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Metal-catalyzed rearrangement of enantiomerically pure alkylidenecyclopropane derivatives as a new access to cyclobutenes possessing quaternary stereocenters†‡

Ahmad Masarwa,[a] Alois Fürstner[b] and Ilan Marek*[a]

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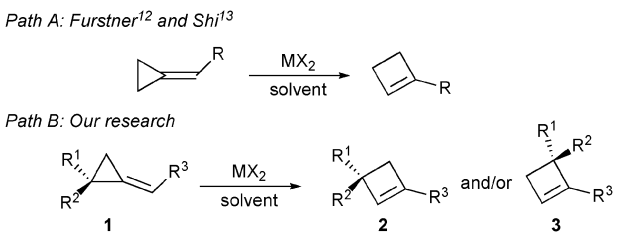
Pd(II)- and Pt(II)-catalyzed ring-expansion of enantiomerically pure alkylidenecyclopropane derivatives leads to the formation of cyclobutene species with a complete preservation of the stereogenic center.

One of the most stimulating and dynamic areas in organic synthesis nowadays is the asymmetric construction of molecules with quaternary carbon stereocenters.[1] Over the last few years, we[2] (mostly in acyclic systems) and others[3] have been involved in the development of such new synthetic strategies and we recently questioned whether it might be possible to develop a simple metal-catalyzed ring-expansion reaction of substituted alkylidenecyclopropanes (ACPs) into cyclobutene derivatives with full conservation of the stereochemical integrity of pre-existing stereogenic centers. Indeed, as far as four-membered rings are concerned, the preparation of enantiomerically pure cyclobutane derivatives (and particularly cyclobutanones) is well known,[4] but the formation of their unsaturated analogs (*i.e.* cyclobutenes)[5] remains challenging. Most of the reports on the formation of cyclobutenes concern the enantioselective [2 + 2] cycloaddition of alkynes and alkenes to lead to polycyclic derivatives in variable enantiomeric excess.[6] However, despite their potential synthetic interest, particularly in various metathesis processes,[7] the formation of enantiomerically enriched (or pure) *mono*cyclic cyclobutene derivatives remains in its complete infancy[8] and therefore drove our curiosity. Alkylidenecyclopropane derivatives have proved their usefulness by their unique reactivity with transition-metal catalysts.[9,10] Such transformations, based on the release of the high level of strain, can be performed either at the distal or proximal bonds of the three-membered ring as well as on the exoalkylidene moiety.[11] In the particular context of the formation of cyclobutenes, it was recently reported by Fürstner and Aïssa[12] and by Shi and coworkers[13] that Pt(II) and Pd(II) catalyze respectively the ring-expansion of alkylidenecyclopropanes into non-substituted cyclobutene derivatives (Scheme 1, Path A). We were therefore interested to study the regioselectivity of such ring-expansion using substituted alkylidenecyclopropanes **1**; would it lead to the formation of one or two regioisomers of the cyclobutenes (**2** and/or **3** respectively, Scheme 1, Path B)? Moreover, starting from enantiomerically enriched **1**, we could then expect to gain access to enantiomerically enriched cyclobutenes.

We were pleased to see that treatment of alkylidenecyclopropanes **1a,j** with either a catalytic amount of $PtCl_2$ or Pd(II) resulted in the clean formation of the isomer **2** in good yields as described in Table 1. When the ring-expansion is performed with Pt(II) (Table 1, condition A), the reaction proceeds smoothly for alkylidenecyclopropanes possessing aromatic and aliphatic groups on the double bond (Table 1, entries 1–5 and 6 respectively). However, the best experimental conditions found when non-activated aryl groups are used (Table 1, entries 1 and 2) are in toluene at 80 °C in the presence of one atmosphere of CO[12,14] (without addition of CO, the yield doesn't exceed 30% for the formation of **2a**). A single regioisomer was formed, suggesting a clean ring-expansion reaction. For aryl groups on the double bond possessing electron-donating groups, the more classical conditions (DCE, 80 °C) were used and a single regioisomer **2** was also obtained (Table 1, entries 3 and 4). However, when a bulky substituent is present on the aromatic group of the alkylidenecyclopropane (**1e**, Table 1, entry 5) or when the double bond is substituted by an aliphatic group (**1f**, Table 1, entry 6), the second isomers **3e** and **3f** respectively are detected in the crude reaction mixture in the range of 10 to 12%. The same trend was observed when Shi's conditions (condition B) were used as described in Table 1. Palladium acetate and copper bromide catalyzed the reaction to afford **2** in moderate yield but gave single isomers. However and in contrast to the Pt(II)-catalyzed reactions, the Pd(II)-catalyzed ring-expansion of alkylidenecyclopropane possessing an aliphatic substituent on the double bond doesn't proceed (when **1f** was treated



Scheme 1 Possible products for the ring-expansion of **1**.

[a] *The Mallat Family Laboratory of Organic Chemistry, Schulich Faculty of Chemistry and the Lise Meitner-Minerva Center for Computational Quantum Chemistry, Technion-Israel Institute of Technology, Haifa 32000, Israel. E-mail: chilanm@tx.technion.ac.il; Fax: +972 4 829 3709*
[b] *Max-Planck-Institute fur Kohlenforschung, D-45470 Mülheim/Ruhr, Germany*

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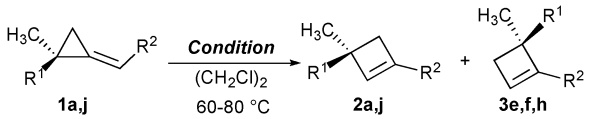
‡ Electronic supplementary information (ESI) available: Experimental details. See DOI: 10.1039/b910465h

Table 1 Pt(II)- and Pd(II)-catalyzed ring-expansion of ACPs



Condition A: $PtCl_2$ (10 mol%)

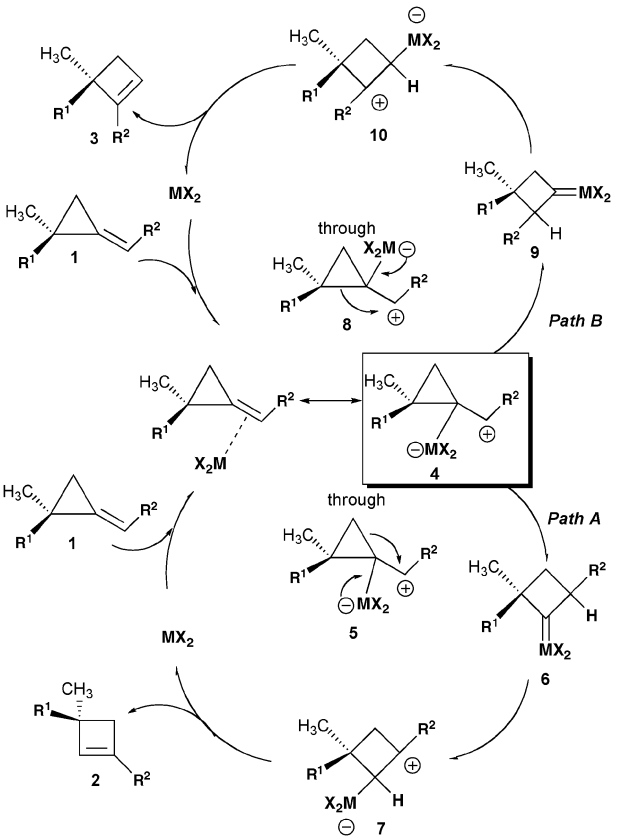
Condition B: $Pd(OAc)_2$ (10 mol%), $CuBr_2$ (20 mol%)

Entry	R^1	R^2	Cond.	**2** : **3**[a]	Yield (%)[b]
1 (**1a**)	C_2H_5	C_6H_5	A	**2a** : **3a** >99 : 1	70[c]
2 (**1b**)	C_2H_5	*p*-Me-C_6H_4	A	**2b** : **3b** >99 : 1	74[c]
3 (**1c**)	C_2H_5	3,5-Br_2-C_6H_3	A	**2c** : **3c** >99 : 1	56
4 (**1d**)	C_2H_5	*p*-MeO-C_6H_4	A	**2d** : **3d** >99 : 1	82
5 (**1e**)	C_2H_5	*o*-BnO-C_6H_4	A	**2e** : **3e** 90 : 10	80
6 (**1f**)	C_2H_5	$CH_2CH_2C_6H_5$	A	**2f** : **3f** 88 : 12	60
7 (**1a**)	C_2H_5	C_6H_5	B	**2a** : **3a** >99 : 1	55
8 (**1g**)	C_4H_9	C_6H_5	B	**2g** : **3g** >99 : 1	55
9 (**1h**)	C_3H_5	C_6H_5	B	**2h** : **3h** 90 : 10	60
10 (**1i**)	C_2H_5	*p*-Br-C_6H_4	B	**2i** : **3i** 98 : 2	50
11 (**1b**)	C_2H_5	*p*-Me-C_6H_4	B	**2b** : **3b** >99 : 1	65
12 (**1j**)	C_4H_9	*p*-Me-C_6H_4	B	**2j** : **3j** >99 : 1	68
13 (**1d**)	C_2H_5	*p*-MeO-C_6H_4	B	**2d** : **3d** >99 : 1	80
14 (**1e**)	C_2H_5	*o*-BnO-C_6H_4	B	**2e** : **3e** >99 : 1	85

[a] Ratio determined on crude ^1H NMR. [b] Yields of isolated pure products after purification by column chromatography. [c] Reaction performed in toluene under one atmosphere of CO.

under the condition B, no reaction was observed) and only aromatic groups undergo the rearrangement. Interestingly, when the R^2 substituent possesses a remote double bond as in **1h** (Table 1, entry 9), the isomer **3h** appears in moderate amount (10%) which may suggest that an additional coordination of the transition metal intervenes in the ring-cleavage reaction. On the other hand, condition B is less sensitive to steric interactions since **1e** gave only one regioisomer **2e** whereas the Pt(II)-catalyzed reaction led to two isomers **2e** and **3e** in a 9 : 1 ratio. Therefore, the two approaches are nicely complementary although more studies are necessary to fully understand the reasons for such differences. It should be noted that the conversion of alkylidenecyclopropanes into cyclobutenes is almost quantitative, as determined by crude NMR, but as cyclobutenes are relatively unstable, yields of isolated products are usually lower as a result of degradation during the purification by column chromatography.

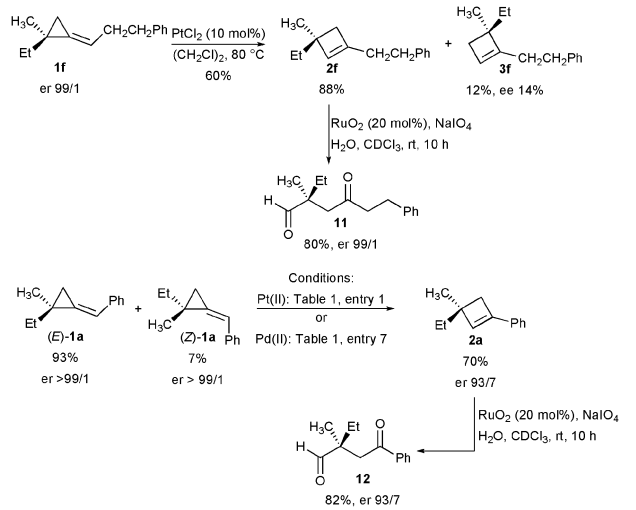
The selective ring-expansion can be rationalized by the following mechanistic hypothesis (Scheme 2). Coordination of the transition metal MX_2 to the alkylidenecyclopropane **1** generates the corresponding cyclopropylmethyl cation **4** that may undergo two different ring-expansions. In path A, the unsubstituted carbon center migrates (as described in **5**) to give



Scheme 2 Mechanistic hypothesis.

the corresponding metal carbene **6**.[15] Subsequent 1,2-hydrogen shift (formation of **7**) and elimination forms the corresponding cyclobutene **2**. On the other hand, when the tertiary alkyl group migrates as depicted in **8**, the metal carbene **9** is formed and after the same 1,2-hydrogen shift and elimination, the isomeric cyclobutene **3** could be obtained. We hypothesized that the migrating carbon acquires a carbanion-like character in the transition state in such a way that the most stable carbanions should migrate faster[16] (primary > tertiary; regiochemistry of the ring-expansion determined by NOE measurement on **2d**, see supplementary information‡).

As the primary alkyl group preferentially migrates in all examined cases, the integrity of the quaternary stereogenic center should remain unaffected in the process. To confirm our assumption, several enantiomerically pure alkylidenecyclopropane derivatives were prepared by the method that we recently described.[17] When **1f** (enantiomeric ratio 99 : 1) was submitted to the Pt(II)-catalyzed ring-expansion, the cyclobutene **2f** was obtained with the same enantiomeric ratio (er 99 : 1) as determined by chiral HPLC after transformation into the linear dicarbonyl species **11** (Scheme 3).[18] However, the minor isomer **3f** was obtained with only 14% ee, demonstrating that racemization occurs during the migration of a tertiary alkyl group (Scheme 2, path B).[19] However, when enantiomerically pure alkylidenecyclopropane derivatives possessing aromatic groups on the double bond were prepared, two geometrical isomers were always obtained.[17] Although the *E*-isomer is always largely predominant, the two isomers have opposite absolute configurations. For instance, **1a** was obtained with an



Scheme 3 Formation of enantiomerically enriched cyclobutene derivatives.

E : Z ratio of 93 : 7 but the absolute configuration of (*E*)-**1a** is (*S*) whereas (*Z*)-**1a** has an (*R*) configuration, both formed with an enantiomeric ratio >99 : 1. When transformed into the corresponding cyclobutene **2a** either with Pt(II) or Pd(II) catalyst (condition described in Table 1, entries 1 and 7 respectively), a complete preservation of the stereochemical information was also found as described in Scheme 3. As both isomers (*E*)- and (*Z*)-**1a** were prepared with enantiomeric ratio >99 : 1, the 93 : 7 enantiomeric ratio of **2a** corresponds to the ratio of the two geometrical isomers.

In conclusion, Pt(II)- and Pd(II)-catalyzed ring-expansion of enantiomerically pure alkylidenecyclopropane derivatives possessing a quaternary stereocenter proceeds smoothly and leads to the corresponding cyclobutene species with complete preservation of the stereochemical information.

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Notes and references

1 E. J. Corey and A. Guzman-Perez, *Angew. Chem., Int. Ed.*, 1998, **37**, 388; B. M. Trost and C. H. Jiang, *Synthesis*, 2006, 369; J. Christoffers and A. Baro, *Adv. Synth. Catal.*, 2005, **347**, 1473.
2 J. P. Das, H. Chechik and I. Marek, *Nat. Chem.*, 2009, **1**, 128; I. Marek, *Chem.–Eur. J.*, 2008, **14**, 7460; I. Marek and G. Sklute, *Chem. Commun.*, 2007, 1683; G. Kolodney, G. Sklute, S. Perrone, P. Knochel and I. Marek, *Angew. Chem.*, 2007, **119**, 9451; G. Sklute and I. Marek, *J. Am. Chem. Soc.*, 2006, **128**, 4642; G. Sklute, D. Amsallem, A. Shibli, J. P. Varghese and I. Marek, *J. Am. Chem. Soc.*, 2003, **125**, 11776.
3 For very recent papers, see: S. R. Levine, M. R. Krout and B. M. Stoltz, *Org. Lett.*, 2009, **11**, 289; K. V. Petrova, J. T. Mohr and B. M. Stoltz, *Org. Lett.*, 2009, **11**, 293; S. Sulzer-Mosse, A. Alexakis, J. Mareda, G. Bollot, G. Bernadinelli and Y. Filinchuk, *Chem.–Eur. J.*, 2009, **15**, 3204; C. Hawner, K. Li, V. Cirriez and A. Alexakis, *Angew. Chem., Int. Ed.*, 2008, **47**, 8211; T. L. May, M. K. Brown and A. H. Hoveyda, *Angew. Chem.*, 2008, **120**, 7468; Y. Matsumoto, K.-I. Yamada and K. Tomioka, *J. Org. Chem.*, 2008, **73**, 4578; A. Wilsily and E. Fillion, *Org. Lett.*, 2008, **10**, 2801; P. Fu, M. L. Snapper and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2008, **130**, 5530; M. Seto, J. L. Roizen and B. M. Stoltz, *Angew. Chem., Int. Ed.*, 2008, **47**, 6873.
4 E. Lee-Ruff and G. Mladenova, *Chem. Rev.*, 2003, **103**, 1449; J. C. Namyslo and D. E. Kaufmann, *Chem. Rev.*, 2003, **103**, 1485.
5 For recent reports on the preparation of cyclobutenes, see: Y. Odabachian and F. Gagosz, *Adv. Synth. Catal.*, 2009, **351**, 379; L. A. Paquette, X. Peng, J. Yang and H.-J. Kang, *J. Org. Chem.*, 2008, **73**, 4548; O. Debleds and J.-M. Campagne, *J. Am. Chem. Soc.*, 2008, **130**, 1562.
6 For recent reports on enantiomerically enriched polycyclic cyclobutenes, see: F. Zhang, N. S. Simpkins and A. J. Blake, *Org. Biomol. Chem.*, 2009, **7**, 1963; T. Shibata, K. Takami and A. Kawachi, *Org. Lett.*, 2006, **8**, 1343; R. Alibes, P. de March, M. Figueredo, J. Font, M. Racamonde and T. Parella, *Org. Lett.*, 2004, **6**, 1449; C. Pichon, C. Alexandre and F. Huet, *Tetrahedron: Asymmetry*, 2004, **15**, 1103; R. Alibes, P. de March, M. Figueredo, J. Font, M. Racamonde, A. Rustullet, A. Alvarez-Larena, J. F. Piniella and T. Parella, *Tetrahedron Lett.*, 2003, **44**, 69; R. Alibes, P. de March, M. Figueredo, J. Font, X. Fu, M. Racamonde, A. Alvarez-Larena and J. F. Piniella, *J. Org. Chem.*, 2003, **68**, 1283; R. Alibes, P. de March, M. Figueredo, J. Font and M. Racamonde, *Tetrahedron Lett.*, 2001, **42**, 6695.
7 B. R. Maughon and R. H. Grubbs, *Macromolecules*, 1997, **30**, 3459; C. W. Bielawski and R. H. Grubbs, *Prog. Polym. Sci.*, 2007, **32**, 1; M. L. Randall, J. A. Tallarico and M. L. Snapper, *J. Am. Chem. Soc.*, 1995, **117**, 9610; W. J. Zuercher, M. Hashimoto and R. H. Grubbs, *J. Am. Chem. Soc.*, 1996, **118**, 6634; K. C. Nicolaou, J. A. Vega and G. Vassilikogiannakis, *Angew. Chem., Int. Ed.*, 2001, **40**, 4441; M. Mori, H. Wakamatsu, K. Tonogaki, R. Fujita, T. Kitamura and Y. Sato, *J. Org. Chem.*, 2005, **70**, 1066; R. E. Giudici and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2007, **129**, 3824; G. S. Weatherhead, J. G. Ford, E. J. Alexanian, R. R. Schrock and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2000, **122**, 1828.
8 K. Hiroi, H. Nakamura and T. Anzai, *J. Am. Chem. Soc.*, 1987, **109**, 1249.
9 For reviews, see: A. Brandi and A. Goti, *Chem. Rev.*, 1998, **98**, 589; M. Lautens, W. Klute and W. Tam, *Chem. Rev.*, 1996, **96**, 49; A. Brandi, S. Cicchi, F. Cordero and A. Goti, *Chem. Rev.*, 2003, **103**, 1213; I. Nakamura and Y. Yamamoto, *Adv. Synth. Catal.*, 2002, **344**, 111; B. M. Trost, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 1; *Methods of Organic Chemistry, Houben-Weyl*, ed. A. de Meijere, Thieme, Stuttgart, 1996, vol. E17.
10 Recent hydro- and carbometalation reactions of cyclopropenes: S. Simaan and I. Marek, *Chem. Commun.*, 2009, 292; W. M. Sherrill and M. Rubin, *J. Am. Chem. Soc.*, 2008, **130**, 13804; S. Simaan and I. Marek, *Org. Lett.*, 2007, **9**, 2569; A. Masarwa, A. Stanger and I. Marek, *Angew. Chem., Int. Ed.*, 2007, **46**, 8039; J. M. Fox and N. Yan, *Curr. Org. Chem.*, 2005, **9**, 719; E. Zohar, M. Ram and I. Marek, *Synlett*, 2004, 1288; E. Zohar and I. Marek, *Org. Lett.*, 2004, **6**, 341; M. Rubin and V. Gevorgyan, *Synthesis*, 2004, 796; M. Rubina, M. Rubin and V. Gevorgyan, *J. Am. Chem. Soc.*, 2004, **126**, 3688; M. Rubina, M. Rubin and V. Gevorgyan, *J. Am. Chem. Soc.*, 2003, **125**, 7198; M. Nakamura, H. Isobe and E. Nakamura, *Chem. Rev.*, 2003, **103**, 1295; I. Nakamura, G. B. Bajracharya and Y. Yamamoto, *J. Org. Chem.*, 2003, **68**, 2297; S. Araki, T. Tanaka, T. Hirashita and J.-I. Setsune, *Tetrahedron Lett.*, 2003, **44**, 8001; M. Rubina, M. Rubin and V. Gevorgyan, *J. Am. Chem. Soc.*, 2002, **124**, 11566; L. A. Liao and J. M. Fox, *J. Am. Chem. Soc.*, 2002, **124**, 14322.
11 I. Marek, S. Simaan and A. Masarwa, *Angew. Chem., Int. Ed.*, 2007, **46**, 7364 (Corrigenda: *Angew. Chem., Int. Ed.*, 2008, **47**, 1982).
12 A. Fürstner and C. Aïssa, *J. Am. Chem. Soc.*, 2006, **128**, 6306.
13 M. Shi, L.-P. Liu and J. Tang, *J. Am. Chem. Soc.*, 2006, **128**, 7430.
14 A. Fürstner, P. W. Davies and T. Gress, *J. Am. Chem. Soc.*, 2005, **127**, 8244; A. Fürstner and P. W. Davies, *J. Am. Chem. Soc.*, 2005, **127**, 15024.
15 A. Fürstner and P. W. Davies, *Angew. Chem., Int. Ed.*, 2007, **46**, 3410.
16 V. L. Heasley, D. F. Shelhammer, L. E. Heasley, D. B. Yeager and G. E. Heasley, *J. Org. Chem.*, 1980, **45**, 4649.
17 S. Simaan, A. Masarwa, P. Bertus and I. Marek, *Angew. Chem., Int. Ed.*, 2006, **45**, 3963.
18 Enantiomeric ratio couldn't be determined on the cyclobutene **2f** by chiral HPLC. The absolute configuration was determined by comparison with calculated CD (see ref. 17).
19 The absolute configuration of the minor isomer wasn't determined.

