Formation of titanacyclobutenes with a spiro-bonded cyclopropane†

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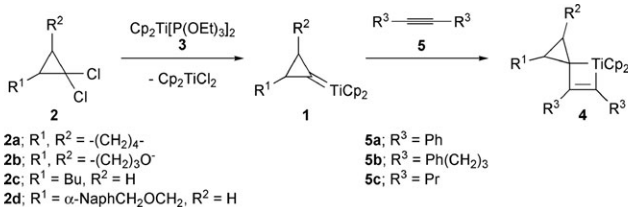
Received (in Cambridge, UK) 25th March 2008, Accepted 24th April 2008
First published as an Advance Article on the web 30th May 2008
DOI: 10.1039/b804930k

The reaction of titanium cyclopropylidene complexes, prepared by the reductive titanation of 7,7-dichlorobicyclo[4.1.0]heptanes, with alkynes produced air and moisture stable titanacyclobutenes with a spiro-bonded cyclopropane.

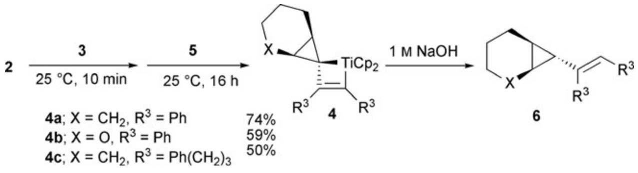
Metallacycles fused with a small ring are an interesting class of compounds because of their unique structure and reactivity. A variety of metallacycles with spiro-bonded cyclopropane rings have been prepared by the reaction of alkylidenecyclopropanes, transition metal complexes and unsaturated compounds, such as alkenes and alkynes.[1] However, the preparation of metallacyclobutenes linked to a cyclopropane in a spirocyclic manner has not been reported, and hence their reactivity and stability are not yet known.

Recently, we reported that titanium cyclopropylidene complexes **1** are readily prepared by the reductive titanation of 1,1-dichlorocyclopropanes **2** with the titanocene(II) reagent $Cp_2Ti[P(OEt)_3]_2$ (**3**).[2] This finding prompted us to investigate the preparation of spirocyclic organotitanium compounds **4** by the reaction of **1** with alkynes **5** (Scheme 1).

Treatment of the titanium cyclopropylidene complex **1a**, prepared by the reductive titanation of 7,7-dichlorobicyclo[4.1.0]heptane (**2a**) with the titanocene(II) reagent **3**, with diphenylacetylene (**5a**) gave spirocyclic titanacyclobutene **4a** as an air and moisture stable brownish-red solid (Scheme 2).‡ The titanacyclobutenes having a bicyclo[4.1.0]heptane moiety, **4b** and **4c**, were also found to be unsusceptible to air and moisture, and could be isolated. The titanacyclobutenes **4** (R^2 = H) having a substituent on their cyclopropane ring were, however, unstable under atmospheric circumstances, and gradually hydrolyzed during isolation. The structure of **4a** was confirmed by an X-ray diffraction study, as shown in Fig. 1.[3] The stereochemistry of **4a** indicates that the *cis*-fused cyclohexane ring shields the most reactive allylic carbon–titanium bond of **4a**. The molecular structure of **4a** also suggests that the titanacycles **4** would be formed through the approach of alkynes from the less sterically-hindered side of cyclopropylidene complexes **1**.



Scheme 1



Scheme 2

Hydrolysis of the isolated titanacyclobutenes **4a–c** produced synthetically useful alkenylcyclopropanes **6a–c** as single isomers in good yields (Table 1). The stereochemistry of titanacyclobutenes **4** are integrally reflected in those of alkenylcyclopropanes **6**. The two substituents (R^3) originating from the alkynes were found to be *cis* to each other. In addition, the NOE experiments of **6a** and **6b** indicated that the alkenyl group of the cyclopropane ring was *trans* with respect to the six-membered ring. Therefore, the protonation of **4** should proceed with the retention of stereochemistry of the carbon–carbon double bond and the cyclopropane ring.

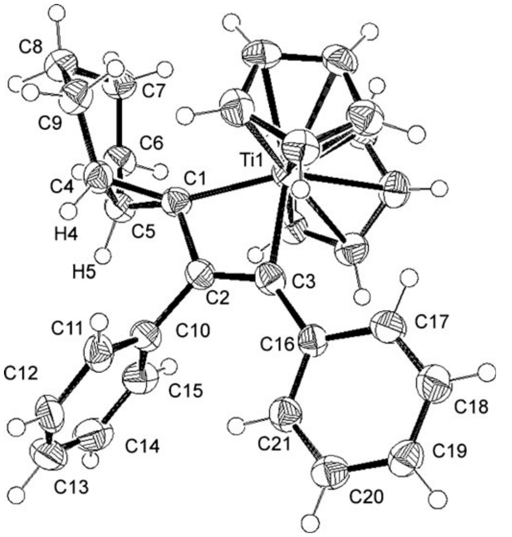


Fig. 1 Molecular structure of titanacyclobutene **4a**. Principal bond lengths (Å) and angles (°): Ti1–C1 2.130(3), Ti1–C3 2.100(3), C1–C2 1.543(4), C2–C3 1.339(4); C1–Ti1–C3 71.22(12), C2–C1–Ti1 82.62(18), C1–C2–C3 117.3(3), C2–C3–Ti1 88.7(2).

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[a] *Department of Applied Chemistry, Graduate School of Engineering, Tokyo University of Agriculture and Technology, Koganei, Tokyo 184-8588, Japan. E-mail: takeda-t@cc.tuat.ac.jp; Fax: +81 42 388 7034; Tel: +81 42 388 7034*
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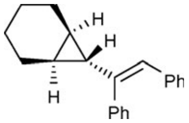
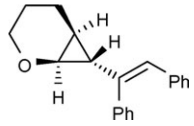
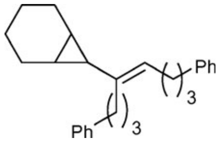
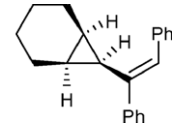
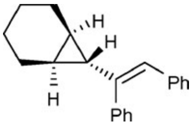
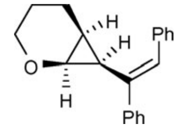
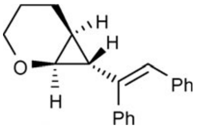
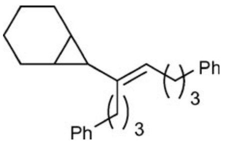
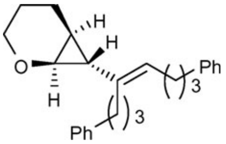
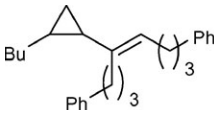
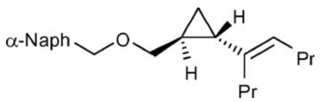
† Electronic supplementary information (ESI) available: Experimental procedure for the hydrolysis of **4** and characterization data for all compounds.

Table 1 Hydrolysis of titanacyclobutenes **4**[a]

Entry	4	Product 6		Yield (%)
1	**4a**		*Z*-**6a**	68
2	**4b**		*Z*-**6b**	67
3	**4c**		*E*-**6c**[b]	86

[a] Carried out in 1 M NaOH/THF (1 : 1) under reflux for 3 h. [b] Single *cis*/*trans* isomer. The stereochemistry was not determined.

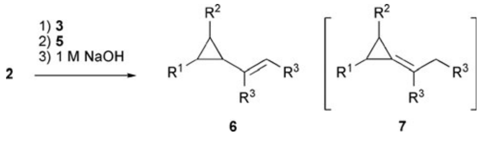
Table 2 Formation of alkenylcyclopropanes **6**[a]

Entry	2	5	Product 6	Yield (%)[b]
1[c]	**2a**	**5a**		*E*-**6a** (78)
				*Z*-**6a** (trace)
2	**2b**	**5a**		*E*-**6b** (36)
				*Z*-**6b** (39)
3	**2a**	**5b**		*E*-**6c** (74)[d,e]
4	**2b**	**5b**		*E*-**6d** (69)
5	**2c**	**5b**		*E*-**6e** (62)[d,e]
6	**2d**	**5c**		*E*-**6f** (46)[f]

[a] All the reactions were performed using a similar procedure, as described in ref. 4. [b] Based on the alkyne **5** used. [c] Carried out using 7 equiv. of **3**. [d] Single *cis*/*trans* isomer. The stereochemistry was not determined. [e] Contaminated with a trace amount of the alkylidenecyclopropane **7**. The yield was corrected for the contaminant. [f] *trans* : *cis* = 89 : 11.

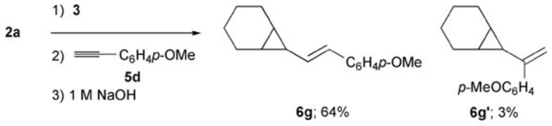
Alkenylcyclopropanes **6** were also obtained along with trace amounts of by-products (alkylidenecyclopropanes **7**) by the *in situ* hydrolysis of titanacyclobutenes **4** without isolation (Scheme 3). Thus, the reaction of **2a** with **5b** afforded the alkenylcyclopropane **6c** after an aqueous work-up (Table 2, entry 3). Similar treatment of carbene complexes **1**, generated from several 1,1-dichlorocyclopropanes **2**, with symmetrical alkynes **5** produced alkenylcyclopropanes **6**. Although no regioselectivity was observed in the reaction of unsymmetrical internal alkynes, the reaction of terminal alkynes proceeded with good regioselectivity; for example, the reaction of **2a** with *para*-methoxyphenylacetylene (**5d**) gave **6g** in 64% yield with a small amount of its regioisomer **6g′** (Scheme 4). As shown in Table 2, entries 3–6, the stereochemistry of **6**, formed by the reaction with aliphatic alkynes, is the same as that obtained by the hydrolysis of isolated **4a–c**. On the contrary, the reaction with **5a** gave either the *E*-isomer predominantly or a mixture of the two stereoisomers (Table 2, entries 1 and 2). The inversion of the double bond geometry of **6a** and **6b**, obtained by the *in situ* hydrolysis, was associated with the inversion of stereochemistry of the cyclopropane ring; *E*-**6a** and **6b** were proved to have a *cis*-configuration.

It was suspected that the formation of *E*-**6a** and **6b** by the *in situ* hydrolysis of **4a** and **4b** was attributable to the action of certain low-valent titanium species. Next, the hydrolysis of **4a** was examined in the presence of titanocene(II) species **3**. After **4a** was mixed with **3** in THF at 25 °C, the mixture was treated with 1 M NaOH (Scheme 5). As expected, *E*-**6a** was exclusively produced in 79% yield. This result clearly shows that the formation of *E*-**6a** and **6b** is due to the reaction of **4a** with low-valent titanium species during the hydrolysis, though the detailed reaction pathway is not clear at present.



Scheme 3

In conclusion, we have demonstrated that titanacyclobutenes having a spiro-bonded cyclopropane were produced by the successive treatment of 1,1-dichlorocyclopropanes with a titanocene(II) reagent and alkynes. Alkenylcyclopropanes are useful intermediates in various organic transformations, such as the magnification to cyclopentenes,[5] and [5 + 2],[6,7] [5 + 2 + 1][7,8] and [5 + 1 + 2 + 1] cycloadditions.[9] Our procedure



Scheme 4

$$\mathbf{4a} + \underset{(2.0\ \text{equiv})}{\mathbf{3}} \xrightarrow[25\ ^\circ\text{C},\ 16\ \text{h}]{1\ \text{M NaOH}} \underset{79\%}{E\text{-}\mathbf{6a}} + \underset{2\%}{Z\text{-}\mathbf{6a}}$$

Scheme 5

for the preparation of alkenylcyclopropanes is versatile and may have wide applications, because a variety of the starting materials are readily available through the dichlorocyclopropanation of alkenes with $CHCl_3$–NaOH.[10]

This work was supported by a Grant-in-Aid for Scientific Research (no. 18350018) and a Grant-in-Aid for Scientific Research on Priority Areas "Advanced Molecular Transformations of Carbon Resources" (no. 19020016) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Notes and references

‡ A representative experimental procedure for the isolation of titanacyclobutenes: To a dry flask charged with finely powdered molecular sieves 4A (1.00 g), magnesium turnings (0.243 g, 10.0 mmol) and Cp_2TiCl_2 (2.49 g, 10.0 mmol) were added THF (20 cm^3) and $P(OEt)_3$ (3.43 cm^3, 20.0 mmol), successively, with stirring, at 25 °C, under argon. After 3 h, a THF (2 cm^3) solution of **2a** (0.660 g, 4.0 mmol) was added to the reaction mixture, which was then stirred for a further 10 min. Then, a THF (2 cm^3) solution of **5a** (0.357 g, 2.0 mmol) was added, and the reaction mixture was stirred for a further 16 h. After filtration through a glass filter, the filtrate was chromatographed over alumina gel (20 g, eluted with hexane (40 cm^3)). The eluate was evaporated to dryness *in vacuo*, giving a brownish-red solid. After the solid had been washed with hexane (3 × 3 cm^3), pure **4a** was obtained (0.668 g, 74%). **4a**: m.p. 196–198 °C (dec.); found: C, 82.73; H, 6.84. $C_{31}H_{30}Ti$ requires C, 82.66; H, 6.71%; δ_H (300 MHz, $CDCl_3$, Me_4Si) 0.85–0.99 (2 H, m), 1.10–1.31 (4 H, m), 1.73–2.06 (4 H, m), 6.11 (10 H, s), 6.58 (2 H, d, J = 7.2 Hz), 6.74 (2 H, d, J = 6.8 Hz), 6.95 (1 H, t, J = 7.2 Hz), 7.05 (2 H, dd, J = 7.5 and 7.5 Hz), 7.16 (1 H, t, J = 7.2 Hz) and 7.24 (2 H, dd, J = 7.5 and 7.5 Hz); δ_C (75 MHz; $CDCl_3$); 22.2, 23.4, 24.7, 85.7, 105.0, 110.9, 124.9, 125.6, 127.6, 127.7, 127.8, 129.8, 137.5, 143.2 and 205.0; ν_{max}/cm^{-1} 3072, 3057, 2975, 2925, 2853, 1591, 1540, 1487, 1476, 1458, 1440, 1382, 1171, 1155, 1066, 1016, 957, 838, 804, 778 and 761.

1. For examples, see: [Ni]: P. Binger, M. J. Doyle and R. Benn, *Chem. Ber.*, 1983, **116**, 1; L. Zhao and A. de Meijere, *Adv. Synth. Catal.*, 2006, **348**, 2484; K. Maeda and S. Saito, *Tetrahedron Lett.*, 2007, **48**, 3173; [Co]: T. Kurahashi and A. de Meijere, *Angew. Chem., Int. Ed.*, 2005, **44**, 7881; S. I. Kozhushkov, J. Foerstner, A. Kakoschke, D. Stellfeldt, L. Yong, R. Wartchow, A. de Meijere and H. Butenschön, *Chem.–Eur. J.*, 2006, **12**, 5642; [Cr]: Y.-T. Wu, T. Kurahashi and A. de Meijere, *J. Organomet. Chem.*, 2005, **690**, 5900; [Ti, Zr]: K. Mashima, N. Sakai and H. Takaya, *Bull. Chem. Soc. Jpn.*, 1991, **64**, 2475; P. Binger, P. Müller, S. Podubrin, S. Albus and C. Krüger, *J. Organomet. Chem.*, 2002, **656**, 288.
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3. Crystal data for compound **4a**: $C_{31}H_{30}Ti$, M = 450.45, 0.35 × 0.30 × 0.05 mm^3, monoclinic, $P2_1/c$, a = 8.3434(2), b = 15.5514(3), c = 17.7460(3) Å, β = 100.736(1)°, V = 2262.26(7) $Å^3$, Z = 4, T = 98 K, D = 1.323 g cm^{-3}, μ(Cu-K_α) = 3.308 mm^{-1}, R_{int} = 0.0817, number of measured/independent reflections = 30475/4083, R = 0.0705 and wR = 0.1786 (all data). CCDC 678446. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b804930k.
4. A representative experimental procedure for the preparation of alkenylcyclopropanes: A THF (2 cm^3) solution of **2a** (124 mg, 0.75 mmol) was added to a THF (3.6 cm^3) solution of **3** (prepared from magnesium turnings (44 mg, 1.8 mmol), Cp_2TiCl_2 (448 mg, 1.8 mmol) and $P(OEt)_3$ (0.62 cm^3, 3.6 mmol) in the presence of molecular sieves 4A (180 mg)) at 25 °C. After the reaction mixture had been stirred for 10 min, a THF (1 cm^3) solution of **5b** (79 mg, 0.3 mmol) was added, and the reaction mixture was refluxed for 5 h. After being cooled to room temperature, the reaction was quenched by the addition of 1 M NaOH (20 cm^3). The insoluble materials were filtered off through Celite and washed with ether (40 cm^3). The layers were separated, and the aqueous layer was extracted with ether (2 × 20 cm^3). The combined organic extracts were dried over Na_2SO_4. After removal of the solvent under a reduced pressure, the residue was purified by PTLC (hexane) to give a mixture of *E*-**6c** and 7-[5-phenyl-1-(3-phenylpropyl)pentylidene]bicyclo[4.1.0]heptane (**7a**) (84 mg; *E*-**6c**: 74%, **7a**: 5%).
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