Synlett M. Bandyopadhyay et al. Letter

Europium-Catalyzed Intramolecular Addition of Carboxylic Acid to Nonactivated Alkenes: An Efficient Route to Aryl-Substituted γ-Butyrolactone

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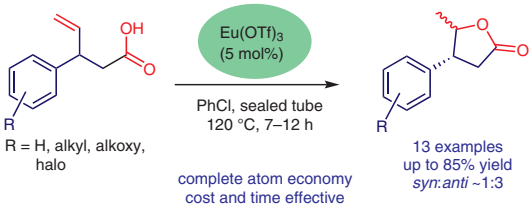

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Abstract Europium(III)triflate has been proved to be an effective catalyst for intramolecular cyclization of aryl-substituted carboxylic acid to afford arylated γ-butyrolactone. Various attractive features, such as broad substrate scope, a wide range of functional group tolerance, operational simplicity, complete atom economy, and good-to-excellent yields have made this new protocol more appealing. Moreover, this method provides a practical alternative to the existing catalysts.

Key words γ-butyrolactones, lanthanide catalyst [Eu(OTf)$_3$], ω-alkenoic acid, intramolecular hydroacyloxylation reaction, O-containing heterocycles

Oxygen heterocycles are important structural units frequently found in various natural products and medicinally important molecules. Tetrahydrofuran[1] and tetrahydropyran[2] rings are commonly found in lignin, macrolide, polyether antibiotic, and various food-flavoring agents.[3] γ-Butyrolactones decorated with various alkyl substituents and functional groups are widely observed in natural products, such as, (+)-whisky lactone, (+)-roccellaric acid, (–)-methylenolactocin, and halenalin (Figure 1); and many of them show significant biological activities.[4,5] γ-Butyrolactones are also considered as useful building blocks for many natural product[4a] syntheses. As a consequence, the synthesis of differently substituted γ-butyrolactone has drawn considerable attention[6] from organic chemists; and a variety of synthetic routes towards γ-butyrolactone has been reported. Amongst all the existing methods, transition-metal-catalyzed routes to butyrolactone via functionalization of nonactivated alkene are quite significant.[7] ω-Alkenoic acids/alcohols and their higher homologues are useful synthetic intermediates which can undergo intramolecular cyclization to afford cyclic lactones and ethers, respectively.

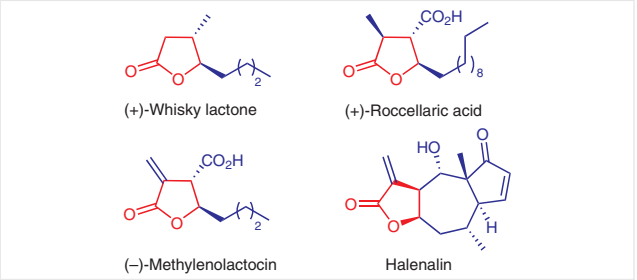

Figure 1 Butyrolactone-containing natural products

Generally, these atom-economical processes of nonactivated C=C bond functionalization are carried out by various transition-metal-catalyzed reactions.[7] Ag(I) triflate[7a] and Cu(II) triflate[7b,c] have been successfully used for intramolecular cyclization of both alkenoic alcohol and carboxylic acid leading to the corresponding ether and lactone, respectively (Scheme 1). Probably, the first example of metal-catalyzed synthesis of γ-butyrolactones was reported way back in 1978[7d] (Scheme 1) by Katzenellenbogen et al. They eventually revealed an efficient method for intramolecular lactonization of 1-pentynoic acid to γ-methylene-γ-butyrolactone catalyzed by Hg(II) catalyst.

Similarly, a wide range of transition metals are known to promote intramolecular hydroalkoxylation of nonactivated alkenes to afford saturated cyclic ethers. Intramolecular hydroalkoxylation of γ- and δ-hydroxy olefins have been successfully converted into cyclic ethers via Pt(II)-,[8a] Sn(IV)-,[8b] Ru(II)-,[8c] and Fe(III)-catalyzed[8d] methods. Even zero-valent gold nanocluster[8e] and Co(salen)[8f] complexes have also been successfully employed for the functionalization of nonactivated olefins. Recently, Nb-based catalytic systems[8g] and Ca(II)[8h] reagents were found to be efficient to promote hydrofunctionalization of nonactivated alkene offering various oxygen heterocycles including lactones.

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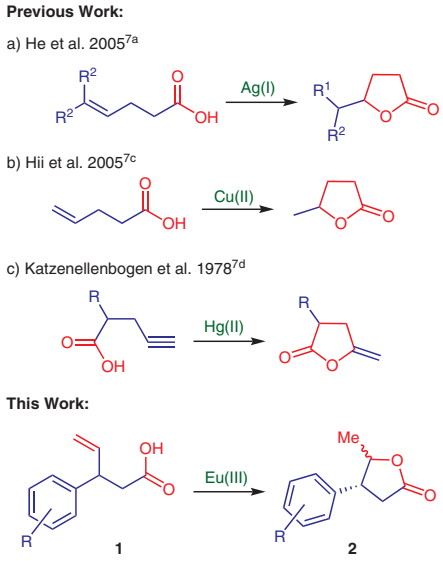


Scheme 1 Intramolecular hydroacyloxylation reaction leading to butyrolactone

Unlike the main group transition metals, rare-earth metals are less famous in the area of organic synthesis. Among all the rare-earth metals, only samarium[9] and scandium[10] reagents are widely used in various organic transformations. On the other hand, the synthetic potential of other lanthanide metal reagents have so far been understudied and consequently explored very little.[11] The rare-earth metal like europium (Eu) remains largely unexplored in organic synthesis; and the reports on its synthetic potential are still limited.[12] Herein, we report the first application of Eu(III) to mediate the conversion of 3-aryl-ω-alkenoic acids to γ-butyrolactone in this publication.

We initially have taken 3-phenyl-ω-alkenoic acid (**1a**) as our model compound; and the reaction was carried out in sealed tube at 120 °C in chlorobenzene as solvent. The catalyst Eu(III) triflate was loaded only with 5 mol%. It was our delight to see that the intramolecular OH addition to the terminal double bond to afford 3-phenyl-γ-butyrolactone (**2a**, Table 1) went smoothly, and clean conversion was observed, but clearly separable two spots were found on TLC. We anticipated that the cyclization process may furnish the mixture of two diastereomers due to the pre-existing aryl group at the 3-position of ω-alkenoic acid. The experimental results proved the anticipation to be true and well-founded. After separation of two diastereomers on silica gel column chromatography, we found that the major isomer was *anti* oriented, while the minor isomer was found to be the *syn* isomer. The ratio of *syn*/*anti* isomers for the same substrate under different reaction conditions was reported to be either the same or opposite to what we observed.

Table 1 Optimization of the Reaction Conditions

Entry	Catalyst	Amount (mol%)	Time (h)	Solvent[a]	Temp (°C)	Yield (%)[b]
1	$Sc(OTf)_3$	2	10	PhH	7 5	ca. 36
2	$Sc(OTf)_3$	2	22	PhCl	100	42
3	$Sc(OTf)_3$	5	36	PhCl	120	40
4	$Tb(OTf)_3$	5	15	MeCN	100	45
5	$Tb(OTf)_3$	5	15	PhCl	120	37
6[c]	$Eu(OTf)_3$	5	7	PhCl	120	70
7	$Eu(OTf)_3$	10	7	PhCl	120	51
8	TfOH	500	15	DCM	r.t	0
9	TfOH	2	24	DCM	40	0
10	TfOH	2	24	PhH	75	<30
11	TfOH	5	7	PhCl	120	<20
12[d,e]	$Eu(OTf)_3$	5	7	PhCl	120	0
13[d,f]	$Eu(OTf)_3$	5	7	PhCl	120	0

[a] Concentration of all solvents: 2.0 (M).
[b] Isolated yield.
[c] Optimized reaction conditions.
[d] Reactions using additives.
[e] 2 mol% of dppf.
[f] 2 mol% of Xantphos.

After reviewing the literature carefully, we have found that the *anti* product was the major product in case of Ag(I) triflate[7a] catalyzed intramolecular addition of alkenoic acid to inert olefin, whereas the *syn* isomer was the major product when the same reaction was promoted by Cu(II) triflate.[7c] Therefore, it could be an interesting issue to study the stereochemical outcome of this reaction under different transition-/rare-earth-metal-catalyzed conditions, when one aryl substituent is present at C-3 of ω-alkenoic acids. But surprisingly enough, no detailed study has been conducted till date. Therefore, we executed this reaction with differently substituted 3-aryl-ω-alkenoic acids under optimized reaction conditions and obtained the *anti*-oriented product as the major product in all cases.

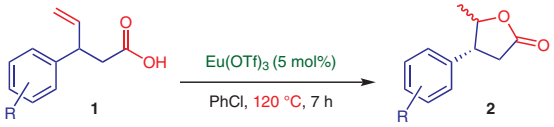
Moreover, under this newly developed conditions, the reaction needed much less time (8–12 h) compared to existing literature procedures (36–48 h).[7c] This may be considered as a major advantage of our newly found reaction conditions. The reaction was also tried with different transition-metal triflates which are not reported earlier for this particular transformation. Sc(III) triflate either in PhH or in PhCl (Table 1, entries 1–3) gave an incomplete conversion even after prolonged heating. Other transition-metal triflates like Tb(III) triflate were screened as catalysts in different solvents. The desired product was isolated but with dissatisfactory yields even after prolonged reaction times (entries 4 and 5).

Since silver and copper triflates were already reported in the literature for the similar reaction, we did not pay at-

tention to them. Best result was obtained by using 5.0 mol% of Eu(III) triflate heating at 120 °C (Table 1, entry 6). Even with an increased amount of catalyst loading (10 mol%), the yield did not improve (entry 7). Triflic acid was also screened as catalyst for this transformation in different solvents at varying temperature (Table 1, entries 8–11), but it failed to provide better result. Either no product was detected, or much inferior yield was obtained.

We were also interested to see whether any additives, like dppf, Xantphos (Table 1, entries 12 and 13), had any beneficial effect on the reaction. All the additives (2.0 mol%) were used under the standard reaction conditions, but none of them was found beneficial.

Table 2 Substrate Scope



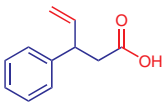
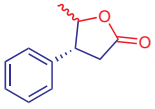
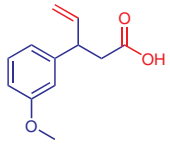
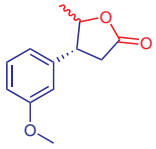
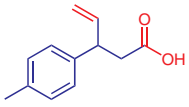
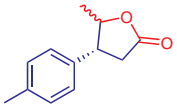
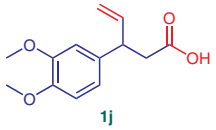
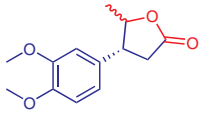
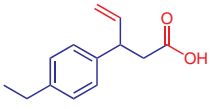
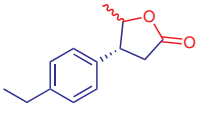
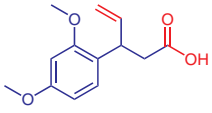
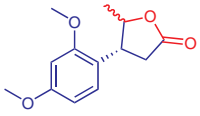
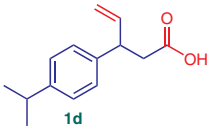
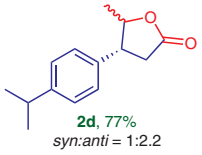
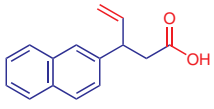
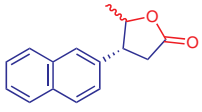
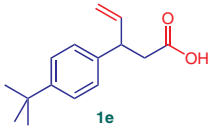
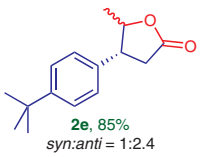
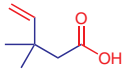
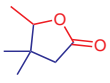
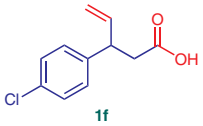
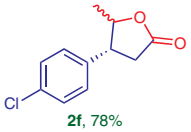
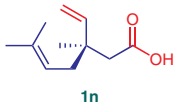
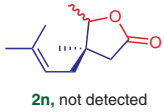
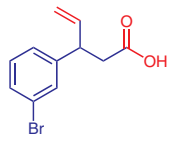
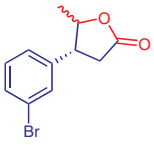
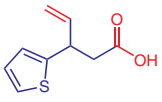
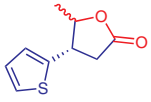
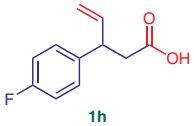
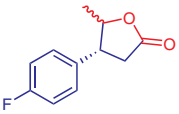
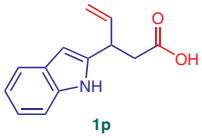
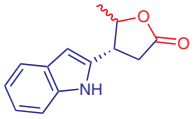
Substrate, product		Substrate, product	
 **1a**	 **2a**, 70% *syn:anti* = 1:2.2	 **1i**	 **2i**, 79% *syn:anti* = 1:2.7
 **1b**	 **2b**, 69% *syn:anti* = 1:2.8	 **1j**	 **2j**, 85% *syn:anti* = 1:2.6
 **1c**	 **2c**, 70% *syn:anti* = 1:2.1	 **1k**	 **2k**, 84% *syn:anti* = 1:2.7
 **1d**	 **2d**, 77% *syn:anti* = 1:2.2	 **1l**	 **2l**, 67% *syn:anti* = 1:1.9
 **1e**	 **2e**, 85% *syn:anti* = 1:2.4	 **1m**	 **2m**, 70%
 **1f**	 **2f**, 78% *syn:anti* = 1:2.6	 **1n**	 **2n**, not detected

Table 2 (continued)

Substrate, product		Substrate, product	
 **1g**	 **2g**, 85% *syn:anti* = 1:2.8	 **1o**	 **2o**, not detected
 **1h**	 **2h**, 83% *syn:anti* = 1:2.8	 **1p**	 **2p**, not detected

After having reached the standard reaction conditions (Table 1, entry 6), we focused our attention to exploring the substrate scope for this reaction. Differently substituted 3-aryl-ω-alkenoic acids (Table 2, 1a–m) were subjected to the optimum reaction conditions. It was observed that all the substrates (**2a**–**m**) were smoothly converted into the product γ-butyrolactones with good-to-excellent yield. It was also observed that the product ratio was always in favor of the *anti* isomer, and the ratio was found to be ca. 3:1 (*anti*/*syn*). We also examined the reaction protocol in the aliphatic system (**1m**,**n**) and observed that alkenoic acid **1m** was smoothly transformed into the corresponding lactone **2m** with the yield in line with the literature precedence, whereas alkenoic acid **1n** did not produce any detectable product **2n** (**1n**). The multiple double bonds present in alkenoic acid **1n** might lead to a complex reaction profile, and no isolable product was identified.

Though a variety of differently substituted 3-aryl-ω-alkenoic acids (**1a**–**m**) were converted smoothly into 3-aryl-γ-butyrolactones with consistent yield and stereoselectivity, the reaction was found to be unsuccessful for the ω-alkenoic acids carrying a heterocycle at 3-position. We tried to convert ω-alkenoic acids decorated with thienyl and indolyl substituents at 3-position (entries **2o**,**p**) to their corresponding γ-butyrolactones, but all our efforts were found to be futile. No detectable product was found in any cases for some unknown reasons.

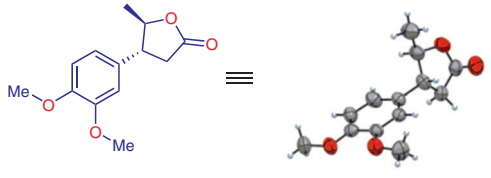
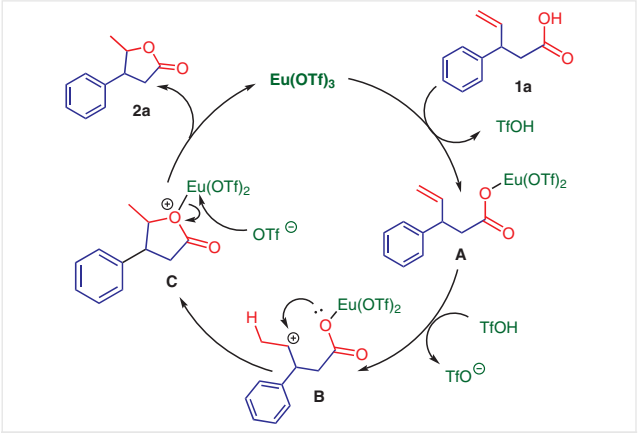


Figure 2 Single-crystal XRD image (ORTEP diagram) of compound **2j** (CCDC 1849393)

We were in quest for the crystal structure of any one of the γ-butyrolactone compounds to confirm the stereochemistry of adjacent aryl and methyl groups present in the title compounds. We were fortunate enough to obtain a single crystal of compound **2j** (Figure 2) suitable for crystallographic analysis. Crystal-structure analysis of the major component isolated by silica gel column chromatography established unambiguously the *anti* relationship between the adjacent aryl and the methyl group of compound **2j** (Figure 2).

We have proposed a mechanistic pathway of the reaction depicted in Scheme 2. Since lanthanides are oxophilic in nature, europium(III) is expected to coordinate to the carboxylic acid group of **1a** to form intermediate **A** (Scheme 2). The triflic acid liberated from metal triflate protonates terminal olefin to give secondary carbocation **B** which undergoes C–O bond formation via nucleophilic attack of the oxygen lone pair to give **C**. Finally, **C** decomposes to afford title compound **2a** and $Eu(OTf)_3$ which initiates another catalytic cycle.



Scheme 2 Plausible reaction mechanism of intramolecular lactonizaton

In summary, we have developed a new Eu(III)-catalyzed intramolecular lactonization reaction of ω-alkenoic acids leading to γ-butyrolactones.[13] To the best of our knowledge, it is the first example to use rare-earth-metal triflate to achieve functionalization of nonactivated terminal double bond. A variety of 3-aryl-γ-butyrolactones can be accessible with good-to-excellent yield. An *anti*-selective product orientation was observed with consistency in a wide range of substrates. Operational simplicity, broad substrate range, good yield, and clean reaction profile made this method more appealing to the chemists. Moreover, our work may be considered as a step forward to popularize the use of rare-earth-metal reagent in organic synthesis.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707820.

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(13) **Typical Procedure for the Preparation of Reference Compound 5-Methyl-4-phenyldihydrofuran-2(3*H*)-one (2a)**
A chlorobenzene (0.2 M) solution of the 3-phenylpent-4-enoic acid (**1a**, 50 mg, 0.284 mmol) was taken in a 10 mL sealed tube, and $Eu(OTf)_3$ (5 mol%) was added to it. Nitrogen gas was flushed into it; the tube was closed and placed it in a silicon oil bath. After 7 h heating the starting material was completely consumed as indicated by TLC, and the reaction was quenched by adding water. Compound was extracted with ethyl acetate (3 × 20 mL). Combined organic layer was washed with brine solution, dried over sodium sulfate, and evaporated to dryness. The crude product was purified on silica gel (mesh 100–200) column chromatography using ethyl acetate in petroleum ether (1:2) as eluent to afford **2a** (35 mg, 70%) as yellow oil. IR: 1775 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.24 (m, 5 H), 4.55 (ddd, *J* = 12, 8.6, 6.2 Hz, 1 H), 3.25 (td, *J* = 11.2, 6.2 Hz, 1 H), 2.95 (dd, *J* = 16, 8.4 Hz, 1 H), 2.79 (dd, *J* = 16, 11.2 Hz, 1 H), 1.42 (d, *J* = 6.4 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.5, 138.2, 129.1, 127.8, 83.2, 49.7, 37.5, 19.2. HRMS: *m/z* $[M + H]^+ - H_2O$ calcd for $C_{11}H_{12}O_2$: 159.0837; found: 159.0843.

