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Transformation of thioacetals to cyclopropanes

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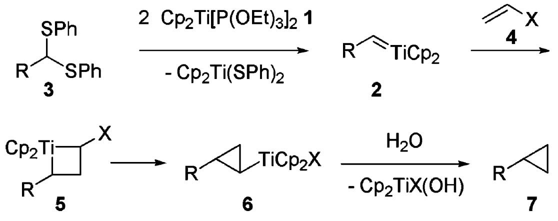
Abstract—Cyclopropanes were obtained by the titanocene(II)-promoted reaction of thioacetals with vinyl pivalate. It was also found that vinycyclopropanes were produced by a similar treatment of thioacetals with the titanocene(II) species in the presence of 1,3-dienes.

Small ring compounds such as cyclopropanes are useful synthetic intermediates because of their ring-opening and ring-enlargement reactions using their strain releases as driving forces.[1] Therefore a variety of methods have been developed for their preparation.[2] We found that alkenylcyclopropanes were produced by the reaction of terminal olefins with titanium alkenylcarbene complexes generated by the treatment of β,γ-unsaturated thioacetals or 1,3-bis(phenylthio)-1-alkenes with the titanocene(II) species $Cp_2Ti[P(OEt)_3]_2$ (**1**).[3] A similar cyclopropanation also proceeds with alkynylcarbene complexes.[4] In contrast to the reactions of alkenyl- and alkynyl-carbene complexes, the major reaction of titanocene alkylidene complexes **2**, prepared from saturated thioacetals **3**, with terminal olefins is olefin metathesis and no cyclopropane derivative is obtained.[5]

The transformation of thioacetals into cyclopropanes is of great value as a reductive cyclopropanation of synthetic equivalents of aldehydes. In order to substantiate such transformation, we examined the reaction of the titanocene-alkylidenes **2** with heteroatom-substituted olefins **4**. Our approach is outlined in Scheme 1; formation of the titanacyclobutane intermediate **5** and subsequent intramolecular substitution afford the cyclopropyltitanocene **6**, which is then hydrolyzed to produce a cyclopropane **7**.



Scheme 1.

Two types of side reactions are probable in the above cyclopropanation (Scheme 2). The first one is a metathesis-type degradation of the titanacycle **5** giving a terminal olefin **8**.[5] If the regioisomeric titanacycle **9** is produced, its β-elimination affords a terminal olefin **10** with two-carbon homologation via the allyltitanium species **11**. Therefore we anticipated that the choice of the leaving group (X) was of crucial importance for the selective formation of the cyclopropanes **7**.

We initially examined the titanocene(II)-promoted reaction of the thioacetal **3a** with various heteroatom-substituted olefins **4** (Table 1). The reactions of **3a** with phenyl vinyl sulfone **4a** and *tert*-butyl vinyl ether **4b** exclusively produced the terminal olefin with one-carbon homologation **8a** via the metathesis-type degradation of the titanacyclobutane **5**. Although the cyclopropane **7a** was obtained in moderate yield by the use of vinyl bromide **4c**, a substantial amount of the terminal olefin **10a** was produced as a by-product. The reaction of **3a** with vinyl acetate **4d** also gave the cyclopropane **7a** along with the vinyl ether, 4-benzyl-2-ethenyloxy-5-phenylpent-2-ene, which was formed by the olefination of the

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Keywords: Cyclopropanation; Titanocene(II) reagent; Thioacetals; Vinyl pivalate; 1,3-Dienes.

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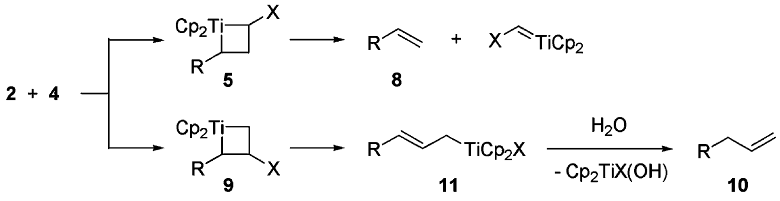


Scheme 2.

Table 1. Titanocene(II)-promoted reaction of the thioacetal **3a** with heteroatom-substituted olefins **4**[a]

Entry	**4**	X	Time (h)	Product/yield (%)		
				7a	**8a**	**10a**
1	**4a**	SO_2Ph	2	—	45	—
2	**4b**	O^tBu	Overnight	—	46	7
3	**4c**	Br	2	45	—	15
4[b]	**4d**	OCOMe	2	34	—	3
5	**4e**	OCO^tBu	2	60	—	2
6[c]	**4e**	OCO^tBu	2	76	—	2

[a] All reactions were carried out using **1** (3 equiv) and **4** (3 equiv) at 25 °C.

[b] 4-Benzyl-2-ethenyloxy-5-phenylpent-2-ene was obtained in 27% yield.

[c] 4 equiv of **1** were used.

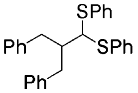
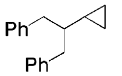
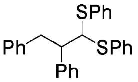
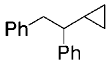
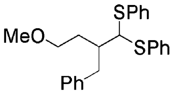
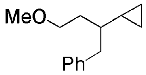
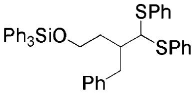
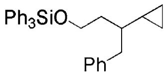
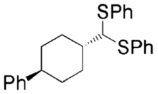
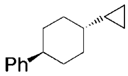
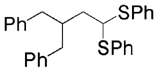
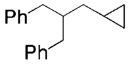
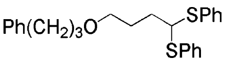
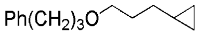
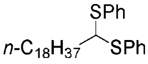
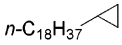
ester carbonyl.[6] In order to suppress the carbonyl olefination, we employed commercially available vinyl pivalate **4e** and found that the cyclopropane **7a** was selectively produced in 60% yield. The yield was further increased by increase of the titanocene(II) reagent to accelerate the desulfurization of the thioacetal **3a**.

In a similar fashion, the titanocene(II)-promoted reaction of various thioacetals **3** with vinyl pivalate **4e** was performed and the corresponding cyclopropanes **7** were obtained. As shown in Table 2, the yield of **7** is dependent on the steric bulkiness of the thioacetal employed. The reaction of the thioacetals **3** possessing an α-substituent gave the cyclopropanes **7** in good yields. The use of less hindered thioacetals, however, led to the decrease of the yields of **7** due to the concomitant formation of the terminal olefin **10**. In such cases, the pure cyclopropane was isolated after treatment of a crude product mixture with MCPBA. These results imply that the regioselectivity of the titanacycle formation (**5** vs **9**) is determined by the extent of the steric repulsion between the substituent of the carbene complex (R) and pivaloyloxyl group of **4e**.

In order to confirm the proposed pathway for the formation of the cyclopropanes **7**, the reaction of **3a** with vinyl pivalate **4e** was quenched with D_2O, and the *trans*-deuterated cyclopropane **12** (85% deuterium incorporation) was isolated in 72% yield (Scheme 3).[7] The formation of **12** indicates that the reaction proceeds via the formation of the cyclopropyltitanocene intermediate **6** as expected.

The typical experimental procedure is as follows: Magnesium turnings (32 mg, 1.3 mmol; purchased from Nacalai Tesque Inc. Kyoto, Japan), Cp_2TiCl_2 (299 mg, 1.2 mmol), and finely powdered molecular sieves 4 A (120 mg) were placed in a flask and dried by heating with a heat gun under reduced pressure (2–3 mmHg). After cooling, THF (2 mL) and $P(OEt)_3$ (0.41 mL, 2.4 mmol) were added successively with stirring at 25 °C under argon. After 3 h, **3a** (128 mg, 0.3 mmol) in

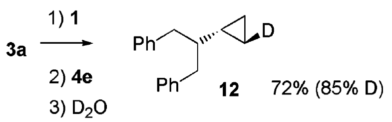
Table 2. Cyclopropanation of thioacetals **3**[a]

Entry	Thioacetal **3**	Cyclopropane **7** (yield/%)
1	 **3a**	 **7a** (76)[b]
2[c]	 **3b**	 **7b** (71)
3	 **3c**	 **7c** (72)
4	 **3d**	 **7d** (73)
5	 **3e**	 **7e** (49)
6	 **3f**	 **7f** (60)
7	 **3g**	 **7g** (46)
8	 **3h**	 **7h** (43)

[a] All the reactions were performed with a similar procedure as described in the text, unless otherwise noted.

[b] Obtained as a mixture of **7a** and **10a**. The yield was determined by NMR analysis.

[c] 3.5 equiv of **1** were used.

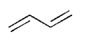
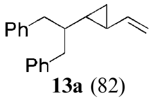
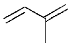
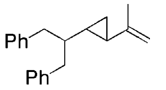
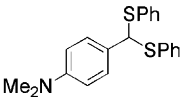
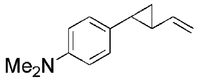
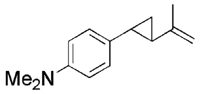


Scheme 3.

THF (1 mL) was added and the mixture was stirred for 10 min. After addition of **4e** (0.13 mL, 0.9 mmol), stirring was continued for 2 h. The reaction was quenched by addition of 1 M NaOH, and the insoluble materials were filtered off through Celite and washed with ether. The organic materials were extracted with ether, and the extract was dried (Na_2SO_4). After removal of the solvent, the residue was purified by PTLC (hexane–AcOEt = 99:1) to give a mixture of **7a** and **10a** (55 mg). The yield of **7a** (76%) was determined by NMR analysis.

The transformation of thioacetals **3** into vinylcyclopropanes **13** was also achieved by their treatment with the titanocene(II) reagent **1** in the presence of conjugated dienes **14**. As noted above, alkenylcyclopropanes were produced by the reaction of alkenylcarbene complexes with terminal olefins.[3] Since it was assumed that the cyclopropanation proceeds through the reductive elimination of 2-alkenyltitanacyclobutane, we anticipated that the similar titanacyclobutane intermediate **15** would be formed by the reaction of titanocene-alkylidenes **2** with **14** (Scheme 4). As expected, the treatment of thioacetals **3** with titanocene(II) reagent **1** in the presence of 1,3-butadiene **14a** or isoprene **14b** gave the vinylcyclopropanes **13** as single stereoisomers (Table 3).[8] The NOE measurement of **13b** indicated that it had *trans*-configuration.[9]

Table 3. Transformation of thioacetals **3** to vinylcyclopropanes **13**[a]

Entry	Thioacetal **3**	Diene **14**	Vinylcyclopropane **13** (yield/%)
1	**3a**	 **14a**	 **13a** (82)
2	**3a**	 **14b**	 **13b** (64)
3	 **3i**	**14a**	 **13c** (60)
4	**3i**	**14b**	 **13d** (52)

[a] All the reactions were performed with a similar procedure as described in Ref. 8, unless otherwise noted.

Takai et al. reported the preparation of cyclopropylsilanes by the chromium(II)-promoted reaction of diiodomethyltrimethylsilane with terminal olefins.[10] Recently the low-valent titanium-mediated reaction of the silane with 1,3-dienes giving (2-vinylcyclopropyl)silanes was also reported.[11] These reactions are suggested to proceed via the formation of metallacyclobutane intermediate and subsequent reductive elimination similarly to the above cyclopropanation of dienes with thioacetals **3**.

Since aldehydes are easily converted to thioacetals, the titanocene(II)-promoted reactions of thioacetals with vinyl pivalate and 1,3-dienes provide convenient tools for the transformation of aldehydes to cyclopropanes.

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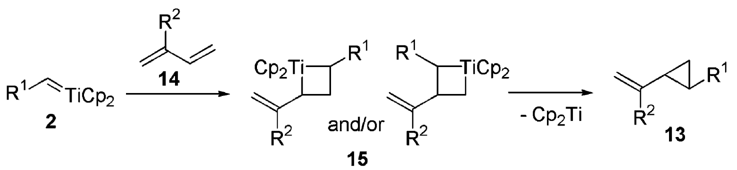

Scheme 4.

4. (a) Takeda, T.; Kuroi, S.; Yanai, K.; Tsubouchi, A.. *Tetrahedron Lett.* **2002**, *43*, 5641; (b) Takeda, T.; Kuroi, S.; Ozaki, M.; Tsubouchi, A. *Org. Lett.* **2004**, *6*, 3207.
5. (a) Fujiwara, T.; Takamori, M.; Takeda, T. *Chem. Commun.* **1998**, 51; (b) Fujiwara, T.; Takeda, T. *Synlett* **1999**, 354; (c) Fujiwara, T.; Kato, Y.; Takeda, T. *Heterocycles* **2000**, *52*, 147; (d) Fujiwara, T.; Kato, Y.; Takeda, T. *Tetrahedron* **2000**, *56*, 4859; (e) Fujiwara, T.; Yanai, K.; Shimane, K.; Takamori, M.; Takeda, T. *Eur. J. Org. Chem.* **2001**, 155; (f) Tsubouchi, A.; Nishio, E.; Kato, Y.; Fujiwara, T.; Takeda, T. *Tetrahedron Lett.* **2002**, *43*, 5755.
6. Horikawa, Y.; Watanabe, M.; Fujiwara, T.; Takeda, T. *J. Am. Chem. Soc.* **1997**, *119*, 1127.
7. The configuration of **12** was determined by NOE experiment.
8. Typical experimental procedure: To a THF (1.5 mL) solution of the titanocene(II) reagent **1**, prepared from magnesium turnings (24 mg, 1 mmol), Cp_2TiCl_2 (224 mg, 0.9 mmol), molecular sieves 4 Å (90 mg), and $P(OEt)_3$ (0.31 mL, 1.8 mmol), was added a THF solution of **14a** (0.9 mL, 1.2 mmol) at 25 °C under argon. After 2 min, **3a** (128 mg, 0.3 mmol) in THF (1 mL) was added to the mixture. After 1 h, the reaction was quenched by addition of 1 M NaOH and the usual workup gave **13a** (65 mg, 82%).
9. ^{1}NMR (300 MHz, $CDCl_3$) spectral data for **13b**: δ 0.20 (ddd, $J = 8.6$, 5.0, 5.0 Hz, 1H), 0.56 (ddd, $J = 8.6$, 4.6, 4.6 Hz, 1H), 0.65–0.78 (m, 1H), 0.96 (ddd, $J = 8.4$, 4.6, 4.6 Hz, 1H), 1.25–1.40 (m, 1H), 1.48 (s, 3H), 2.66 (dd, $J = 6.2$, 3.3 Hz, 4 H), 4.47 (s, 1H), 4.56 (s, 1H), 7.10–7.30 (m, 10H).
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