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Catalytic Cyclopropanol Ring Opening for Divergent Syntheses of γ-Butyrolactones and δ-Ketoesters Containing All-Carbon Quaternary Centers

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Supporting Information Placeholder

ABSTRACT: Catalytic ring opening cross coupling reactions of strained cyclopropanols have been useful for the syntheses of various β-substituted carbonyl products. Among these ring opening cross coupling reactions, the formation of α,β-unsaturated enone byproducts often competes with the desired cross coupling processes and has been a challenging synthetic problem to be addressed. Herein, we describe our efforts in developing divergent syntheses of a wide range of γ-butyrolactones and δ-ketoesters containing all-carbon quaternary centers via copper-catalyzed cyclopropanol ring opening cross couplings with 2-bromo-2,2-dialkyl esters. Our mechanistic studies reveal that unlike the previously reported cases, the formation of α,β-unsaturated enone intermediates is actually essential for the γ-butyrolactone synthesis and also contributes to the formation of the δ-ketoester product. The γ-butyrolactone synthesis is proposed to go through an intermolecular radical conjugate addition to the in situ generated α,β-unsaturated enone followed by an intramolecular radical cyclization to the ester carbonyl double bond. The reactions are effective to build all-carbon quaternary centers and have broad substrate scope.

KEYWORDS: *cyclopropanol, copper catalysis, ring opening, γ-butyrolactone, δ-ketoester, α,β-unsaturated enone, quaternary carbon*

INTRODUCTION

Cyclopropanols, readily available from the Kulinkovich protocol or the Simmons-Smith reaction, are prone to undergo various ring expansion[1] and ring opening[2] reactions due to the intrinsic strain in the three-membered ring system. For example, cyclopropanol ring opening cross coupling reactions promoted by various transition metal catalysts[3] or single electron transferring (SET) oxidants[4] have been utilized to synthesize a wide range of β-substituted ketone products including those embedded in complex natural products and life-saving drug molecules (Figure 1A). In general, these processes go through either a metallo-homoenolate (**2**) or a β-alkyl radical intermediate (**3**) and substituents including aryl, alkyl, alkynyl, alkenyl, acyl, halogen, nitrile, azide, amine, and others can be installed at the β-carbon (cf. **4**). In these ring opening cross coupling processes, transition metal such as palladium-promoted β-H elimination[5] of the metallo-homoenolate **2** and over oxidation[6] of the β-alkyl radical intermediate **3** are two serious competing reaction pathways that can result in the formation of α,β-unsaturated enone byproducts (**5**). Many efforts have been invested to avoid these side reaction pathways and prevent the formation of the enone byproducts. For example, various ligands have been used to suppress the β-H elimination process in palladium-catalyzed cyclopropanol ring opening cross couplings.[7]

To address the issues of α,β-unsaturated enone byproduct formation, we have developed a series of copper-catalyzed cyclopropanol ring opening cross coupling reactions such as trifluoromethylation, trifluoromethylthiolation, amination, and (fluoro)alkylation (Figure 1B).[8] The use of copper catalysts helps to reduce the formation of the enone products in these oxidative ring opening cross couplings because copper catalysts are less prone to β-H elimination in comparison to palladium catalysts. We also developed a novel palladium-catalyzed cyclopropanol ring opening carbonylation to synthesize oxaspirolactions[9] as well as manganese-mediated oxidative cyclopropanol ring opening tandem radical cyclizations to synthesize *N*-heterocycles.[10] In the carbonylation chemistry, the β-H elimination process is reduced because carbon monoxide can occupy the empty orbitals on the palladium center which are required for β-H elimination. In the manganese-mediated oxidative cyclopropanol ring opening radical cyclizations, highly reactive radical acceptors such as isonitriles and electron-deficient double bonds were used to trap the β-alkyl radical intermediate generated in situ before over oxidation or dimerization occurs.

In our continuing interest of developing copper-catalyzed cyclopropanol ring opening cross coupling reactions, we wondered the possibility of building all-carbon quaternary centers via cyclopropanol ring opening alkyl-alkyl cross couplings with 2-bromo-2,2-dialkylesters (Figure 1C). All-carbon quaternary centers, while prevalently exist in many functional molecules including bioactive natural products, small-molecule therapeutics, and agrochemicals, still present a challenge for synthetic chemists.[11] Alkyl-alkyl cross coupling reactions to build all-carbon quaternary centers are rare and various side reaction pathways can compete with the desired coupling. By finely tuning the reaction conditions, we not only realized the desired cross coupling reaction to synthesize δ-ketoesters (cf. **9**) containing all-carbon quaternary centers, but also discovered a novel γ-butyrolactone synthesis (cf. **8**) via a tandem sequence of C-C bond cleavage followed by C-C and C-O formations. Our mechanistic studies indicate that unlike the previously reported cross coupling reactions which occur via a metallo-homoenolate (**2**) or a β-alkyl radical intermediate (**3**), the formation of γ-butyrolactones is likely to go through the α,β-unsaturated enone intermediate (cf. **5**) derived from the corresponding cyclopropanol start material followed by copper-catalyzed conjugate addition and oxidative lactone formation. Herein, we report the details of our research efforts.

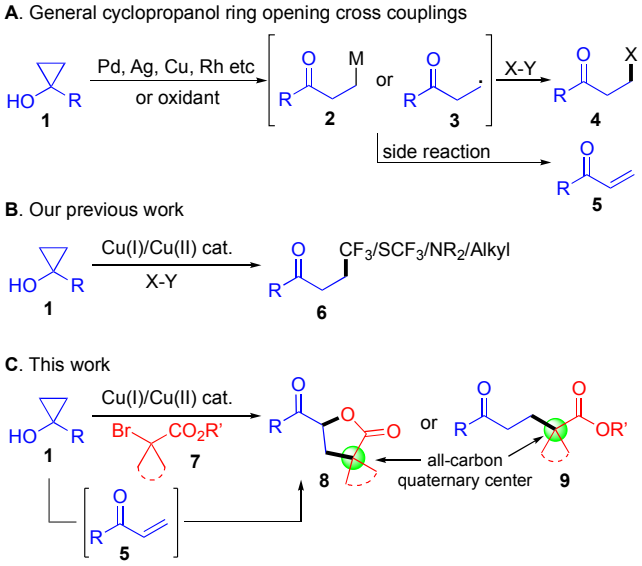
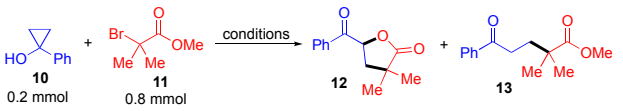


Figure 1. Prior arts and this work.

RESULTS

Reaction Condition Optimization

Our investigation started with 1-phenyl-1-cyclopropanol **10** and methyl 2-bromo-2,2-dimethyl acetate **11** (Table 1). Upon the treatment of **10** (0.2 mmol) and **11** (0.8 mmol) with CuI (0.1 equiv.) as catalyst, phenanthroline (Phen, 0.2 equiv.) as ligand, and K_2CO_3 (2.0 equiv.) as base in MeCN at 80 °C for 12 h, the reaction conditions we established for our previous cyclopropanol ring opening fluoroalkylation process,[8c] surprisingly, γ-butyrolactone **12** was obtained as the main product in 27% yield with only a trace amount of cross coupling product **13** we were expecting. The structure of **12** was unambiguously confirmed by x-ray crystallography analysis.[12] The unexpected formation of γ-butyrolactone **12** was very exciting because this process not only built a C-C bond with an all-carbon quaternary center, but also a C-O bond to form a γ-butyrolactone. At this stage, we speculated that the formation of **12** might be a continued copper-catalyzed formal C-H oxidative lactonization[13] after the formation of **13**, which was eventually proved not to be the case as we continued our investigation. Nevertheless, this interesting observation as well as the importance of γ-butyrolactones in natural products and other bioactive molecules[14] prompted us to establish a general procedure to enable efficient access of γ-butyrolactone products from readily available cyclopropanols and α-bromoesters directly. Our continuing reaction condition optimization revealed that the addition of 1.0 equiv. of KI dramatically increased the yield for the formation of **12** (63%) and **13** (10%, entry 2). After evaluating different bases, copper catalysts, and ligands, we learned that (i) K_2CO_3 was superior to other bases such as $KHCO_3$, Na_2CO_3, $NaHCO_3$, and Cs_2CO_3; (2) $Cu(OTf)_2$ was more effective than CuI, $CuCl_2$, and CuBr; (3) Phen was better than other nitrogen-based chelating ligands (**L1-6**) we explored. Slightly increase the amount of **11** to 4.5 equiv. was able to enhance the formation of **12** in 82% yield (80% isolated yield) and reduce the formation of **13** to 6% yield (entry 16). The need for an excess amount of **11** is because it serves as both the cross coupling partner and the terminal oxidant in the lactonization process. During these investigations, we also learned that switch base from K_2CO_3 to KOAc (entry 17) produced **13** as the major product in 64% yield with 9% of **12**. This observation offered an opportunity to develop a divergent approach to produce either **12** or **13** as the dominant product as needed. We then switched to organic bases and discovered that the yield of **13** could be improved to 71% with diisopropylamine (iPr_2NH, entry 18). After a quick evaluation of several copper catalysts and ligands and reducing the amount of **11** to 3.0 equiv., product **13** was produced in 78% yield (73% isolated yield, entry 25) with 12% yield of **12** by using a combination of CuCl (0.1 equiv.) and **L5** (0.2 equiv.). Further decreasing the amount to **11** to 2.0 equiv. only slightly reduced the yield of **13** to 75% (entry 26). Products **12** and **13** can be separated readily by flash column chromatography on silica gel.



entry	reaction conditions (equiv.)	yield **12**[a]	**13**[a]
1	CuI (0.1), Phen (0.2), K_2CO_3 (2.0), MeCN, 80 °C	27%	trace
2	CuI (0.1), Phen (0.2), K_2CO_3 (2.0), KI (1.0), MeCN, 80 °C	63%	10%
3	CuI (0.1), Phen (0.2), $KHCO_3$ (2.0), KI (1.0), MeCN, 80 °C	47%	16%
4	CuI (0.1), Phen (0.2), Na_2CO_3 (2.0), KI (1.0), MeCN, 80 °C	48%	14%
5	CuI (0.1), Phen (0.2), $NaHCO_3$ (2.0), KI (1.0), MeCN, 80 °C	31%	15%
6	CuI (0.1), Phen (0.2), Cs_2CO_3 (2.0), KI (1.0), MeCN, 80 °C	34%	16%
7	$CuCl_2$ (0.1), Phen (0.2), K_2CO_3 (2.0), KI (1.0), MeCN, 80 °C	56%	8%
8	CuBr (0.1), Phen (0.2), K_2CO_3 (2.0), KI (1.0), MeCN, 80 °C	53%	12%
9	$Cu(OTf)_2$ (0.1), Phen (0.2), K_2CO_3 (2.0), KI (2.0), MeCN, 80 °C	74%	6%
10	$Cu(OTf)_2$ (0.1), L1 (0.2), K_2CO_3 (2.0), KI (1.0), MeCN, 80 °C	51%	5%
11	$Cu(OTf)_2$ (0.1), L2 (0.2), K_2CO_3 (2.0), KI (1.0), MeCN, 80 °C	40%	5%
12	$Cu(OTf)_2$ (0.1), L3 (0.2), K_2CO_3 (2.0), KI (1.0), MeCN, 80 °C	27%	10%
13	$Cu(OTf)_2$ (0.1), L4 (0.2), K_2CO_3 (2.0), KI (1.0), MeCN, 80 °C	12%	12%
14	$Cu(OTf)_2$ (0.1), L5 (0.2), K_2CO_3 (2.0), KI (1.0), MeCN, 80 °C	64%	10%
15	$Cu(OTf)_2$ (0.1), L6 (0.2), K_2CO_3 (2.0), KI (1.0), MeCN, 80 °C	23%	11%
16[b]	**$Cu(OTf)_2$ (0.1), Phen (0.2), K_2CO_3 (2.0), KI (2.0), MeCN, 80 °C**	**82%(80%)**	**6%**
17	CuI (0.1), Phen (0.2), KOAc (2.0), KI (1.0), MeCN, 80 °C	9%	64%
18	CuI (0.1), Phen (0.2), iPr_2NH (2.0), KI (1.0), MeCN, 80 °C	15%	71%
19	CuCl (0.1), Phen (0.2), iPr_2NH (2.0), KI (1.0), MeCN, 80 °C	15%	75%
20	$CuCl_2$ (0.1), Phen (0.2), iPr_2NH (2.0), KI (1.0), MeCN, 80 °C	17%	69%
21	CuBr (0.1), Phen (0.2), iPr_2NH (2.0), KI (1.0), MeCN, 80 °C	17%	68%
22	$Cu(OTf)_2$ (0.1), Phen (0.2), iPr_2NH (2.0), KI (1.0), MeCN, 80 °C	14%	6%
23	CuCl (0.1), L1 (0.2), iPr_2NH (2.0), KI (1.0), MeCN, 80 °C	13%	64%
24	CuCl (0.1), L5 (0.2), iPr_2NH (2.0), KI (1.0), MeCN, 80 °C	14%	77%
25[c]	**CuCl (0.1), L5 (0.2), iPr_2NH (2.0), KI (1.0), MeCN, 80 °C**	**12%**	**78%(73%)**
26[d]	CuCl (0.1), **L5** (0.2), iPr_2NH (2.0), KI (1.0), MeCN, 80 °C	8%	75%

[a]Yield by NMR with trimethoxybenzene as internal reference and isolated yield in parenthesis; 12 h reaction time; [b]4.5 equiv. **11**; [c]3.0 equiv. **11**; [d]2.0 equiv. **11**.

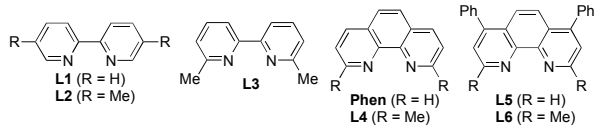


Table 1. Reaction condition optimization.

Substrate Scope

With a divergent strategy established to access either the γ-butyrolactone or δ-ketoester products, the substrate scope study of both transformations was subsequently conducted (Table 2 and Table 3). For the syntheses of γ-butyrolactones, the reaction has a broad substrate scope and tolerates a variety of functional groups. A wide range of 1-arylcyclopropanol substrates underwent the desired cross coupling and lactonization to afford the corresponding γ-butyrolactone products. Functional groups such as ketone, lactone, fluoride (**14**), iodide (**15**), benzyl ether (**17**), tosylate (**19**), sulfonamide (**20**) and carbamate (**25**) are well tolerated. Heteroaromatics including pyrrole (**22**), furan (**23**), indole (**24**, **25**), and thiophene (**27**) are compatible as well. In general, substrates with an electron-neutral or electron-rich aryl group gave higher reaction yield than electron-deficient ones (cf. **16**). 1-Alkylcyclopropanol is effective as well, but it requires an all carbon quaternary center at the α-position of the newly formed ketone (**30**). For the case of **31**, a mixture of diastereomers (1.2:1) was obtained.

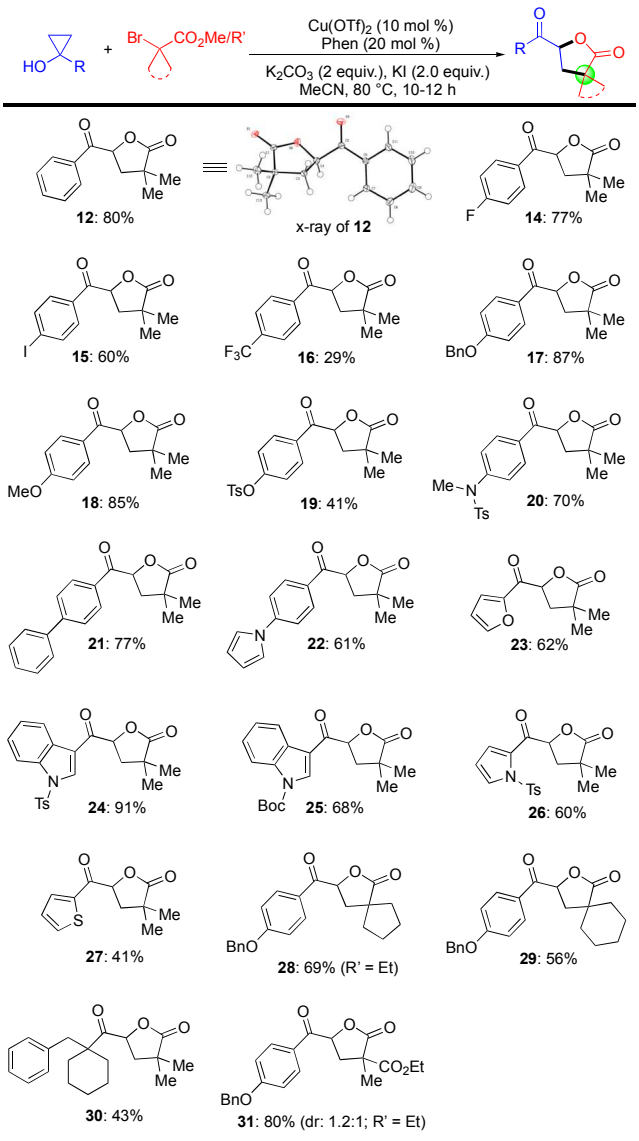


Table 2. Substrate scope for the γ-butyrolactone synthesis.

The substrate scope for the synthesis of δ-ketoester is even broader than the γ-butyrolactone synthesis (Table 3). In addition to 1-arylcyclopropanol and 1-heteroarylcyclopropanol substrates (with reaction condition **A**), which worked well for the γ-butyrolactone synthesis, various 1-alkyl substituted cyclopropanols are effective substrates as well (cf. **48**, **56**-**63**). For the latter, a modified reaction condition was used (reaction condition **B**), in which KI was removed and Phen was used to replace **L5**. Remote olefin (**62**) or conjugated enones (**54** and **55**) are tolerated. For the case of **55**, no electrocyclic cyclobutene ring opening product was observed. In addition to halogens, alkyl ethers, carbamates, and sulfonamides, more labile functional groups such as TBS-ether (**55** and **60**), benzoate (**59**), and free alcohol (**63**) are compatible under the relatively mild reactions.

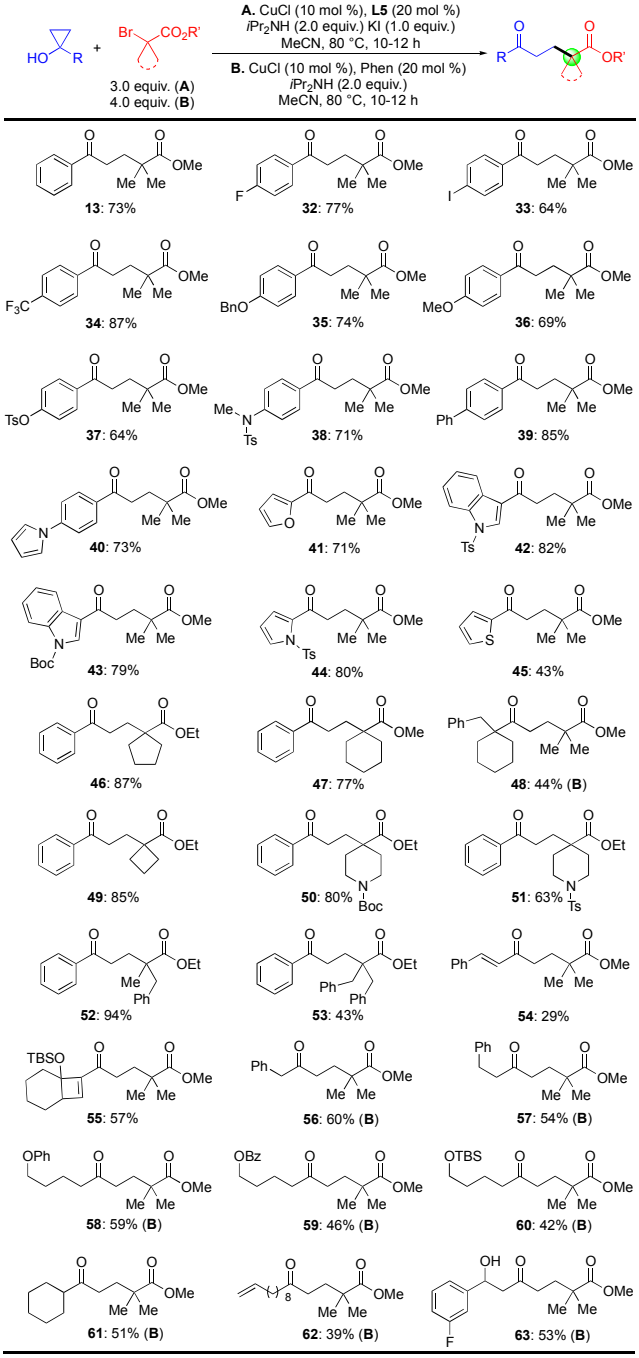


Table 3. Substrate scope for the δ-ketoester synthesis.

Mechanistic Studies

To provide insights about the reaction mechanisms of these two divergent synthetic transformations, a series of experiments were conducted (Figure 2). We initially speculated that the formation of the γ-butyrolactone product (cf. **18**) might be derived from the corresponding cyclopropanol ring opening cross coupling product (cf. **36**) via a formal α-C-H oxidative lactonization process; therefore, we treated purified **36** with the standard reaction conditions for the γ-butyrolactone synthesis (Eq. 1). However, we didn't observe the formation of γ-butyrolactone **18** and recovered **36** in 95% yield, which indicates that **18** was not derived from **36**. Another possibility for the formation of **18** might be from an α,β-unsaturated enone (cf. **64**), while the α,β-unsaturated enone formation is often considered as an undesired side reaction pathway in the previously reported transition metal-catalyzed cyclopropanol ring opening cross coupling reactions. Recently, Lei and coworkers reported an interesting nickel-catalyzed radical type addition of α-bromoesters to styrenes and α,β-unsaturated enones to form γ-butyrolactones.[15] Inspired by their discovery, we treated α,β-unsaturated enone **64** with α-bromoester **11** under the γ-butyrolactone formation conditions and γ-butyrolactone product **18** was produced in 70% yield (Eq. 2). This result supports that the formation of **18** is from enone **64**, not from δ-ketoester **36**. We then treated a mixture of **64** and **11** with the two standard cross coupling reaction conditions for the δ-ketoester synthesis (Table 3). The formation of both **18** and **36** were observed, but the yield for **36** was low and a significant amount of γ-butyrolactone product **18** was produced (Eq. 3). The product distribution is different from the results we obtained in Table 3, where **36** was produced as the major product. These observations indicate that the enone pathway only partially contributes to the formation of δ-ketoester **36** and the direct ring opening cross coupling between **66** and **11** without going through the enone intermediate is still the major pathway. This notion was corroborated by the reaction of enone **65** with **11** under the standard δ-ketoester formation condition **B** (Eq. 4), from which only 14% of the desired product **57** was obtained, significantly lower than the direct cross coupling result (57%, Table 3).

We then probed the controlling factors for the enone formation. We first treated cyclopropanol **66** with stoichiometric amount of $Cu(OTf)_2$/Phen with K_2CO_3 as base (Eq. 5). Ethyl ketone **67**, a cyclopropanol ring opening protonation product, was produced along with dimeric product **68** and other unidentifiable products, but enone **64** was not one of them. We then added KI to the reaction mixture (Eq. 6). In this case, we did observe the formation of enone **64** in 28% yield together with 18% of dimer **68** and 30% of recovered **66**. This result indicates that KI is facilitating the formation of the enone intermediate, presumably via β-iodoketone intermediate **69** followed by a base-promoted elimination. K_2CO_3 was then removed from the reaction system (Eq. 7). Without the base, after 1 h reaction, **69** was detected as the major product (30-40% yield based on crude NMR analysis) in the reaction mixture and it underwent rapid elimination on silica gel column to give enone **64**. Additionally, when cyclopropanol **66** was treated with stoichiometric amount of CuCl/Phen without base and KI (Eq. 8), most of **66** could be recovered with 18% of **67** and 16% of **68**, but no enone **64** formation. The involvement of β-iodoketone intermediate **69** was further confirmed by the fact that γ-butyrolactone product **18** was obtained after subjecting **69** to the reaction conditions of $Cu(OTf)_2$/Phen with K_2CO_3 in MeCN at 80 °C (Eq. 9).

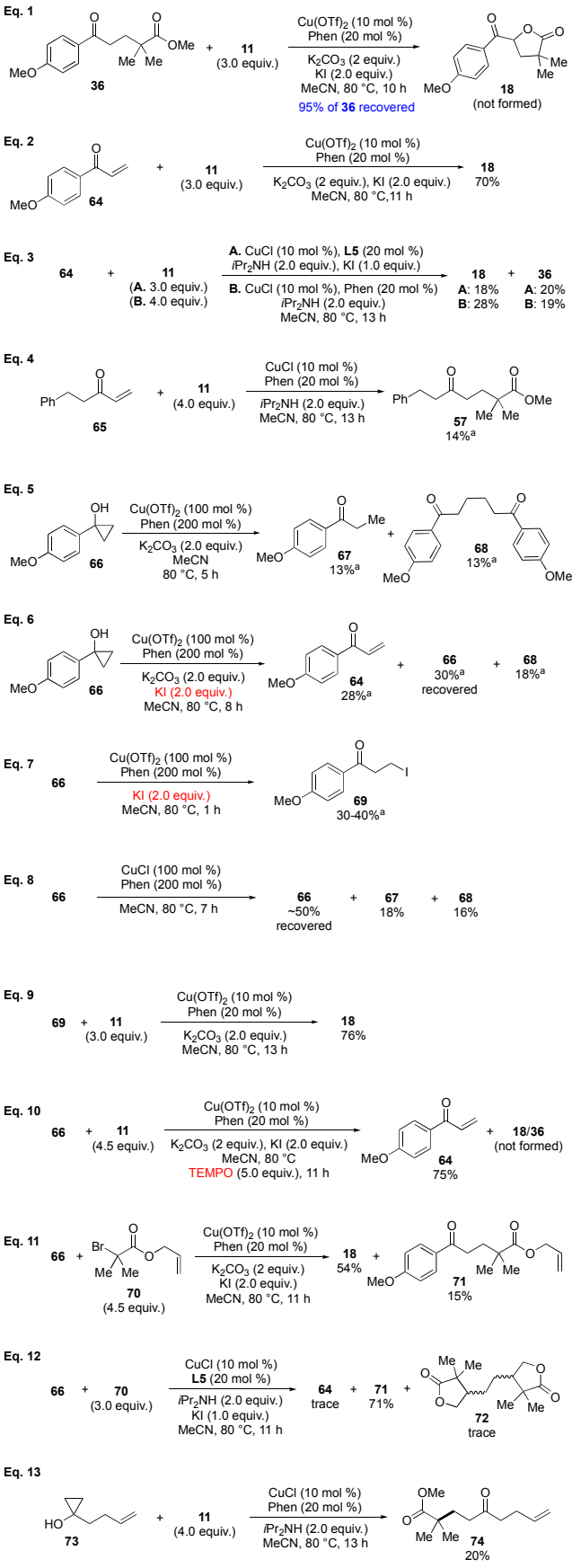


Figure 2. Mechanistic studies. [a]Yield based on ^{1}H NMR analysis with 1,3,5-trimethoxybenzene as internal reference.

Our further investigation showed that both the direct cross coupling pathway and γ-butyrolactone formation pathway are inhibited by TEMPO (Eq. 10). In this case, enone **64** was produced in 75% yield. TEMPO may interfere with the β-alkyl radical intermediate generated from **66** or the α-alkyl radical (cf. **F**, Figure 3) derived from **11**. The former could still result in enone **64** via a subsequent base-promoted elimination of the β-TEMPO-ketone intermediate. Copper-catalyzed α-alkyl radical formation from α-bromoester such as **11** has been commonly proposed and widely used in organic synthesis[16] and polymer synthesis.[17] We then prepared allyl α-bromoester **70** to probe this process and were expecting that the α-radical could be intercepted by the intramolecularly tethered double bond via a 5-*exo*-*trig* cyclization process. Interestingly, under the standard γ-butyrolactone synthesis conditions, desired γ-butyrolactone **18** was formed 54% yield along with δ-ketoester **71** in 15% yield (Eq. 11). When **70** was subjected to the standard δ-ketoester synthesis conditions (Eq. 11), **71** was obtained in 71% yield with a trace amount of **64** and dimer **72** detected. The observation of **72** suggests the α-radical formation, but the α-radical reacts faster with enone **64** generated in situ or the copper-homoenolate derived from **66** to provide desired product **18** or **71** as the dominant ones. The involvement of copper-homoenolate was supported by the formation of product **74** from cyclopropanol **73** which contains an intramolecularly tethered olefin for a potential 6-*exo*-*trig* radical cyclization. Since the yield of **74** is low (20%) and the reaction is quite complex, the formation of a β-alkyl radical (cf. **B**, Figure 3) cannot be completely eliminated.

Based on the above experimental results, a plausible reaction mechanism was proposed in Figure 3 by using **10** and **11** as model substrates. The catalytic cycle is expected to start with a Cu^{II} species derived from $Cu(OTf)_2$ or oxidation of CuCl by **11**. Ligand exchange with cyclopropanol **10** would generate alkoxide intermediate **A**, which would undergo a ring opening process to provide β-alkyl radical **B** (potentially stabilized by the resulting Cu^{I}) or copper-homoenolate **C**. **B**/**C** could then react with KI to form β-iodoketone **D**. Base (K_2CO_3 or iPr_2NH)-promoted elimination would convert **D** to enone **E**. The latter would react with radical intermediate **F** derived from the reaction of Cu^{I} with **11** to form a new radical intermediate **H**. At this stage, the involvement of copper-enolate **G** cannot be ruled out. Intermediate **H** would then undergo two possible pathways to form carbocation intermediate **K**, then to product **12** after the loss of a methyl group. The first pathway would involve an addition of the α-radical of **H** to the ester carbonyl π-bond to form a new carbon-centered radical **I** which is stabilized by the two adjacent oxygen atoms. This electron rich radical would be readily oxidized to carbocation **K** by Cu^{II} in the reaction system. The other pathway would involve a Cu^{II}-mediated oxidation of radical intermediate **H** to carbocation **J**. Nucleophilic attack of the newly formed carbocation by the carbonyl group of the ester would give rise to **K**. While plausible, the oxidation of radical **H** to **J** with a carbocation right next to an electron-withdrawing ketone would require much higher energy than the radial cyclization pathway.[15] Additionally, radical **H** could be quenched by a hydrogen abstraction process to provide δ-ketoester product **13**, but this is not the major pathway for the formation of **13**. Under the δ-ketoester formation conditions, the majority of the δ-ketoester is likely to be obtained via a direct cross coupling reaction between **B**/**C** and **F**/**G**.

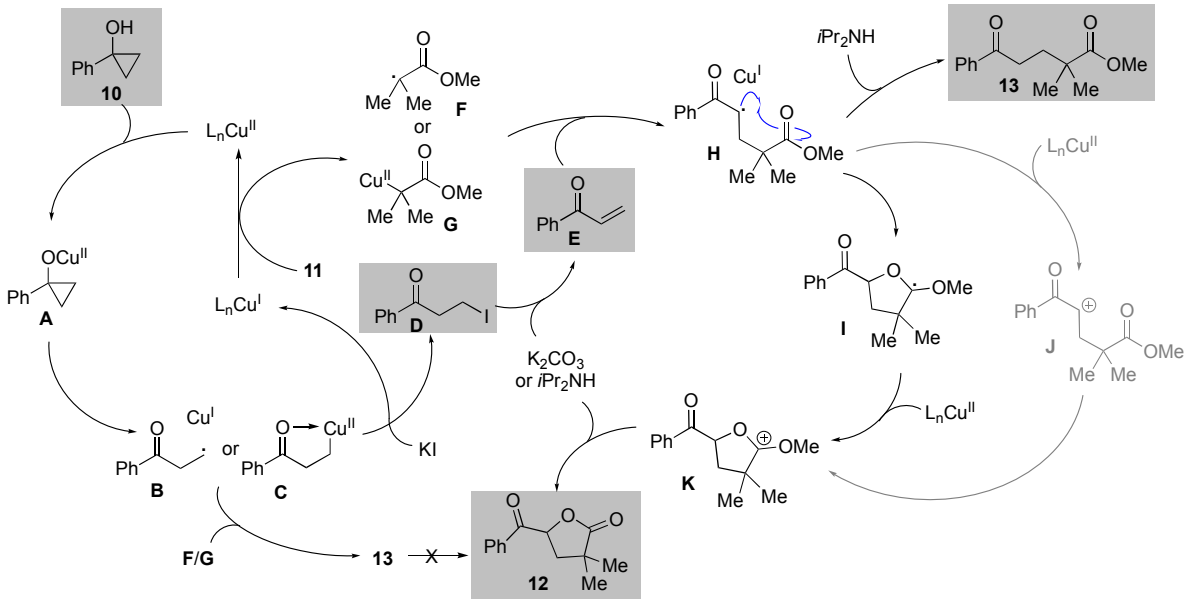


Figure 3. Proposed reaction mechanism for the formation of **12** and **13**.

CONCLUSIONS

In summary, we have developed two divergent copper-catalyzed cyclopropanol ring opening reactions to form either δ-ketoesters or γ-butyrolactones. The reaction conditions are mild and tolerate a wide range of functional groups. Our mechanistic studies revealed an unprecedented reaction mechanism involving the formation of enone intermediate, which is often considered as one of the main byproducts in many cyclopropanol ring opening reactions. This novel reaction mechanism is expected to guide the development of new cyclopropanol ring opening reactions and to provide mechanistic insights about some of the existing transition metal catalyzed cyclopropanol ring opening reactions.

EXPERIMENTAL

γ-Butyrolactone synthesis procedure:

A mixture of the cyclopropanol substrate (0.2 mmol), 2-bromo-2,2-dialkylester (0.9 mmol), $Cu(OTf)_2$ (7.2 mg, 0.02 mmol), Phen (7.2 mg, 0.04 mmol), K_2CO_3 (55.2 mg, 0.4 mmol), and KI (66.4 mg, 0.4 mmol) was dissolved in MeCN (2 mL) and stirred at 80 °C for 10-12 h. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2 (30 mL) for three times. The combined organic extract was then washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography with hexane and ethyl acetate as eluents to provide the desired γ-butyrolactone product.

δ-Ketoester synthesis procedure:

Condition A: A mixture of the cyclopropanol substrate (0.2 mmol), 2-bromo-2,2-dialkylester (0.6 mmol), CuCl (2.0 mg, 0.02 mmol), **L5** (13.2 mg, 0.04 mmol), iPr_2NH (56μL, 0.4 mmol), and KI (33.2 mg, 0.2 mmol) was dissolved in MeCN (2 mL) and stirred at 80 °C for 10-12 h. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2 (30 mL) for three times. The combined organic extract was then washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography with hexane and ethyl acetate as eluents to provide the desired δ-ketoester product. **Condition B**: **L5** was replaced with **Phen** and KI was removed from the reaction system. The rest remains the same as described in condition A.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information including experimental procedures and compound characterization is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.xxxxx.

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Notes

The authors declare no competing financial interests.

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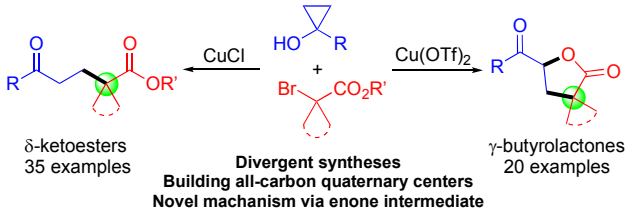
CuCl
Cu(OTf)2
HO
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Br
CO2R'
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OR'
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δ-ketoesters
35 examples
γ-butyrolactones
20 examples
Divergent syntheses
Building all-carbon quaternary centers
Novel machanism via enone intermediate