

Copper-Catalyzed Intermolecular Oxidative [3 + 2] Cycloaddition between Alkenes and Anhydrides: A New Synthetic Approach to γ -Lactones

Liangbin Huang, Huanfeng Jiang,* Chaorong Qi, and Xiaohang Liu

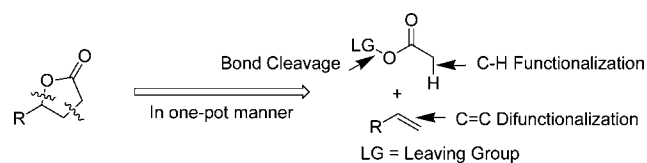
School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou 510640, P. R. China

Received July 10, 2010; E-mail: jianghf@scut.edu.cn

Abstract: A new copper-catalyzed oxidative [3 + 2] cycloaddition of alkenes with anhydrides using oxygen as the sole oxidant to afford γ -lactones has been developed. This catalyzed cyclization process has a broad substrate scope and affords γ -lactones in good to excellent yields.

The discovery of new transformations through olefin difunctionalization continues to attract broad interest because of their high potential for application in natural product and bioactive compound synthesis.^{1,2} Recent progress in this specific area has been made with respect to carboamination,^{3–6} carboetherification,^{7,8} carbohalogenation,^{9,10} and carboesterification¹¹ of alkenes. It is surprising, however, that among these difunctionalization reactions, few can achieve the formation of C(sp³)–C(sp³) bonds,^{11–13} despite their ubiquitous nature. To address this issue, we envisioned using cheap acetic anhydride as a carboesterification agent for the alkene difunctionalization under copper catalysis,¹⁴ that is, copper-mediated intermolecular cycloaddition with subsequent C(sp³)–H/C–O bond cleavage and C(sp³)–C(sp³)/C–O bond formation would provide an expedient route to diverse lactone rings from simple precursors (Scheme 1).^{12,15,16}

Scheme 1



Our initial investigations of Cu-catalyzed carboesterification of olefins focused on the cycloaddition of acetic anhydride to styrene (**1a**). To our delight, when **1a** was treated with 10 mol % Cu(OTf)₂, 30 mol % LiBr, and 1 equiv of NaOAc in 2 mL of Ac₂O, carboesterification of styrene indeed proceeded readily under 1 atm air at 100 °C to give the γ -lactone product **2a** in moderate yield (Table 1, entry 1). Further investigation of the additives led to the discovery that LiBr was the best halide for this reaction (entries 2–5).¹⁷ The reaction did not occur without Cu(OTf)₂ or O₂ (entries 6 and 7). Elevating the temperature to 120 °C and running the reaction under 1 atm O₂ increased the yield to 88% (entries 8 and 9).¹⁸ When *tert*-butylhydroperoxide (TBHP) or 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) was used as the oxidant, benzaldehyde was obtained instead of the γ -lactone product **2a** and up to 30% of the styrene was recovered. When the solvent was changed to AcOH, the yield of **2a** dropped to zero. Screening of other copper salts, solvents, and bases showed that both copper(I) and copper(II) were effective in the catalysis and that use of the anhydride as the solvent was essential (see the Supporting Information).

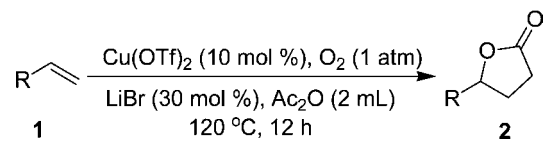
Table 1. Screening of Reaction Conditions^a

entry	catalyst	additive	oxidant	temp (°C)	yield (%) ^b
1	Cu(OTf) ₂	LiBr	air	100	62
2	Cu(OTf) ₂	NaBr	air	100	57
3	Cu(OTf) ₂	NBu ₄ Br	air	100	42
4	Cu(OTf) ₂	–	air	100	nr
5	Cu(OTf) ₂	KI	air	100	nr
6	–	LiBr	air	100	nr
7	Cu(OTf) ₂	LiBr	– ^c	100	nr
8	Cu(OTf) ₂	LiBr	air	120	73
9	Cu(OTf) ₂	LiBr	1 atm O ₂	120	88 (86)
10	Cu(OTf) ₂	LiBr	TBHP	120	0
11	Cu(OTf) ₂	LiBr	DDQ	120	0
12 ^d	Cu(OTf) ₂	LiBr	1 atm O ₂	120	0

^a Reaction conditions: All reactions were performed with **1a** (1 mmol) and Cu catalyst (10 mol %) under air with NaOAc (1 equiv) and the additive (30 mol %) in 2 mL of Ac₂O for 12 h. ^b Determined by GC. The value in parentheses is an isolated yield. ^c Under a N₂ atmosphere. ^d Using 2 mL of AcOH as the solvent.

Subsequently, we explored the generality of the reaction with other alkenes under the optimized conditions. As shown in Table 2, the desired reaction products were synthesized in generally high yields. A series of para-substituted styrenes, including both electron-withdrawing groups (Table 2, entries 1–3) and a weakly electron-donating group (entry 4), were converted into their corresponding γ -lactones in excellent yields. Moreover, 1-methoxy-4-vinylbenzene with the strongly electron-donating methoxy group afforded the corresponding γ -lactone **2f** in 76% yield (entry 5). Increasing the steric demand ortho to the vinyl group by substitution with a methyl group afforded high yield of **2h** (entry 7). Even the slightly sterically demanding 1,1-disubstituted olefin **1i** offered **2i** in 79% yield (entry 8). To our delight, highly electron-deficient 1,2,3,4,5-pentafluoro-6-vinylbenzene also provided a good result (entry 10). It is especially worth mentioning that when conjugated dienes were employed as substrates (entries 11 and 12), the desired products **2l** and **2m** were isolated in 87 and 93% yield, respectively, with exclusive selectivity toward the terminal olefin. The generality of this unique transformation was also demonstrated by the successful carboesterification of a linear aliphatic alkene (83% yield; entry 13) and 1-(but-3-en-1-ynyl)benzene (71% yield; entry 14). Unfortunately, the nonterminal olefin **1p** failed to afford the desired product (entry 15).

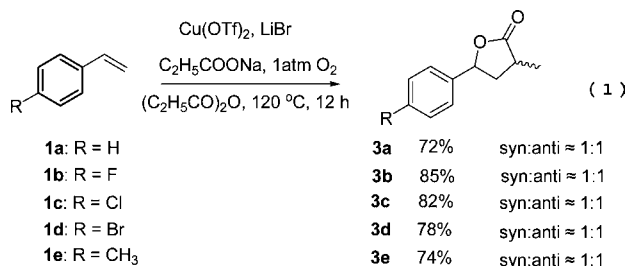
Importantly, when propionic anhydride was used as the substrate, acceptable yields of γ -lactones were obtained, although the syn/anti ratio was ~1:1 (eq 1). This allows the selective synthesis of

Table 2. Substrate Scope of the Carboesterification of Alkenes with Acetic Anhydride^a


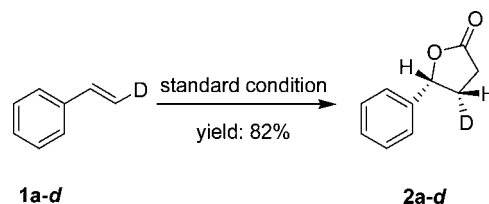
entry	alkene	product	yield ^b (%)
1			92
2			89
3			90
4			85
5			76
6			92
7			82
8			79
9			90
10			73
11			87
12			93
13			83
14			71
15		-	nr

^a Reaction conditions: All reactions were performed with **1** (1 mmol), Cu catalyst (10 mol %), NaOAc (1 equiv), and LiBr (30 mol %) under 1 atm O₂ in 2 mL of Ac₂O at 120 °C for 12 h. ^b Isolated yield.

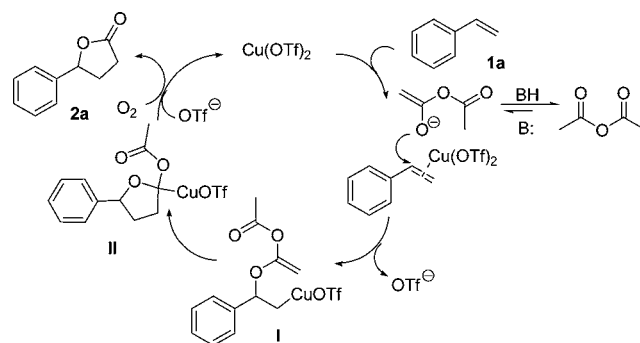
α,γ-disubstituted γ-lactones simply by choosing the correct olefins and anhydrides.



In order to obtain information about oxycupration process, stereospecifically deuterium-labeled styrene (*E*)-**1a-d** was prepared (see the Supporting Information) and then cyclized using acetic anhydride under the standard conditions (Scheme 2). The reaction afforded a single stereoisomer of product **2a-d**, and the ¹H NMR resonance at *J* = 7.2 Hz for the trans isomer was absent while the ¹H NMR resonance at *J* = 6.8 Hz for the cis isomer was still present, indicating that oxycupration proceeded with overall cis selectivity.

Scheme 2. Labeling Experiment Involving Styrene

On the basis of the above results and other experiments,¹⁹ a tentative mechanism for the Cu(II)-catalyzed intermolecular carboesterification of alkenes is proposed in Scheme 3. First, the Cu(OTf)₂ coordinates with alkene **1a** and the enol of the anhydride.²⁰ Subsequently, a cis oxycupration to form intermediate **I** is followed by the formation of **II** through intramolecular insertion into the enol.^{3,4,14e,21} Finally, with the aid of molecular oxygen, **II** affords the product **2a** and regenerates Cu(II) to complete the catalytic cycle.

Scheme 3. Tentative Mechanism for the Cu(II)-Catalyzed Carboesterification of Alkenes

In conclusion, we have developed a new Cu-catalyzed method for the formation of C(sp³)-C(sp³) and C-O bonds through carboesterification of alkenes with anhydrides, allowing the facile synthesis of γ-lactones. This catalyzed cyclization process uses oxygen as the sole oxidant, has a broad substrate scope, and affords γ-lactones in good to excellent yields. Ongoing research involves the extension of carboesterification to other substrates and further investigations of the synthesis of chiral lactone rings as well as detailed mechanistic studies. The results will be reported in due course.

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Note Added after ASAP Publication. Discussion of yield for compound **2h** has been corrected in the version reposted December 1, 2010.

Supporting Information Available: Experimental procedures and characterization of compounds **2a–o** and **3a–e**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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