J|A|C|S COMMUNICATIONS

Published on Web 05/20/2006

Palladium-Catalyzed Ring Enlargement of Aryl-Substituted Methylenecyclopropanes to Cyclobutenes

Min Shi,*,† Le-Ping Liu,‡ and Jie Tang‡

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China, and Department of Chemistry, East China Normal University, 3663 Zhongshanbei Lu, Shanghai 200062, China

Received March 14, 2006; E-mail: mshi@pub.sioc.ac.cn

Methylenecyclopropanes (MCPs) **1** are highly strained but readily accessible molecules that have served as useful building blocks in organic synthesis.[1,2] MCPs undergo a variety of ring-opening reactions in the presence of transition metal and Lewis acid catalysts because the relief of ring strain provides a potent thermodynamic driving force.[3,4] Several pathways for the cleavage of both proximal and distal bonds of MCPs catalyzed by transition metals have been reported.[2a,5] Herein, we report a new such reaction in which palladium-catalyzed ring enlargement of aryl-substituted MCPs **1** to the corresponding cyclobutenes **2** occurs in the presence of metal bromides in 1,2-dichloroethane (DCE) under mild conditions.

Cyclobutenes are mainly used in cycloaddition and photochemical reactions,[6] and a few strategies have been reported for their synthesis. One of the most common routes to cyclobutenes is the photochemical or thermal [2 + 2] cycloaddition reaction of an alkyne and an alkene.[7] In our ongoing investigation of the transformation of MCPs, we envisioned that, if a metal carbene intermediate was generated at the C_1 position of MCPs, a ring enlargement would take place to give the corresponding cyclobutene product.[8] In this paper, we disclose a new Pd-catalyzed method for the synthesis of 1-aryl cyclobutenes.

Using (2-benzyloxy)phenylmethylenecyclopropane (**1a**) as the substrate, we investigated the feasibility of the proposed reaction and found the optimal reaction conditions for the formation of the corresponding cyclobutene, **2a**. The results are summarized in Table 1. Palladium chloride and palladium bromide catalyzed the reaction to afford **2a** in 62 and 84% yields, respectively, within 24 h at room temperature in DCE (entries 1 and 2). Palladium acetate and bis(triphenylphosphine)palladium chloride did not catalyze this reaction under the same conditions (entries 3 and 4). Bis(nitrile)-palladium halides, the more soluble Pd(II) catalysts, did not give better results than palladium halides (entries 5−7). However, in the presence of metal bromides such as copper bromide,[9] zinc bromide, and magnesium bromide, **2a** was produced in excellent conversions and high yields under $Pd(OAc)_2$ catalysis (entries 8−12). Chloride and iodide salts are less effective than the bromide salts (entries 13−15). Next, we examined the effect of solvent choice on this reaction (entries 16−22). The reaction proceeded smoothly in THF, toluene, dichloromethane, chloroform, and dioxane, but the yields of **2a** were not as high as those within DCE (entries 16−20). In both acetonitrile and diethyl ether, only a trace of **2a** was formed (entries 21 and 22). Other metal catalysts, such as $RhCl(PPh_3)_3$, $RuCl_3$, $PtCl_2$, and $Au(PPh_3)Cl$, did not catalyze this reaction under identical conditions.

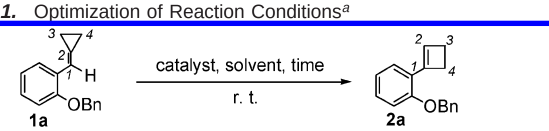
Using the optimal reaction conditions, we carried out the palladium-catalyzed ring enlargement of a variety of MCPs **1** and found that the corresponding cyclobutenes **2** were obtained in moderate to high yields (Table 2). The product structures were determined by ^{1}H and ^{13}C NMR spectroscopic data, HRMS, and microanalysis. Furthermore, the X-ray crystal structure of **2l**[10] was determined and is presented in the Supporting Information.[11]

An electron-donating group on the aromatic ring of **1** significantly promoted the reaction, and these reactions were complete within 3 h at room temperature to give the corresponding cyclobutenes **2** in good yields and conversions (Table 2, entries 2−4, 7, 9, and 11−15). On the other hand, having either an electron-withdrawing group or no substituent on the aromatic ring retarded the reaction (entries 1, 5, 6, and 10). For MCP **1i**, higher temperature (80 °C) and longer reaction time were required to give the corresponding cyclobutenes **2i** in high yield and conversion (entry 8). It should be noted that, if R is an alkyl group, no reaction occurred even at high temperature (80 °C).

A plausible mechanism for this unusual ring enlargement of **1** to **2** is presented in Scheme 1. Regioselective bromopalladation of MCPs **1**[5a,12] with $PdBr_2$, which might be produced in situ from $Pd(OAc)_2$ and MBr_n (M = Cu, Zn, Mg, Li), affords intermediate **A**.[13] Intermediate **A** undergoes β-hydrogen elimination to form intermediate **B**, which subsequently generates palladium carbenoid **C** via hydropalladation with a reversed regioselectivity. Via an α-bromo migration,[14] **C** is transformed to a palladium carbene **D**,[15] which yields the product **2**[8] and regenerates the palladium bromide catalyst. To test the plausibility of this proposed mechanism, we designed a deuterium labeling experiment. When deuterated substrate **1a-*d*** was subjected to the standard reaction conditions, cyclobutene **2a-*d*** (>99% D incorporation)[16] with the deuterium at the 2-position was obtained in 83% yield (Scheme 2). This result is consistent with the mechanism proposed in Scheme 1.

In conclusion, we have found a versatile palladium-catalyzed ring enlargement reaction where methylenecyclopropanes are con-

Table 1. Optimization of Reaction Conditions[a]



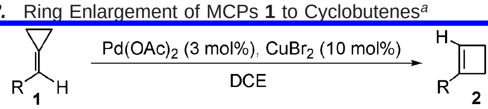
entry	catalyst	solvent	time/h	**2a** yield/[%][b] (conv./[%])[c]
1	$PdCl_2$	DCE	24	62 (85)
2	$PdBr_2$	DCE	24	84 (92)
3	$Pd(OAc)_2$	DCE	24	N. R.
4	$Pd(PPh_3)_2Cl_2$	DCE	24	N. R.
5	$Pd(CH_3CN)_2Cl_2$	DCE	24	trace
6	$Pd(CH_3CN)_2Br_2$	DCE	24	64 (74)
7	$Pd(PhCN)_2Br_2$	DCE	24	73 (87)
8	***$Pd(OAc)_2$, $CuBr_2$***	***DCE***	***3***	***93 (>99)***
9	$Pd(OAc)_2$, LiBr	DCE	24	69 (83)
10	$Pd(OAc)_2$, $ZnBr_2$	DCE	3	91 (>99)
11	$Pd(OAc)_2$, $NiBr_2$	DCE	24	trace
12	$Pd(OAc)_2$, $MgBr_2$	DCE	12	81 (>99)
13	$Pd(OAc)_2$, LiCl	DCE	24	trace
14	$Pd(OAc)_2$, $CuCl_2$	DCE	24	trace
15	$Pd(OAc)_2$, NaI	DCE	24	N. R.
16	$Pd(OAc)_2$, $CuBr_2$	THF	24	39 (53)
17	$Pd(OAc)_2$, $CuBr_2$	toluene	3	70 (>99)
18	$Pd(OAc)_2$, $CuBr_2$	CH_2Cl_2	3	77 (>99)
19	$Pd(OAc)_2$, $CuBr_2$	$CHCl_3$	3	77 (>99)
20	$Pd(OAc)_2$, $CuBr_2$	dioxane	24	79 (95)
21	$Pd(OAc)_2$, $CuBr_2$	CH_3CN	24	trace
22	$Pd(OAc)_2$, $CuBr_2$	Et_2O	24	trace

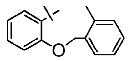
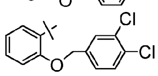
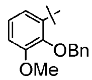
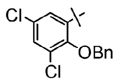
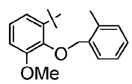
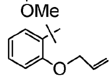
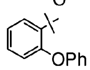
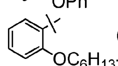
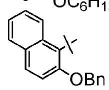
[a] Reaction conditions: **1a** (0.3 mmol), palladium catalyst (3 mol %), bromide (10 mol %), solvent (2.0 mL). [b] Isolated yields. [c] Starting material consumed after column chromatography.

† Chinese Academy of Sciences.
‡ East China Normal University.

10.1021/ja061749y CCC: $33.50

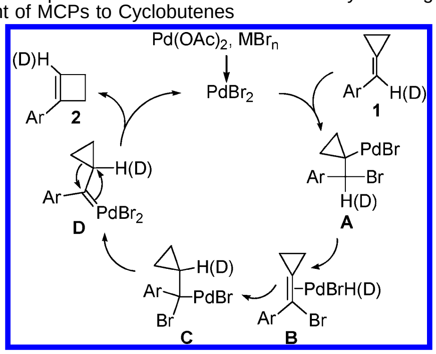
Table 2. Ring Enlargement of MCPs **1** to Cyclobutenes[a]



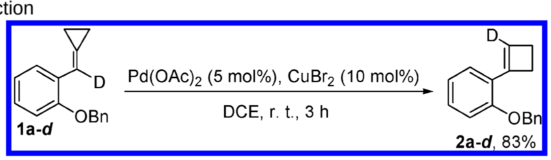
entry	R	temp./°C	time/h	yield/[%][b] (conv./[%])[c]
1	C_6H_5 (**1b**)	80	24	**2b**, 46 (68)
2	*p*-$CH_3C_6H_4$ (**1c**)	r.t.	3	**2c**, 52 (>99)
3	*p*-$CH_3OC_6H_4$ (**1d**)	r.t.	1	**2d**, 60 (>99)
4	*o,p*-$(CH_3O)_2C_6H_3$ (**1e**)	r.t.	3	**2e**, 74 (>99)
5	*p*-ClC_6H_4 (**1f**)	80	24	**2f**, 41 (60)
6	*m*-ClC_6H_4 (**1g**)	80	24	**2g**, 38 (62)
7	 (**1h**)	r.t.	3	**2h**, 89 (>99)
8	 (**1i**)	80	10	**2i**, 91 (>99)
9	 (**1j**)	r.t.	3	**2j**, 91 (>99)
10	 (**1k**)	80	24	**2k**, 64 (82)
11	 (**1l**)	r.t.	3	**2l**, 93 (>99)
12	 (**1m**)	r.t.	3	**2m**, 91 (>99)
13	 (**1n**)	r.t.	3	**2n**, 85 (>99)
14	 (**1o**)	r.t.	3	**2o**, 83 (>99)
15	 (**1p**)	r.t.	3	**2p**, 90 (>99)

[a] Reactions were carried out by use of MCP **1** (0.3 mmol) in 1,2-dichloroethane (DCE) (2.0 mL) with palladium acetate (2.0 mg, 3 mol %) and copper(II) bromide (7.0 mg, 10 mol %). [b] Isolated yields. [c] Starting material consumed after column chromatography.

Scheme 1. Proposed Mechanism for the Pd-Catalyzed Ring Enlargement of MCPs to Cyclobutenes



Scheme 2. Deuterium Labeling Experiment of the Ring Enlargement Reaction



verted into the corresponding cyclobutene compounds. This represents a new ring-opening isomerization reaction pathway of methylenecyclopropane and a novel approach for the synthesis of 1-aryl-substituted cyclobutenes. In this manner, a series of cyclobutenes was obtained under mild conditions in moderate to good yields.

Acknowledgment. We thank the State Key Project of Basic Research (Project 973) (No. G2000048007), Shanghai Municipal Committee of Science and Technology (04JC14083), Chinese Academy of Sciences (KGCX2-210-01), and the National Natural Science Foundation of China for financial support (20025206, 203900502, and 20272069).

Supporting Information Available: ^{1}H and ^{13}C NMR, MS, HRMS, and analytic data of the compounds shown in Tables 1 and 2 and Schemes 1 and 2, X-ray crystal structure of **2k**, and a detailed description of experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Synthesis of MCPs: Brandi, A.; Goti, A. *Chem. Rev.* **1998**, *98*, 589.
(2) For recent reviews, see: (a) Nakamura, I.; Yamamoto, Y. *Adv. Synth. Catal*. **2002**, *344*, 111. (b) Brandi, A.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Rev.* **2003**, *103*, 1213. (c) Nakamura, E.; Yamago, S. *Acc. Chem. Res.* **2002**, *35*, 867.
(3) Selected recent articles about transition metal catalyzed reactions of MCPs: (a) Nakamura, I.; Oh, B. H.; Saito, S.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1298. (b) Camacho, D. H.; Nakamura, I.; Saito, S.; Yamamoto, Y. *J. Org. Chem.* **2001**, *66*, 270. (c) Lautens, M.; Meyer, C.; Lorenz, A. *J. Am. Chem. Soc.* **1996**, *118*, 10676. (d) Saito, S.; Masuda, M.; Komagawa, S. *J. Am. Chem. Soc.* **2004**, *126*, 10540. (e) Brase, S.; de Meijere, A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2545. (f) Shi, M.; Wang, B.-Y.; Huang, J.-W. *J. Org. Chem.* **2005**, *70*, 5606.
(4) Selected recent articles about Lewis acid mediated reactions of MCPs: (a) Huang, J.-W.; Shi, M. *Synlett* **2004**, 2343. (b) Shi, M.; Xu, B.; Huang, J.-W. *Org. Lett.* **2004**, *6*, 1175. (c) Xu, B.; Shi, M. *Org. Lett.* **2003**, *5*, 1415. (d) Shi, M.; Shao, L.-X.; Xu, B. *Org. Lett.* **2003**, *5*, 579. (e) Patient, L.; Berry, M. B.; Kilburn, J. D. *Tetrahedron Lett.* **2003**, *44*, 1015 and references cited therein.
(5) (a) Ma, S.; Lu, L.; Zhang, J. *J. Am. Chem. Soc.* **2004**, *126*, 9645. (b) Siriwardana, A. I.; Kamada, M.; Nakamura, I.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 5932.
(6) Selected recent articles about cyclobutenes: (a) Feng, J.; Szeimies, G. *Eur. J. Org. Chem.* **2002**, 2942. (b) Kniep, C. S.; Padias, A. B.; Hall, H. K., Jr. *Tetrahedron* **2000**, *56*, 4279. (c) Mislin, G. L.; Miesch, M. *J. Org. Chem.* **2003**, *68*, 433. (d) Delas, C.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **2001**, *123*, 7937. (e) Tantillo, D. J.; Hoffmann, R. *J. Am. Chem. Soc.* **2001**, *123*, 9855. (f) Murakami, M.; Hasegawa, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4874. (g) Liu, Y.; Liu, M.; Song, Z. *J. Am. Chem. Soc.* **2005**, *127*, 3662.
(7) For the synthesis of cyclobutenes, see: (a) *Carbocyclic Four-member Ring Compounds, Houben-Weyl, Methods of Organic Chemistry*; de Meijere, A., Ed.; Thieme: Stuttgart, 1997; Vol. 17f, E 17e-f. (b) Hall, H. K., Jr.; Padias, A. B. *J. Polym. Sci, Part A: Polym. Chem.* **2003**, *41*, 625. (c) Leigh, W. J.; Postigo, J. A. *Can. J. Chem.* **1995**, *73*, 191. (d) Barbero, A.; Cuadrado, P.; Garcia, C.; Rincon, J. A.; Pulido, F. J. *J. Org. Chem.* **1998**, *63*, 7531. (e) Juteau, H.; Gareau, Y. *Synth. Commun.* **1998**, *28*, 3795. (f) Huang, D.-J.; Rayabarapu. D. K.; Li, L.-P.; Sambaiah, T.; Cheng, C.-H. *Chem.*—*Eur. J.* **2000**, *6*, 3706. (g) Takahashi, T.; Shen, B.; Nakajima, K.; Xi, Z. *J. Org. Chem.* **1999**, *64*, 8706. (h) Villeneuve, K.; Tam, W. *Angew. Chem., Int. Ed.* **2004**, *43*, 610. (i) Winkler, J. D.; Melaughlin, E. C. *Org. Lett.* **2005**, *7*, 227.
(8) For the cycloisomerization of α-cyclopropanyl metal carbene to cyclobutene, see: (a) Furstner, A.; Davies, P. D.; Gress, T. *J. Am. Chem. Soc.* **2005**, *127*, 8244. (b) Nieto-Oberhuber, C.; López, S.; Muñoz, M. P.; Cardenas, D. J.; Buñuel, E.; Nevado, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6146. (c) Trost, B. M.; Tanoury, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 1636. (d) Trost, B. M.; Trost, M. K. *Tetrahedron Lett.* **1991**, *32*, 3647. (e) Nieto-Oberhuber, C.; López, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*, 6178.
(9) For $CuBr_2$ (2.0 equiv) mediated ring-opening reaction of MCPs giving dibrominated compounds, see: Zhou, H.-W.; Huang, X.; Chen, W.-L. *Synlett* **2003**, 2080.
(10) The crystal data of **2k** have been deposited in CCDC with number 289394.
(11) The ^{1}H and ^{13}C NMR spectroscopic data of compounds **2b**, **2c**, and **2d** (see the Supporting Information) are similar to those reported in previous publications. See refs 7c, 7d, and (a) Wilt, J. W.; Kosturik, J. M.; Orlowski, R. C. *J. Org. Chem.* **1965**, *30*, 1052. (b) Hill, E. A.; Engel, M. R. *J. Org. Chem.* **1971**, *36*, 1536. (c) Kirmse, W.; Krzossa, B.; Steenken, S. *J. Am. Chem. Soc.* **1996**, *118*, 7473.
(12) For recent articles on halopalladation to multi carbon−carbon bonds, see: (a) Ma, S.; Lu, X. *Chem. Commun.* **1990**, 733. (b) Ma, S.; Lu, X. *J. Org. Chem.* **1991**, *56*, 5120. (c) Ma, S.; Zhu, G.; Lu, X. *J. Org. Chem.* **1993**, *58*, 3692. (d) Zhu, Z.; Zhang, Z. *J. Org. Chem*. **2005**, *70*, 3339.
(13) Another route for the formation of intermediate **A** and the corresponding mechanism was presented in Supporting Information as Scheme SI-2.
(14) For the migration of α-halo to a metal center, see: (a) McCrindle, R.; Arsenault, G. J.; Gupta, A.; Hampden-Smith, M. J.; Rice, R. E.; McAlees, A. J. *J. Chem. Soc., Dalton Trans.* **1991**, 949. (b) McCrindle, R.; Ferguson, G.; McAlees, A. J.; Arsenault, G. J.; Gupta, A.; Jennings, M. C. *Organometallics* **1995**, *14*, 2741. (c) Bernardi, F.; Bottoni, A.; Miscione, G. P. *Organometallics* **2001**, *20*, 2751.
(15) For an article on palladium carbene, see: (a) Fillion, E.; Taylor, J. *J. Am. Chem. Soc.* **2003**, *125*, 12700 and references therein. (b) Nakamura, I.; Bajracharya, G. B.; Mizushima, Y.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 4328. (c) Yamamoto, Y.; Kuwabara, S.; Ando, Y.; Nagata, H.; Nishiyama, H.; Itoh, K. *J. Org. Chem.* **2004**, *69*, 6697 and references cited therein.
(16) Determined by ^{1}H and ^{13}C NMR spectroscopic data (see the Supporting Information).

JA061749Y