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Carbometalation–Carboxylation of 2,3-Allenols with Carbon Dioxide: A Dramatic Effect of Halide Anion

Suhua Li,[†] Bukeyan Miao,[‡] Weiming Yuan,[‡] and Shengming Ma*[,†,‡]

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, P. R. China, and Shanghai Key Laboratory of Green Chemistry and Chemical Process, Department of Chemistry, East China Normal University, 3663 North Zhongshan Lu, Shanghai 200062, P. R. China

masm@sioc.ac.cn

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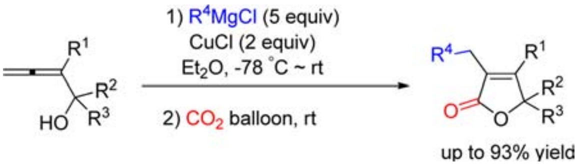
ABSTRACT



The cyclic organometallic intermediates formed via CuCl-mediated highly regio- and stereoselective carbomagnesiation of 2,3-allenols with Grignard reagents may smoothly react with carbon dioxide to afford 2(5*H*)-furanones. A dramatic effect of the halide anion from the Grignard reagent (Br vs Cl) for CO_2 activation was observed. The reaction proceeded smoothly under mild conditions to afford the products in 58–93% yields.

Much attention has been paid to the development of new and efficient methodologies for the synthesis of 2(5*H*)-furanones,[1] a class of important heterocycles with a broad range of potential biological activities.[2] On the other hand, carbon dioxide is one of the most attractive C1 synthons in organic synthesis as it is a type of renewable, nontoxic, abundant, and economical resource.[3] There are a few reports on the synthesis of 2(5*H*)-furanones from the reaction of alkynols with Grignard reagents with or without Cp_2TiCl_2 followed by quenching with inletting CO_2 gas or pouring into dry ice.[4] Recently, we have developed an efficient regio- and stereospecific CuCl-mediated carbomagnesiation of differently substituted 2,3-allenols with primary, secondary alkyl, or aromatic Grignard reagents followed by iodination to synthesize fully substituted allylic alcohols (Scheme 1).[5] We envisioned that the cyclic intermediates **A** formed in situ in the reaction would react with CO_2 to form γ-hydroxy *Z*-alkenoic carboxylic acid, which would be followed by lactonization to produce butenolides. Herein, we report such a transformation in which a dramatic halide anion effect for CO_2 activation was observed and a CO_2 balloon was used without continuous release of CO_2 to the environment.

After the CuCl-mediated carbometalation of *n*-BuMgBr with allenol **1a**, CO_2 was introduced into reaction vessel by

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[†] Chinese Academy of Sciences.

[‡] East China Normal University.

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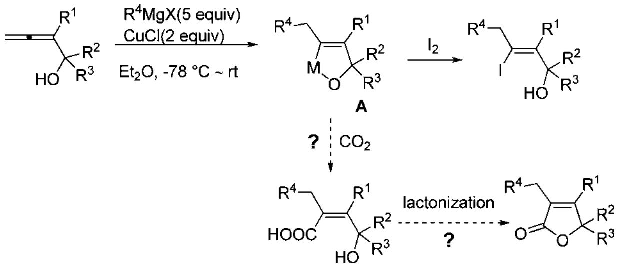
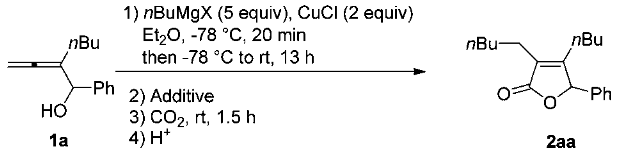
Scheme 1. Our Previous Work and Proposed Synthesis of 2(5*H*)-Furanones



installation of a CO_2 balloon and **2aa** was formed in 45% yield (Table 1, entry 1). We believed that the reason for the low yield might be the low reactivity of the intermediate **A** toward CO_2. When HMPA or CsF was added as an additive before quenching of the intermediate **A** with CO_2, the yield of **2aa** dropped to 23% (Table 1, entries 2 and 3). To our delight, when LiCl was used, the yield of **2aa** was raised to 79% (Table 1, entry 4). With such an observation of the unique effect of halide anion, we further used *n*-BuMgCl instead of *n*-BuMgBr: interestingly, the yield was further improved to 87% (Table 1, entry 5)!

Table 1. Optimization of Reaction Conditions for the Synthesis of 2(5*H*)-Furanone **2aa**[a]



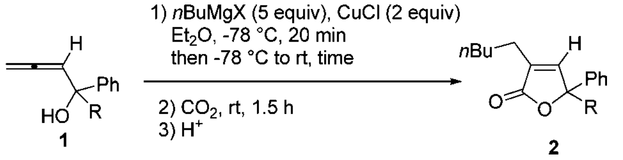
entry	X	additive (equiv)	NMR yield of **2aa** (%)
1	Br	none	45
2	Br	HMPA (2)	23
3	Br	CsF (2)	23
4	Br	LiCl (2)	79
5[b]	**Cl**	**none**	**85 (87)**[c]

[a] The reaction was conducted using 1 mmol of **1**, 2 mmol of CuCl, 5 mmol of *n*-BuMgBr (2 M in Et_2O), and a CO_2 balloon in 6 mL of Et_2O. [b] The reaction was conducted with 1 mmol of **1**, 2 mmol of CuCl, 5 mmol of *n*-BuMgCl (2 M in Et_2O), and a CO_2 balloon in 6 mL of Et_2O. The first step finished after 15 h. [c] Isolated yield in parentheses.

Subsequently, other organomagnesium chlorides and organomagnesium bromides were compared (Table 2). When *n*-C_4H_9MgBr was used, lactone **2ba** was obtained in low yield (Table 2, entry 1) while with *n*-C_4H_9MgCl, **2ba** was isolated in 72% yield (Table 2, entry 2); the halide anion effect also exists in the reaction of secondary 2,3-allenol **1c** (Table 2, entries 3 and 4).[6]

On the basis of these results, the scope of this reaction was then studied using organomagnesium chlorides. The results show in Table 3 indicated that 2(5*H*)-furanones were formed in moderate to excellent yields: R^1 can be alkyl, phenyl, benzyl, or H; R^2 may be alkyl, phenyl, methyl, or H. Primary (Table 3, entries 1−3), secondary (Table 3, entries 4−13), and tertiary 2,3-allenols (Table 3, entry 14) all produced the lactones in moderate to good yields. Grignard reagents such as CyMgCl (entry 4), *i*-PrMgCl (entry 5), and PhMgCl (entry 6) were examined in this reaction producing moderate to good yields of 2(5*H*)-furanones. To check the practicality, this reaction was scaled up to 1.12 g (7 mmol)

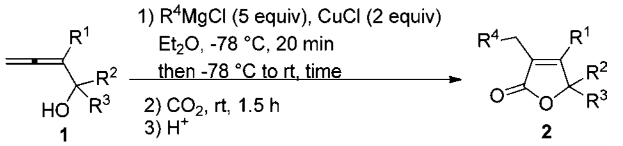
Table 2. Effect of Halide Anion



entry	R	*n*-BuMgX	time (h)	yield of **2** (%)
1[a]	CH_3 (**1b**)	$^nC_4H_9MgBr$	13	48[d] (**2ba**)
2[b]	CH_3 (**1b**)	$^nC_4H_9MgCl$	14	72 (**2ba**)
3[a]	H (**1c**)	$^nC_4H_9MgBr$	13	44[d] (**2ca**)
4[b]	H (**1c**)	$^nC_4H_9MgCl$	13	78 (**2ca**)
5[c]	H (**1c**)	$^nC_4H_9MgI$	24	complicated

[a] The reaction was conducted using 1 mmol of **1**, 2 mmol of CuCl, 5 mmol of *n*BuMgBr (2 M in Et_2O), and a CO_2 balloon in 6 mL of Et_2O. [b] The reaction was conducted with 1 mmol of **1**, 2 mmol of CuCl, 5 mmol of BuMgCl (2 M in Et_2O), and a CO_2 balloon in 6 mL of Et_2O. [c] The reaction was conducted using 1 mmol of **1**, 2 mmol of CuCl, 5 mmol of *n*BuMgI (2 M in Et_2O), and a CO_2 balloon in 6 mL of Et_2O. [d] NMR yield.

Table 3. Synthesis of 2(5*H*)-Furanones[a]



entry	$R^1/R^2/R^3$	R^4 MgCl	time (h)	isolated yield (%)
1	nC_6H_{13}/H/H (**1d**)	$^nC_4H_9$	10	75 (**2da**)
2	$^nC_4H_9$/H/H (**1e**)	$^nC_4H_9$	10	73 (**2ea**)
3	Bn/H/H (**1f**)	$^nC_4H_9$	12	88 (**2fa**)
4	H/Ph/H (**1c**)	Cy	13	68 (**2cb**)
5	H/Ph/H (**1c**)	^{i}Pr	13	58 (**2cc**)
6	H/Ph/H (**1c**)	Ph	13	75 (**2cd**)
7	H/4-ClC_6H_4/H (**1g**)	$^nC_4H_9$	12	76 (**2ga**)
8	H/1-naphthyl/H (**1h**)	$^nC_4H_9$	13.5	61 (**2ha**)
9	H/nC_5H_{11}/H (**1i**)	$^nC_4H_9$	12	65 (**2ia**)
10	H/Cy/H (**1j**)	$^nC_4H_9$	14	67 (**2ja**)
11	Ph/Me/H (**1k**)	$^nC_4H_9$	13	76 (**2ka**)
12[b]	Ph/Me/H (**1k**)	$^nC_4H_9$	11	81 (**2ka**)
13	Ph/Ph/H (**1l**)	$^nC_4H_9$	14	82 (**2la**)
14	H/nC_6H_{13}/Me (**1m**)	$^nC_4H_9$	13	64 (**2ma**)

[a] The reaction was conducted with 1 mmol of **1**, 2 mmol of CuCl, 5 mmol of R^4 MgCl (2 M in Et_2O), and a CO_2 balloon in 6 mL of Et_2O. [b] The reaction was conducted using 7 mmol of **1k** (1.12 g scale).

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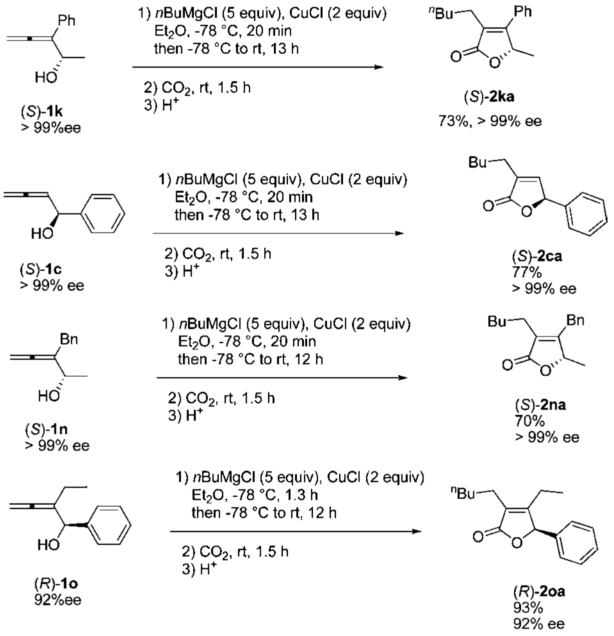
affording **2ka** in 81% yield (Table 3, entry 12). It should be noted that in some cases the premature protonation product was observed as the minor byproduct and the reaction of **1c** with 3 equiv of n-C$_4$H$_9$MgCl afforded a lower yield of **2ca** after 24 h.

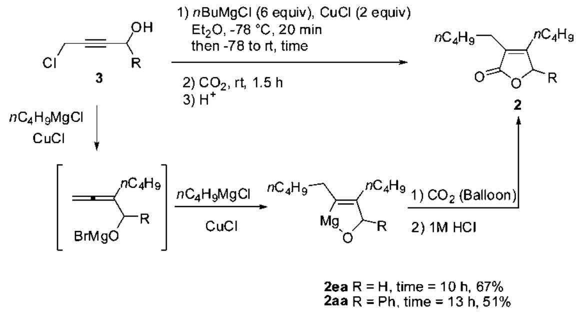
When the optically active 2,3-allenols *S*-**1k** *S*-**1c**, *S*-**1n4,** and *S*-**1o** were applied, optically active 2(5*H*)-furanones *S*-**2ka**, *S*-**1ca**, *S*-**2na**, and *R*-**2oa** were prepared in 70–92% yields without obvious racemization (Scheme 2).

Scheme 2. Synthesis of Optically Active 2(5*H*)-Furanones



2(5*H*)-Furanones **2ea** and **2aa** may also be synthesized directly from 4-chlorobut-2-yn-1-ol (**3**) with the in situ synthesis of the allenol,[7] carbomagnesiation, carboxylation with CO$_2$, and lactonization in one pot (Scheme 3).

Scheme 3. Synthesis of 2(5*H*)-Furanones **2ea** and **2aa** in One Step from 4-Chlorobut-2-yn-1-ol



It should be noted that three carbon–carbon bonds and a carbon–oxygen bond were formed in this transformation.

In conclusion, we have developed a very convenient method to synthesize 2(5*H*)-furanones using 2,3-allenols, organomagnesium chlorides, and carbon dioxide provided in the form of a balloon as the starting materials. *It is interesting to observe a dramatic chloride effect of the Grignard reagents for this carboxylation with CO$_2$*: the yields with RMgCl are much higher than those with RMgBr. Optically active 2(5*H*)-furanones were synthesized from optically active 2,3-allenols. As a result of usefulness of the products and the easy availability of various 2,3-allenols,[5,7,8] the reaction may be potentially useful in organic and medicinal chemistry. Further studies in this area are in progress in our laboratory.

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Supporting Information Available. Spectroscopic data, general procedure, and ^{1}H/^{13}C NMR spectra of all the products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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