of mechanistic data and favored reaction pathways. (Energies in kcal/mol; $\Delta G^{\ddagger}$ refers to activation free energy barrier and ΔG_{rxn} to reaction free energy of the corresponding step.)

DOI: 10.1021/jacs.5b08347
J. Am. Chem. Soc. 2016, 138, 518−526

Interestingly, when we added the base hppH to peroxide **24** in another experiment, rapid conversion to the corresponding alcohol **2** was also seen (see Scheme 7). This reactivity was

Scheme 7. Preparation and Study of Reactivity of Peroxide 24 as Key Intermediate Leading to C−C Cleaved *versus* C−H Hydroxylated Products



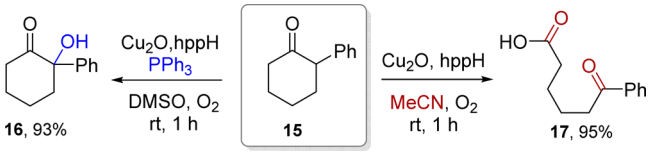
remarkable and would be consistent with the exclusive selectivity for the α-hydroxy ketone **2** in the Cu-catalyzed aerobic oxidation of **1** in the presence of hppH, as compared to lower selectivity when the reactions were performed with alternative bases (e.g., entries 9 and 11 in Table 1).[42]

In line with this, DBU was not effective as reductant (Scheme 7). With a longer lifetime of the peroxide intermediate in this case, it can undergo homolytic cleavage (likely catalyzed by Cu salt) to eventually also give C−C cleaved product **3** (via Route A, Scheme 6 or Scheme 4). Moreover, non-oxide Cu salts appear to be more effective in de-peroxidation, since $CuCl_2$ gave rise to efficient conversion to **3**. Overall, a competition between reduction of peroxide **24** by hppH versus homolytic bond scission (de-peroxidation that is catalyzed by the added Cu salt) takes place.

These results suggest that two competing pathways are active, resulting in either the C−C cleaved product **3** (via Route A, see Figure 3) or the C−H hydroxylated product **2** (via reduction of the peroxide in Route B). The controlling factor to selectively give α-hydroxy ketone **2** appears to be the rapid reduction of the peroxide.

Thus, we hypothesized that if a reductant better than hppH was added, then selective C−H functionalization could potentially also be achieved for more-activated substrates (such as α-phenyl ketone **15**), since the slightly more-favored homolytic cleavage of the corresponding peroxide may then be outcompeted. To our delight, this was indeed seen, with hydroxylated ketone **16** obtained exclusively when a stoichiometric amount of PPh_3 was added under otherwise standard Cu_2O/hppH/DMSO catalytic conditions (Scheme 8).

Scheme 8. Demonstration of Switchability of C−C Cleavage versus C−H Hydroxylation on Activated Substrate 16[a]



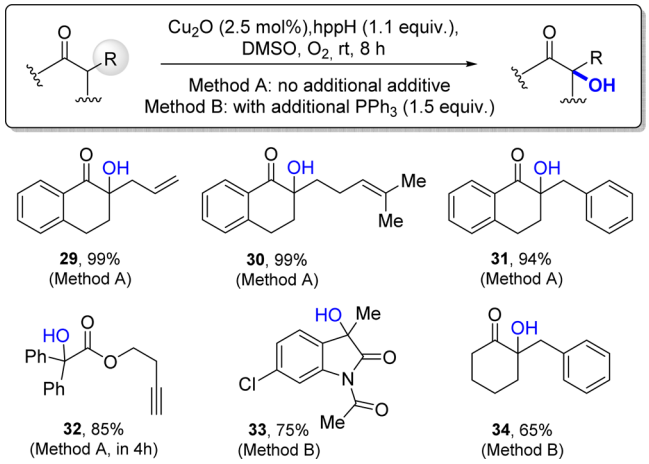
[a]Reagents: Cu_2O (5 mol%), hppH (1.1 equiv), PPh_3 (1.5 equiv).[44]

To probe our mechanistic picture in reverse, it can be implied that if we accelerated the homolytic scission of the peroxide, this should allow to steer toward the C−C fragmented product exclusively. Previous electrochemical studies suggested that the oxidizing ability and stability of Cu salts strongly depends also on the medium.[43] To create a more-reactive Cu species, we replaced the reaction solvent DMSO by MeCN (guided also by our observations in Table 1, entries 16, 18). Indeed, selective C−C fragmentation of α-phenyl ketone **15** to **17** as exclusive product was now seen with MeCN (Scheme 8).

These results support our mechanistic proposals and showcase the tunability toward exclusive selectivity for C−H hydroxylated or C−C cleaved products.

Additional Examples of Cu-Catalyzed α-Hydroxylation. Having identified the key factors necessary to achieve selective hydroxylation even of activated substrates, we subsequently applied our insights to the α-hydroxylation of a wider range of carbonyl compounds. Scheme 9 presents the

Scheme 9. Exploration of the Scope of α-Hydroxylation



results. The method proved to be compatible with alkene (**29**, **30**), alkyne, ester (**32**), amide (**33**) functional groups as well as otherwise readily oxidizable benzylic sites (**31**, **34**).[24]

On the Role of Copper. The mechanistic studies showed that the observed reactivity is consistent with a hydroperoxide as key catalytic intermediate whose fate ultimately dictates the product selectivity (C−C cleavage versus C−H hydroxylation, see Figure 3). While the formation of the hydroperoxide is eased by Cu salts, it is important to note that addition of exogenous Cu salt may not necessarily be required. Our tests with ketone **1** in the presence of hppH (1.1 equiv) in DMSO showed that without the addition of exogeneous Cu_2O, hydroxylation was also seen, albeit more slowly [i.e., 21% conversion to **2** was seen without and 46% with added Cu_2O (5 mol%) after 2 h]. However, even without added Cu salt, truly Cu-free conditions are challenging to achieve. While we utilized "trace-metal-free DMSO" [copper content ≤5 μg/kg (for TraceSELECT, ≥99.99995%)], our trace metal analysis of hppH indicated significantly greater amounts of copper being present (917 μg/kg, see Supporting Information). An initiation process triggered by the trace copper cannot be ruled out. Alternatively, the reactivity in the absence of added Cu salt may also be consistent with radical-based autoxidation or enolate-derived reactivity. However, it is important to note that the

DOI: 10.1021/jacs.5b08347
J. Am. Chem. Soc. 2016, 138, 518−526

overall product selectivities are dependent on whether Cu salt was added (as well as the type of Cu salt and conditions, see Table 1 and Scheme 7),[45] consistent with the facilitation of deperoxidation of the hydroperoxide as another mechanistic role of the Cu salt.

CONCLUSIONS

In summary, we herein examined the factors that control selectivities in α-C−H bond hydroxylation versus C−C bond cleavage of ketones under homogeneous Cu catalysis. The roles of substrate, additive, solvent, and catalyst were investigated. Specifically, it was found that α-alkyl-substituted ketones selectively generate α-hydroxy ketones under Cu_2O/DMSO/hppH conditions. More-activated substrates (e.g., α-phenyl) give rise to C−C bond activation in addition to hydroxylation, but this inherent selectivity can be overturned through the addition of an exogeneous reductant to yield the hydroxylated product exclusively. *In situ* React IR studies, experiments, and computational investigations suggest that the reactivity is consistent with the intermediacy of a hydroperoxide whose formation is catalyzed by [Cu]/O_2. Various alternative mechanisms that have previously been proposed could be ruled out. As opposed to literature proposals, computational studies predict that, upon homolytic scission of the peroxide, spontaneous C−C cleavage should take place to yield the formal C−C cleaved product. With appropriate test experiments on the separately prepared hydroperoxide intermediate, we uncovered that hppH is able to reduce the peroxide to the α-hydroxy ketone, while other bases (such as DBU) are ineffective.[46] Given the widespread biological existence of this or similar structural motifs, we anticipate that this finding will also be of wider relevance to understand enzymatic reactivities as well as the fate of peroxide species *in vivo* in the context of oxidative stress[47] or metastatic cancer.[29c] The data suggest that the relative rates of peroxide reduction (leading to ROH) versus deperoxidation (leading to C−C cleavage) control the overall product selectivity. For more-activated substrates, a base-mediated anionic peroxide fragmentation may also be competitive (see Route D, Figure 3). However, more-efficient reductants (such as phosphines) allow even for more-activated substrates (e.g., α-phenyl) to selectively generate the α-hydroxy ketone (**16**). Removal of all reductants (i.e., use of alternative base) and appropriate choice of solvent or Cu salt to encourage deperoxidation allows switching to selective C−C activation (product **17**). We anticipate that these findings will aid the deeper mechanistic understanding and development of *selective* transformations in the context of homogeneous oxidative catalysis.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b08347.

Details on experimental procedures, spectroscopic data, trace metal analyses, additional ReactIR studies, computational information, Cartesian coordinates of calculated species, and complete ref 34 (PDF)

AUTHOR INFORMATION

Corresponding Author

*franziska.schoenebeck@rwth-aachen.de

Author Contributions

§A.S.-K.T. and A.K. contributed equally.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank the MIWF NRW and the RWTH Aachen University for financial support. We thank Dr. J. A. Allen and Dr. M. Adamczyk from Mettler-Toledo GmbH for access to their ReactIR instrument as well as their invaluable technical assistance. We thank S. Thoröe (Uniklinik, RWTH Aachen) for trace metal analyses.

REFERENCES

(1) (a) Bäckvall, J.-E. *Modern Oxidation Methods*, 2nd ed.; Wiley-VCH: Weinheim, 2011. (b) Cavani, F.; Teles, J. H. *ChemSusChem* **2009**, *2*, 508. (c) Arpentinier, P.; Cavani, F.; Trifiro, F. *The Technology of Catalytic Oxidations*; Editions Technip: Paris, 2001. (d) Bielanski, A.; Haber, J. *Oxygen in Catalysis*; Marcel Dekker: New York, 1991. (e) Sheldon, R. A.; Kochi, J. K. *Metal Catalyzed Oxidations of Organic Compounds*; Academic Press: New York, 1981.

(2) For selected examples and reviews, see: (a) Zakzeski, J.; Bruijnincx, P. C. A.; Jongerius, A. L.; Weckhuysen, B. M. *Chem. Rev.* **2010**, *110*, 3552. (b) Collinson, S. R.; Thielemans, W. *Coord. Chem. Rev.* **2010**, *254*, 1854. (c) Rahimi, A.; Ulbrich, A.; Coon, J. J.; Stahl, S. S. *Nature* **2014**, *515*, 249. (d) Nguyen, J. D.; Matsuura, B. S.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2014**, *136*, 1218. (e) Rinaldi, R. *Angew. Chem., Int. Ed.* **2014**, *53*, 8559. (f) Bruijnincx, P. C. A.; Weckhuysen, B. M. *Nat. Chem.* **2014**, *6*, 1035.

(3) For selected reviews, see: (a) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400. (b) Punniyamurthy, T.; Velusamy, S.; Iqbal, J. *Chem. Rev.* **2005**, *105*, 2329. (c) Sigman, M. S.; Jensen, D. R. *Acc. Chem. Res.* **2006**, *39*, 221. (d) Shi, Z.; Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3381. (e) Roduner, E.; Kaim, W.; Sarkar, B.; Urlacher, V. B.; Pleiss, J.; Gläser, R.; Einicke, W.-D.; Sprenger, G. A.; Beifuß, U.; Klemm, E.; Liebner, C.; Hieronymus, H.; Hsu, S.-F.; Plietker, B.; Laschat, S. *ChemCatChem* **2013**, *5*, 82.

(4) Stahl, S. S. *Science* **2005**, *309*, 1824.

(5) For representative reviews, see: (a) Himes, R. A.; Karlin, K. D. *Curr. Opin. Chem. Biol.* **2009**, *13*, 119. (b) Que, L.; Tolman, W. B. *Nature* **2008**, *455*, 333. (c) Chufán, E. E.; Puiu, S. C.; Karlin, K. D. *Acc. Chem. Res.* **2007**, *40*, 563. (d) Rosenzweig, A. C.; Sazinsky, M. H. *Curr. Opin. Struct. Biol.* **2006**, *16*, 729. (e) Mirica, L. M.; Ottenwaelder, X.; Stack, T. D. P. *Chem. Rev.* **2004**, *104*, 1013. (f) Lewis, E. A.; Tolman, W. B. *Chem. Rev.* **2004**, *104*, 1047. (g) Solomon, E. I.; Chen, P.; Metz, M.; Lee, S.-K.; Palmer, A. E. *Angew. Chem., Int. Ed.* **2001**, *40*, 4570. (h) Mahadevan, V.; Gebbink, R. J. M. K.; Stack, T. D. P. *Curr. Opin. Chem. Biol.* **2000**, *4*, 228. (i) Klinman, J. P. *Chem. Rev.* **1996**, *96*, 2541. (j) Solomon, E. I.; Sundaram, U. M.; Machonkin, T. E. *Chem. Rev.* **1996**, *96*, 2563.

(6) (a) Osako, T.; Ohkubo, K.; Taki, M.; Tachi, Y.; Fukuzumi, S.; Itoh, S. *J. Am. Chem. Soc.* **2003**, *125*, 11027. (b) Mirica, L. M.; Vance, M.; Rudd, D. J.; Hedman, B.; Hodgson, K. O.; Solomon, E. I.; Stack, T. D. P. *Science* **2005**, *308*, 1890. (c) Herres-Pawlis, S.; Verma, P.; Haase, R.; Kang, P.; Lyons, C. T.; Wasinger, E. C.; Flörke, U.; Henkel, G.; Stack, T. D. P. *J. Am. Chem. Soc.* **2009**, *131*, 1154. (d) Rolff, M.; Schottenheim, J.; Decker, H.; Tuczek, F. *Chem. Soc. Rev.* **2011**, *40*, 4077. (e) Hoffmann, A.; Citek, C.; Binder, S.; Goos, A.; Rübhausen, M.; Troeppner, O.; Ivanovic-Burmazovic, I.; Wasinger, E. C.; Stack, T. D. P.; Herres-Pawlis, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 5398. (f) Esguerra, K. V. N.; Fall, Y.; Lumb, J.-P. *Angew. Chem., Int. Ed.* **2014**, *53*, 5877. (g) Esguerra, K. V. N.; Fall, Y.; Petitjean, L.; Lumb, J.-P. *J. Am. Chem. Soc.* **2014**, *136*, 7662.

(7) For examples of Cu-catalyzed aerobic oxidations, see: (a) Xu, B.; Lumb, J. P.; Arndtsen, B. A. *Angew. Chem., Int. Ed.* **2015**, *54*, 4208. (b) Shang, M.; Sun, S.-Z.; Dai, H.-X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 3354. (c) Lee, Y. E.; Cao, T.; Torruellas, C.; Kozlowski, M. C. *J.*

DOI: 10.1021/jacs.5b08347
J. Am. Chem. Soc. 2016, 138, 518−526

Am. Chem. Soc. **2014**, *136*, 6782. (d) Zhang, H.; Yao, B.; Zhao, L.; Wang, D.-X.; Xu, B.-Q.; Wang, M.-X. *J. Am. Chem. Soc.* **2014**, *136*, 6326. (e) Xu, H.; Qiao, X.; Yang, S.; Shen, Z. *J. Org. Chem.* **2014**, *79*, 4414. (f) Roane, J.; Daugulis, O. *Org. Lett.* **2013**, *15*, 5842. (g) Genovino, J.; Lütz, S.; Sames, D.; Touré, B. B. *J. Am. Chem. Soc.* **2013**, *135*, 12346. (h) Zhang, H.; Zhao, L.; Wang, D.-X.; Wang, M.-X. *Org. Lett.* **2013**, *15*, 3836. (i) Suess, A. M.; Ertem, M. Z.; Cramer, C. J.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 9797. (j) Gallardo-Donaire, J.; Martin, R. *J. Am. Chem. Soc.* **2013**, *135*, 9350. (k) Yu, J.; Yang, H.; Jiang, Y.; Fu, H. *Chem. - Eur. J.* **2013**, *19*, 4271. (l) Bhadra, S.; Dzik, W. I.; Goosßen, L. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 2959. (m) Jover, J.; Maseras, F. *Chem. Commun.* **2013**, *49*, 10486. (n) Zhang, J.; Liu, Y.; Chiba, S.; Loh, T.-P. *Chem. Commun.* **2013**, *49*, 11439. (o) Boess, E.; Schmitz, C.; Klussmann, M. *J. Am. Chem. Soc.* **2012**, *134*, 5317. (p) Zhang, G.; Ma, Y.; Wang, S.; Zhang, Y.; Wang, R. *J. Am. Chem. Soc.* **2012**, *134*, 12334. (q) Guo, S.; Qian, B.; Xie, Y.; Xia, C.; Huang, H. *Org. Lett.* **2011**, *13*, 522.

(8) For recent examples of Cu-catalyzed oxygenations with O_2, see: (a) Wang, T.; Jiao, N. *J. Am. Chem. Soc.* **2013**, *135*, 11692. (b) Su, Y.; Sun, X.; Wu, G.; Jiao, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 9808. (c) Liu, Q.; Wu, P.; Yang, Y.; Zeng, Z.; Liu, J.; Yi, H.; Lei, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 4666. (d) Xu, Z.; Zhang, C.; Jiao, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 11367. (e) Wang, H.; Wang, Y.; Liang, D.; Liu, L.; Zhang, J.; Zhu, Q. *Angew. Chem., Int. Ed.* **2011**, *50*, 5678. (f) Zhang, C.; Jiao, N. *J. Am. Chem. Soc.* **2010**, *132*, 28. (g) Garcia-Bosch, I.; Company, A.; Frisch, J. R.; Torrent-Sucarrat, M.; Cardellach, M.; Gamba, I.; Güell, M.; Casella, L.; Que, L.; Ribas, X., Jr.; Luis, J. M.; Costas, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 2406. (h) Chiba, S.; Zhang, L.; Lee, J.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 7266.

(9) For recent reviews, see: (a) Allen, S. E.; Walvoord, R. R.; Padilla-Salinas, R.; Kozlowski, M. C. *Chem. Rev.* **2013**, *113*, 6234. (b) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 11062.

(10) (a) Allpress, C. J.; Miłaczewska, A.; Borowski, T.; Bennett, J. R.; Tierney, D. L.; Arif, A. M.; Berreau, L. M. *J. Am. Chem. Soc.* **2014**, *136*, 7821. (b) He, C.; Guo, S.; Huang, L.; Lei, A. *J. Am. Chem. Soc.* **2010**, *132*, 8273. (c) Zou, L.-H.; Priebbenow, D. L.; Wang, L.; Mottweiler, J.; Bolm, C. *Adv. Synth. Catal.* **2013**, *355*, 2558. (d) Atlamsani, A.; Bregeault, J.-M. *Synthesis* **1993**, *1993*, 79. (e) Capdevielle, P.; Audebert, P.; Maumy, M. *Tetrahedron Lett.* **1984**, *25*, 4397. (f) Sayre, L. M.; Jin, S.-J. *J. Org. Chem.* **1984**, *49*, 3498.

(11) Zhang, L.; Bi, X.; Guan, X.; Li, X.; Liu, Q.; Barry, B.-D.; Liao, P. *Angew. Chem., Int. Ed.* **2013**, *52*, 11303.

(12) (a) Tang, C.; Jiao, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 6528. (b) Subramanian, P.; Indu, S.; Kaliappan, K. P. *Org. Lett.* **2014**, *16*, 6212.

(13) Huang, X.; Li, X.; Zou, M.; Song, S.; Tang, C.; Yuan, Y.; Jiao, N. *J. Am. Chem. Soc.* **2014**, *136*, 14858.

(14) (a) Capdevielle, P.; Audebert, P.; Maumy, M. *Tetrahedron Lett.* **1984**, *25*, 4397. (b) Ogata, Y.; Sawaki, Y.; Shiroyama, M. *J. Org. Chem.* **1977**, *42*, 4061.

(15) Fraser, M. S.; Hamilton, G. A. *J. Am. Chem. Soc.* **1982**, *104*, 4203.

(16) Bordwell, F. G.; Knipe, A. C. *J. Am. Chem. Soc.* **1971**, *93*, 3416.

(17) Examples of natural products with this structural motif are hamigeran A and the precursors of the antibiotics daunomycin, vindoline, kjellmanianone, and doxycycline. See: (a) Wellington, K. D.; Cambie, R. C.; Rutledge, P. S.; Bergquist, P. R. *J. Nat. Prod.* **2000**, *63*, 79. (b) Davis, F. A.; Clark, C.; Kumar, A.; Chen, B.-C. *J. Org. Chem.* **1994**, *59*, 1184.

(18) For a recent overview, see: Streuff, J. *Synlett* **2013**, *24*, 276.

(19) For reviews, see: (a) Chen, B.-C.; Zhou, P.; Davis, F. A.; Ciganek, E. *Org. React.* **2003**, *62*, 1. (b) Smith, A. M. R.; Hii, K. K. *Chem. Rev.* **2011**, *111*, 1637. (c) Janey, J. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4292.

(20) See the following for examples using different salts. (a) Mn salt: Christoffers, J. *J. Org. Chem.* **1999**, *64*, 7668. (b) Co salt: Baucherel, X.; Levoirier, E.; Uziel, J.; Juge, S. *Tetrahedron Lett.* **2000**, *41*, 1385. (c) Ce salt: Christoffers, J.; Werner, T.; Frey, W.; Baro, A. *Chem. - Eur. J.* **2004**, *10*, 1042. (d) For a review, see: Christoffers, J.; Baro, A.; Werner, T. *Adv. Synth. Catal.* **2004**, *346*, 143.

(21) (a) Chuang, G. J.; Wang, W.; Lee, E.; Ritter, T. *J. Am. Chem. Soc.* **2011**, *133*, 1760. (b) El-Qisairi, A. K.; Qaseer, H. A. *J. Organomet. Chem.* **2002**, *659*, 50.

(22) (a) For an early precedence, see: Gardner, J. N.; Carlon, F. E.; Gnoj, O. *J. Org. Chem.* **1968**, *33*, 3294. (b) A recent report: Liang, Y.-F.; Jiao, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 548. (c) For an enantioselective variant, see: Sim, S.-B. D.; Wang, M.; Zhao, Y. *ACS Catal.* **2015**, *5*, 3609.

(23) Arai, T.; Sato, T.; Noguchi, H.; Kanoh, H.; Kaneko, K.; Yanagisawa, A. *Chem. Lett.* **2006**, *35*, 1094.

(24) While an 8 h reaction time was chosen, not all substrates necessarily need this long a reaction time.

(25) In the absence of any substituent in the α-position, oxidation to the diketone results.

(26) (a) Costas, M.; Mehn, M. P.; Jensen, M. P.; Que, L., Jr. *Chem. Rev.* **2004**, *104*, 939. (b) Kim, E.; Chufan, E. E.; Kamaraj, K.; Karlin, K. D. *Chem. Rev.* **2004**, *104*, 1077. (c) Lewis, E. A.; Tolman, W. B. *Chem. Rev.* **2004**, *104*, 1047. (d) Herres-Pawlis, S.; Binder, S.; Eich, A.; Haase, R.; Schulz, B.; Wellenreuther, G.; Henkel, G.; Rübhausen, M.; Meyer-Klaucke, W. *Chem. - Eur. J.* **2009**, *15*, 8678. (e) Donoghue, P. J.; Gupta, A. K.; Boyce, D. W.; Cramer, C. J.; Tolman, W. B. *J. Am. Chem. Soc.* **2010**, *132*, 15869. (f) Kim, S.; Ståhlberg, J.; Sandgren, M.; Paton, R. S.; Beckham, G. T. *Proc. Natl. Acad. Sci. U. S. A.* **2014**, *111*, 149.

(27) (a) vam Rheenen, V. *Tetrahedron Lett.* **1969**, *10*, 985. (b) Arora, P. K.; Sayre, L. M. *Tetrahedron Lett.* **1991**, *32*, 1007. (c) Ram, R. N.; Singh, L. *Tetrahedron Lett.* **1995**, *36*, 5401.

(28) Rudler, H.; Denise, B. *J. Mol. Catal. A: Chem.* **2000**, *154*, 277.

(29) (a) Zhang, L.; Ang, G. Y.; Chiba, S. *Org. Lett.* **2011**, *13*, 1622. (b) Chiba, S. *Bull. Chem. Soc. Jpn.* **2013**, *86*, 1400. (c) Zhu, P.; Tong, B. M. K.; Wang, R.; Chen, J. P.; Foo, S.; Chong, H. C.; Wang, X. L.; Ang, G. Y.; Chiba, S.; Tan, N. S. *Cell Death Dis.* **2013**, *4*, e552.

(30) Weber, M.; Weber, M.; Kleine-Boymann, M. *Ullmann's Encyclopedia of Industrial Chemistry*, 6th ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2004; Vol. *26*, p 503.

(31) (a) Dinca, E.; Hartmann, P.; Smrček, J.; Dix, I.; Jones, P. G.; Jahn, U. *Eur. J. Org. Chem.* **2012**, *2012*, 4461. (b) Wetter, C.; Jantos, K.; Woithe, K.; Studer, A. *Org. Lett.* **2003**, *5*, 2899. (c) Wetter, C.; Studer, A. *Chem. Commun.* **2004**, 174. (d) Vogler, T.; Studer, A. *Synthesis* **2006**, *24*, 4257. (e) Wienhöfer, I. C.; Studer, A.; Rahman, M. T.; Fukuyama, T.; Ryu, I. *Org. Lett.* **2009**, *11*, 2457. (f) Lindner, J.-P.; Studer, A. *Chem. - Eur. J.* **2011**, *17*, 4090. (g) Pouliot, M.; Renaud, P.; Schenk, K.; Studer, A.; Vogler, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 6037. (h) Hayashi, M.; Shibuya, M.; Iwabuchi, Y. *Synlett* **2012**, *23*, 1025.

(32) See, for example, Schemes 6, 346, and 624 in ref 9a.

(33) (a) For an early reference, see: Baillie, A. C.; Thomson, R. H. *J. Chem. Soc. C* **1966**, 2184. (b) See also: Jin, S.-J.; Arora, P. K.; Sayre, L. M. *J. Org. Chem.* **1990**, *55*, 3011.

(34) Frisch, M. J.; et al. *Gaussian 09*, Revision A.02; Gaussian, Inc.: Wallingford, CT, 2009.

(35) For recent reports on the adequate performance of M06-2X in treating radicals, see: (a) Zhao, Y.; Truhlar, D. G. *J. Phys. Chem. A* **2008**, *112*, 1095. (b) Wodrich, M. D.; Corminboeuf, C.; Wheeler, S. E. *J. Phys. Chem. A* **2012**, *116*, 3436. (c) Manini, P.; Capelli, L.; Reale, S.; Arzillo, M.; Crescenzi, O.; Napolitano, A.; Barone, V.; d'Ischia, M. *J. Org. Chem.* **2008**, *73*, 7517.

(36) Tano, T.; Ertem, M. Z.; Yamaguchi, S.; Kunishita, A.; Sugimoto, H.; Fujieda, N.; Ogura, T.; Cramer, C. J.; Itoh, S. *Dalton Trans.* **2011**, *40*, 10326.

(37) For a recent mechanistic study on the deperoxidation step with alternative metal salts, see: Spier, W.; Neuenschwander, U.; Hermans, I. *Angew. Chem., Int. Ed.* **2013**, *52*, 1581.

(38) We saw no difference in reactivity or product distribution when we employed additional equivalents of water in the reaction. A moisture (or hydroxide)-induced fragmentation of the peroxides is therefore unlikely.

DOI: 10.1021/jacs.5b08347
J. Am. Chem. Soc. 2016, 138, 518−526

(39) It has also been suggested that the substrate itself may function as H-atom donor. Since **15** should be the superior H-atom donor, this scenario can be ruled out. For more information on this theme, see, for example: (a) Neuenschwander, U.; Meier, E.; Hermans, I. *ChemSusChem* **2011**, *4*, 1613. (b) Turra, N.; Neuenschwander, U.; Hermans, I. *ChemPhysChem* **2013**, *14*, 1666.
(40) The following procedure was followed: Riahi, A.; Muzart, J.; Abe, M.; Hoffmann, N. *New J. Chem.* **2013**, *37*, 2245.
(41) Formation of $Ph_3P{=}O$ was verified by ^{31}P NMR. For a very early precedence of peroxide reduction by phosphine, see: Challenger, F.; Wilson, V. K. *J. Chem. Soc.* **1927**, 209.
(42) Our efforts to unambiguously characterize the hppH-derived byproduct resulting from peroxide reduction have so far been unsuccessful.
(43) Ukpong, E. J.; Akpanudo, N. W.; Prasad, J. *Afr. J. Pure Appl. Chem.* **2010**, *4*, 38.
(44) For the unactivated ketone **1**, we see under the conditions quoted in Scheme 8, 25% of the C−C cleaved product **3** (see also Table 1, entry 18). However, using $Cu(NO_3)$ as oxidant in AcOH/H_2O (5:1) at 120 °C for 16 h gives product **3** in 65% yield.
(45) Under addition of ZnO or MgO, the analogous product selectivity is seen as for Cu_2O in tests with substrate **1**.
(46) For information on peroxyl radical-trapping antioxidants and inhibitors, see: (a) Nam, T.-G.; Nara, S. J.; Zagol-Ikapitte, I.; Cooper, T.; Valgimigli, L.; Oates, J. A.; Porter, N. A.; Boutaud, O.; Pratt, D. A. *Org. Biomol. Chem.* **2009**, *7*, 5103. (b) Ingold, K. U.; Pratt, D. A. *Chem. Rev.* **2014**, *114*, 9022. (c) Haidasz, E. A.; Shah, R.; Pratt, D. A. *J. Am. Chem. Soc.* **2014**, *136*, 16643.
(47) Halliwell, B. *Biochem. Soc. Trans.* **2007**, *35*, 1147.

DOI: 10.1021/jacs.5b08347
J. Am. Chem. Soc. 2016, 138, 518−526