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Copper-Catalyzed Oxidative Cyclization of Carboxylic Acids

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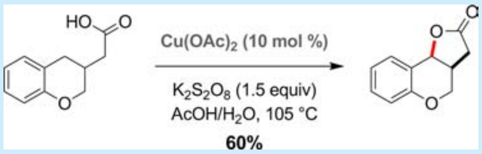
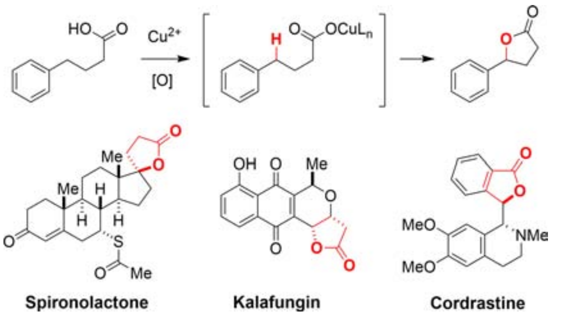
S *Supporting Information*

ABSTRACT: A method for converting C−H to C−O bonds through oxidative cyclization of carboxylic acids to generate lactone products is described. The reaction employs catalytic amounts of $Cu(OAc)_2$ and potassium persulfate as the terminal oxidant and is performed open to air in an aqueous acetic acid solvent system. Preliminary mechanistic studies suggest that substrate oxidation likely proceeds by sulfate radical anion and that the Cu catalyst has no influence on the product-determining step. These conclusions differ from related investigations that propose the intermediacy of a carboxylate radical.



The selective conversion of sp^3 C−H to C−O bonds in complex molecules remains an outstanding challenge in synthetic chemistry.[1,2] The majority of methods for C−H hydroxylation rely on a combination of intrinsic differences in C−H bond reactivity and substrate−catalyst steric interactions to bias reaction outcomes. A smaller number of technologies exploit intermediate alkoxy or acyloxy radical oxidants to promote intramolecular C−H functionalization.[3,4] Such methods generally offer a level of precision in controlling site-selectivity that is unrivaled by more conventional O-atom transfer processes.[5,6] Here, we describe our efforts to develop an oxidation reaction that transforms carboxylic acids to lactone products (Scheme 1). Following available precedent, this reaction was envisioned to occur through the intermediacy of a putative Cu carboxylate or acyloxy radical species, either of which could effect subsequent 1,5-H atom abstraction.[7] Such a process would offer predictable control over product selectivity, avoid complications from overoxidation of the product, and enable direct synthesis of value-added lactone derivatives.

Scheme 1. Oxidative Cyclization of Carboxylic Acids for Lactone Synthesis



Our decision to explore conditions for promoting carboxylic acid oxidative cyclization was inspired by a small number of published reports highlighting the viability of such a process.[7] In particular, work by Nikishin and co-workers has demonstrated that modest yields (20−40%) of γ- and δ-lactone mixtures are formed in reactions of linear alkanoic acids with stoichiometric amounts of $CuCl_2$ and $Na_2S_2O_8$.[7e] A carboxyl radical intermediate is posited as the active oxidant, as both CO_2 and alkyl chloride side products are detected. Intrigued by these findings and cognizant of alternate protocols for oxidizing carboxylate anions, we initiated studies to advance a general, catalytic method for oxidative cyclization of carboxylic acids.[4a−c,8]

Initial exploratory experiments to optimize conditions for lactone formation were performed with 4-phenylbutyric acid **1** as a model substrate. Guided by prior reports, **1** was treated with 10 mol % of $Cu(OAc)_2{\cdot}H_2O$ and $K_2S_2O_8$ in aqueous CH_3CN (Table 1). No reaction ensued when this mixture was stirred at room temperature; however, upon warming the solution to 65 °C, 35% of the desired lactone **2** was produced along with 10% of ketone **3** (Table 1, entry 1). Elevating the reaction temperature (105 °C) resulted in a slight increase in conversion of starting material to **2** (Table 1, entry 2). Replacing CH_3CN with sulfolane as a polar cosolvent was deleterious to reaction performance (Table 1, entry 3); in contrast, AcOH offered demonstrable improvement, yielding ~60% of the desired product (Table 1, entry 4). It appears that both solvent and temperature influence the overall efficiency of this process, whereas the choice of copper catalyst does not (Table 1, entries 5 and 6).[9] Of the terminal oxidants screened, including different persulfate salts and Oxone, $K_2S_2O_8$ was most effective (Table 1, entries 4, 7−10). Control experiments using other transition-metal acetates afforded substantially reduced quantities of lactone **2** compared to reactions catalyzed with cupric ion (Table 1, entries 10−12). These results closely mirror those obtained in the absence of any added catalyst (Table 1, entry 13). Finally, it is worth noting that oxidation of **1** using conditions described by Nikishin (1 equiv $CuCl_2$, 1 equiv $Na_2S_2O_8$, neat H_2O, 90 °C) or with stoichiometric amounts of ceric ammonium nitrate (CAN) gave only 35% and 20% of **2**, respectively (Table 1, entries 14 and 15).[7e,10]

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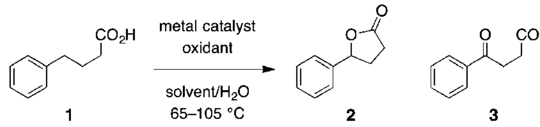
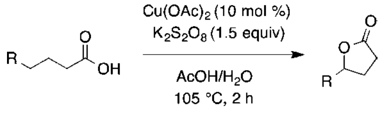
Table 1. Optimization of Catalytic Reaction Conditions

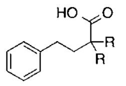
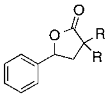
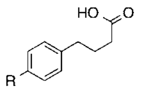
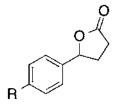
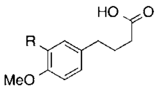
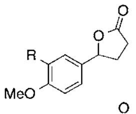
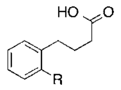
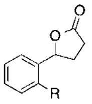
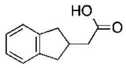
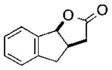
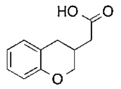
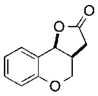
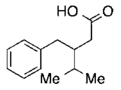
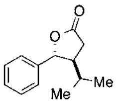
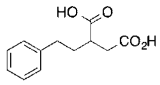
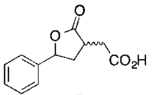
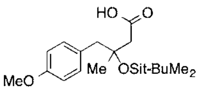
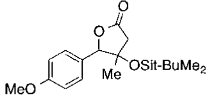
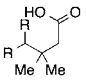
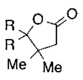
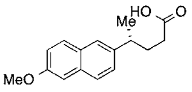
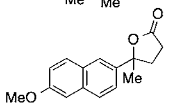


entry	catalyst[a]	oxidant[b]	solvent	T (°C)	2/3/1[c]
1	$Cu(OAc)_2{\cdot}H_2O$	$K_2S_2O_8$	CH_3CN	65	35:10:30
2	$Cu(OAc)_2{\cdot}H_2O$	$K_2S_2O_8$	CH_3CN	105	40:10:20
3	$Cu(OAc)_2{\cdot}H_2O$	$K_2S_2O_8$	sulfolane	105	20:5:50
4	**$Cu(OAc)_2{\cdot}H_2O$**	**$K_2S_2O_8$**	**AcOH**	**105**	**60:10:20**
5	**$Cu(SO_4){\cdot}5H_2O$**	**$K_2S_2O_8$**	**AcOH**	**105**	**60:10:20**
6	**$CuCl_2{\cdot}2H_2O$**	**$K_2S_2O_8$**	**AcOH**	**105**	**60:10:15**
7	$Cu(OAc)_2{\cdot}H_2O$	$Na_2S_2O_8$	AcOH	105	50:5:25
8	$Cu(OAc)_2{\cdot}H_2O$	$(NH_4)_2S_2O_8$	AcOH	105	40:5:40
9	$Cu(OAc)_2{\cdot}H_2O$	Oxone	AcOH	105	20:10:55
10	$Co(OAc)_2{\cdot}2H_2O$	$K_2S_2O_8$	AcOH	105	20:10:15
11	$Ni(OAc)_2{\cdot}4H_2O$	$K_2S_2O_8$	AcOH	105	20:10:20
12	$Zn(OAc)_2{\cdot}2H_2O$	$K_2S_2O_8$	AcOH	105	25:10:30
13	none	$K_2S_2O_8$	AcOH	105	20:10:30
14	1 equiv $CuCl_2$	$Na_2S_2O_8$	H_2O	90	35:5:50
15	none	CAN[d]	AcOH	105	20:0:75

[a] Reaction performed with 0.1 equiv of catalyst in a 1:1 mixture of solvent/H_2O. In the absence of H_2O, no reaction is observed. [b] Reaction performed with 1.5 equiv of oxidant. [c] Reaction yields and product ratios estimated by ^1H NMR integration against an internal standard (4-nitrotoluene). [d] CAN = ceric ammonium nitrate.

Table 2. Lactonization of Aliphatic Carboxylic Acids



entry	substrate	product[a]		yield (%)[b]
1			R = H R = Me	59 57
2			R = OMe R = Br R = NHAc	75 42 46[c]
3			R = Br R = NO_2	53 25
4			R = OMe R = Br	70 21
5				59[d]
6				60[d]
7				45[e]
8				55[f]
9				35[g]
10			R = Me R = $(CH_2)_4$	35 21
11	 *ee* = 99.9%			16[h]

[a] All reactions were conducted on a 0.5 mmol scale at a substrate concentration of 0.1 M. [b] Isolated yield after purification by chromatography. [c] Reaction performed in 1:1 CH_3CN/H_2O at 85 °C. [d] The *cis*-diastereomer was formed exclusively. [e] Product obtained as a single *trans*-diastereomer. [f] Product obtained as a 1:1 mixture of diastereomers. [g] Product obtained as a single diastereomer (stereochemistry unassigned). [h] Product obtained as a racemic mixture; see the Supporting Information for details.

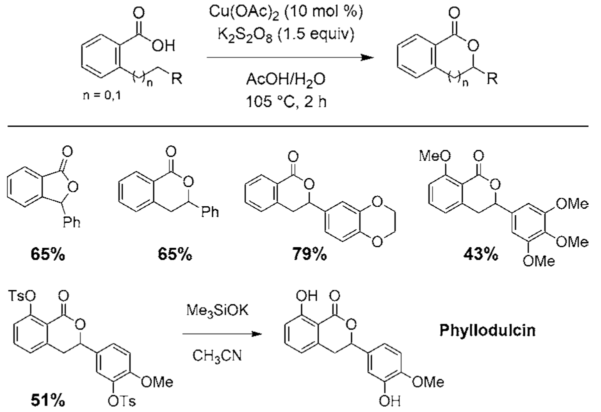
Our optimized catalytic C−H oxidation protocol is functional with both aliphatic and aromatic carboxylic acids (Table 2 and Scheme 2).[11] For aliphatic derivatives, 5-membered lactone products are formed preferentially. Isolated yields for substrates bearing γ-benzylic centers are generally above 40%. In many cases, reactions give few overoxidized byproducts, and unreacted starting material accounts for the majority of the mass balance.[12] Of note, electron-rich arene substrates are superior to those with electron-withdrawing substituents (Table 2, entries 2−4), a finding consistent with our proposed mechanism (vide infra). Although this method shows a strong preference for benzylic oxidation, acyloxylation of 3° C−H bonds does occur in conformationally constrained substrates (Table 2, entry 10). Reactions with optically active 3° substrates, however, are found to give racemic product (Table 2, entry 11). Evident limitations notwithstanding, the overall process uses low-cost reagents, can be run open to air, and is easy to perform.

Oxidative cyclization of benzoic acid substrates is strongly biased (>20:1 selectivity) toward six-membered ring lactone formation (Scheme 2). As with aliphatic carboxylic acids, substrates containing electron-rich arene groups engage effectively, a feature that distinguishes this process from methods for C−H hydroxylation.[13] Benzo-fused lactones are common elements in a number of plant-derived natural products, including phyllodulcin and related structures.[14,15]

Successful lactone production in aqueous AcOH solution in combination with the absence of detectable amounts of decarboxylated side products in reaction mixtures has led us to question the likelihood of a carboxylate radical as the active oxidant in this transformation (as has been proposed for related Cu-mediated reactions).[7e] We have noted that decarboxylation occurs with 2-indanylacetic acid **4** under closely related conditions using $AgNO_3$ and $K_2S_2O_8$ (Scheme 3).[16] None of the 2-methylindanone product **5** or related compounds appear as side products in the $Cu(OAc)_2$-catalyzed reaction.

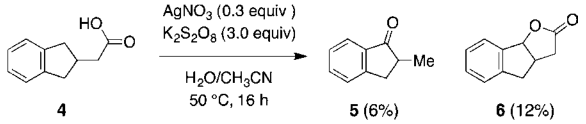
We have performed a series of experiments to clarify the role of the carboxylic acid in this oxidation reaction. Absent knowledge of the rate-determining step, we have obtained kinetic isotope effect data by conducting both intra- and intermolecular competition experiments (Scheme 4). Under our optimized $Cu(OAc)_2$-catalyzed conditions, both methods give equivalent KIE values within error of the measurements (1.9 ± 0.1 and 2.2 ±

Scheme 2. Oxidative Cyclization of Arene Carboxylic Acids[a]

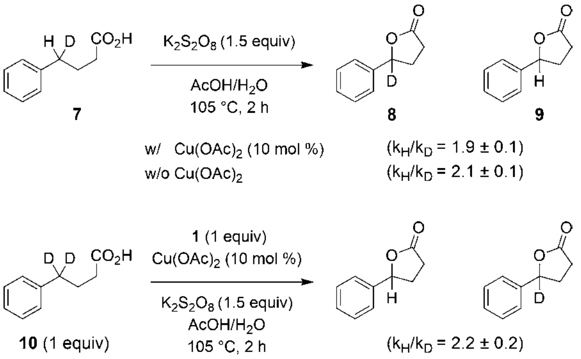


[a]Product lactones are common structural elements in natural products, as exemplified by phyllodulcin.

Scheme 3. Silver-Catalyzed Decarboxylation of 2-Indanylacetic Acid



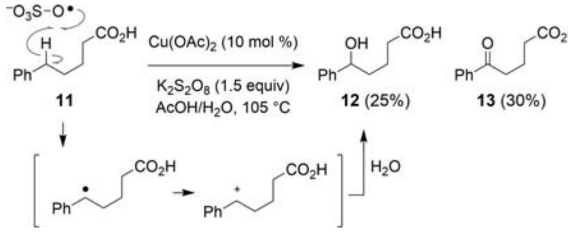
Scheme 4. Kinetic Isotope Effect Measurements Implicate Sulfate Radical As the Active Oxidant



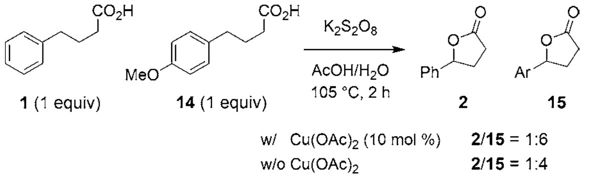
0.2, respectively). The fact that these experiments afford the same KIE value discounts a mechanism involving rate-determining carboxylate radical formation. Notably, a KIE of 2.1 ± 0.1 has also been measured with substrate **7** under conditions in which Cu(OAc)$_2$ is absent. This latter result implicates sulfate radical, $SO_4^{\bullet -}$ (or possibly acetoxy radical, $MeCO_2^{\bullet}$), as the active oxidant responsible for initiating the cyclization process.

A proposed mechanism involving C−H abstraction by $SO_4^{\bullet -}$ is supported by both literature precedent and by additional observations that we have made.[17,18] Sulfate radical can be generated from persulfate, $S_2O_8^{2-}$, and is known to react rapidly with saturated hydrocarbons.[19] In the presence of cupric ion, it is possible that an intermediate alkyl radical is trapped and/or oxidized to a carbocation. Formation of either a radical or cationic species accounts for the generation of racemic lactone from an enantiomerically pure substrate (Table 2, entry 11). This proposal is also consistent with oxidation of 5-phenylvaleric acid **11**, which gives both ketone and alcohol products (Scheme 5). In this case, the rate of six-membered lactone formation does not compete with the rate at which H$_2$O intercepts the putative carbocation.[20] Interestingly, a competition between 4-phenylbutyric acid **1** and the *p*-MeO derivative **14** affords a 1:6 mixture of products, a ratio that is similar to that obtained when Cu(OAc)$_2$ is excluded from the reaction (Scheme 6). This final result suggests that oxidation by $SO_4^{\bullet -}$ is product-determining and that Cu(OAc)$_2$ has effectively no influence on selectivity. The evident role of cupric salt on reaction efficiency, however, is clear from the data shown in Table 1. Future studies will aim to elucidate its unique function in this process.

Scheme 5. Product Distribution with 5-Phenylvaleric Acid as Substrate



Scheme 6. Competition Experiments Show No Effect of Copper Catalyst on Product Selectivity



Lactonization of aliphatic and aromatic carboxylic acids has been shown to proceed under the action of catalytic Cu(OAc)$_2$ and K$_2$S$_2$O$_8$ as the terminal oxidant. In general, reaction performance is highest for substrates bearing benzylic C−H bonds and that are predisposed to furnish butyrolactone products. The scope of this process and the identification of conditions to effect catalytic turnover distinguish our findings from prior art. In addition, preliminary mechanistic experiments have provided evidence for a pathway that does not involve carboxylate radical formation and for which the Cu catalyst has no influence on product selectivity. Studies to reveal the ambiguous role of cupric ion in promoting oxidative lactonization are expected to give way to advances in this technology.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03176.

Experimental details, characterization data, and NMR and IR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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