Palladium(II)-catalyzed ring enlargement of 2-(arylmethylene)cyclopropylcarbinols: strong effect of substituent electronic nature on the reaction pathway†

Guo-Qiang Tian,[a] Zhi-Liang Yuan,[b] Zhi-Bin Zhu[b] and Min Shi*[ab]

Received (in College Park, MD, USA) 25th March 2008, Accepted 25th April 2008
First published as an Advance Article on the web 8th May 2008
DOI: 10.1039/b804932g

In the presence of Pd(II) catalyst and copper(II) bromide, 2-(arylmethylene)cyclopropylcarbinols undergo ring enlargement to deliver (arylcyclobutenyl)carbinols or hydrogenated furans in good yields under mild conditions; mechanisms accounting for the distinct products have been proposed on the basis of control and deuterium labeling experiments.

Methylenecyclopropanes (MCPs) are generally used as building blocks in organic synthesis for their ready accessibility as well as diverse reactivity driven by the relief of ring strain. Over the past decades, a series of review articles have been published on the transformations of these *exo*-methylene three-membered carbocycles.[1] Transition metal catalysts, now one of the most powerful tools for synthetic chemists, have played an increasingly important role in these transformations.[2,3] Recently, we showed that, catalyzed by palladium acetate and metal bromide, MCPs could undergo ring enlargement to provide the cyclobutene motif efficiently.[4] Almost at the same time, Fürstner and Aïssa reported a similar transformation promoted by platinum.[5]

2-(Arylmethylene)cyclopropylcarbinols **1** are another kind of MCP bearing an additional hydroxymethyl group[6] and, as demonstrated by our group, can undergo a variety of transformations triggered by the nucleophilic hydroxyl group under milder conditions.[7] In view of this, we hypothesized that the tethered hydroxyl group might accelerate transition metal-assisted reactions or trap the reaction intermediates of MCPs. Herein, we wish to report the palladium(II) chloride-catalyzed ring enlargement of 2-(arylmethylene)cyclopropylcarbinols in the presence of copper(II) bromide to furnish (arylcyclobutenyl)carbinols or hydrogenated furans in good yields depending on the substituents on the benzene ring.

The initial examination was performed using (*E*)-[2-(4-methoxybenzylidene)cyclopropyl]methanol **1a** as the substrate upon treatment with $Pd(OAc)_2$ and $CuBr_2$ at room temperature (20 °C) in dichloromethane (DCM). We found that the starting material disappeared rapidly and complex product mixtures were obtained within 0.2 h (Table S1,† entry 1). When the temperature was decreased to 0 °C, to our delight, we found that the ring expanded products **2a** and **3a** were obtained in good total yield (75%) along with moderate selectivity, with a ratio 5 : 1, within 0.5 h (entry 2). The structure of **2a** has been further confirmed by X-ray diffraction (ESI†).[8] Compared with the method described in our previous paper,[4] this procedure needs a much lower activation energy, indicating that the hydroxymethyl group does play an important role in accelerating the reaction rate. Following that, we next screened the reaction conditions in detail. When the reaction was carried out in 1,2-dichloroethane (DCE) a similar result was obtained, although toluene, THF, diethyl ether and acetonitrile were not suitable solvents for this reaction (entries 3–7). $Pd(OAc)_2$ or $CuBr_2$ alone did not promote the transformation (entries 8 and 9). Combination of $Pd(OAc)_2$ with other copper salts such as $Cu(OTf)_2$, $CuCl_2$, $Cu(OAc)_2$ or CuBr did not give an effective catalytic system (entries 10, 12–14). If the catalytic system contained K_2CO_3, no reaction occurred (entry 11). On the other hand, on the examination of some other metal bromides such as $NiBr_2$, NaBr, $MgBr_2$, $ZnBr_2$, and LiBr, only $NiBr_2$ gave a satisfactory result (entries 15–20). These results suggest that $PdBr_2$ might be the real active catalyst in this transformation. Actually, the same products were produced when either $PdBr_2$ or $PdCl_2$ was loaded as the sole catalyst, although in low yields (entries 21 and 22). Continuous experiments showed that the combination of $PdCl_2$, $CuBr_2$ (0.03 or 0.06 mmol) and $NaHCO_3$ could catalyze this transformation smoothly to afford cyclobutenylcarbinols **2a** and **3a** in good total yields along with high selectivities, with the ratio 12 : 1, within 0.5 h (entries 24 and 25).

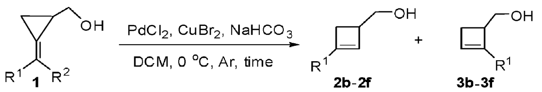
With the optimal conditions identified, we next examined the scope of the transformation. Substrates **1**, bearing electron-donating groups on the benzene ring, underwent ring expanding reactions smoothly to provide the corresponding (arylcyclobutenyl)carbinols **2b**–**2f** and **3c**–**3e** in good total yields and good-to-excellent selectivities within 1 h (Table 1, entries 1–5). (*Z*)-2-(4-Methoxybenzylidene)cyclopropyl]-methanol (*Z*)-**1a** delivered the same products as its (*E*)-isomer in slightly lower yield and selectivity under the standard conditions (entry 6). However, when these reaction conditions were applied to (*E*)-(2-benzylidenecyclopropyl)methanol **1g** which does not have substituent on the benzene ring or substrates **1h** and **1i** bearing electron-withdrawing groups on

---

[a] *State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai, China 200032. E-mail: Mshi@mail.sioc.ac.cn*
[b] *School of Chemistry and Molecular Engineering, East China University of Science and Technology, 130 Meilong Road, Shanghai, China 200237*

† Electronic supplementary information (ESI) available: Experimental procedures and spectroscopic data for all compounds. CCDC 665100 and 674227. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b804932g

Table 1 Formation of (arylcyclobutenyl)carbinols from 2-(arylmethylene)cyclopropylcarbinols



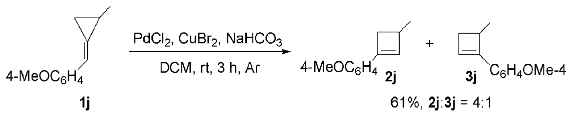
Entry[a]	R^1/R^2	Time/h	Yield[b] (%) (**2** : **3**)
1[c]	3-BnOC$_6$H$_4$/H, **1b**	1	75 (**2b**)
2	3,4,5-(MeO)$_3$C$_6$H$_2$/H, **1c**	0.5	89 (13 : 1) (**2c** : **3c**)
3	2,5-(MeO)$_2$C$_6$H$_3$/H, **1d**	0.5	70 (22 : 1) (**2d** : **3d**)
4	4-MeC$_6$H$_4$/H, **1e**	1	70 (17 : 1) (**2e** : **3e**)
5[c]	3-MeC$_6$H$_4$/H, **1f**	1	68 (**2f**)
6	H/4-(MeO)C$_6$H$_4$, (*Z*)-**1a**	0.5	83 (5 : 1) (**2a** : **3a**)
7[d]	C$_6$H$_5$/H, **1g**	2	88 (21 : 1) (**2g** : **3g**)
8[c,d]	4-BrC$_6$H$_4$/H, **1h**	6	61 (**2h**)
9[c,d]	4-ClC$_6$H$_4$/H, **1i**	10	23 (**2i**)

[a] All reactions were carried out with **1** (0.3 mmol), PdCl$_2$ (0.015 mmol), CuBr$_2$ (0.06 mmol), NaHCO$_3$ (0.15 mmol) in 1.0 mL of dichloromethane under an argon atmosphere. [b] Isolated yields. [c] A trace of **3** was observed. [d] 2 mg of MS 4 Å were added.

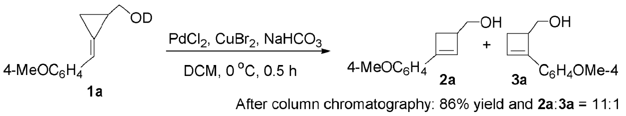
the benzene ring, the reactions were sluggish to afford the corresponding products in sharply lower yields, even upon prolonged reaction time, and most of the starting materials **1** were recovered. After a series of trials and errors, we found that adding molecular sieves (4 Å, 2 mg for 0.3 mmol of **1**) improved the situation to some extent, although a large amount of molecular sieves would suppress the reaction. As a result, the corresponding (arylcyclobutenyl)carbinols **2g**–**2i** and **3g** were obtained in 23–88% total yields (entries 7–9).

To clarify the role of the hydroxymethyl group in this transformation, a control experiment using dehydroxylated substrate **1j** as the substrate was carried out under the standard conditions, and we found that the corresponding ring expanded products **2j** and **3j** were obtained in lower yield and selectivity at elevated temperature (20 °C) even after a longer reaction time (Scheme 1). This result clearly suggested that the hydroxyl group plays an important role in this process. To gain more mechanistic insight into the effects of the hydroxyl group, we carried out deuterium labeling experiments as shown in Scheme 2. The deuterium atom on the hydroxyl group did not shift into the products **2** and **3** and the results are very similar as those shown in entry 25 of Table S1.† When the hydroxyl group was protected by a benzyl group, a similar result was obtained after a longer reaction time (see the ESI†). However, when the hydroxyl group was replaced by an amino group, no reaction occurred, indicating that just the hydroxyl group would work by accelerating the reaction rate *via* coordination to the palladium center.

As noted above, products **2** and **3** were formed in lower yields and most of the starting materials **1** were recovered in the absence of 4 Å molecular sieves when using substrates **1** with an electron-withdrawing group on the benzene ring in the presence of PdCl$_2$ (5 mol%) and CuBr$_2$ (20 mol%). However, when these reactions were carried out under an air atmosphere in the presence of PdCl$_2$ (5 mol%) and 2.5 equiv. of CuBr$_2$, products **4** and *anti*-**5**[9] were the dominant products (Table 2, entries 2–5). As for (*E*)-(2-benzylidenecyclopropyl)methanol, **1g**, which does not have a substituent on the benzene ring, also cleanly underwent this type of transformation to provide **4g** and *anti*-**5g** in good total yield (entry 1). (*Z*)-[2-(4-Fluorobenzylidene)cyclopropyl]methanol (*Z*)-**1k** gave the same products as its (*E*)-isomer, but in a lower yield (Table 2, entry 6). It should be noted that 47% of *anti*-**5h** could be converted to **4h**† if it was stored at 0 °C for 6 days, indicating that compounds **4** are more thermodynamically stable. A control experiment was carried out to evaluate the S$_N$2′ reaction pathway of *anti*-**5h** in the presence of NaBr (1.0 equiv.) under the standard conditions (Scheme 3). It was found that **4h** was formed in 16% yield after 24 h, suggesting that this S$_N$2′ reaction was relatively sluggish and compounds **4** and *anti*-**5** were formed through two different reaction pathways.



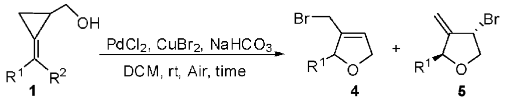
Scheme 1 Effects of the hydroxyl group.



Scheme 2 Deuterium labeling experiment.

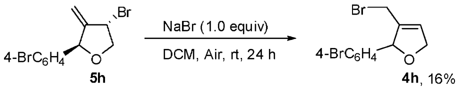
Plausible reaction mechanisms have been proposed for these two distinct transformations (Scheme 4). In process I, the hydroxy group in compound **1** first coordinates to PdX$_2$ (X = Cl or Br) to form a chelated intermediate **A**, which then produces a zwitterionic intermediate **B** (this process might be the rate-determining step of the transformation). This zwitterionic intermediate is stabilized by the cyclopropylmethyl group[10] and reinforced by the electron-donating group substituted benzene ring. Rearrangement of this "non-classical" zwitterionic species produces carbene intermediates **C** and **D** *via* path a and path b, respectively. The final products of (arylcyclobutenyl)carbinols **2** and **3** are furnished by a following 1,2-hydrogen shift.[4,5] In process II, a partially charged zwitterionic intermediate **E**[11] rather than the totally changed zwitterionic intermediate **B** might exist, which presumably

Table 2 Formation of dihydrofurans and tetrahydrofurans

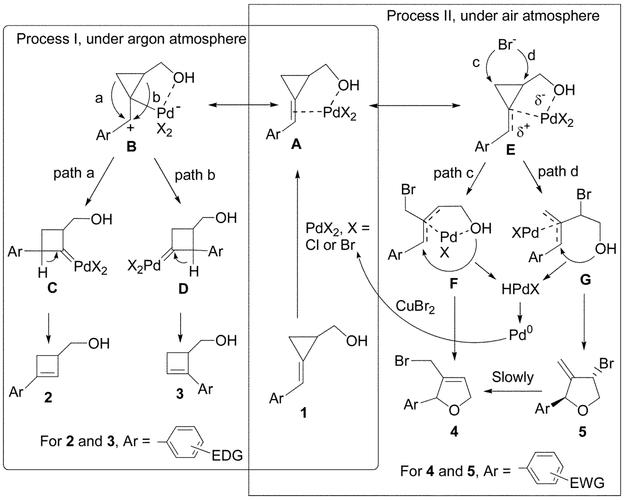


Entry[a]	R^1/R^2	Time/h	Yield[b] (%) (**4** : **5**)
1	C$_6$H$_5$/H, **1g**	12	85 (3 : 1) (**4g** : **5g**)
2	4-BrC$_6$H$_4$/H, **1h**	12	81 (3 : 1) (**4h** : **5h**)
3	4-ClC$_6$H$_4$/H, **1i**	12	82 (3 : 1) (**4i** : **5i**)
4	4-FC$_6$H$_4$/H, **1k**	12	97 (3 : 1) (**4k** : **5k**)
5	2,3-Cl$_2$C$_6$H$_3$/H, **1l**	12	70 (3 : 1) (**4l** : **5l**)
6	H/4-FC$_6$H$_4$, (*Z*)-**1k**	32	27 (3 : 1) (**4k** : **5k**)

[a] All reactions were carried out with **1** (0.3 mmol), PdCl$_2$ (0.015 mmol), CuBr$_2$ (0.75 mmol), NaHCO$_3$ (0.40 mmol) in 1 mL of dichloromethane under an air atmosphere. [b] Isolated yields.



Scheme 3 Control experiment.



Scheme 4 Proposed mechanisms for the two distinct processes.

comes about due to the electronic nature of the electron-withdrawing substituents on the benzene ring. Then, intermediate **E** is attacked from two different orientations by a bromide anion to form π-allylpalladium intermediates **F** and **G** *via* path c and path d, respectively.[12] Subsequent attack of the π-allylpalladium intermediates by the tethered hydroxyl group furnishes the corresponding two products of dihydrofuran **4** and tetrahydrofuran **5**, respectively. In addition, reductive elimination of the forming palladium(II) halide hydride (HPdX) intermediate gives a Pd^0 species, which is oxidized by $CuBr_2$ to regenerate the active catalyst. An alternative mechanism of the reactions under air, similar to a Wacker-type reaction, is provided in the ESI.†

Concerning the operation of process I, two points should be outlined: (a) 0.2 equiv. of $CuBr_2$ (>0.05 equiv. of $PdCl_2$) is necessary because traces of substrate **1** follow process II and subsequently result in the formation of catalytically inactive Pd^0 species although the bromine atom is not incorporated in the products. (b) Adding 4 Å molecular sieves could get rid of the forming water and subsequently decrease the density of nucleophilic bromide anions, accordingly improving the yields of (arylcyclobutenyl)carbinols **2** and **3** especially for substrates **1** with electron-withdrawing groups on the benzene ring.

In conclusion, we have developed an efficient method for ring enlargement of 2-(arylmethylene)cyclopropylcarbinols catalyzed by palladium(II) chloride in the presence of copper(II) bromide. Substrates with electron-donating groups on the benzene ring undergo rearrangement smoothly to provide (arylcyclobutenyl)carbinols in good yields and selectivities under mild conditions. While, substrates with electron-withdrawing groups on the benzene ring produce dihydrofurans and tetrahydrofurans in good total yields in the presence of stoichiometric amounts of $CuBr_2$. Mechanisms have been proposed for these two distinct reaction processes. We think that carbene species might be involved in the formation of (arylcyclobutenyl)carbinols and a π-allylpalladium intermediate would account for the production of the dihydrofuran and tetrahydrofuran products.

We thank the Shanghai Municipal Committee of Science and Technology (04JC14083, 06XD14005) and the National Natural Science Foundation of China for financial support (20472096, 20672127, and 20732008).

Notes and references

1 For reviews, see: (*a*) P. Binger and H. M. Büch, *Top. Curr. Chem.*, 1987, **135**, 77; (*b*) A. Goti, F. M. Cordero and A. Brandi, *Top. Curr. Chem.*, 1996, **178**, 1; (*c*) A. Brandi, S. Cicchi, F. M. Cordero and A. Goti, *Chem. Rev.*, 2003, **103**, 1213; (*d*) E. Nakamura and S. Yamago, *Acc. Chem. Res.*, 2002, **35**, 867.

2 For reviews, see: (*a*) I. Nakamura and Y. Yamamoto, *Adv. Synth. Catal.*, 2002, **344**, 111; (*b*) M. Rubin, M. Rubina and V. Gevorgyan, *Chem. Rev.*, 2007, **107**, 3117.

3 For selected articles, see: (*a*) D. H. Camacho, I. Nakamura, S. Saito and Y. Yamamoto, *Angew. Chem., Int. Ed.*, 1999, **38**, 3365–3367; (*b*) M. Lautens, C. Meyer and A. Lorenz, *J. Am. Chem. Soc.*, 1996, **118**, 10676; (*c*) M. Lautens and Y. Ren, *J. Am. Chem. Soc.*, 1996, **118**, 9597; (*d*) S. Saito, M. Masuda and S. Komagawa, *J. Am. Chem. Soc.*, 2004, **126**, 10540; (*e*) M. Shi, B.-Y. Wang and J.-W. Huang, *J. Org. Chem.*, 2005, **70**, 5606; (*f*) I. Nakamura, B. H. Oh, S. Saito and Y. Yamamoto, *Angew. Chem., Int. Ed.*, 2001, **40**, 1298; (*g*) N. Tsukada, A. Hibuya, I. Nakamura and Y. Yamamoto, *J. Am. Chem. Soc.*, 1997, **119**, 8123; (*h*) M. Suginome, T. Matsuda and Y. Ito, *J. Am. Chem. Soc.*, 2000, **122**, 11015; (*i*) M. E. Scott, Y. Bethuel and M. Lautens, *J. Am. Chem. Soc.*, 2007, **129**, 1482; (*j*) S. Brase and A. de Meijere, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2545; (*k*) I. Nakamura, T. Nemoto, Y. Yamamoto and A. de Meijere, *Angew. Chem., Int. Ed.*, 2006, **45**, 5176.

4 M. Shi, L.-P. Liu and J. Tang, *J. Am. Chem. Soc.*, 2006, **128**, 7430.

5 A. Fürstner and C. Aïssa, *J. Am. Chem. Soc.*, 2006, **128**, 6306.

6 For the preparation of 2-(arylmethylene)cyclopropylcarbinols, see: (*a*) A. Turcant and L. M. Corre, *Tetrahedron Lett.*, 1976, **17**, 985; (*b*) L. M. Corre, A. Hercouet and B. Bessieres, *J. Org. Chem.*, 1994, **59**, 5483.

7 (*a*) G.-Q. Tian and M. Shi, *Org. Lett.*, 2007, **9**, 2405; (*b*) G.-Q. Tian and M. Shi, *Org. Lett.*, 2007, **9**, 4917; (*c*) L.-X. Shao, M.-H. Qi and M. Shi, *Tetrahedron Lett.*, 2008, **49**, 165.

8 Crystal data for **2a** (CCDC 665100): $C_{12}H_{14}O_2$; M = 190.23; crystal color, habit: colorless, prismatic; crystal system: monoclinic; lattice type: primitive; a = 46.33(2), b = 5.461(3), c = 8.220(4) Å, β = 92.926°, V = 2077.2(18) Å^3; space group: $P2(1)/c$; Z = 8; D_{calc} = 1.217 g cm^{-3}; F_{000} = 816; diffractometer: Rigaku AFC7R; residuals: R, wR: 0.0677, 0.1706. F_{000} = 1232; diffractometer: Rigaku AFC7R; residuals: R; wR: 0.0928, 0.2064.

9 The *anti*-configuration of **5** was tentatively assigned on the basis of NOESY spectroscopy (see the ESI†).

10 (*a*) F. A. Carey and R. J. Sundberg, *Advanced Organic Chemistry*, Plenum Press, New York, 5th edn, 1998, pp. 221, 419; (*b*) C. J. Lancelot, D. J. Cram and P. v. R. Schleyer, in *Carbonium Ions*, ed. G. A. Olah and P. v. R. Schleyer, Wiley, New York, 1972, vol. III, p. 1347.

11 (*a*) D. M. Kalendra and B. R. Sickles, *J. Org. Chem.*, 2003, **68**, 1594; (*b*) J.-M. Xu, B.-K. Liu, W.-B. Wu, C. Qian, Q. Wu and X.-F. Lin, *J. Org. Chem.*, 2006, **71**, 3991.

12 (*a*) S. Ma, L. Lu and J. Zhang, *J. Am. Chem. Soc.*, 2004, **126**, 9645; (*b*) I. Nakamura, H. Itagaki and Y. Yamamoto, *J. Org. Chem.*, 1998, **63**, 6458; (*c*) I. Nakamura, A. I. Siriwardana, S. Saito and Y. Yamamoto, *J. Org. Chem.*, 2002, **67**, 3445; (*d*) D. H. Camacho, I. Nakamura, B. H. Oh, S. Saito and Y. Yamamoto, *Tetrahedron Lett.*, 2002, **43**, 2903.