closures to give [3:2:1] bicyclic systems, such as the AC rings of **3**, can be troublesome, although strategies for success have been reported by Coates,[20] based on elegant pioneering studies of Raphael and co-workers.[21]

The most effective synthon for the C-2 carbonyl group proved to be the vicinal diol **9b**, obtained via a Rubottom reaction.[22] Sodium periodate cleavage, followed by routine processing of the olefinic group, led to the keto aldehyde **10**. In view of the aforementioned prospects for the aldol condensation, we were gratified to find that treatment of **10** with a dilute solution of sodium carbonate in aqueous methanol afforded **11** in 90% yield.

It now remained to install the functionality on the A ring, and we planned to intersect with intermediate **13b**, which had been prepared (in racemic form) by Funk and Bolton in their elegant synthesis of α-pipitzol.[9] Of several routes examined, the one preferred involved conversion of **11** into the α-enone **12**, followed by conjugate addition of methyl to give **13a**. Hydrogenolytic cleavage of the cyclopropane ring, followed by reoxidation of the secondary alcohol, then afforded **13b** in chiral nonracemic form. This material had spectroscopic (^{1}H NMR, FTIR, MS) and TLC properties[23] identical with those of a sample of the racemic modification prepared by Funk and Bolton.[9] In keeping with their precedent, selenium dioxide oxidation then afforded (−)-α-pipitzol **3**, which was spectroscopically identical with the racemic material[9] except for the optical rotation, $[\alpha]_D = -141°$.

Acknowledgment. We are grateful to Professor R. Funk for samples and spectra of racemic modifications of compounds **13b** and **3**.

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(23) R_f 0.61 (10% ethyl acetate/petroleum ether); $[\alpha]_D^{20}$ −141° (*c* 0.22, $CHCl_3$); IR ($CHCl_3$) 3456, 1752, 1675, 1640 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.06 (s, 1 H, CO*H*), 2.81 (s, 1 H, H-7), 2.39 (m, 1 H, H-2), 2.09 (t, 1 H, $J_{9,10}$ = 8.4 Hz, H-9), 2.04 (s, 3 H, C*H*$_3$), 1.94–1.45 (m, 4 H, H-10, H-10′, H-11, H-11′), 1.36 (d, 3 H, $J_{CH_3,12}$ = 7.1 Hz, *gem*-dimethyl C*H*$_3$), 1.00 (s, 3 H, *gem*-dimethyl C*H*$_3$); HRMS (CI/NH_3) 249.1492 (M + H)$^+$, calcd for $C_{15}H_{20}O_3$ 249.1485.

Articles

Copper-Mediated Oxygenation of Aldehydes and Internal Cannizzaro-like Rearrangement of Phenylglyoxal

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Under the influence of Cu(II) in MeOH containing py and Et_3N, $PhCH_2CHO$ undergoes competitive O_2-dependent conversions to PhCHO and phenylglyoxal. The latter, as the MeOH hemiacetal, undergoes a Cu(II)-catalyzed rearrangement to PhCHOHCOOMe and a Cu(II) oxidation to PhCOCOOMe, and there appears to be an independent O_2-mediated production of PhCOCOOH. Phenylglyoxal also undergoes oxidative cleavage to PhCOOH, but does not give rise to PhCHO. The homologous aldehyde $PhCH_2CH_2CHO$ is converted mainly via $PhCH_2CHO$ to a product mixture derived from the latter. This result is interpreted in terms of preferential C–C cleavage of an α-hydroxyperoxide intermediate initially formed from $PhCH_2CH_2CHO$. The alternative pathway for this intermediate, dehydration to α-keto aldehyde $PhCH_2COCHO$, is barely competitive, because the independently prepared α-keto aldehyde gives a distinct set of products under the reaction conditions. The preference for cleavage over dehydration explains the previously published finding of a stepwise degradation of long-chain aldehydes to formate units by the Cu(II)–py–Et_3N–MeOH–O_2 system. Product comparisons using either an O_2 atmosphere or a N_2 atmosphere (with varying equivalents of Cu^{II}) permit a distinction between stoichiometric Cu(II) oxidations and O_2-dependent reactions. Mechanisms are proposed for the observed transformations.

In the mid 1960s Backman and co-workers reported that aliphatic aldehydes could be autoxidized to α-keto aldehydes under the influence of a Cu(II) salt in MeOH containing excess pyridine and Et_3N,[1] but the synthetic utility was limited on account of competing C–C cleavage reaction(s) leading to a stepwise chain shortening of the aldehyde. These workers presumed that the chain-shortening process involved mainly a methoxide-induced cleavage of α-keto aldehyde to methyl formate and the next lower aldehyde homologue. We recently studied the autoxidation of benzylic ketones using the Cu(II)–py–Et_3N–MeOH system and found that in this case, the aldehyde-forming C–C cleavage occurs in competition with, and not subsequent to, generation of α-dicarbonyl compound.[2] Furthermore, when C–C cleavage of α-diketone did occur, this required the presence of water and Cu(II) as oxidant and led to chain-shortened *acid* rather than aldehyde. On the basis of substantial precedent in published studies on base-catalyzed[3,4] and/or metal-cata-

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Scheme I

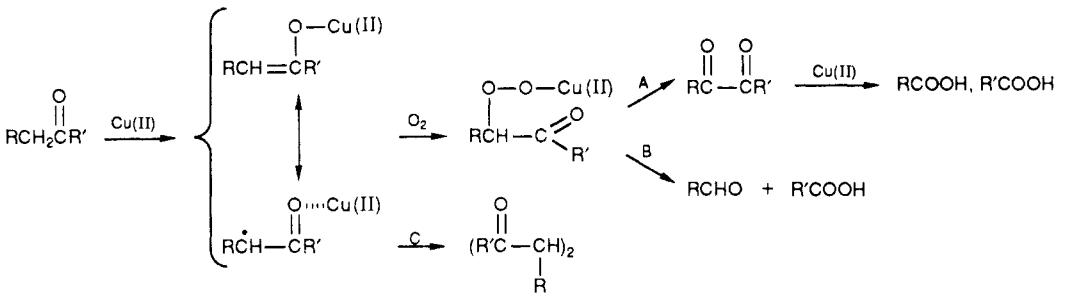

Table I. Products of Oxidation of $PhCH_2CHO$ (PA), PhCOCHO (PG), $PhCH_2CH_2CHO$ (3-PP), and $PhCH_2COCHO$

substrate, conditions[a]	yield,[b] % PhCOCHO (PG)	PhCHO	PhCHOHCOOH (MA)	(MM) PhCHOHCOOMe	PhCOCOOH	PhCOCOOMe	PhCOOH	PhCOOMe	total recovery
$PhCH_2CHO$, O_2	0	62.1	5.2	2.9	9.9	1.6	7.6	1.5	90.8
PhCOCHO, O_2	0	0	18.0	9.1	32.9	21.8	3.7	0	85.5
PhCOCHO, O_2, 3-Å sieves	3.0	0	14.6	11.2	24.6	26.5	5.1	0.5	85.5
PhCOCHO, N_2	28.3	0	6.2	10.0	4.2	37.3	2.2	0	88.2
PhCOCHO, N_2, 3-Å sieves	43.8	0	8.0	8.2	5.7	19.2	2.0	0	86.9
$PhCH_2CH_2CHO$, O_2	0	58.3	4.1	3.7	7.4	1.1	10.2	1.6	86.4
$PhCH_2COCHO$, O_2	0	34.8	0	1.3	25.7	3.5	19.3	5.2	89.8

[a] General conditions: substrate (2 mmol), $Cu(NO_3)_2py_2$ (2 mmol), Et_3N (30 mmol), and py (30 mmol) in MeOH (40 mL), 12 h, 25 °C under O_2 (2.3 atm) or N_2. PhCOCHO was used as the commercially available monohydrate, and 2 mmol of H_2O was added in the reactions of $PhCH_2CHO$ and $PhCH_2CH_2CHO$. $PhCH_2COOH$, $PhCH_2COOCH_3$, and $PhCH_2CHOHCOOH$ were recovered unchanged under these conditions. [b] The data represent an average of three or four experiments.

lyzed[1,5-11] autoxidation of carbonyl compounds, we have written a mechanism (Scheme I) involving a Cu(II)-α-hydroperoxide intermediate which partitions between dehydration (path A) and C–C cleavage (path B).[2]

The present report describes the extension of our ketone studies to aldehydes. The results are consistent with the mechanism shown in Scheme I and indicate that cleavage to chain-shortened aldehyde (path B) predominates over dehydration (path A), especially in the absence of benzylic activation. In addition, we have observed a copper-catalyzed, methanol-mediated rearrangement of phenylglyoxal to methyl mandelate. A comparative product study analysis under N_2 and O_2 is used to obtain mechanistic information that governs the various competitive reaction pathways.

Results

Our previous studies on deoxybenzoin (1, R = R′ = Ph) and its α-methyl derivative established that a Cu(II)-induced oxidative α-coupling (path C, Scheme I) competes with oxygenation pathways and occurs cleanly in the absence of O_2.[2] Dehydrodimer formation is generally observed when ketones are treated with Cu(II) under anaerobic conditions,[2,5] though it has not been documented for aldehydes. We found that the ketones $PhCH_2COCH_3$ and $PhCH(CH_3)COCH_3$ are converted to 3,4-diphenyl- and 3,4-dimethyl-3,4-diphenyl-2,5-hexanedione, respectively, as mixtures of *meso* and *d,l* isomers, using the "Brackman" conditions in CH_3OH solvent at 50–55 °C under N_2, in yields that are higher than those reported using, e.g., PbO_2 as an oxidative coupling agent.[12] In contrast, the corresponding aldehydes, $PhCH_2CHO$ and $PhCH(CH_3)CHO$, are recovered largely as their dimethyl acetals under N_2, together with mixtures of products of Cu(II)-mediated oxidative coupling and aldol condensation.[13] The anaerobic product mixtures have been characterized only in part, with the help of product analyses on reactions conducted in CH_3CN where solvent-derived acetal formation is precluded. Details are given in the Experimental Section.

Under 1 atm of O_2, complex mixtures of products were obtained, reflecting both O_2-dependent and O_2-independent reactions. However, the anaerobic products, which are incidental to this study, could be effectively eliminated by running the reactions at 20 psi (2.3 atm) of O_2.

Table I shows the products obtained for the reactions of $PhCH_2CHO$ (phenylacetaldehyde, PA) and PhCOCHO (phenylglyoxal, PG) at 2.3 atm of O_2 under the Brackman conditions. If the original Brackman theory regarding C–C cleavage was correct, the α-keto aldehyde PG would be the intermediate leading to production of the chain-shortened aldehyde (PhCHO) from PA. Since PG is supplied commercially as the hydrate, we added 1 equiv of H_2O to all reactions not using PG as the starting material in order to maintain a constant initial mole fraction of solvent water. It is clear that the production of PhCHO in high yield from PA and the lack of PhCHO formed from PG rules out PG as the intermediate leading to C–C cleavage of PA.

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Table II. Effect of Cu(II)–Substrate Stoichiometry on the Distribution of Oxidation Products of PhCOCHO under N_2[a]

$Cu(NO_3)_2py_2$ (mmol)	yield,[b] %						
	PhCOCHO	PhCH(OH)COOH	PhCH(OH)COOMe	PhCOCOOH	PhCOCOOMe	PhCOOH	total recovery
0.5	65.2	2.6	2.7	1.4	17.4	0.9	90.2
2.0	28.3	6.2	10.0	4.2	37.3	2.2	88.2
4.0	3.2	11.4	17.9	14.3	37.4	5.4	89.6

[a] General conditions: $PhCOCHO·H_2O$ (2 mmol), copper salt, Et_3N (30 mmol), and py (30 mmol) in MeOH (40 mL), 12 h, 25 °C. [b] The data represent an average of two or three experiments.

Table III. Control Experiments on Methyl Mandelate and Methyl Benzoylformate

substrate, conditions[a]	yield,[b] %					
	PhCH(OH)COOH	PhCH(OH)COOMe	PhCOCOOH	PhCOCOOMe	PhCOOH	total recovery
PhCH(OH)COOMe, O_2	14.8	22.8	27.4	14.0	6.1	85.1
PhCH(OH)COOMe, N_2	9.9	45.8	9.6	19.5	4.6	89.4
PhCOCOOMe, O_2	–	–	68.6	22.5	3.3	94.4

[a] General conditions: substrate (2 mmol), $Cu(NO_3)_2py_2$ (2 mmol), Et_3N (30 mmol), py (30 mmol), and H_2O (2 mmol) in MeOH (40 mL), 12 h, 25 °C, under O_2 (2.3 atm) or N_2. [b] The data represent an average of two experiments.

The formation of mandelic acid and benzoylformic acid derivatives from PA is a consequence of the conversion of PA to PG which occurs in competition with the production of PhCHO, since the same products form starting with PG itself. We found that the benzoylformates are formed from PG under both 2.3 atm of O_2 and N_2 atmospheres, indicating that Cu(II) alone is capable of carrying out this oxidation anaerobically. The formation of the mandelates from PG is suggestive of a nonredox intramolecular Cannizzaro rearrangement. The fact that PG was recovered unchanged from reactions run in the absence of Cu(II) (under O_2 or N_2) indicates that the rearrangement is catalyzed by Cu(II). Although the yield of mandelic acid and its ester from PG was higher in the presence of O_2 compared to N_2, this is probably a consequence of the maintenance of the copper catalyst in the +2 oxidation state and not a direct action of O_2.

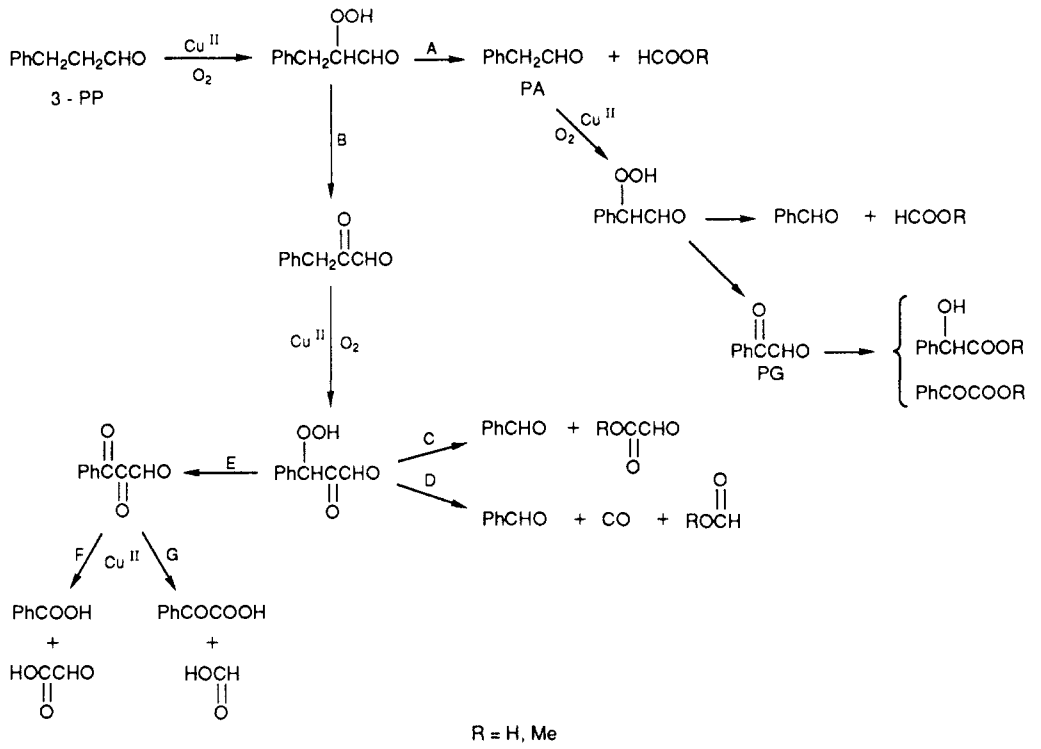
The product distributions arising from PG under O_2 (2.3 atm) and N_2 (with a varying amount of Cu(II) oxidant) were compared in an effort to distinguish the relative contributions by copper–O_2 vis-a-vis stoichiometric Cu(II) in the oxidation of PG to the benzoylformates. In the case using a Cu(II)–PG stoichiometry of 1:1, the yield of acid PhCOCOOH increased markedly upon changing from N_2 to O_2, whereas the yield of the ester PhCOCOOMe decreased slightly. Since the ester–acid balance is sensitive to the amount of water present in the reaction at any time (e.g., the esters can hydrolyze to acids), the O_2 vs N_2 results could reflect the fact that the former reaction contains more total water as a consequence of O_2 reduction. In order to check this possibility, the reactions of PG in both the N_2 and 2.3 atm of O_2 conditions were run in the presence of 3-Å sieves. The 3-Å sieves are incapable of removing all water from MeOH but were expected to maintain a fairly constant low H_2O concentration for the two reactions. The results (Table I) indicate that H_2O content plays only a partial role in explaining the difference between the N_2 and O_2 results: with 3-Å sieves, the benzoylformate acid/ester ratio is 0.9 in O_2 but only 0.3 in N_2, though the percent PG converted is low in the N_2 case. In experiments which varied the Cu(II)–PG stoichiometry under N_2 (Table II), an increase in [Cu(II)] from 25% to 200% of [PG] increased the percent conversion of PG to products, thereby permitting a better comparison of product distribution with the O_2 reaction. The finding that the yield of PhCOCOOMe is much greater and the yield of PhCOCOOH much smaller in the N_2 case than in the O_2–3-Å sieves case suggests the existence of an O_2-dependent route leading directly to PhCOCOOH that is distinct from the Cu(II) oxidations leading to the benzoylformates in general.

Additional control experiments performed in order to assess directly the fate of any mandelate or benzoylformate ester product under the reaction conditions are shown in Table III. The greater yield of mandelic acid from its ester in the O_2 case is interpreted in terms of the production of extra H_2O on account of some O_2 reduction, leading to a greater extent of hydrolysis. Mandelic acid itself was inert to both O_2 and N_2 reaction conditions (data not shown). Methyl benzoylformate was partially hydrolyzed in the O_2 conditions, and a small amount of oxidation to PhCOOH occurred as well. Similar results were obtained under N_2 (data not shown). Benzoylformic acid was recovered unchanged (O_2 or N_2), except for a small amount (4–5%) of oxidation to PhCOOH (data not shown).

Under no condition was $PhCH_2COOH$ or its methyl ester observed as a final product from PA. Since a control study showed that these materials are inert to the reaction conditions employed (under O_2 or N_2), it is clear that an aldehyde-to-acid oxidation of PA does not occur.

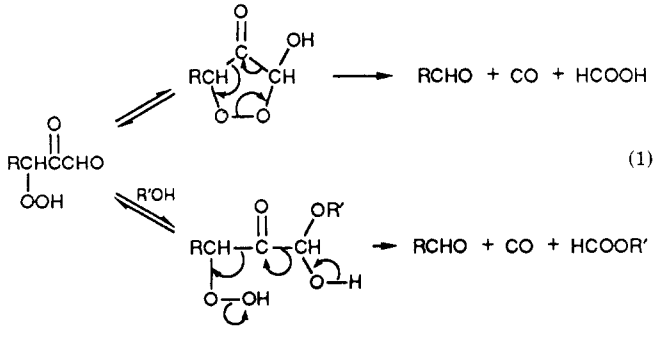
Our choice of ketone $PhCH_2COPh$ and aldehyde $PhCH_2CHO$ for mechanistic studies on the copper-mediated oxidations was predicated on the basis of simplifying the reaction stoichiometry, e.g., the Ph group limits these substrates to a single C–C cleavage, unlike the situation for long-chain aldehydes. However, since the reactivity of PA is biased by benzylic activation, the partitioning of competitive reaction pathways observed for this substrate might not be relevant to aliphatic aldehydes in general. In order to address this question, we examined the oxidation of $PhCH_2CH_2CHO$ (3-phenylpropionaldehyde, 3-PP) and compared the results to those obtained for PA under the same reaction conditions (2.3 atm of O_2). A very similar product distribution was obtained (e.g., ~60% PhCHO is formed in both cases, see Table I), consistent with an initial oxygenation of 3-PP to its α-hydroperoxide and cleavage of the latter to PA (path A of Scheme II). The alternative fate of the 3-PP-derived α-hydroperoxide would be dehydration to $PhCH_2COCHO$, which would in turn undergo further transformation, two pathways for which (paths C and D) would also produce PhCHO. In an effort to assess directly the partitioning among the various possible pathways (Scheme II) that can rationalize the product spectrum obtained from 3-PP, we synthesized the crucial intermediate $PhCH_2COCHO$ and determined its fate independently under the reaction conditions. The

Scheme II



data (Table I) indicate a significantly different product distribution for $PhCH_2COCHO$ than for either PA or 3-PP. Most noteworthy is the lower yield of PhCHO from $PhCH_2COCHO$, the production of substantial benzoylformates but only a trace of mandelates, and the generation of relatively high levels of both PhCOOH and PhCOOMe. Neither $PhCH_2COOH[CH_3]$ nor $PhCH_2CHOHCOOH$ (independently shown to be inert to the reaction conditions) were detected as products from $PhCH_2COCHO$.

Path D in Scheme II is included in light of a recent study by a Japanese group on copper-mediated oxygenation of cyclohexanone, in which the presumed 3-hydroperoxy-1,2-cyclohexanedione intermediate undergoes a CO-generating double C–C cleavage reaction to yield the half-aldehyde of glutaric acid.[14] This type of cleavage could conceivably occur for the β-hydroperoxy-α-keto aldehyde generated from $PhCH_2COCHO$ in our reactions (shown in eq 1 as following either cyclic or "open" mechanisms) as



(1)

an alternative to glyoxylate production (path C). We found evidence for production of HCOCOOH (spot test) in the reaction of both the parent aldehyde 3-PP and $PhCH_2COCHO$, but CO (phosphomolybdate assay) was not detected reproducibly. However, CO was also not detected in the oxidation under the basic Brackman conditions of 1,2-cyclohexanedione, even though the latter, as well as $PhCH_2COCHO$, readily produced CO for 60–180 min when oxygenation was carried out using $CuCl_2$ in CH_3OH without added base according to ref 14.

Since the Cu(II)-catalyzed rearrangement of PhCOCHO to mandelic acid derivatives generates a chiral center, we thought that the use of an optically active copper catalyst might result in asymmetric induction. Some preliminary studies were conducted using *N,N*-dimethyl-L-histidine as a Cu(II) ligand, amine methylation being required to prevent Schiff base formation with the carbonyl substrate. We examined a variety of reaction conditions under N_2 in an effort to maximize the occurrence of the rearrangement reaction and minimize the competing Cu(II) oxidation reaction, but synthetically useful yields and enantiomeric enrichments have not yet been realized. Further studies, including the use of nonoxidant transition metal ions and other chiral auxiliary ligands, will be needed to assess whether this reaction has potential as a useful asymmetric synthesis.

In our previous ketone study,[2] we found that the introduction of an α-methyl group in $PhCH_2COPh$ greatly decreased reactivity toward "Brackman" oxygenation. This was unexpected, since α-methyl substitution in *base*-catalyzed autoxidation of ketones *increases* reactivity, and we invoked a steric interference to the participation of the Cu(II) catalyst to explain our result. In the present study, however, the introduction of an α-methyl group into the aldehyde PA did not have a retarding influence; $PhCH(CH_3)CHO$ was rapidly converted in 96.6% yield to acetophenone (which was itself inert to further oxidative transformation). Thus, the previously invoked steric argument appears to apply only to the ketone case. This could be the case if the steric effect occurs in the generation of the Cu(II) enolates (which are the probable substrates for oxygenation); the enolate derived from $PhCH(CH_3)$-

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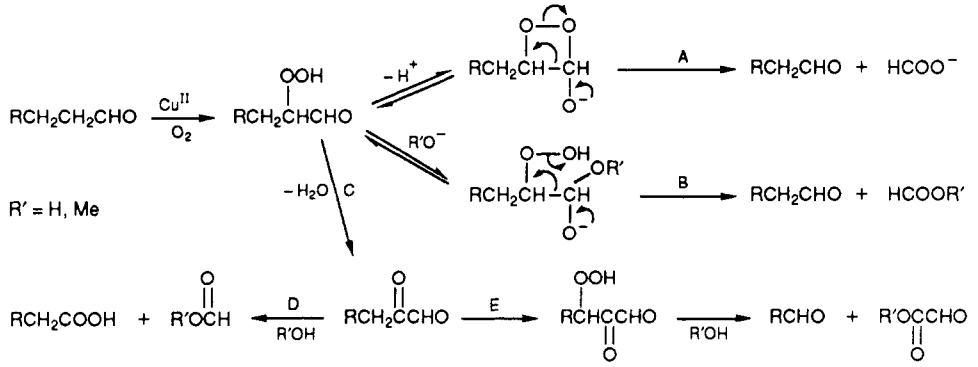
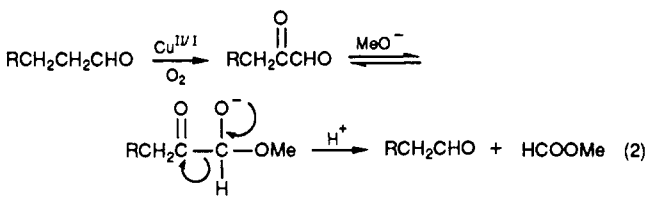
Scheme III



COPh would be severely crowded in a way which does not arise for either $PhCH_2COPh$ or $PhCH(CH_3)CHO$.

Discussion

The degradation of long-chain aldehydes observed by Brackman and co-workers was described to proceed via sequential generation of α-keto aldehydes followed by a methoxide-induced cleavage to the next lower aldehyde (eq 2).[1] This mechanism accounted for the fact that the



major products were methyl formate and acetic acid, the latter presumably arising from oxidation of CH_3CHO generated at the end of the chain degradation. However, we believed that the proposed expulsion of highly basic aliphatic carbonyl anions ($RC{=}O^-$) under the mild MeOH–Et_3N conditions was unlikely. In our study comparing the ketones $PhCH_2COPh$ and PhCOCOPh,[2] the formation of PhCHO only in the former case indicated that even $PhC(=O)^-$ could not be displaced in the MeOH–Et_3N–py system. Rather, we interpreted the C–C cleavage leading to the lower aldehyde in terms of the α-hydroperoxide intermediate that *precedes* the α-ketocarbonyl compound (see Scheme I).

A similar reaction manifold (Scheme III) was envisioned for the aldehydes studied here. According to this scheme, the course of α-oxygenation is determined by the partitioning of the α-hydroperoxide intermediate between C–C cleavage, giving chain-shortened aldehyde (paths A or B) and dehydration to α-keto aldehyde (path C). The former routes would permit for repetitive reactions, and both cyclic dioxetane (path A) and "open" (path B) mechanisms have been considered in the chemical literature,[3,4,15,16] the former leading to HCOOH and the latter leading to HCOOMe. If path C were followed, the α-keto aldehyde could be cleaved in part to chain-shortened *acid* (path D),[2,17] in this case effectively terminating the chain-shortening process. Alternatively, a resumption of the chain-shortening process would occur if the α-keto aldehyde underwent oxygenation to a β-hydroperoxy-α-keto aldehyde, which then cleaved to glyoxylic acid (or methyl ester) and an aldehyde of two shorter carbon number (path E). The fact that Brackman and co-workers observed relatively clean degradation of long-chain aldehydes to formate units and CH_3CHO suggests that the initial α-hydroperoxide prefers C–C cleavage (paths A or B) over dehydration (path C), and that when path C occurs, it is followed mainly by path E.

The above prediction was tested in the current study through investigating the reaction manifold for $PhCH_2CH_2CHO$ (3-PP) described in Results (Scheme II). The product distribution obtained from 3-PP was almost identical to that obtained independently from PA, but significantly different from that obtained independently from α-keto aldehyde $PhCH_2COCHO$ (Table I). This indicates that the main reaction pathway for 3-PP involves C–C cleavage rather than dehydration of the α-hydroperoxide intermediate. Since partitioning of this intermediate is unaffected by benzylic activation, it is clear that C–C cleavage is the preferred outcome of α-oxygenation. Thus, the stepwise, chain-shortening of long-chain aldehydes observed by Brackman and co-workers occurs not from cleavage of successively generated α-keto aldehydes but as a consequence of efficient C–C cleavage at the α-hydroperoxide stage that precedes the α-keto aldehyde.

In regard to the reaction outcome for $PhCH_2COCHO$, the lack of production of $PhCH_2CHOHCOOH$ rules out the occurrence of the Cannizzaro-like rearrangement observed for PhCOCHO. Instead, the generation of substantial amounts of PhCHO, PhCOCOOH, and PhCOOH (Scheme II) indicates that paths C, E–G, and E–F are all competitive, the latter being required to rationalize the yield of PhCOOH in excess of that expected from oxidation of PhCHO and PhCOCOOH. Although path D (CO generation) appears to be significant only under nonbasic reaction conditions, it is included in the overall mechanistic profile shown here.

The lack of production of $PhCH_2COOH$ from $PhCH_2COCHO$ indicates that α-oxygenation is greatly preferred over the type of oxidative α-dicarbonyl cleavage we found previously for benzil. Certainly, the unavailability of an oxygenatable α-C in benzil makes oxidative cleavage to PhCOOH the only recourse here. However, $PhCH_2COCHO$ exists mainly in the enol form, $PhCH{=}C(OH)CHO$,[18] on account of resonance, and may therefore be particularly susceptible to oxygenation rather than oxidative cleavage at the α-dicarbonyl bond. Thus, the reactivity of $PhCH_2COCHO$ is probably not predictive of the fate of nonbenzylic α-keto aldehydes in general that may form in the "Brackman" oxidation of long-chain aldehydes.

The reactions undergone by phenylglyoxal (PG) do not pertain to the mechanism of oxidative degradation of

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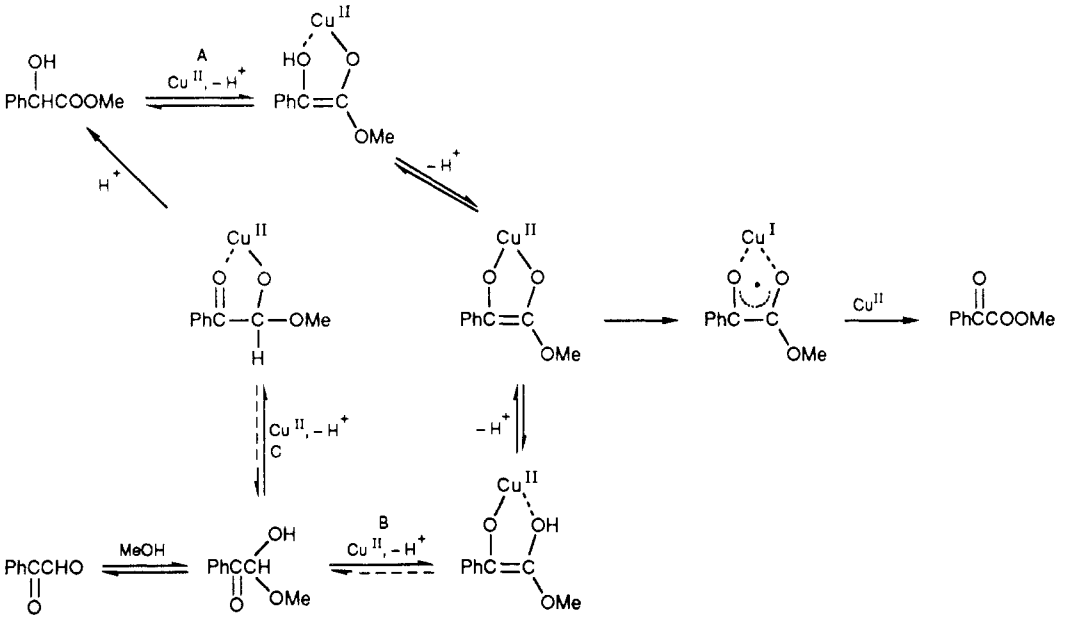
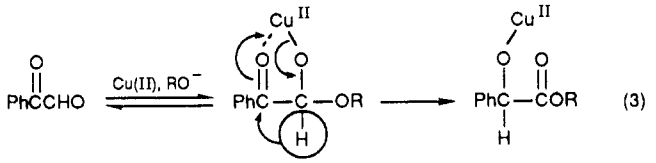
Scheme IV



long-chain aldehydes but are important in terms of the overall characterization of the chemistry studied here. One reaction involved a Cu(II)-catalyzed intramolecular Cannizzaro-like rearrangement to the mandelic acid skeleton. The Cannizzaro reaction has been reported to be catalyzed by some (mainly Group I and II) metal ions in aqueous base,[19] but no information in regard to Cu(II) or other transition metals has appeared. However, the proposed mechanism[19] involves a 1,2-hydride shift, similar to that occurring in the base-catalyzed rearrangement,[20] where the metal ion stabilizes the anionic transition state, and thus a similar mechanism should be possible in the case of Cu(II) (eq 3). Since mandelic acid (MA) is not esterified



(3)

under our reaction conditions, the generation of methyl mandelate (MM) would require that the rearrangement in eq 3 occur for the methanol hemiacetal (R = Me) of PG (or possibly the acetal[21]). Whether the rearrangement also occurs for the hydrate (R = H) cannot be determined, since the MA formed in the reaction can be rationalized on the basis of hydrolysis of the ester MM. Notwithstanding, in view of our observed rearrangement of PG, it is curious that an analogous benzilic acid rearrangement of benzil was completely absent under the same reaction conditions.[2]

The second reaction undergone by PG is its conversion to the benzoylformates. Since PG undergoes rearrangement to MA/MM, the benzoylformates could arise either from oxidation of the aldehyde group of PG or oxidation of the alcohol group of MA/MM. Although MM was transformed under the Brackman conditions to nearly the same product mixture as results from PG, MA itself was inert to such conditions. This means that if a mandelate-to-benzoylformate oxidation is involved, it is occurring at the ester (MM) and not acid (MA) stage. The inertness of the acid MA compared to the ester MM can be explained in terms of a required α-C deprotonation for oxidation to take place. We favor a mechanism in which Cu(II) coordination induces formation of the enolate of MM (Scheme IV, path A), in which case the oxidation can be viewed in analogy to the well-known enediolate oxidations by Cu(II).[22]

By comparing the results obtained using MM as substrate to the results starting with PG as substrate, the following observations can be made: (i) Under N_2, more PhCOCOOMe is obtained from PG than from MM, indicating that the latter is not an obligatory intermediate in the formation of PhCOCOOMe from PG. (ii) Under N_2, the yield of PhCOCOOMe from PG decreases sharply when the amount of water available in the reaction is reduced by the presence of 3-Å sieves. The most reasonable pathway for a Cu(II) oxidation of PG to PhCOCOOMe is via the hemiacetal, which allows for a Cu(II)-induced enolization to the same enediolate as that formed from MM (Scheme IV, path B). If this is the case, the requirement for water in the oxidation can be explained on the basis of discouraging conversion of PG to the acetal $PhCOCH(OCH_3)_2$, which would be inert to oxidation.

Scheme IV invokes a common *dianionic* intermediate (as the Cu(II) complex) in the oxidation of MM and PG (as the methanol hemiacetal) PhCOCOOMe. We show the oxidation as proceeding through a two-step sequence of one-electron oxidations, since the semidione-like intermediate would be expected to be reasonably stable.[23] However, a concerted two-electron oxidation via an enediolate-bridged binuclear Cu(II) species may alternatively be involved. Also shown in the lower left corner of this scheme is the Cannizzaro-like rearrangement for PG, which

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(20) Alexander, E. R. *J. Am. Chem. Soc.* **1947**, *69*, 289. Doering, W. von. E.; Taylor, T. I.; Schoenewaldt, E. F. *J. Am. Chem. Soc.* **1948**, *70*, 455. Neville, O. K. *J. Am. Chem. Soc.* **1948**, *70*, 3499.

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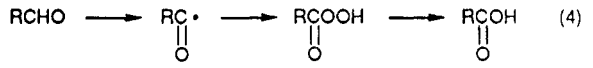
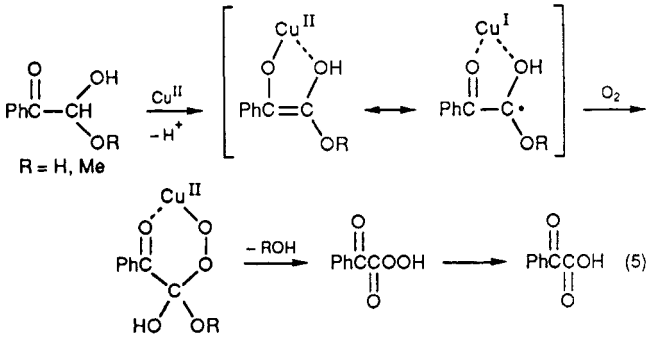
was above considered (eq 3) in terms of O-deprotonation of the hemiacetal (path C), as a 1,2-hydride shift. However, it is now apparent that an alternative mechanism for the rearrangement of PG is one involving C_β-deprotonation of the hemiacetal (path B) and reprotonation of the enediolate intermediate at C_α (the reverse of path A). If such prototropic (rather than hydridotropic) reorganization is in force for PhCOC(=O)H, it is clear why we did not observe the benzilic rearrangement for PhCOC(=O)Ph in our previous study.[2] In view of the inertness of MA, and other data comparisons in Tables I–III, it is sufficient to consider the reaction in Scheme IV as proceeding only at the level of MM and PhCOCH(OH)(OMe), without having to invoke the involvement of MA and $PhCOCH(OH)_2$. If this interpretation is correct, the obvious rationale would be the greater enolization tendency of esters compared to acids.

Finally, our finding that the yield of PhCOCOOH from PG in the O_2 reactions is greater than can be accounted for by the hydrolysis of PhCOCOOMe (see Results), suggested that there is an O_2-dependent route for this transformation that is independent of the chemistry shown in Scheme IV. There are two possibilities for such oxidation. One is the well-known transition metal mediated (chain) oxygenation of aldehydes to acids that proceeds via acyl radical and peracid intermediates (eq 4).[24] Al-



(4)

though PG may be particularly susceptible to this type of reaction, we have not observed simple aldehyde-to-acid oxidation for the other aldehydes in our study (PhCHO, $PhCH_2CHO$, $PhCH_2CH_2CHO$, and $PhCH_2COCHO$). An alternative explanation is a mechanism (eq 5) involving oxygenation of the Cu(II) enolate of the hydrate (or hemiacetal) of PG, which could theoretically occur in the same manner as the general α-oxygenations of carbonyl compounds discussed above.



(5)

Experimental Section

General Methods and Materials. ^1H NMR spectra were obtained at 60 and 200 MHz with Varian A 60-A, EM-360, and XL-200 spectrometers. Chemical shifts are reported as δ ppm downfield from Me_4Si and were referenced to Me_4Si in $CDCl_3$, to sodium 3-(trimethylsilyl)-1-propanesulfonate in D_2O, and to the solvent peak in acetone-d_6. ^{13}C NMR spectra were obtained at 50.3 MHz, and chemical shifts are reported relative to the $CDCl_3$ signal at 77.0 ppm. IR spectra were recorded on either a Beckman IR10 or a Perkin-Elmer 1420 spectrophotometer. Mass spectra were obtained on a Kratos MS-25A instrument. Melting points were measured with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Analytical and preparative TLC were run using silica gel 60 plates. $Cu(NO_3)_2py_2$ was obtained as described previously.[2] Benzylglyoxal was synthesized according to ref 18. *N,N*-Dimethyl-L-histidine was prepared according to ref 25: ^1H NMR (D_2O) δ 8.43 (s, 1 H), 7.18 (s, 1 H), 3.70 (t, 1 H), 3.27 (d, 2 H), 2.79 (s, 6 H).

Methyl benzoylformate (Aldrich) was diluted with ether and washed with aqueous Na_2CO_3 to remove benzoylformic acid. All other organic substrates were the highest grade obtainable from Aldrich and were used as is, except for hydrocinnamaldehyde, which was fractionally distilled before use. Commercial phenylacetaldehyde contains a small amount of polystyrene oxide, which is not readily removed, but which does not affect the reaction course. Inorganic chemicals were ACS reagent grade. The methanol used as solvent contained 0.1% water.

Reaction Procedure. N_2 reactions were initiated by the addition of the organic substrate to a solution of the remaining ingredients (see Tables I–III for quantities) in MeOH preequilibrated with and maintained under N_2 at 25 °C. O_2 reactions were conducted in a pressure bottle as previously described.[2] In the case of experiments conducted to test for generation of CO, a two-hole neoprene stopper was utilized, the additional hole serving as an outlet to permit a slow bleeding of the O_2 through a pinch clamp into a solution of phosphomolybdic acid. CO production is indicated by a color change from yellow to blue-green.[26] Under the "Brackman" reaction conditions, no color change was apparent for either benzylglyoxal or 1,2-cyclohexanedione, the latter serving as our reference compound for which CO production was reported.[14] However, by using the same apparatus but changing the reaction conditions to those of ref 14 ($CuCl_2$ in CH_3OH without added base) CO production was seen for both compounds for 90–180 min.

Quantitative Product Determination. The yield of benzaldehyde was obtained by acidification of the reaction mixture with 3 N HCl to pH 1, distillation of the $PhCHO–H_2O–CH_3OH$ azeotrope in vacuo, and quantitation of the (2,4-dinitrophenyl)hydrazone, as described before.[2] Quantitation of the other products was carried out on separate experimental runs by an NMR integration method using weighed amounts of an integration reference which gave resonances distant from those of the products; usually hexamethylbenzene in $CDCl_3$ and sodium acetate in D_2O. For these measurements, workup involving initial acidification (HCl, pH 1) of the reaction mixture prior to solvent removal was found to mediate acid–ester interchange, resulting in artifactual product distributions (e.g., in a control study, mandelic acid was partly converted to methyl mandelate). In contrast, solvent removal prior to acidification was found to yield reliable product distributions. Thus, after removal of solvent, the residue was diluted with water (80 mL) and acidified to pH 1 with 3 N HCl, and the aqueous layer was extracted with three 80-mL portions of diethyl ether. Extraction of the combined ether layer with aqueous $NaHCO_3$ removed the acidic products (mandelic, benzoylformic, and benzoic acids), and the remaining organic layer was saved for analysis of the neutral products as described below.

The water layer was reacidified and extracted with ether, and the ether layer was evaporated to afford a mixture of the three carboxylic acid products. TLC indicated no other materials were present. The yield of mandelic acid was determined (^1H NMR, D_2O) by integration of the 1 H singlet appearing at δ 5.2 with respect to the methyl singlet of CH_3COONa added as a weighed amount to the entire reaction product. An aliquot of this same solution was treated with $NaBH_4$, which reduced the benzoylformic acid to mandelic acid. Using the same NMR integration technique, the yield of benzoylformic acid was calculated from the increased intensity of the 1 H signal at δ 5.2. From the latter spectrum, the yield of PhCOOH was then calculated from the integrated intensity of the aromatic signal after subtracting the fraction due to mandelic acid. The relative yield of the three acids in the original product mixture was confirmed independently by an analysis of the aromatic region of the 200-MHz ^1H NMR spectrum, where a 2 H dd resonance for PhCOOH (δ 8.1) and a 2 H dd resonance for PhCOCOOH (δ 8.2) are well separated from the remaining multiplet of signals at 7.3–7.7 δ. A control using measured quantities of the three acids established that this

(24) Reference 11, p 359.

(25) Reinhold, V. N.; Ishikawa, Y.; Melville, D. B. *J. Med. Chem.* **1968**, *11*, 258.

(26) Feigl, F. *Spot Tests in Organic Analysis*; Elsevier: New York, 1966.

method of analysis gave reliable data and was more convenient than a derivatization/GC method.

The ether layer containing the nonacidic products was subsequently evaporated, giving the combined methyl ester products (and PhCOCHO, when it was present). The yield of each individual component was again determined by NMR integration using as internal standard a measure weight of hexamethylbenzene added to the entire product mixture. Each ester exhibits a distinct methyl signal (3 H) in the ^{1}H NMR spectrum (δ 3.7 for PhCHOHCOOMe, δ 3.85 for PhCOOMe, and δ 3.90 for PhCOCOOMe), which could be utilized to calculate the yield relative to hexamethylbenzene (18 H). The yield of PhCOCHO was calculated either from the ^{1}H NMR spectrum, by subtraction of the total ester integration from the aryl H resonance, or by weighing the (2,4-dinitrophenyl)hydrazone derivative obtained by adding 2,4-DNP reagent after diluting the product mixture with MeOH and dilute aqueous HCl.

Bubbling H_2S through the original (pH 1) water layer, filtration of CuS, and evaporation of the filtrate left a solid residue which could be analyzed for glyoxylic acid by a spot-test method[26] (a positive test was obtained only in the case $PhCH_2CH_2CHO$ was used as substrate).

Anaerobic Coupling Products. Treatment of $PhCH_2CHO$ and $PhCH(CH_3)CHO$ with the "Brackman" oxidant under N_2 gave mainly the corresponding methanol-derived acetals and, in addition, complex mixtures of oxidation products. Two approaches were used to help identify the nature of these latter products: (i) carrying out the reactions under N_2 in CH_3CN to avoid acetal formation and (ii) carrying out the anaerobic MeOH reactions on the corresponding ketones, $PhCH_2COCH_3$ and $PhCH(CH_3)COCH_3$. In all cases below, the reaction components and conditions were as described above (Brackman conditions) except as noted, and product identities are assigned on the basis of 200-MHz ^{1}H NMR spectra of fractions from preparative TLC, without characterization of pure compounds. The yield data given is approximated from the integrated 200-MHz spectrum of the total reaction product mixture, using the integral of the aryl H peak as 100%.

(a) Oxidation of $PhCH_2COCH_3$ in CH_3OH at 50–55 °C for 15 h, followed by the usual workup, gave a 98% crude yield of a 61:39 mixture of the *d,l* and *meso* isomers of 3,4-diphenyl-2,5-hexanedione. The minor isomer: ^{1}H NMR ($CDCl_3$) δ 1.88 (s, 3 H, CH_3), 4.63 (s, 1 H, CH), 7.23–7.43 (m, 5 H, Ar H); mp 198 °C, assigned as *meso* on the basis of ref 12, which reports a mp of 204–206 °C. The major isomer: ^{1}H NMR ($CDCl_3$) δ 2.15 (s, 3 H, CH_3), 4.41 (s, 1 H, CH), 6.95–7.40 (m, 5 H, Ar H), assumed to be the *d,l* isomer (lit.[12] mp 102–104 °C).

(b) Oxidation of $PhCH(CH_3)COCH_3$, prepared according to ref 27, in CH_3OH or CH_3CN at 50–55 °C for 40 h, gave, after the usual workup, ~5% unreacted starting material, and ~95% yield of a 2:1 mixture of the isomeric 3,4-dimethyl-3,4-diphenyl-2,5-hexanediones (*d,l* and *meso*): ^{1}H NMR ($CDCl_3$) δ (major) 1.65 (s, 6 H), 2.08 (s, 6 H), and 7.20–7.55 (m, 10 H); δ (minor) 1.66 (s, 6 H), 2.12 (s, 6 H), 7.20–7.55 (m, 10 H). This compound, as a mixture of isomers, has been partially characterized previously.[28]

(c) Oxidation of $PhCH_2CHO$. In CH_3CN at 25 °C for 16 h, ~82% of the aldehyde was converted to a mixture of oxidation products, only one of which, formed in ~10% yield, exhibited interpretable ^{1}H NMR ($CDCl_3$) signals at δ 5.19 (s) and 9.70 (s), consistent with 2,3-diphenylbutanedial. **In CH_3OH** at 25 °C for 16 h, ~30% of the starting material was recovered, ~32% was converted to the known (Aldrich) dimethyl acetal, $PhCH_2CH(OCH_3)_2$, and ~38% was transformed to unidentified oxidation products which contained a trace of the known[29] aldol dehydration product, 2,4-diphenyl-2-butenal.

(d) Oxidation of $PhCH(CH_3)CHO$. In CH_3CN at 25 °C for 16 h, ~94% conversion occurred to mainly a single (~90%) 2,4-DNP-positive product oil, which is very susceptible to autoxidation, and which we have assigned as the O–C-coupled dehydrodimer, (*E*)-2,5-diphenyl-2-methyl-3-oxa-4-hexenal: ^{1}H NMR ($CDCl_3$) δ 1.786 (s, 3 H, C_2-CH_3), 2.156 (d, 3 H, J = 1.4 Hz, C_5-H), 6.468 (q, 1 H, J = 1.4 Hz, C_3-H), 7.2–7.5 (m, 10 H, Ar H), 9.665 (s, 1 H, CHO); the observed $^4J_{HH}$ coupling of 1.4 Hz is only consistent with the assigned *E* stereochemistry; ^{13}C NMR ($CDCl_3$) δ 13.11, 20.40, 125.21, 125.37, 125.64, 126.34, 126.53, 127.50, 127.78, 127.98, 128.32, 128.57, 128.97, 129.95, 133.09, 137.14, 137.35, 198.53; HRMS (40 eV) calcd for $C_{18}H_{18}O_2$ m/z 266.1352, found 266.1320 (M^+, 4); IR (neat, cm^{-1}) 1598, 1645, 1735. **In CH_3OH** at 25 °C for 22 h, the above pentenal was formed in ~10% yield together with other unidentified products (~55%), accompanying ~20% of the recovered starting material and ~10% of the corresponding known (Pfaltz & Bauer H07970) dimethyl acetal $PhCH(CH_3)CH(OCH_3)_2$: ^{1}H NMR ($CDCl_3$) δ 1.26 (d, 3 H, J = 7.1 Hz, CH_3), 3.05 (m, 1 H, C_2-H), 3.24 and 3.38 (2 s, 3 H each, diastereotopic methoxys), 4.4 (d, 1 H, J = 7.5 Hz, C_1-H), 7.50–7.65 (m, 5 H, Ar H). The spectral data of one of the unidentified products is consistent with the cyclic aldehyde hydrate hemiacetal of the oxidatively coupled dimer (2,3-dimethyl-2,3-diphenylbutanedial), 3,4-dimethyl-3,4-diphenyl-2-methoxy-5-hydroxytetrahydrofuran, or a related isomer: ^{1}H NMR ($CDCl_3$) δ 1.21 and 1.24 (2 s, 3 H each), 3.54 (s, 3 H, methoxy), 5.90 and 6.41 (2 m, 1 H each, C_2- and C_5-H); EIMS (40 eV) m/z 297 $(M - 1)^+$.

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Registry No. PG, 1074-12-0; MA, 90-64-2; MM, 4358-87-6; $PhCH_2COCH_3$, 103-79-7; D,L-$CH_3CO[CH(Ph)]_2COCH_3$, 69373-32-6; *meso*-$CH_3CO[CH(Ph)_2COCH_3$, 69373-33-7; D,L-$CH_3CO(C(Ph)(CH_3))_2COCH_3$, 126036-66-6; *meso*-$CH_3CO(C(Ph)(CH_3))_2COCH_3$, 126036-67-7; CHOCH(Ph)CH(Ph)CHO, 126036-68-8; (±,*E*)-CHOC(Ph)(CH_3)OCH=C(CH_3)Ph, 126036-69-9; $Cu(NO_3)_2Py_2$, 14842-51-4; $PhCH_2CHO$, 122-78-1; $Ph(CH_2)_2CHO$, 104-53-0; $PhCH_2COCHO$, 56485-04-2; PhCHO, 100-52-7; $Ph(CO)_2OH$, 611-73-4; $Ph(CO)_2OMe$, 15206-55-0; $PhCO_2H$, 65-85-0; PhCOOMe, 93-58-3; $PhCH(CH_3)COCH_3$, 769-59-5; $PhCH(CH_3)CHO$, 93-53-8.

Supplementary Material Available: ^{1}H and ^{13}C NMR spectra for (*E*)-2,5-diphenyl-2-methyl-3-oxa-4-hexenal and the ^{1}H NMR spectrum for a compound tentatively identified as 3,4-dimethyl-3,4-diphenyl-2-methoxy-5-hydroxytetrahydrofuran (6 pages). Ordering information is given on any current masthead page.

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