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$PdCl_2$-Catalyzed Oxidative Cycloisomerization of 3-Cyclopropylideneprop-2-en-1-ones

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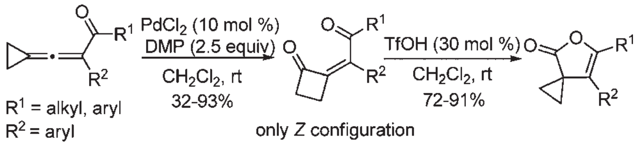
ABSTRACT



A novel $PdCl_2$-catalyzed oxidative cycloisomerization of 3-cyclopropylideneprop-2-en-1-ones, providing a facile synthesis of highly strained functionalized 2-alkylidenecyclobutanones via furan-fused cyclobutene intermediates, is reported. An interesting route to 2(3*H*)-furanones with a spiro-cyclopropane unit from the obtained 2-alkylidenecyclobutanones via a ring-contraction rearrangement reaction is also realized.

The four-membered ring is an important structural motif, existing in many bioactive natural products,[1] and also serves as a key intermediate in the synthesis of structurally complex targets by ring-opening reactions[2] which make its preparation of great interest in organic synthesis. However, efficient methods for the synthesis of these compounds are limited compared to those for other carbocyclic systems.[3] In the past, several advanced strategies involving transition-metal-catalyzed ring expansion of cyclopropanes via cyclopropyl carbenes have been established for the synthesis of cyclobutanes and cyclobutenes.[4] The groups of Trost, Echavarren, and Fürstner reported the synthesis of various isomeric bicyclic cyclobutenes by transtition-metal-mediated cycloisomerization of tethered enynes via cyclopropyl metal carbenes.[5] Alternatively, Shi and Fürstner discovered that monosubstituted cyclobutenes could be prepared through cyclopropyl metal carbenes derived from methylenecyclopropanes (MCPs).[6] Furthermore, Tang reported the synthesis of cyclobutenyl esters via silver(I)-catalyzed decomposition of diazocarbonyl precursors forming the cyclopropyl metal carbenes,[7a] and Liu developed a gold-catalyzed oxidative ring expansion of alkynylcyclopropanes via cyclopropyl gold carbenes to afford cyclobutenyl ketone.[7b] Despite these elegant achievements, the progress of novel synthetic methods

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[§] Prof. Huang passed away on March 6, 2010. He had been fully in charge of this project. At this moment, Prof. Luling Wu is finishing all the projects with help from Prof. Shengming Ma.

(1) (a) Hansen, T. V.; Stenstrom, Y. *Organic Synthesis: Theory and Applications*, Vol. 5; Elsevier Science: Dordrecht, 2001, p 1. (b) Dembitsky, V. M. *J. Nat. Med.* **2008**, *62*, 1.

(2) (a) Lee-Ruff, E.; Mladenova, G. *Chem. Rev.* **2003**, *103*, 1449. (b) Gauvry, N.; Lescop, C.; Huet, F. *Eur. J. Org. Chem.* **2006**, 5207.

(3) (a) Winkler, J. D.; Bowen, C. M.; Liotta, F. *Chem. Rev.* **1995**, *95*, 2003. (b) Hoffmann, N. *Chem. Rev.* **2008**, *108*, 1052. (c) Inanaga, K.; Takasu, K.; Ihara, M. *J. Am. Chem. Soc.* **2005**, *127*, 3668. (d) Canales, E.; Corey, E. J. *J. Am. Chem. Soc.* **2007**, *129*, 12686. (e) Shibata, T.; Takami, K.; Kawachi, A. *Org. Lett.* **2006**, *8*, 1343.

(4) (a) Masarwa, A.; Fürstner, A.; Marek, I. *Chem. Commun.* **2009**, 5760. (b) Kleinbeck, F.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 9178. (c) Trost, B. M.; Xie, J.; Maulide, N. *J. Am. Chem. Soc.* **2008**, *130*, 17258. (d) Markham, J. P.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 9708.

(5) (a) Trost, B. M.; Tanoury, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 1636. (b) Trost, B. M.; Trost, M. K. *Tetrahedron Lett.* **1991**, *32*, 3647. (c) Nieto-Oberhuber, C.; Lopez, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178. (d) Nieto-Oberhuber, C.; Lopez, S.; Munoz, M. P.; Cardenas, D. J.; Bunuel, E.; Nevado, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6146. (e) Fürstner, A.; Davies, P. W.; Gress, T. *J. Am. Chem. Soc.* **2005**, *127*, 8244. (f) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2008**, *47*, 6754.

(6) (a) Shi, M.; Liu, L. P.; Tang, J. *J. Am. Chem. Soc.* **2006**, *128*, 7430. (b) Fürstner, A.; Aïssa, C. *J. Am. Chem. Soc.* **2006**, *128*, 6306.

(7) (a) Xu, H.; Zhang, W.; Shu, D.; Werness, J. B.; Tang, W. *Angew. Chem., Int. Ed.* **2008**, *47*, 8933. (b) Li, C.-W.; Pati, K.; Lin, G.-Y.; Abu Sohel, S. M.; Hung, H.-H.; Liu, R.-S. *Angew. Chem., Int. Ed.* **2010**, *49*, 9891.

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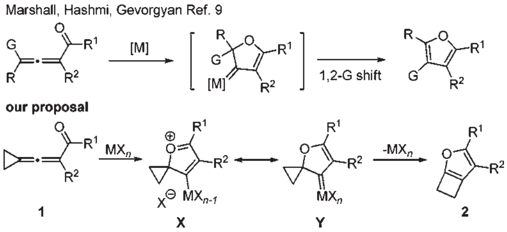
via cyclopropyl metal carbene intermediates leading readily to the selective formation of the four-membered ring with new structural features for further elaboration is still of current interest.

Yet, increasing attention has been paid to a metal-catalyzed cyclization/1,2-migration domino methodology which provides rapid access to complex molecular frameworks.[8] Particularly, the cyclization of allenyl ketones via 1,2-migration of various groups is an efficient approach for the synthesis of highly substituted furans (Scheme 1).[9] Marshall and Hashmi have shown an efficient approach for the assembly of the furan ring via a formal 1,2-hydrogen shift of allenyl ketones.[9b−d] Gevorgyan has reported the metal-catalyzed cyclization of allenyl ketones with 1,2-alkyl migration as a key step in the formation of highly substituted furans.[9e]

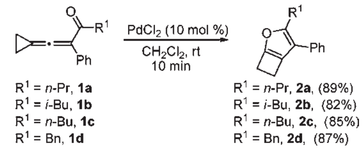
Scheme 1. Transition Metal Catalyzed Cycloisomerization of 1,2-Allenylketones and 3-Cyclopropylideneprop-2-en-1-ones **1**



Based on these reports and our interest in the chemistry of cyclopropane,[10] we envisioned that under the activation of π-carbophilic metals, cyclization of cyclopropylideneprop-2-en-1-ones **1** would afford cyclopropyl metal carbenes **Y**, which could undergo C−C bond cleavage and a subsequent 1,2-shift to form furan-fused cyclobutenes **2**, which are interesting precusors for the synthesis of other important molecules (Scheme 1).

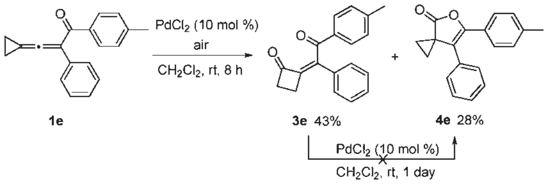
We first examined the reaction of **1a** (R^1 = *n*-Pr) in the presence of a catalytic amount of a metal salt under N_2 at rt to explore the possibility of forming furan-fused cyclobutene **2a** (Scheme 2). Fortunately, **2a** was obtained in 89% yield after flash chromatography on neutral Al_2O_3. We determined the scope of the reaction when R^1 = alkyl groups with 10 mol % $PdCl_2$ under N_2 at rt and the furan-fused cyclobutenes **2b**, **2c**, and **2d** were obtained in 82−87% yield (Scheme 2).

Scheme 2. Cycloisomerization of 3-Cyclopropylideneprop-2-en-1-ones **1** To Afford Furan-Fused Cyclobutenes **2**



To further expand the scope of this reaction, we carried out the reaction of **1e** wherein R^1 is an aryl group; however the desired furan-fused cyclobutene product was not isolated presumably because this compound is unstable under the reaction conditions. Surprisingly, the reaction proceeded smoothly to give two new products, 2-alkylidenecyclobutanone (**3e**) in 43% yield and 2(3*H*)-furanone (**4e**) in 28% yield, in the presence of 10 mol % $PdCl_2$ in an open air flask (Scheme 3). The structures of **3e**[11] and **4e**[12] were further confirmed by the single crystal X-ray diffraction analysis. We next carried out the reaction of **3e** in the presence of 10 mol % $PdCl_2$; however, **4e** was not formed, indicating that the formation of **3e** and **4e** are competitive in the reaction (Scheme 3).

Scheme 3. Reaction of **1e** in the Presence of 10 mol % $PdCl_2$ under Open Air Conditions



We proposed a plausible mechanism for for the preparation of **3e** and **4e** (Scheme 4). $PdCl_2$ may activate the relatively electron-rich C−C double bond and trigger the nucleophilic attack of the carbonyl oxygen at the C4 atom of the allenone moiety to form the spirocyclic oxonium **X**. The latter intermediate would evolve into the Pd(II) carbenoid **Y**, and subsequent bond cleavage followed by elimination of the metal would provide the intermediate compound **2e**. The next step is most likely to be a single-electron oxidation of **2e** by the oxygen in air to furnish the radical cation **A**. The cationic center in intermediate **A** is trapped by water to afford the radical species **B**, which after proton elimination gives the hydroxy radical **C**. The latter could be further oxidized into the corresponding

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(8) (a) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395. (b) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (c) Shapiro, N. D.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 9244. (d) Kirsch, S. F.; Binder, J. T.; Liébert, C; Menz, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 5878. (e) Trost, B. M; Xie, J. *J. Am. Chem. Soc.* **2008**, *130*, 6231.

(9) (a) Sheng, H.; Lin, S.; Huang, Y. Z. *Tetrahedron Lett.* **1986**, *27*, 4893. (b) Marshall, J. A.; Robinson, E. D. *J. Org. Chem.* **1990**, *55*, 3450. (c) Marshall, J. A.; Wallace, E. M. *J. Org. Chem.* **1995**, *60*, 796. (d) Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2285. (e) Dudnik, A. S.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2007**, *46*, 5195. (f) Kim, J. T.; Kel'in, A. V.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2003**, *42*, 98. (g) Sromek, A. W.; Rubina, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2005**, *127*, 10500. (h) Sromek, A. W.; Kel'in, A. V.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2004**, *43*, 2280. (i) Dudnik, A. S.; Xia, Y.; Li, Y.; Gevorgyan, V. *J. Am. Chem. Soc.* **2010**, *132*, 7645.

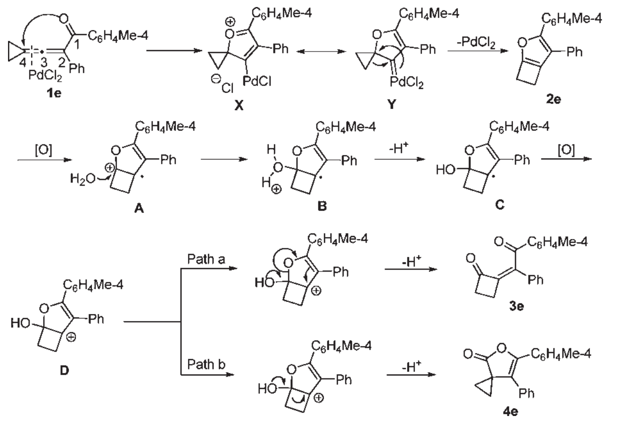
(10) (a) Su, C.; Cao, J.; Huang, X.; Wu, L.; Huang, X. *Chem.—Eur. J.* **2011**, *17*, 1579. (b) Huang, X.; Zhou, H. *Org. Lett.* **2002**, *4*, 4419. (c) Chen, W.; Cao, J.; Huang, X. *Org. Lett.* **2008**, *10*, 5537. For synthesis of MCPs, see: (d) Brandi, A.; Goti, A. *Chem. Rev.* **1998**, *98*, 589. For recent reviews, see: (e) Brandi, A.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Rev.* **2003**, *103*, 1213. (f) Nakamura, E.; Yamago, S. *Acc. Chem. Res.* **2002**, *35*, 867.

(11) For X-ray crystal data for **3e,** see Supporting Information.

(12) For X-ray crystal data for **4e**, see Supporting Information.

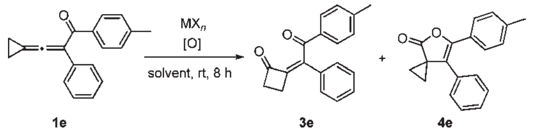
cation **D**, and subsequent loss of a proton and cleavage of the dihydrofuran ring would lead to the 1,4-dicarbonyl compound **3e** with a four-membered ring (Path a). Alternatively, elimination of a proton and ring contraction would produce the furanone derivative **4e** with a spirocyclopropane at the 3-position (Path b).

Scheme 4. Plausible Mechanism for the Formation of **3e** and **4e**



Efforts were made to optimize the reaction conditions and improve the selectivity of the reaction. As indicated in Table 1, $AgNO_3$, $Pd(OAc)_2$, AgOTf, and $Au(PPh_3)OTf$ all sluggishly catalyzed the reaction and only gave lower yields of a mixture of **3e** and **4e**, compared to $PdCl_2$ (Table 1, entries 2–5). The reaction proceeded smoothly in THF, CH_3OH, and toluene, but the yield and selectivity were not obviously improved (Table 1, entries 6–8). Considering the oxidation of the intermediate might be the key step in the reaction, various oxidants were then screened[13] (Table 1, entries 9–13). Gratifyingly, the yield of **3e** was improved to 84% when 2.5 equiv of Dess-Martin periodinane (DMP) were employed, and the formation of **4e** was not observed (Table 1, entry 11). The yield dropped to 77% when the loading of $PdCl_2$ was reduced to 5 mol % (Table 1, entry 14). Thus, using DMP as the oxidant and 10 mol % $PdCl_2$ as the catalyst, this reaction could highly selectively produce functionalized 2-alkylidenecyclobutanones **3**.

Table 1. Optimization of the Reaction Conditions for the Selective Formation of **3e**[a]



	MX$_n$ (10 mol %)	[O] (equiv)	solvent[b]	yield of **3e** (%)[c]	yield of **4e** (%)[c]
1	$PdCl_2$	air	CH_2Cl_2	43	28
2	$AgNO_3$	air	CH_2Cl_2	33	6
3	$Pd(OAc)_2$	air	CH_2Cl_2	11	trace
4	AgOTf	air	CH_2Cl_2	14	0
5	$Au(PPh_3)OTf$	air	CH_2Cl_2	36	22
6	$PdCl_2$	air	THF	42	19
7	$PdCl_2$	air	CH_3OH	44	22
8	$PdCl_2$	air	toluene	32	30
9	$PdCl_2$	O_2	CH_2Cl_2	33	37
10	$PdCl_2$	$PhI(OAc)_2$ (2.5)	CH_2Cl_2	24	17
11	$PdCl_2$	DMP (2.5)	CH_2Cl_2	84	0
12	$PdCl_2$	DTBP (2.5)	CH_2Cl_2	16	trace
13	$PdCl_2$	MCPBA (2.5)	CH_2Cl_2	trace	trace
14	$PdCl_2$[d]	DMP (2.5)	CH_2Cl_2	77	0

[a] Unless otherwise specified, the reaction was carried out using **1e** (0.15 mmol) in 3 mL of solvent in an open air atmosphere at room temperature. [b] The solvent was used as received without further purification. [c] Isolated yields. [d] 5 mol % $PdCl_2$ was used.

The scope of the reaction is described in Table 2. When R^2 was an aryl group, the R^1 substituent could be an aryl, a heteroaryl, or an alkyl group and the corresponding products **3** were obtained in moderate to good yields (Table 2, entries 1–9). As for the more electron-deficient **1h** and **1i**, **3h** and **3i** were produced in moderate yields (Table 2, entries 4 and 5). When R^1 was a 2-thienyl group, the reaction only afforded **3k** in 32% yield (Table 2, entry 7). The nature and position of substituents on the aromatic R^2 seem to have little effect on this reaction with R^1 being Ph or Tol. Thus the reactions all proceeded smoothly to give the products **3m**–**3p** in good yields from **1m**–**1p**, which have different aromatic R^2 substitutions (Table 2, entries 11–14). However, when R^2 was a 2-naphthyl group, **3q** was obtained in 56% yield (Table 2, entry 15).

We also examined the reactivity of furan-fused cyclobutenes **2c** and **2d** upon treatment with DMP (2.5 equiv). These products were successfully converted to functionalized 2-alkylidenecyclobutanones **3c** and **3d** in 64% and 66% yields (Scheme 5), confirming that the furan-fused cyclobutene is the key intermediate in the formation of **3e** from **1e** (Scheme 4).

Attempts to selectively form furanones **4** from allenyl ketones **1** by screening various reaction conditions were unsuccessful. As a result of the inherent ring strain, functionalized 2-alkylidenecyclobutanones **3** may show interesting reactivity in organic synthesis. Thus, considering the ready availability of **3** with our protocol, we envisioned that a possible route to **4** from **3** may be realized via a ring-contraction reaction of cyclobutane mediated by a Brønsted acid as shown in Scheme 6. The proton may selectively activate the cyclic carbonyl oxygen of **3** to form **E**; intramolecular nucleophilic attack of the acyclic carbonyl oxygen at

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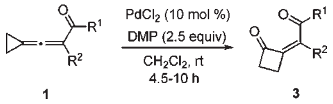
[13] (a) Brasholz, M.; Reissig, H.-U. *Angew. Chem., Int. Ed.* **2007**, *46*, 1634. (b) Alcaide, B.; Almendros, P.; Carrascosa, R.; Torres, M. R. *Eur. J. Org. Chem.* **2010**, *5*, 823. (c) Li, Y.; Pattenden, G.; Rogers, J. *Tetrahedron Lett.* **2010**, *51*, 1280.

[14] The reaction of **1e** could be easily scaled up to 1.084 g, conducted with just 3 mol % of $PdCl_2$ and 2.1 equiv of DMP, affording **3e** in 72% yield.

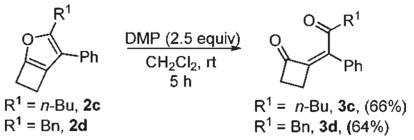
Table 2. Scope of the Reaction for the Highly Selective Formation of **3**[a]



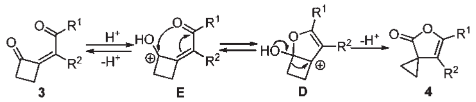
	1		
entry	R^1	R^2	**3** (yield %)[b]
1	(**1e**) 4-MeC$_6$H$_4$	Ph	**3e** (84)[14]
2	(**1f**) Ph	Ph	**3f** (91)
3	(**1g**) 4-FC$_6$H$_4$	Ph	**3g** (70)
4	(**1h**) 4-MeOC$_6$H$_4$	Ph	**3h** (55)[c]
5	(**1i**) 3,4,5-(MeO)$_3$C$_6$H$_2$	Ph	**3i** (64)[c]
6	(**1j**) 2-furyl	Ph	**3j** (63)
7	(**1k**) 2-thienyl	Ph	**3k** (32)
8	(**1a**) *n*-Pr	Ph	**3a** (83)
9	(**1b**) *i*-Bu	Ph	**3b** (85)
10	(**1l**) 4-ClC$_6$H$_4$	2-MeOC$_6$H$_4$	**3l** (93)
11	(**1m**) 4-MeC$_6$H$_4$	4-MeC$_6$H$_4$	**3m** (72)
12	(**1n**) Ph	3-MeC$_6$H$_4$	**3n** (77)
13	(**1o**) Ph	4-MeOC$_6$H$_4$	**3o** (90)
14	(**1p**) Ph	4-FC$_6$H$_4$	**3p** (81)
15	(**1q**) Ph	2-naphthyl	**3q** (56)

[a] Unless otherwise specified, the reaction was carried out using **1e** (0.15 mmol) in the presence of 10 mol % PdCl$_2$ and 2.5 equiv of DMP in 3 mL of CH$_2$Cl$_2$ in open air at rt. [b] Isolated yields. [c] The reaction was conducted at 0 °C.

Scheme 5. Conversion of **2** upon Treatment with DMP

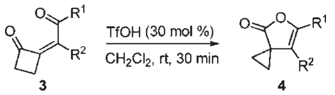


Scheme 6. Proposed Reaction Pathways for the Formation of **4** from **3** Mediated by Brønsted Acid



the cationic carbon atom would take place to yield the intermediate **D** which are proposed in Scheme 4. **D** would then undergo ring contraction and subsequent loss of a proton to finally afford **4**.

Table 3. Scope of the Reaction of **3** with TfOH for the Highly Selective Formation of **4**[a]



	3		
entry	R^1	R^2	**4** (yield %)[b]
1	(**3e**) 4-MeC$_6$H$_4$	Ph	**4e** (82)
2	(**3f**) Ph	Ph	**4f** (88)
3	(**3g**) 4-FC$_6$H$_4$	Ph	**4g** (83)
4	(**3h**) 4-MeOC$_6$H$_4$	Ph	**4h** (72)
5	(**3b**) *i*-Bu	Ph	**4b** (91)
6	(**3l**) 4-ClC$_6$H$_4$	2-MeOC$_6$H$_4$	**4l** (66)
7	(**3m**) 4-MeC$_6$H$_4$	4-MeC$_6$H$_4$	**4m** (77)
8	(**3n**) Ph	3-MeC$_6$H$_4$	**4n** (82)
9	(**3o**) Ph	4-MeOC$_6$H$_4$	**4o** (80)
10	(**3q**) Ph	2-naphthyl	**4q** (84)

[a] Unless otherwise specified, the reaction was carried out using **3e** (0.1 mmol) mediated by 30% TfOH in 3 mL of CH$_2$Cl$_2$ in open air at rt. [b] Isolated yields.

Thus, we started to examine the reactivity of **3e** in the presence of TfOH (30 mol %) in CH$_2$Cl$_2$ at rt. To our delight, the expected product **4e** was cleanly obtained in 82% yield (Table 3, entry 1). The results summarized in Table 3 show that various furanones of type **4** could be obtained smoothly in moderate to high yields using the current protocol. Here, It should be mentioned that the 2(3*H*)-furanones with the spiro-three-membered ring should be valuable intermediates in organic synthesis due to the presence of a highly strained spiro-cyclopropyl ring.

In conclusion, we have developed a cyclization of 3-cyclopropylideneprop-2-en-1-ones in the presence of π-philic metals leading to furan-fused cyclobutenes, which are versatile intermediates for further elaboration. In the presence of PdCl$_2$ and DMP, a highly selective formation of functionalized 2-alkylidenecyclobutanones can be realized. Furthermore, we have developed an efficient route toward 2(3*H*)-furanones with a spiro-three-membered ring at the 3-position from 2-alkylidenecyclobutanones. Due to the easy availability of the starting materials and synthetic potential of these products, this method should be useful in organic synthesis, and further studies in this area are underway in our laboratory.

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Supporting Information Available. Experimental procedure and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.