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# Diastereoselective Addition of Allyltitanocenes to Cyclic Enones

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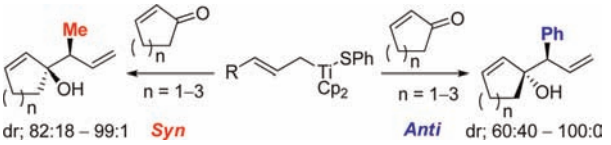
## ABSTRACT




**The reaction of allyltitanocenes with five- to seven-membered cyclic enones proceeded with good to high diastereoselectivity depending on the ring size of enones. The stereochemistry of the major isomers produced by the reaction of cinnamyltitanocene was opposite to that of crotyltitanocene.**

Regio- and stereoselective construction of acyclic systems is a central theme in organic synthesis, and efficient new methodologies are still anticipated.[1] Our recent efforts in this area have focused on the stereoselective construction of multistereogenic centers including a quaternary carbon by the reaction of allyltitanium species with ketones.[2] Similar steric discrimination of a carbonyl based strategy for the construction of adjacent stereocenters has also been examined using organoboron,[3] tin,[4] silicon,[5] zinc,[6] zirconium,[7] aluminum,[8] and samarium[9] species. However, in most of these reactions, high diastereoselectivity is observed only when aldehydes and highly sterically crowded alkyl methyl ketones are employed.

Our recent observations[2a] in the reaction of allyltitanocenes with ketones, where even a small difference between methyl and ethyl groups induced a high level of diastereoselectivity, prompted us to further investigate the diastereoselective allylation of ketones possessing two differently hybridized carbons bonded to the carbonyl group. Herein, we report a stereoselective preparation of cycloalkenols **1** by the reaction of allyltitanocenes **2** with five- to seven-membered cyclic enones **3**, in which unprecedented ring-size dependence of selectivity was observed.

The allyltitanocenes **2** were readily prepared by the desulfurizative titanation of allylic sulfides **4** with titanocene(II)-1-butene complex **5** (Scheme 1). We first examined the reaction of crotyltitanocene **2a** with 2-cyclopentenone (**3a**) and found that only the 1,2-addition product **1a** was produced with moderate diastereoselectivity (entry 1, Table 1). In contrast, the reaction of **2a** with 2-cyclohexenone (**3b**) and 2-cycloheptenone (**3c**) proceeded with much higher diastereoselectivity (entries 2 and 3).

(1) For a recent review, see: O'Brien, A. G. *Tetrahedron* **2011**, *67*, 9639.

(2) (a) Yatsumonji, Y.; Nishimura, T.; Tsubouchi, A.; Noguchi, K.; Takeda, T. *Chem.—Eur. J.* **2009**, *15*, 2680. (b) Takeda, T.; Nishimura, T.; Yatsumonji, Y.; Noguchi, K.; Tsubouchi, A. *Chem.—Eur. J.* **2010**, *16*, 4729.

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(4) (a) Yasuda, M.; Hirata, K.; Nishino, A.; Yamamoto, A.; Baba, A. *J. Am. Chem. Soc.* **2002**, *124*, 13442. (b) Schmidtmann, E. S.; Oestreich, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 4634.

(5) Tietze, L. F.; Knizel, T.; Schmatz, S. *J. Am. Chem. Soc.* **2006**, *128*, 11483.

(6) (a) Ren, H.; Dunet, G.; Mayer, P.; Knochel, P. *J. Am. Chem. Soc.* **2007**, *129*, 5376. (b) Dunet, G.; Mayer, P.; Knochel, P. *Org. Lett.* **2008**, *10*, 117.

(7) Katkin, A. N.; Whitby, R. J. *Tetrahedron Lett.* **1999**, *40*, 9353.

(8) Peng, Z.; Blumke, T. D.; Mayer, P.; Knochel, P. *Angew. Chem., Int. Ed.* **2010**, *49*, 8516.

(9) Takaki, K.; Kusudo, T.; Uebori, S.; Nishiyama, T.; Kamata, T.; Yokoyama, M.; Takehira, K.; Makioka, Y.; Fujiwara, Y. *J. Org. Chem.* **1998**, *63*, 4299.

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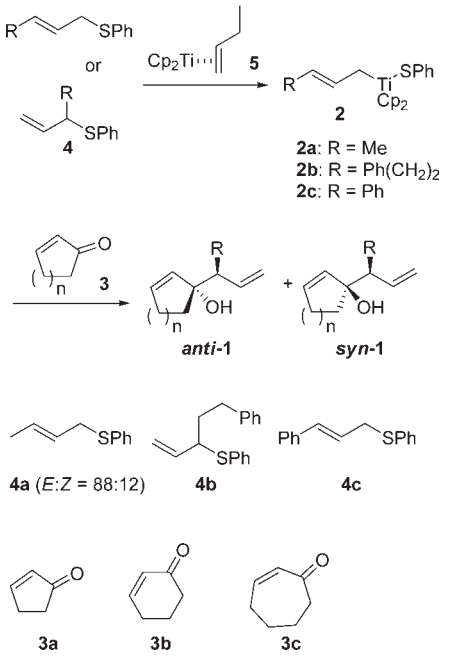
**Scheme 1.** Diastereoselective Addition of Allyltitanocenes **2** to Cyclic Enones **3**




The reactions of allyltitanocene **2b** generated by the desulfurizative titanation of branched sulfide **4b** with cyclic enones **3** produced the unsaturated alcohols **1d**–**f** with similar diastereoisomeric ratios. All these reactions were completely regioselective, and no formation of 1,4-addition product was observed.

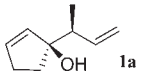
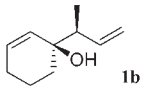
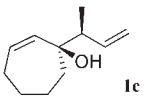
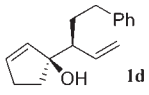
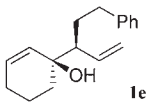
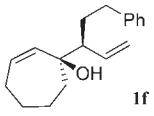
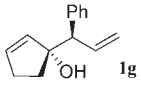
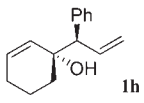
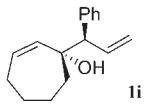
Unlike the reaction of alkyl and aralkyl group substituted allyltitanocenes **2a** and **2b**, the reaction of cinnamyltitanocene **2c** with 2-cyclopentenone (**3a**) produced the homoallylic alcohol **1g** with total diastereoselectivity. It is of interest that the opposite ring-size dependence of selectivity was observed; the diastereoselectivity decreased with the increase of carbon number of cyclic enones as shown in Table 1.[10]

The observed ring-size dependence of selectivity suggests that the stereochemical pathway of the reaction of cinnamyltitanocene **2c** is different from that of alkyl or aralkyl group substituted allyltitanocenes **2a** and **2b**.

Then we examined the relative configuration of homoallylic alcohols **1** by X-ray single crystal analysis. The cyclohexenol **1e** was first transformed into the crystalline lactone **6a** by hydroboration (9-BBN/THF/reflux/2 h)–oxidation (3 M $NaOH/H_2O_2$/room temperature/18 h) and following TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)-oxyl) oxidation ($TEMPO/PhI(OAc)_2/CH_2Cl_2$/room temperature/18 h) of the resulting diol **7a** (Scheme 2). The stereochemistry of the major isomer of **1e** was determined to be *syn* based on the X-ray analysis of the lactone **6a** (see Figure 1a).[11]

On the other hand, it was confirmed that the stereochemistry of the major isomer of **1h** obtained by the reaction of cinnamyltitanocene **2c** with 2-cyclohexenone (**3b**) was found to be *anti* after it was transformed into the lactone **6b** (see Figure 1b).[12] Furthermore, the X-ray

**Table 1.** Titanocene(II)-Promoted Reaction of Allyl Sulfides **4** with 2-Cycloalkenones **3**

| entry | 4 | 3 | 1 | yield, %[a] (dr)[b] |
|---|---|---|---|---|
| 1 | **4a** | **3a** |  **1a** | 87 (82:18) |
| 2 | **4a** | **3b** |  **1b** | 82 (95:5) |
| 3 | **4a** | **3c** |  **1c** | 70 (99:1) |
| 4 | **4b** | **3a** |  **1d** | 62 (74:26) |
| 5 | **4b** | **3b** |  **1e** | 86 (96:4) |
| 6 | **4b** | **3c** |  **1f** | 72 (100:0) |
| 7 | **4c** | **3a** |  **1g** | 72 (100:0) |
| 8 | **4c** | **3b** |  **1h** | 67 (73:27) |
| 9 | **4c** | **3c** |  **1i** | 62 (60:40) |

[a] Isolated yield based on allylic sulfide **4** used. [b] Determined by GC analysis.

(10) A typical experimental procedure is as follows: To a THF (12 mL) suspension of $Cp_2TiCl_2$ (996 mg, 4.0 mmol) was added a 1.54 M hexane solution of BuLi (5.2 mL, 8.0 mmol) at −78 °C under argon. After 1 h, a THF (8 mL) solution of **4c** (329 mg, 2.0 mmol) was added dropwise over 5 min to the mixture and stirring was continued for 15 min at the same temperature and then at 0 °C for 45 min. After the reaction mixture was stirred at −78 °C for 30 min, **3a** (197 mg, 2.4 mmol) in THF (4 mL) was added, and the reaction mixture was further stirred for 18 h. The reaction was quenched by the addition of a mixture of 1 M NaOH (5 mL) and THF (5 mL), and insoluble materials were filtered off through Celite and washed with ether. The organic materials were extracted with ether and dried over $Na_2SO_4$. After removal of the solvent, the residue was purified by silica gel column chromatography (hexane/AcOEt = 95:5, v/v) to give **1g** (287 mg, 72%).

(11) The crystal data of **6a** have been deposited in CCDC as number 865236.

(12) The crystal data of **6b** have been deposited in CCDC as number 865235.

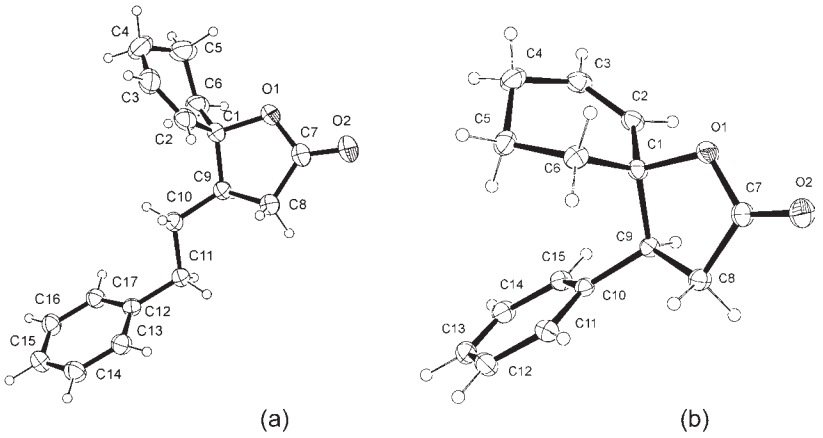
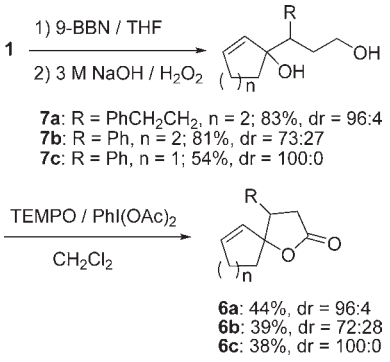
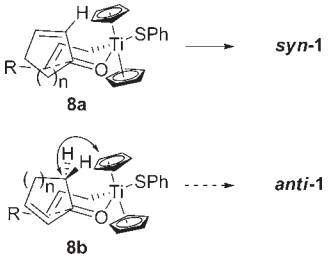



**Figure 1.** (a) ORTEP view of molecular structure of **6a**. Selected bond distances (Å) and angles (deg): C2−C3 1.304(3), C5−C6 1.517(3); C1−C2−C3 124.17(18), C1−C6−C5 112.46(16). (b) ORTEP view of molecular structure of **6b**. Selected bond distances (Å) and angles (deg): C2−C3 1.3309(15), C5−C6 1.5305(14); C1−C2−C3 124.00(10), C1−C6−C5 112.26(8).

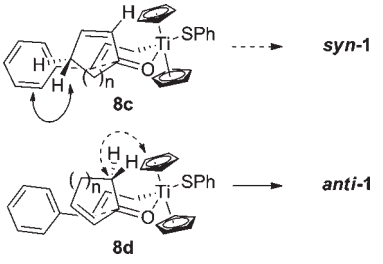
**Scheme 2.** Transformation of Homoallylic Alcohols **1** into Lactones **6**




**Scheme 3.** Transition States for the Reaction of **4a** and **4b**




**Scheme 4.** Transition States for the Reaction of **4c**




analysis of the crystalline lactone **6c** (see Supporting Information)[13] indicated that the cyclopentenol **1g** obtained by the reaction of **2c** with 2-cyclopentenone (**3a**) had *anti* stereochemistry.

The *syn* selectivity observed in the reaction of allyltitanocene **2b** with 2-cyclohexenone (**3b**) is explained by the chairlike cyclic transition states **8** (Scheme 3). The transition state **8b** leading to the *anti*-isomer ***anti*-1** is destabilized by the steric repulsion between the α-methylene of enone and the Cp ring indicated by a double-headed arrow. As a result, the reaction proceeds via the transition state **8a** in which the double bond of enone is located in an axial position to give ***syn*-1**. The ring-size dependence of selectivity is well explained by the unfavorable steric repulsion in the less stable transition state **8b** which increases with increasing the carbon number of enone. On the basis of this result, the stereochemistry of all other major isomers of the reaction of **2a** and **2b** with cyclic enones **3** is assumed to be *syn*.

In the reaction of cinnamyltitanocene **2c**, the steric interaction between the α-methylene hydrogens of enones **3** and the phenyl group of **2c** becomes significant (Scheme 4). Since the chairlike transition state **8c** is destabilized by such steric interaction between the two overlapped carbocycles, the *anti*-alcohol **1g** was exclusively produced via the more favored transition state **8d**. The moderate to low diastereoselectivity observed in the reactions of **2c** with

(13) The crystal data of **6c** have been deposited in CCDC as number 865234.

2-cyclohexenone (**3b**) and 2-cycloheptenone (**3c**) is reasonably explained by the unfavorable increased steric repulsion between the Cp ring and α-methylene of enone in the transition state **8d**.

In conclusion, it should be noted that the present reaction is the first regio- and diastereoselective addition of allylmetals to cyclic enones. This reaction provides a useful method for the preparation of stereochemically defined cycloalkenols. Further study on the synthetic application and extension of this methodology to the construction of a variety of acyclic unsaturated systems is now under investigation.

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**Supporting Information Available.** Experimental procedures and full characterization of all compounds. This material is available free of charge via Internet at http://pubs.acs.org.

The authors declare no competing financial interest.