Ring-opening Bis(alkoxycarbonylation) Reaction of Methylenecyclopropanes Catalyzed by Palladium in the Presence of Copper(I) Salt

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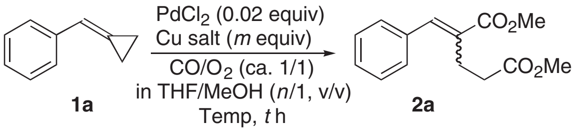
A palladium-catalyzed ring-opening bis(alkoxycarbonylation) reaction of methylenecyclopropanes in the presence of copper(I) salt was achieved under normal pressure of carbon monoxide and oxygen to give the corresponding α-methyleneglutarates.

Carbonylation is an important reaction in organic synthesis to provide efficient entries to a variety of useful homologated carbonyl compounds.[1] We have reported the selective mono- and bis(alkoxycarbonylation) reactions of terminal olefins catalyzed by palladium in the presence of copper salts under normal pressure of carbon monoxide and oxygen. Furthermore, γ-butyrolactones and γ-butyrolactams were prepared from homoallylic alcohols and amine derivatives under the similar conditions, respectively.[2,3] Bis(alkoxycarbonylation) reaction of olefins generally affords succinate derivatives.[2–5] In order to prepare glutarate derivatives via a direct introduction of two carbonyl groups, the bis(alkoxycarbonylation) reaction[2] of cyclopropylbenzene was carried out. However, the desired glutarate derivatives were not detected. Among the cyclopropane derivatives, methylenecyclopropanes are versatile building blocks in organic synthesis due to unique chemical reactivity derived from ring strain to undergo a variety of ring-opening reactions. Further attractive feature of them is their surprising stability.[6] Herein we describe a ring-opening bis(alkoxycarbonylation) reaction of methylenecyclopropanes catalyzed by palladium in the presence of CuCl under remarkably mild conditions to afford the corresponding α-methyleneglutarates.[7]

First, the bis(alkoxycarbonylation) reaction of benzylidenecyclopropane (**1a**) was carried out in the presence of a 0.02 equiv of $PdCl_2$ and 1.5 equiv of CuCl under normal pressure of carbon monoxide and oxygen in MeOH at rt; the desired carbonylated product, a 85/15 mixture of dimethyl (*E*)- and (*Z*)-α-benzylideneglutarate (**2a**), was obtained in 61% yield (Table 1, Entry 1). It was confirmed that in the absence of $PdCl_2$ or CuCl, the glutarate **2a** was not formed, respectively (Entries 2 and 15). Other copper salts CuBr and CuI were less effective than CuCl (Entries 1, 16, and 17), and $CuOTf(C_6H_6)_{0.5}$ showed similar reactivity (Entries 5 and 18). The reaction proceeded smoothly even when the amount of CuCl was reduced, especially with 0.5 equiv of CuCl (Entries 1, 3–5, 13, and 14). Bis(ethoxycarbonylation) reaction also proceeded when EtOH was used as a solvent instead of MeOH (Entry 6). By addition of THF as a cosolvent (Entries 5, 8, 10, and 12) and/or lowering the reaction temperature (Entries 7, 9, and 11), E/Z ratio was slightly enhanced although the reaction was retarded. When the reaction was carried out at 0 °C in THF/MeOH (1/1, v/v), (*E*)-glutarate **2a** was selectively obtained in 68% yield with the E/Z ratio of 93/7 (Entry 9).

Table 1. Bis(alkoxycarbonylation) reaction of **1a**



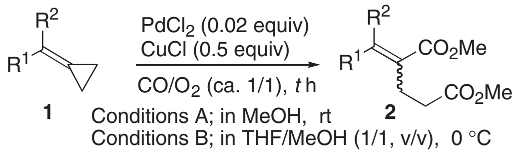
Entry	Cu salt	*m*	*n*	Temp	*t*/h	Yield/%	E/Z[a]
1	CuCl	1.5	0	rt	2	61	85/15
2[b]	CuCl	1.5	0	rt	24	nd[c]	—
3	CuCl	1.0	0	rt	2	62	85/15
4	CuCl	0.5	0	rt	2	60	86/14
5	CuCl	0.5	0	rt	14	75	86/14
6[d]	CuCl	0.5	0	rt	14	72	84/16
7	CuCl	0.5	0	0 °C	48	48	90/10
8	CuCl	0.5	1	rt	14	78	89/11
9	CuCl	0.5	1	0 °C	48	68	93/7
10	CuCl	0.5	2	rt	24	71	91/9
11	CuCl	0.5	2	0 °C	48	43	93/7
12	CuCl	0.5	5	rt	48	34	91/9
13	CuCl	0.1	0	rt	14	52	85/15
14	CuCl	0.05	0	rt	36	24	86/14
15	—	—	0	rt	24	nd[c]	—
16	CuBr	1.5	0	rt	18	11	85/15
17	CuI	1.5	0	rt	48	5	84/16
18	$CuOTf(C_6H_6)_{0.5}$	0.5	0	rt	20	72	85/15

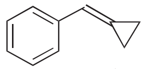
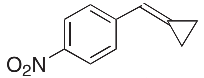
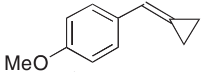
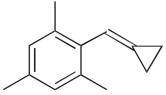
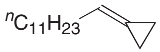
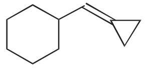
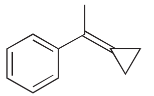
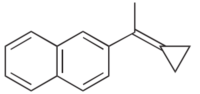
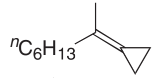
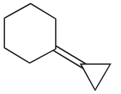
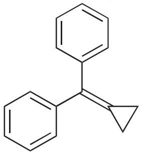
[a] The ratios were determined by 400 MHz ^1H NMR spectra. [b] The reaction was carried out without $PdCl_2$. [c] The signal of product **2a** was not detected in the ^1H NMR spectrum of a mixture of the crude products. [d] EtOH was used instead of MeOH and the ethyl ester corresponding to **2a** was obtained.

Various methylenecyclopropanes **1** were subjected to bis(alkoxycarbonylation) reaction in MeOH at rt (Conditions A) or in THF/MeOH (1/1, v/v) at 0 °C (Conditions B). As shown in Table 2, the corresponding two carbon-homologated glutarates **2** were obtained in good chemical yields.[8–10] Benzylidenecyclopropanes **1a**–**1d** furnished (*E*)-α-benzylideneglutarates **2a**–**2d** selectively (Entries 1–6). Alkylidenecyclopropanes **1e** and **1f** afforded the α-alkylideneglutarates in good chemical yields (Entries 7–9). In the reaction of (cyclohexylmethylidene)cyclopropane (**1f**), (*Z*)-**2f** was mainly produced. When the carbonylation was carried out in THF/MeOH at 0 °C, production of (*E*)-**2f** was slightly increased. Bis(alkoxycarbonylation) reaction of tetrasubstituted olefinic substrates **1g**–**1k** also proceeded to give tetrasubstituted olefins **2g**–**2k** in good chemical yields (Entries 10–15). In contrast to **1a**, (α-methylbenzylidene)cyclopropane (**1g**) gave (*Z*)-**2g** preferentially (Entries 1 and 10, 2 and 11).

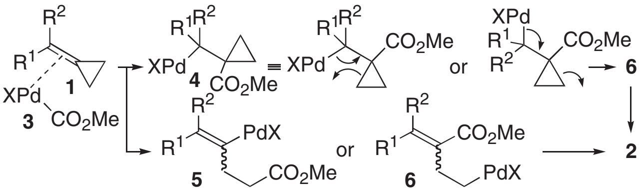
Although the precise mechanism of the present ring-opening bis(alkoxycarbonylation) reaction is still an open question, two possible pathways are shown in Scheme 1. The carbopalladation of a double bond in **1** with (methoxycarbonyl)palladium inter-

Table 2. Bis(alkoxycarbonylation) reaction of **1**



Entry	1		Conditions	t/h	Yield/%	E/Z[a]
1		**a**	A	14	75	86/14
2			B	48	68	93/7
3	 O$_2$N	**b**	A	14	94	80/20
4	 MeO	**c**	A	14	80	89/11
5		**d**	A	34	95	90/10
6			B	72	29	92/8
7	 ^{n}C$_{11}$H$_{23}$	**e**	A	14	75	48/52
8		**f**	A	20	78	12/88
9			B	48	55	37/63
10		**g**	A	14	88	17/83
11			B	48	57	14/86
12		**h**	A	14	91	17/83
13	 ^{n}C$_6$H$_{13}$	**i**	A	14	91	16/84
14		**j**	A	14	73	—
15		**k**	A	72	55	—

[a]The ratios were determined by 400 MHz ^{1}H NMR spectra.



Scheme 1.

mediate **3**, formed in the presence of CuCl, gives **4**,[2] which undergoes ring-opening *cis*- or *trans*-β-carbon elimination followed by the second carbonylation.[7] Another pathway via a cleavage of proximal cyclopropane C–C bond, probably through oxidative addition of **3**, giving intermediate **5** or **6** could not be ruled out. The stereochemistry of the double bonds in the products **2**, however, could not be elucidated well yet even by both mechanisms.[11]

As described above, bis(alkoxycarbonylation) reaction toward methylenecyclopropanes was realized by utilizing palladium and copper salt under remarkably mild conditions to afford the corresponding α-methyleneglutarates in good yields. It is noteworthy that (*E*)-olefins **2a**–**2d** were selectively produced by the reaction of mono-aromatic-substituted substrates **1a**–**1d**, whereas (*Z*)-olefins **2g**–**2i** were obtained from tetrasubstituted olefinic substrates **1g**–**1i**. Further studies are now in progress in our laboratory.

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References and Notes

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2 K. Inomata, S. Toda, H. Kinoshita, *Chem. Lett.* **1990**, 1567; S. Toda, M. Miyamoto, H. Kinoshita, K. Inomata, *Bull. Chem. Soc. Jpn.* **1991**, *64*, 3600; T. Mizutani, Y. Ukaji, K. Inomata, *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1251.

3 Enantioselective version of the bis(alkoxycarbonylation) reaction: Y. Ukaji, M. Miyamoto, M. Mikuni, S. Takeuchi, K. Inomata, *Bull. Chem. Soc. Jpn.* **1996**, *69*, 735; S. Takeuchi, Y. Ukaji, K. Inomata, *Bull. Chem. Soc. Jpn.* **2001**, *74*, 955; T. Aratani, K. Tahara, S. Takeuchi, Y. Ukaji, K. Inomata, *Chem. Lett.* **2007**, *36*, 1328.

4 a) D. E. James, J. K. Stille, *J. Am. Chem. Soc.* **1976**, *98*, 1810. b) Y. Tamaru, M. Hojo, Z. Yoshida, *J. Org. Chem.* **1991**, *56*, 1099. c) T. Yokota, S. Sakaguchi, Y. Ishii, *J. Org. Chem.* **2002**, *67*, 5005.

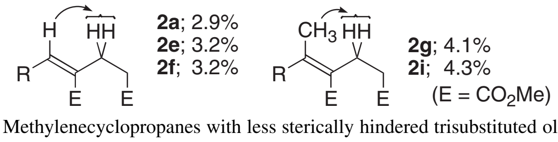
5 Bis(alkoxycarbonylation) reaction of 2-methyl-1-alkenes was reported to produce glutarates in low yield: see ref. 4a.

6 a) A. Brandi, A. Goti, *Chem. Rev.* **1998**, *98*, 589. b) I. Nakamura, Y. Yamamoto, *Adv. Synth. Catal.* **2002**, *344*, 111. c) A. Brandi, S. Cicchi, F. M. Cordero, A. Goti, *Chem. Rev.* **2003**, *103*, 1213. d) M. Rubin, M. Rubina, V. Gevorgyan, *Chem. Rev.* **2007**, *107*, 3117. e) N. Hayashi, Y. Hirokawa, I. Shibata, M. Yasuda, A. Baba, *J. Am. Chem. Soc.* **2008**, *130*, 2912.

7 Palladium-catalyzed ring-opening copolymerization of methylenecyclopropanes with CO was recently reported: S. Kim, D. Takeuchi, K. Osakada, *J. Am. Chem. Soc.* **2002**, *124*, 762; D. Takeuchi, A. Yasuda, T. Okada, J. Kuwabara, K. Osakada, K. Tomooka, *Helv. Chim. Acta* **2006**, *89*, 1574.

8 A representative procedure for the bis(alkoxycarbonylation) reaction of **1a** (Table 2, Entry 2): Under an Ar atmosphere, PdCl$_2$ (1.90 mg, 0.011 mmol), CuCl (25 mg, 0.25 mmol) was placed in a flask and a MeOH (2 mL) solution of **1a** (64 mg, 0.49 mmol) and THF (2 mL) were added. The Ar atmosphere was replaced with CO/O$_2$ (ca. 1/1, v/v) and the reaction mixture was stirred for 48 h at 0 °C. A saturated aqueous solution of NaHCO$_3$ was added and the insoluble substance was filtered off. After the filtrate was extracted with ethyl acetate, the combined extracts were washed with water and brine, dried over Na$_2$SO$_4$, and condensed in vacuo. The residue was purified by TLC on silica gel to give **2a** (83 mg, 68%, E/Z = 93/7).

9 The stereochemistry of double bond in **2** was determined by NOE measurement. Representative data were shown below:



10 Methylenecyclopropanes with less sterically hindered trisubstituted olefinic moiety were not stable enough under the reaction conditions. For example in the case of **1a**, the small amount of unidentified by-products were observed in the crude ^{1}H NMR spectrum. However, a succinate derivative derived from direct carbonyl insertion of **4a** and a product such as methyl 5-phenyl-3,4-pentadienoate or methyl 3-phenyl-2-vinylacrylate, which could be generated from **5a** or **6a** via β-hydrogen elimination, were not detected at least.

11 The palladium-catalyzed reaction mechanism via addition–elimination vs. the direct cleavage of cyclopropane C–C bond was discussed. See: M. Suginome, T. Matsuda, Y. Ito, *J. Am. Chem. Soc.* **2000**, *122*, 11015 and ref. 6b.

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