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Copper-Catalyzed Desaturation of Lactones, Lactams and Ketones under pH-Neutral Conditions

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Abstract

A copper-catalyzed desaturation method is reported, which is suitable for converting lactones, lactams and cyclic ketones to their α,β-unsaturated counterparts. The reaction does not require strong base/acid or sulfur/selenium reagents, and can be carried out through a simple one-step operation. The protocol uses inexpensive catalysts and reagents, exhibits excellent scalability and functional group tolerance. Notably, *t*-butanol is the only stoichiometric byproduct produced, and over oxidation is not observed. The reaction mechanism has been investigated through control experiments, deuterium labelling, radical clock, EPR, HRMS and kinetic studies. The data obtained are consistent with a reaction pathway involving a reversible α-deprotonation by a Cu(II)-O^{t}Bu species, followed by further oxidation of the resulting Cu enolate.

Introduction

Methods that prepare and modify carbonyl compounds have been critical in organic synthesis.[1] Among numerous carbonyl-involved transformations, desaturation reactions, namely converting a saturated carbonyl compound to the corresponding α,β-unsaturated counterpart, is of particular interest for syntheses of complex and biologically relevant molecules.[2] First, the electrophilic α,β-unsaturated structural motif is commonly found in many bioactive natural products (Fig. 1), which has been an important inspiration for developing new pharmaceutical agents.[3] On the other hand, the desaturation process could be coupled with other transformations, which leads to β-functionalization[2a,4] or simultaneous α,β-difunctionalization of carbonyl compounds.[5]

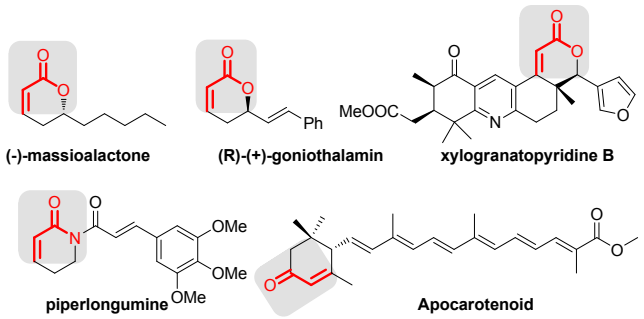
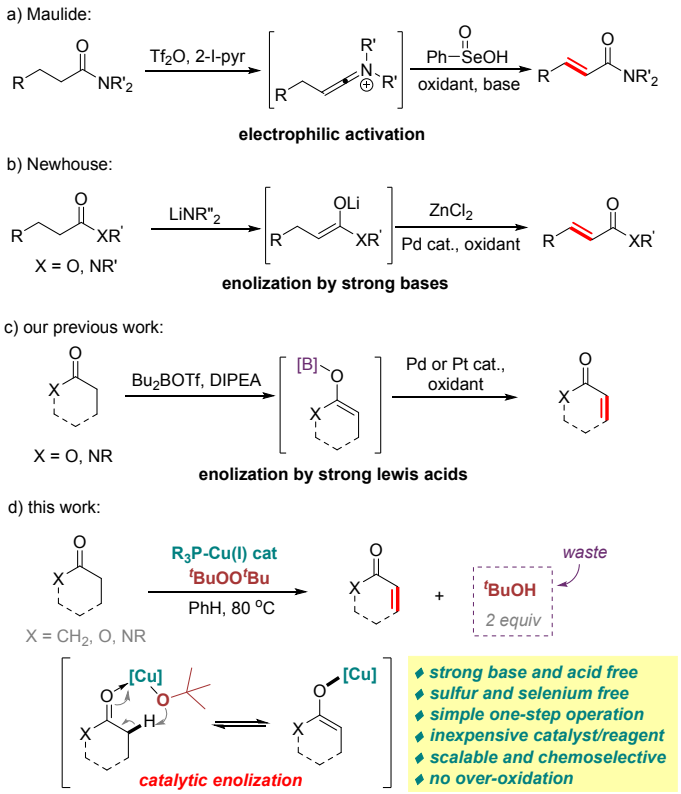


Figure 1. Representative natural products containing α,β-unsaturated carbonyl moieties.

To date, desaturation of ketones and aldehydes has been extensively developed;[2] among various creative strategies, the palladium-catalyzed oxidation offers a direct, efficient and mild approach, and has been widely utilized in complex molecule syntheses.[6] By contrast, the corresponding reactions with common esters and amides have been much less developed. Classical approaches typically involve introducing a sulfur or selenium-based leaving group to the α-carbon followed by an elimination process.[7] Recently, through an electrophilic activation approach, an impressive one-pot chemoselective

selenium(IV)-mediated amide-desaturation was reported by Maulide and co-workers (Scheme 1a).[8] Regarding catalytic strategies, Newhouse has systematically developed a suite of palladium-catalyzed dehydrogenation of esters, amides, nitriles, ketones and carboxylic acids,[9] which were effectively enabled by enolate formation with a novel lithium anilide and subsequent transmetalation to zinc (Scheme 1b). Alternatively, a soft enolization approach has been adopted by us for direct desaturation of various esters and amides under either palladium[10] or platinum catalysis[11] (Scheme 1c). While effective, these established catalytic methods require either stoichiometric strong bases or strong Lewis acids for carbonyl enolization due to reduced acidity of the α C–H bonds in esters and amides (compared to ketones and aldehydes); as a consequence, byproducts are heavily produced in these processes.

Scheme 1. Recent Advances on Desaturation of Esters and Amides

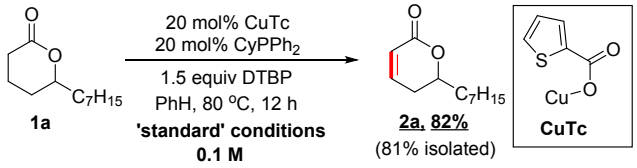


Inspired by Stahl's seminal mechanistic studies on the palladium-catalyzed ketone dehydrogenation,[6g] an intriguing question is whether *catalytic enolization* of lactones and lactams could be realized using a dual functional catalyst that contains a more Lewis acidic metal and a more basic X ligand (better than carboxylates). Serving as both a Lewis acid and an oxidation catalyst, the metal complex could first activate the carbonyl substrate through soft enolization and then participate in the subsequent dehydrogenation process. To continuously supply the base, as well as to maintain a relatively neutral reaction medium and minimize byproduct formation, it could be strategically attractive to slowly generate the basic X ligand from the oxidant. In addition, it would also be appealing if earth abundant first-row transition metals could be employed as catalysts. Herein, we describe our initial development of a copper-catalyzed oxidation method that can effectively convert a range of saturated lactones, lactams and ketones to the corresponding unsaturated conjugated carbonyls (Scheme 1d). The reaction is operated under near pH-neutral conditions with *t*-butanol as the only stoichiometric byproduct formed.

Results and Discussion

In 2014, Han,[12] Patel[13] and Hartwig[14] independently reported a Cu-catalyzed sequential dehydrogenation of simple alkanes followed by Kharasch–Sosnovsky-type[15] allylic functionalization. Shortly after, the Antonchick group disclosed a single example of a Cu-catalyzed dehydrogenation of a special 1,4-diketone.[16] Concurrently, the Su group reported a novel Cu/2,2'-bipyridine (bpy)-catalyzed TEMPO-mediated system for dehydrogenative β-functionalization[17] and later multi-desaturation reactions[18] via radical abstractions. While highly efficient, the scope has been mainly focused on ketones/aldehydes and selective mono-dehydrogenation was difficult. The challenge for the selective mono-dehydrogenation is likely due to that, comparing to the α C–H bond in the substrate (~89-94 kcal/mol), the allylic C–H bond of the initially formed unsaturated product is typically weaker (~87 kcal/mol) and tends to be more reactive with radical species.[19] In addition, from the prospect of polar effect,[20] the α C–H bond is generally more electronically deficient than allylic C–H bonds, therefore less competitive to be abstracted by an electrophilic oxygen-based radical.

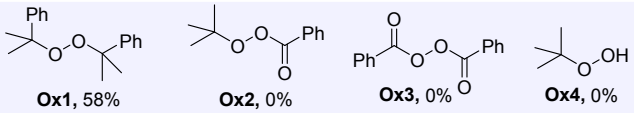
Table 1. Selected Optimization Studies[a]



Entry	Variations from the 'standard' conditions	Yield (%) of **2a**[a,b]
1	Without **CuTc**	0
2	Without **$CyPPh_2$**	trace
3	Without **DTBP**	0
4	**C1-6** instead of **CuTc**	Listed below
5	**L1-16** instead of **$CyPPh_2$**	Listed below
6	**Ox1-4** instead of **DTBP**	Listed below
7	10 mol% **CuTc** and 10 mol% **$CyPPh_2$**	58
8	solvent = toluene	60
9	solvent = PhF	68
10	solvent = 1,4-dioxane	0
11	solvent = DCE	20
12	temp = 70 °C	76
13	temp = 60 °C	42
14	C = 0.05 M	48[c]
15	C = 0.2 M	72
16	none	**82**

CuOAc **C1**, 78%	CuCl **C2**, 20%	CuSPh **C3**, 0%	$Cu(CH_3CN)_4PF_6$ **C4**, 0%	$Cu(OAc)_2$ **C5**, trace	$Cu_2(OTf)_2$•PhMe **C6**, trace

 **L1**, 10%	**PAr_3 (L4-9)**	$^tBuPPh_2$ **L10**, 76%	Cy_3P **L12**, 56%
bpy **L2**, 14%	Ar = Ph, 64%	$^iPrPPh_2$ **L11, 82%**	
1,10-phen **L3**, trace	Ar = *p*-Me-C_6H_4, 66%	SPhos, **L13**, 0%	
	Ar = *p*-OMe-C_6H_4, 72%	XPhos, **L14**, 0%	
	Ar = *p*-F-C_6H_4, 68%	XantPhos, **L15**, 0%	
	Ar = *p*-CF_3-C_6H_4, 48%	dppb, **L16**, 0%	
	Ar = 3,5-*di*-CF_3-C_6H_3, 28%		



[a] Each reaction was run on a 0.2 mmol scale in a sealed 4 mL vial for 12 h. [b] Yields were determined by ^1H NMR using CH_2Br_2 as the internal standard. [c] 50% of **1a** was observed.

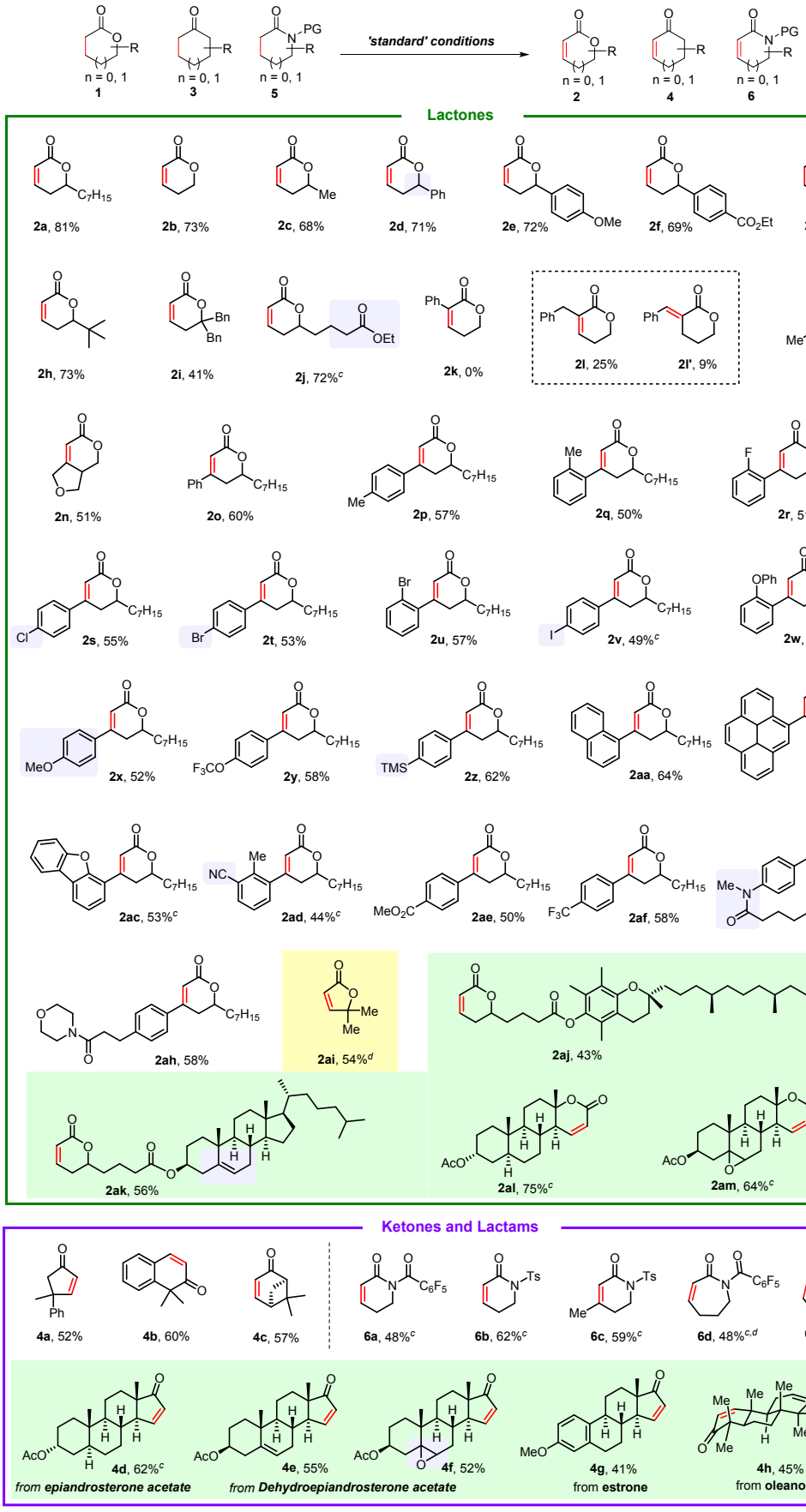
To address the selectivity challenge, we hypothesized that, using a more basic X ligand, such as *t*-butoxide, and a softer L ligand (that can have a stronger *trans* influence), deprotonation of the α C–H bond could be achieved in a cooperative manner under relatively mild conditions (i.e. lower reaction temperature). As a consequence, it is expected that the undesired radical-mediated further oxidation could be minimized. To test this hypothesis, phosphines were first examined as the ancillary ligand and di-*t*-butylperoxide (DTBP) was employed as the oxidant in order to slowly generate the basic *t*-butoxide ligand. To our delight, when using lactone **1a** as the model substrate, the desired α,β-unsaturated lactone product **2a** was isolated in 81% yield at 80 °C when using copper(I) thiophene-2-carboxylate (CuTc)/$CyPPh_2$ (20 mol%) as the metal/ligand combination (Table 1). The role of each reactant was then explored through control experiments. Clearly, the copper catalyst, the phosphine ligand and DTBP are all essential to this transformation (entries 1-3). Besides CuTc, a variety of other copper (I) and (II) complexes has also been tested as catalysts (entry 4). While CuOAc was almost equally effective, other Cu(I) species, such as CuCl, CuSPh and $Cu(MeCN)_4PF_6$, were much less efficient, suggesting the importance of the carboxylate ligand (*vide infra*, Mechanistic Studies). Cu(II) complexes, including $Cu_2(OTf)_2$•PhMe and $Cu(OAc)_2$ (effective catalyst in Su's reactions[17,18]), gave no or trace desired product.

While the majority of the prior Cu-mediated oxidation reactions employ pyridine-type ligands,[21] phosphine ligands were found to be more effective in this transformation (entry 5).[22] Pyridine, bpy and 1,10-phen (**L1**-**L3**) all gave low yields of the product. Simple triarylphosphines are excellent ligands. Regarding the electronic effect of the ligand (**L4**-**L9**), the more electron-rich PAr_3 outperformed the electron-deficient ones. Interestingly, the monoalkyl diarylphosphines were found most efficient. Both ^{t}Bu and ^{i}Pr-substituted phosphines (**L10** and **L11**) can give comparable yields to $CyPPh_2$, but the trialkyl PCy_3 ligand (**L12**) gave a lower yield. In addition, Buchwald ligands (**L13** and **L14**) and bidentate phosphine ligands (**L15** and **L16**) have also been examined, whereas all gave low efficiency or no reactivity.

As one of the most stable peroxide species with decomposition temperature over 100°C, DTBP was found to be a superior oxidant. Cumyl peroxide (**Ox1**) delivered the desired product in a moderate yield; other peroxides, including ^{t}BuOOBz (**Ox2**), BPO (**Ox3**) and TBHP (**Ox4**), failed to yield any product (entry 6). Decreasing the catalyst/ligand loading to 10 mol% still afforded **2a** in 58% yield (entry 7). A survey of different solvents suggested aromatic solvents to be optimal (entries 8-11); in contract, the more polar solvents, e.g. 1,4-dioxane and DCE, gave no product or only 20% yield, respectively. Although 80 °C was the best reaction temperature, the reaction can still proceed even at 60 °C (entries 12 and 13). Finally, running the reaction at a lower concentration gave a lower conversion with most of the starting material recovered (entry 14), while a higher concentration led to more substrate decomposition (entry 15).

With the optimized conditions in hand, the substrate scope was explored (Table 2). First, substitutions at the various positions of δ-lactones were tolerated (**2a-2ah**).[23] δ-Alkyl- or aryl-substituted substrates all worked well, giving satisfactory yields of the corresponding products. In the presence of an additional enolizable linear ester, the desaturation of δ-lactones (**1j**) still occurred selectively at the lactone moiety. The α-phenyl substituted δ-lactone gave no desired product (**2k**); instead, the α-dimer was formed as the major side product (*vide infra*, Scheme 4). When the phenyl group was replaced with a benzyl group, a pair of isomers of dehydrogenation products was obtained in low yields (**2l**). The β-methyl substituted δ-lactone afforded a high yield (**2m**) using *i*-$PrPPh_2$ as the ligand. The fused lactone (**1n**) was also a suitable substrate. The functional group compatibility was examined based on β-aryl-substituted δ-lactones (**2o**-**2ah**). Gratifyingly, a wide range of functional groups were

Table 2. Substrate Scope with Lactones, Lactams and Ketones

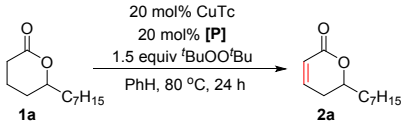


[a] Each reaction was run on a 0.2 mmol scale in a sealed 4 mL vial for 12 h. [b] Isolated yields. [c] 20 mol% $^{i}PrPPh_2$ was used. [d] The reaction was run at 100 °C. Ts= *p*-toluenesulfonyl.

tolerated, including aryl fluoride (**2r**), chloride (**2s**), bromide (**2t** and **2u**), iodide (**2v**), ethers (**2w**, **2x** and **2y**), silyl (**2z**), nitrile (**2ad**), ester (**2ae**), trifluoromethyl (**2af**), electron-rich arenes (**2w**, **2x** and **2ac**), polyaromatic (**2ab**) and tertiary amides (**2ag** and **2ah**). Five and seven-membered lactones were found less reactive, though unsaturated γ-lactone (**2ai**) was still obtained in a moderate yield. Gratifyingly, δ-lactones derived from bioactive natural products, such as α-tocopherol (**2aj**), cholesterol (**2ak**), androsterone (**2al**), and dehydroepiandrosterone (**2am**), also smoothly afforded the desired desaturation products. Note that the allylic and benzylic C–H bonds in these substrates were tolerated.

The feasibility of desaturating ketones and lactams was also tested with the Cu-catalyzed protocol. β,β-disubstituted or α,α-disubstituted cyclopentanones and cyclohexanones were competent substrates (**4a-4c**). Particularly, this method could be employed to desaturate a number of sterically encumbered steroid-based substrates (**4d-4h**). In addition, protected six- or seven- membered lactams could all afford the corresponding unsaturated products in moderate yields (**6a-6e**). Reactions with linear esters and amides were not fruitful under the current conditions likely due to further reduced acidity of the α hydrogens, which is the topic of the ongoing study.

Scheme 2. Gram-scale Reactions

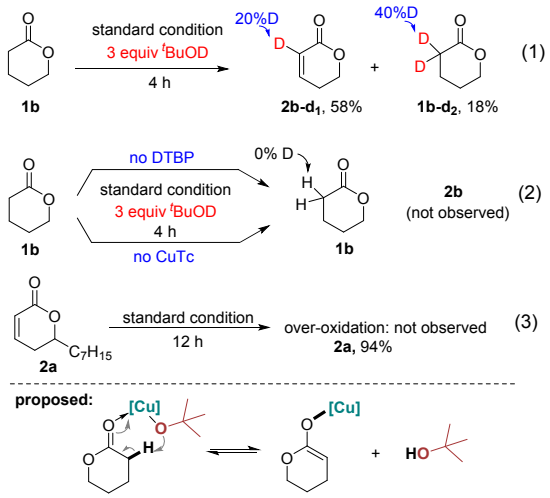


To investigate the practicality of this method, gram and decagram-scale reactions were carried out. On a 20.0 mmol scale, the desired α,β-unsaturated lactone **2a** was isolated in 86% yield when $CyPPh_2$ was used (Scheme 2). The 100 mmol scale reaction employed inexpensive PPh_3 as the ligand,[24] which afforded 13.4 g of product **2a**.

Mechanistic Studies

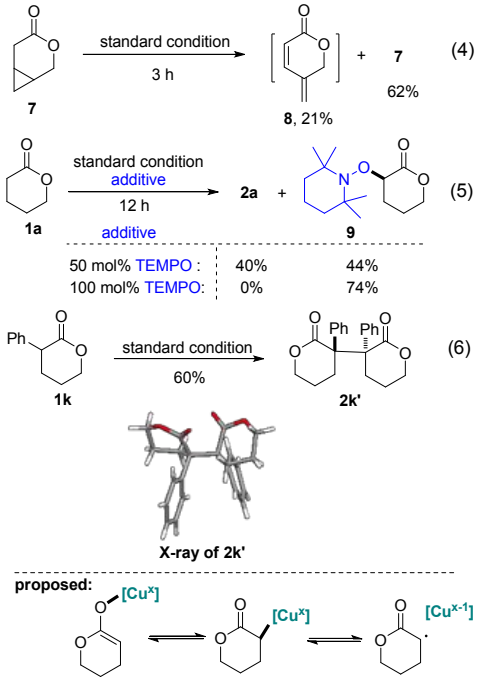
Efforts were then carried out to obtain some mechanistic insights into the Cu-catalyzed dehydrogenation reaction. First, perhaps, the most interesting question is *how the α C–H bond is cleaved*. To address this question, a number of control experiments were conducted (Scheme 3). Running the reaction of substrate **1b** under the standard reaction conditions except in the presence of 3 equiv ^{t}BuOD in 4 h provided the desaturated product in 58% yield with 20% D incorporation at the α position (Eq 1). The recovered **1b** was found to contain 40% D at the α position. On the other hand, no deuterium incorporation was found when running the same reaction in the absence of DTBP or Cu (Eq 2), suggesting an important role of the proposed [^{t}BuO-Cu] species. The H/D exchange phenomenon indicates that the copper enolate formation is likely reversible. Thus, from a microscopic reversibility viewpoint, the cleavage of the α C–H bond should come from a deprotonation process,[25,16] which could be the key for the proposed catalytic enolization. In addition, given that over-oxidation was not observed even after subjecting the unsaturated product (**2a**) to the standard condition (Eq 3), as well as the tolerance of weak benzylic and allylic C–H bonds (**2d-2f** and **2ak**), the alternative α C–H abstraction pathway by highly reactive free ^{t}BuO· radical is unlikely.

Scheme 3. Cleavage of the α C–H Bond



The second question is *how the β C–H bond is cleaved*. To answer this question, understanding the property of the generated copper enolate would be important. Similar to Su's observation,[17a] the copper enolate also exhibits sufficient radical character (Scheme 4). First, the reaction of the cyclopropane-containing lactone (**7**) gave a transient ring-opening product (**8**), which decomposed after a longer reaction time (Eq 4). The C–C cleavage pattern for such a ring-fused cyclopropane is consistent with the previously reported radical-mediated pathway.[26] In addition, a persistent radical, e.g. TEMPO, can effectively trap the α radical generated in the reaction (Eq 5). Moreover, when the α-phenyl substituted δ-lactone (**1k**) was employed, the α dimer was formed in 60% yield (Eq 6). This is likely due to that such α radical species is stable enough to dissociate and form a dimer. Thus, in addition to being basic, the copper enolate intermediate also has a notable radical property.

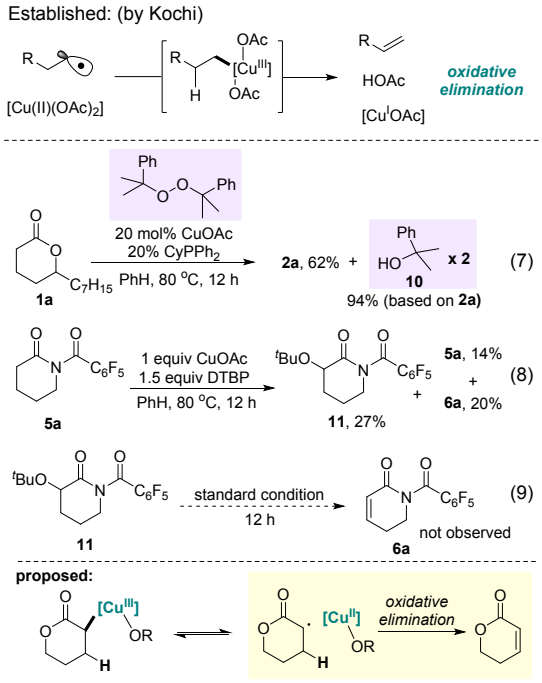
Scheme 4. Radical Character of the Copper Enolate



Given the radical character of the copper enolate, the β C–H bond of the enolate is anticipated to be significantly weakened. Early studies by Kochi show that alkyl radicals can react with Cu(II) salts to give olefins; this process was described as a "oxidative elimination" reaction (Scheme 5).[27] A transient Cu(III)-alkyl intermediate was proposed and carboxylate ligands on copper (e.g. OAc) were critical for this

transformation. Similarly, in this Cu-catalyzed dehydrogenation reaction, carboxylate-type X ligands were also found to be essential (*vide supra*, Table 1). Thus, we questioned whether a similar "oxidative elimination" process could have occurred in this system.[28] A number of experiments were then carried out. While it is difficult to quantify the ^{t}BuOH generated in the reaction, the use of heavier cumyl peroxide (**Ox1**) afforded the corresponding alcohol **10** in 94% yield based on the desaturated product generated (Eq 7). In the prior $Cu(OAc)_2$/TEMPO-assisted dehydrogenation, the β C–H abstraction occurred with an α-oxygenated species (e.g. TMEPO-substituted ketones).[17a] In our system, the α-oxygenated species was not observed with lactones. In contrast, the α-^{t}BuO-substituted product (**11**) was only observed when treating lactam **5a** with stoichiometric CuOAc in the absence of phosphine ligands (Eq 8); however, subjecting compound **11** to the standard catalytic conditions gave no desired desaturation product (Eq 9). These results indicate that the α-oxygenated species is unlikely to be an intermediate in this reaction, which represents a main difference from the $Cu(OAc)_2$/TEMPO system.[17a] Hence, in our system the β C–H scission possibly occurs with either the copper enolate or the enolate radical species.

Scheme 5. Cleavage of the β C–H bond



Kinetic studies. To better understand the catalytic system, the kinetic profiles of the reaction were obtained (Fig. 2). A short induction period (~10 min) was observed. The reaction then proceeded with a fast initial rate (0.4 mM/min), and became slower after 3 hours (at around 50% conversion). The production formation was plateaued after 6 hours. Notably, in the first 6 hours, the mass balance was nearly perfect, indicating that there was almost no decomposition of the starting material in this period. The catalyst system then became inactive after 6 hours; the ^{31}P NMR of the reaction mixture suggests that a significant amount of phosphine oxide was formed at this stage. It is also not surprising that decomposition of **1a** started to occur after the death of the catalyst.

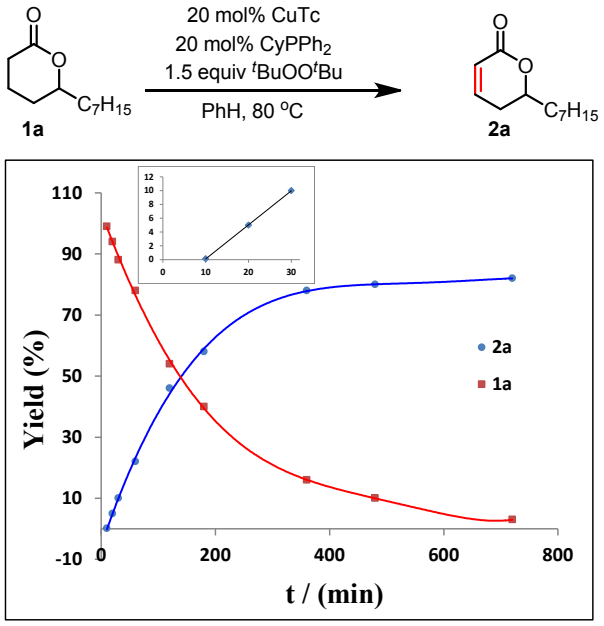
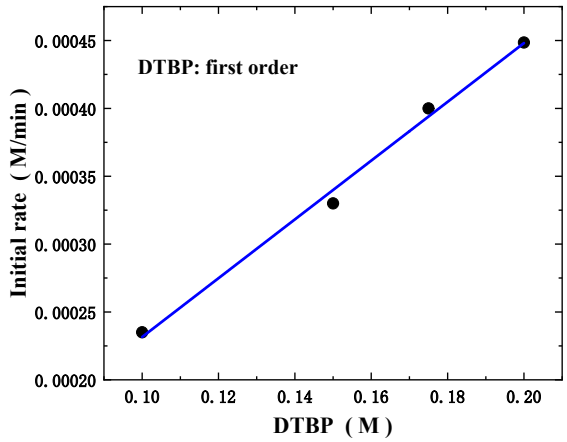
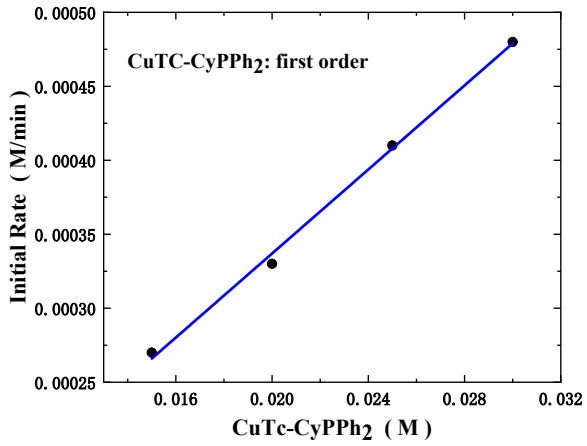


Figure 2. The Kinetic Profile of the Cu-Catalyzed Desaturation of Lactone 1a under the Standard Conditions





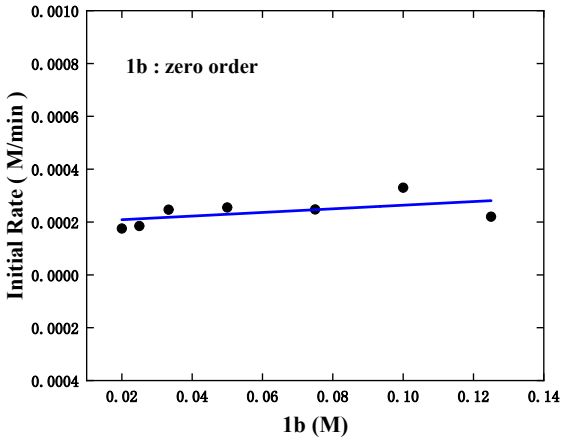
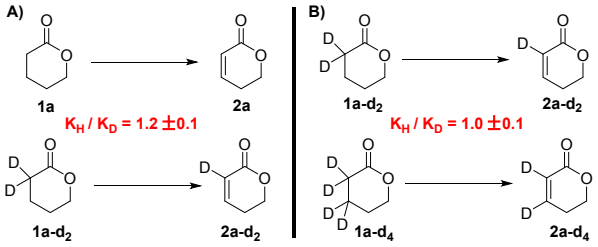


Figure 3. Measurement of the Reaction Rate Dependence of the Oxidant (DTBP), the Copper Catalyst and the Substrate (1b)

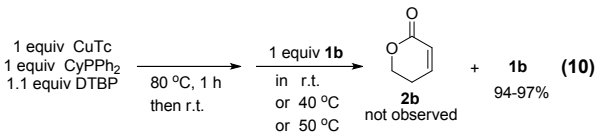
To gain insights into the turnover limiting step (TLS) and the resting state of the catalyst, the reaction orders of each component have been determined using the initial-rate method (Fig. 3). The rate of reaction shows first-order dependences on the catalyst and the oxidant (DTBP), but pseudo zero-order on the lactone substrate (**1b**). In addition, the parallel kinetic isotope effect (KIE) studies show that no primary KIE was observed at either the α or β position (Scheme 6), which indicates that C–H bond cleavage is unlikely involved in the TLS, though a small K_H/K_D ratio (1.2, repeated twice) was observed at the α position. The kinetic feature of this reaction represents another difference from the $Cu(OAc)_2$/TEMPO system,[17a] which has the α C–H cleavage as the TLS.

Scheme 6. Kinetic Isotope Effect Studies.



Based on the results of the kinetic study, further experiments have been carried out to probe the TLS and resting state of the catalyst. First, the induction period was found to be notably shortened under a higher concentration of DTBP. In addition, when first mixing CuTc and $CyPPh_2$ in benzene at 80 °C for 0.5 h and then adding the substrate and DTBP, the induction period still existed. However, when mixing CuTc, $CyPPh_2$ and DTBP at 80 °C first before adding the substrate,[29] no induction period was observed (for details, see Supporting Information). These results suggest that the copper (I) species, i.e. [LCu(I)OAc], is unlikely to be involved in the catalytic cycle. To examine whether the TLS involves participation of the lactone substrate, stoichiometric phosphine ligand, Cu(I)Tc and DTBP were first stirred at 80 °C for 1 h before reacting with substrate **1b** at room temperature, 40 °C and 50 °C, respectively (Eq 10). No desired desaturation product was observed with most substrate **1b** untouched in all these reactions after 24 h, which implies that the TLS should not be a step before the substrate enters the catalytic cycle. Considering the pseudo-zero order dependence with the substrate concentration as well as a small KIE at the α position and no KIE at the β position, we postulated that the

TLS could be a step after the α C–H deprotonation but before the β C–H cleavage, which also involves reaction with DTBP (due to the first order dependence on [DTBP]).



Proposed catalytic cycle. While some mechanistic details of this reaction remain unclear and still under investigation, the data above allow us to propose a hypothesis for the Cu-catalyzed desaturation of lactones (Fig. 4). Elegant mechanistic studies by Warren show that Cu(I) could react with DTBP to generate a LCu(II)O^{t}Bu species (**B**) and a *t*-butyl oxo-radical that can undergo quick combination with another equivalent of Cu(I) to give the same species **B**.[21e,f] This process is anticipated to be the reason for the induction period, which is consistent with a fact that higher [DTBP] shortened the induction period. The LCu(II)O^{t}Bu species **B** could then coordinate to the carbonyl substrate and promote the subsequent reversible deprotonation of the α-C–H bond. The resulting LCu(II)-enolate **D** or **E** could then react with DTBP to afford a Cu(III) intermediate **F** that undergoes fast oxidative elimination, according to Kochi's study,[27,30] to afford the desaturated product and ultimately regenerate the LCu(II)O^{t}Bu species **B**.[31]

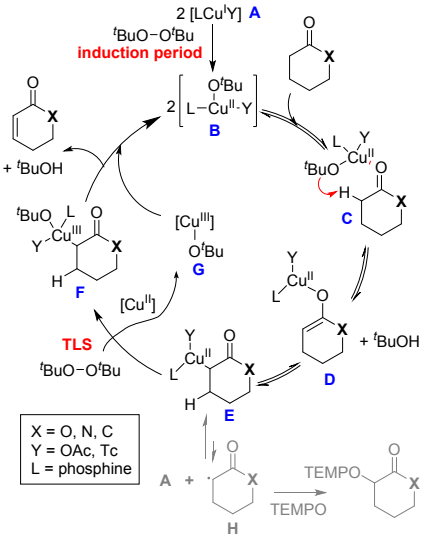


Figure 4. Proposed Simplified Catalytic Cycle

Based on the kinetic studies, the TLS is proposed to be the reaction between the LCu(II)-enolate and DTBP. This proposal is consistent with the KIE experiments (*vide supra*, Scheme 6), as the β C–H cleavage is expected to be after the TLS and the α C–H cleavage to be before the TLS and reversible (equilibrium isotope effect). In addition, peroxides are known to be capable of oxidizing Cu(II) to Cu(III),[32] though other pathways involving oxidation of the potential α radical intermediate **H** cannot be excluded at this stage. Consequently, the resting state of the catalyst is postulated to be the LCu(II)-enolate and/or other Cu(II) species (**B** or **C**), given that these species could all be in equilibrium. While it remains difficult to identify the exact Cu(II) species as the resting state(s),[33] EPR spectrum of the reaction mixture clearly indicated the existence of Cu(II) species (see Supporting Information). In addition, ESI high-resolution mass spec (HRMS) of the reaction mixture captured the masses of the Cu(II) species instead of Cu(I) or Cu(III) species (see Supporting Information). Taken together, all the data are consistent with the proposed reaction pathway. Finally, it is noteworthy that copper carboxylates often exist in a dimeric

form,[34] thus it is highly possible that dinuclear copper species are involved and the actual catalytic cycle is much more complex. Further detailed characterization of the reaction intermediates is underway.

Conclusion

In summary, the development of a Cu-catalyzed desaturation of lactones, lactams and cyclic ketones is described. The reaction does not require stoichiometric strong bases or acids, and is sulfur/selenium-free, showing high functional group tolerance. It uses a first-row transition-metal catalyst and an inexpensive reagent with *t*-butanol formed as the only stoichiometric byproduct. In addition, this method is scalable, operationally simple, and avoids over-oxidation. Preliminary mechanistic studies reveal an unusual reversible deprotonation of the carbonyl α C−H bonds, radical character of the copper enolate intermediate, and a critical role of the DTBP oxidant. Future efforts will involve further enhancement of the reaction efficiency and substrate scope through catalyst design and better understanding of the structure and reactivity of the copper enolate intermediate.

ASSOCIATED CONTENT

Text, figures, tables, and CIF files giving experimental procedures, kinetics data, and crystallographic information. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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