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Copper-Mediated Reaction of Oxazirconacyclopentenes with But-2-ynedioates: A New Pathway for the Formation of α-Methylene-δ-lactone Derivatives[†]

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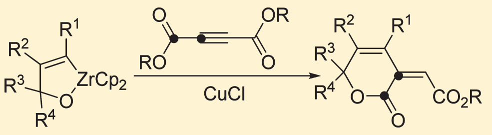
Supporting Information

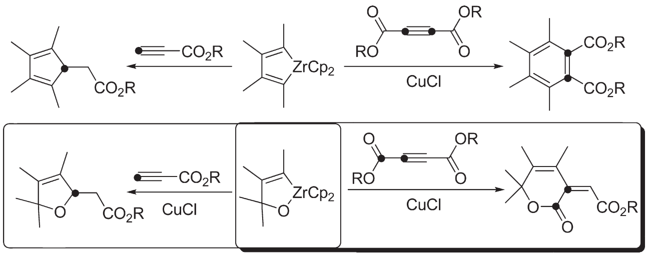
ABSTRACT: Oxazirconacyclopentenes reacted with but-2-ynedioates in the presence of CuCl via tandem Michael addition/nucleophilic substitution to afford α-methylene-δ-lactone derivatives.



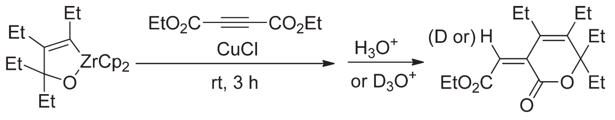
The formation of cyclized compounds is an essential process in organic synthesis, and metallacycles can be important intermediates for transformation into cyclic compounds.[1] In this regard, five-membered zirconacycles, which can be easily prepared by reductive coupling of two molecules of unsaturated compounds on a zirconocene(II) species[2] and can participate in a number of organic reactions,[3] are especially attractive. Recently, it has been reported that zirconacyclopentadiene reacted with but-2-ynedioates in the presence of CuCl, resulting in a 1,2-cycloaddition, to afford phthalate derivatives.[4] The zirconacyclopentadienes reacted with propynoates, resulting in a 1,1-cycloaddition, to afford cyclopentadienylacetate derivatives.[5] Furthermore, oxazirconacyclopentenes reacted with the propynoates in the presence of CuCl, resulting in a 1,1-cycloaddition, to afford 2-(2,5-dihydrofuran-2-yl)acetate derivatives.[6] In all the above reactions, the last intramolecular cyclization occurred at the carbon of the original triple bond (Scheme 1). However, there has been no report for the intramolecular cyclization of zirconacycles and acetylenic ester directly occurring at the carbon of carbonyl, to the best of our knowledge. Herein we report a novel reaction of oxazirconacyclopentenes with but-2-ynedioates in the presence of CuCl, affording α-methylene-δ-lactone derivatives, in which the last intramolecular cyclization occurred at the carbon of the carbonyl via nucleophilic substitutions.

A typical procedure is as follows. To a solution of oxazirconacylopentene in THF (5 mL), prepared from Cp_2ZrCl_2 (292 mg, 1 mmol), EtMgBr (1 M THF solution, 2 mL, 2 mmol), 3-hexyne (114 μL, 1 mmol), and pentan-3-one (106 μL, 1 mmol) according to the reported procedure,[2e,k] was added diethyl but-2-ynedioate (170 mg, 1 mmol) and CuCl (198 mg, 2 mmol). The reaction mixture was stirred at room temperature for 3 h and quenched with 3 N HCl solution (Scheme 2). After separation and purification by column chromatography, α-methylene-δ-lactone **2a** was obtained in 83% yield. Deuteriolysis instead of hydrolysis of the reaction mixture afforded the monodeuterated compound **3a** in 82% yield with 92% deuterium incorporation. This result indicates that one metal−carbon bond remained before hydrolysis.

Scheme 1



Scheme 2



1a

2a: 83%
3a: 82%, (D > 92%)

α-Methylene-δ-lactone skeletons are frequently found in natural products and medicaments.[7] Various substituent groups make α-methylene-δ-lactones as excellent candidates in activity of medicaments. The reaction described here allowed the efficient synthesis of various substituted α-methylene-δ-lactones.

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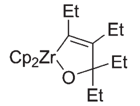
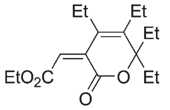
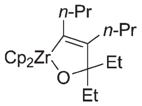
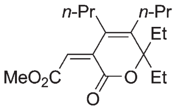
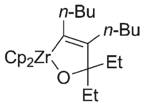
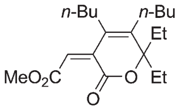
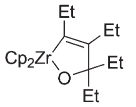
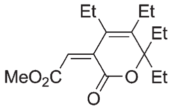
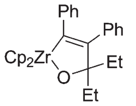
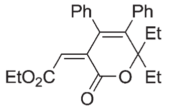
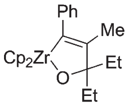
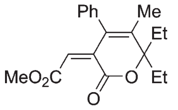
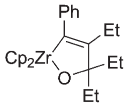
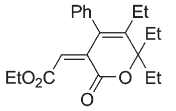
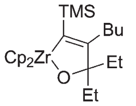
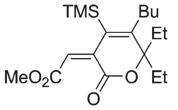
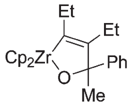
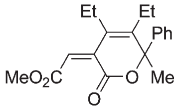
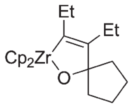
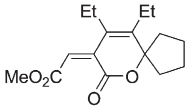
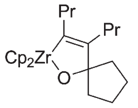
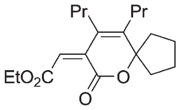
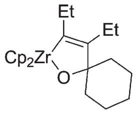
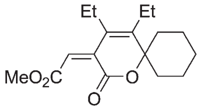
Table 1. Reaction of Oxazirconacycles with But-2-ynedioates in the Presence of CuCl

Entry	Oxazirconacycles	Product	Yield (%)[a]
1	 (1a)	 (2a)	83
2	 (1b)	 (2b)	81
3	 (1c)	 (2c)	78
4	 (1a)	 (2d)	86
5	 (1d)	 (2e)	48
6	 (1e)[b]	 (2f)	47
7	 (1f)[c]	 (2g)	54
8	 (1g)[d]	 (2h)	49
9	 (1h)	 (2i)[e]	52
10	 (1i)	 (2j)	41
11	 (1j)	 (2k)	53
12	 (1k)	 (2l)	48

[a] Isolated yield. [b] A 1:1 mixture of two regioisomers. [c] A 6:1 mixture of two regioisomers; major isomer is shown. [d] A 20:1 mixture of two regioisomers; major isomer is shown. [e] A 1.1:1 mixture of two diastereoisomers.

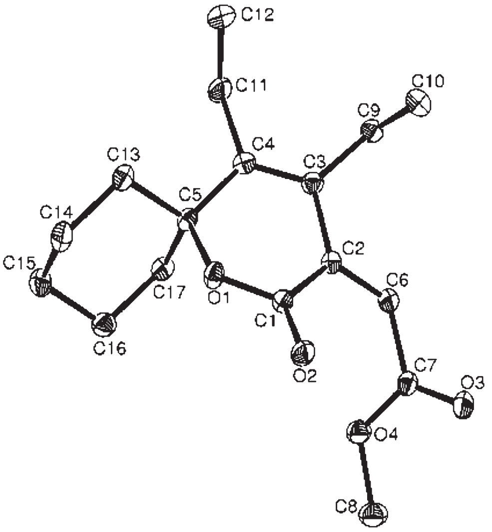
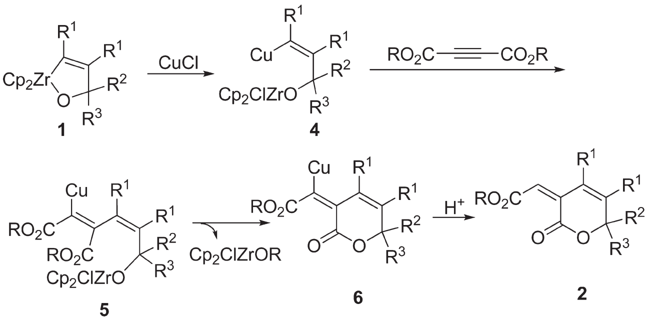


Figure 1. Perspective view of **2l**.

Scheme 3

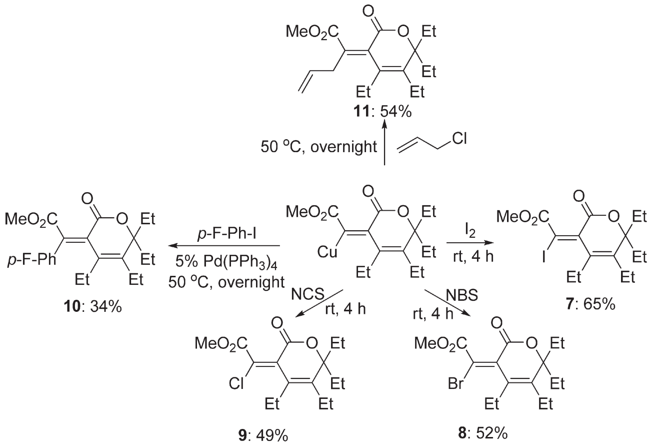


Some representative examples of the reaction are summarized in Table 1. Reaction of both monocyclic (entries 1−9) and spirocyclic (entries 10−12) oxazirconacyclopentenes with but-2-ynedioate gave the corresponding α-methylene-δ-lactone derivatives in good to high yields after hydrolysis. When unsymmetrical alkynes were used, the formation of two regioisomers (entries 6−8) was observed. For PhC≡CMe, the ratio of the two isomers is 1:1. For PhC≡CEt, the ratio of the two isomers is 6:1. For TMSC≡CBu^n, the ratio of the two isomers is 20:1. When unsymmetrical ketone was used, a 1.1:1 mixture of diastereoisomer was formed (entry 9). To our delight, the crystals of **2l** were suitable for an X-ray diffraction analysis, and its structure was confirmed as α-methylene-δ-lactone (Figure 1). It is noteworthy that when diethyl maleate and fumarate were used instead of but-2-ynedioates, the reaction resulted in the formation of a complicated reaction mixture.

To elucidate the lactone ring formation before hydrolysis or after hydrolysis, the following experiments were conducted. The reaction mixture of the oxazirconacyclopentene **1a** and dimethyl but-2-ynedioate in the presence of CuCl was treated with iodine at room temperature for 3 h, and the iodinated compound **7** was obtained without hydrolysis. Moreover, on monitoring of the reaction by NMR, the ^{13}C NMR (C_6D_6, Me_4Si) spectrum showed a signal at 90.50 ppm assigned to an sp^3 carbon of the lactone ring, consisting of the sp^3 carbon of the lactone ring in the product **2d**. These results show that the lactone ring formed before hydrolysis.

On the basis of the results obtained here, the following reaction mechanism can be proposed for the formation of α-methylene-δ-lactone (Scheme 3). In the first step the Zr−C bond of is transmetalated to Cu−C bond to give **4**.[8,3m−3o] The

Scheme 4



intermediate **4** then adds to the triple bond of but-2-ynedioate via Michael addition to give metallodiene derivative **5**, which undergoes intramolecular nucleophilic substitution on the ester group with elimination of Cp$_2$ClZrOR to form γ-metallo-α-methylene-δ-lactone **6**. Hydrolysis of **6** affords α-methylene-δ-lactone derivative **2**.

The remaining Cu−C bond of intermediate **6** could be converted into functionalized α-methylene-δ-lactones by coupling with various electrophilies such as iodine, NBS, allyl chloride, and 1-fluoro-4-iodobenzene to afford the corresponding products in good yields (Scheme 4).

In summary, an unprecedented reaction of oxazirconacyclopentens with but-2-ynedioates to afford γ-metallo-α-methylene-δ-lactones has been developed. This method enhances the synthetic utility of five-membered oxazirconacycles by providing highly functionalized α-methylene-δ-lactone derivatives through a multicomponent reaction in one pot.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Text, figures, a table, and a CIF file giving all experimental details and characterization data for all compounds and crystallographic data for compound **2l**. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ DEDICATION

[†]Dedicated to Professor Christian Bruneau on the occasion of his 60th birthday.

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