Synthetic Methods

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Highly Diastereoselective Construction of Acyclic Systems with Two Adjacent Quaternary Stereocenters by Allylation of Ketones**

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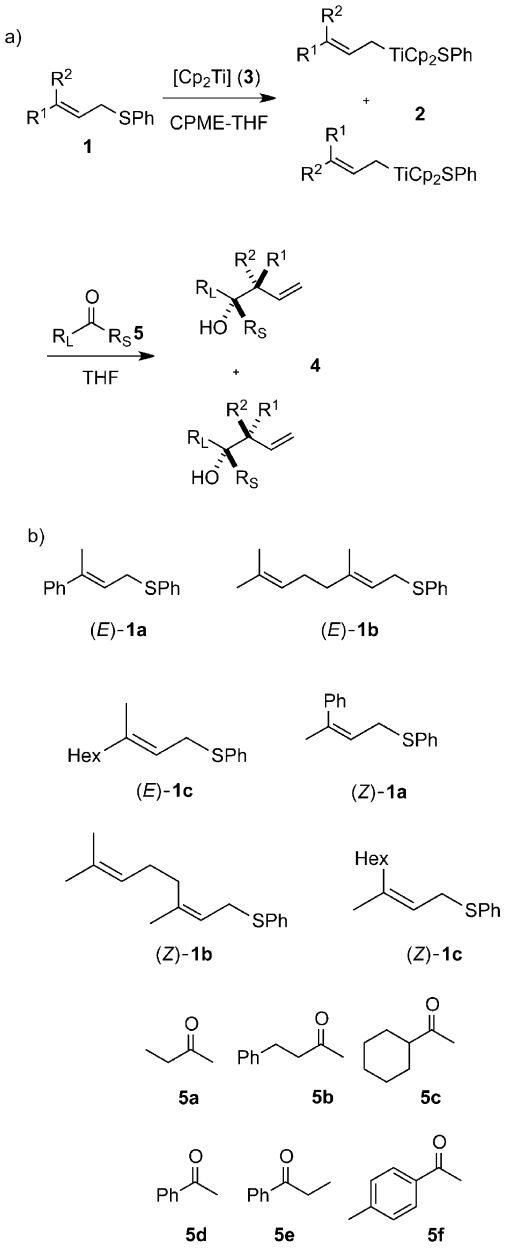
Diastereoselective construction of acyclic systems bearing multiple stereogenic centers is one of the most challenging areas in organic synthesis.[1] Reaction of allylmetals with unsymmetrical carbonyl compounds is a major approach to this challenge. Recently much attention has been paid to diastereoselective allylation of ketones with various γ-monosubstituted allylmetals such as organoboron,[2] silicon,[3] tin,[4] zinc,[5] titanium,[6] indium,[7] vanadium,[8] and samarium[9] species. A much more arduous task is the stereoselective construction of acyclic systems having two adjacent quaternary carbon atoms, and only most recently highly stereoselective construction of such systems by the allylation of ketones has been achieved by Knochel and co-workers[10] and Marek and co-workers[11] using γ,γ-disubstituted allylzinc reagents. The approach by Marek and co-workers enjoys a synthetic advantage in that the reaction is stereospecific and both the diastereomers are obtained by using the different geometrical isomers of allylzinc reagents generated in situ from terminal alkynes, organocopper reagents, and the Simons–Smith–Furukawa zinc carbenoid. The allylation, however, has only been applied to aryl, hetaryl, and styryl ketones, and the allylation of aliphatic ketones has not been elucidated yet.

We have shown that allyltitanocenes are excellent reagents for diastereoselective construction of tertiary homoallylic alcohols bearing multiple chiral centers, and even a small difference between two alkyl groups attached to the carbonyl group induces a high level of diastereoselectivity.[6c–e] These results prompted us to further investigate the more challenging stereoselective construction of acyclic systems having two contiguous quaternary carbon atoms using γ,γ-disubstituted allyl sulfides **1** (Scheme 1).

To construct such systems with high stereoisomeric purity, both the formation of allyltitanocenes and their reaction with ketones must be highly stereoselective. As we reported earlier,[6c] thermodynamically stable allyltitanocenes having an *E* configuration are preferentially produced from both stereoisomers of γ-monosubstituted allyl sulfides. The *E* allyltitanocenes thus formed react with ketones via the well-established chairlike six-membered transition state to produce *anti*-homoallylic alcohols with high diastereoselectivity.

In accordance with the previous results, the reaction of the allyltitanocene **2**, generated by the desulfurizative titanation



Scheme 1. a) Formation of γ,γ-disubstituted allyltitanocenes and their reaction with ketones. b) The γ,γ-disubstituted allyl sulfides **1** and ketones **5** used for this study.

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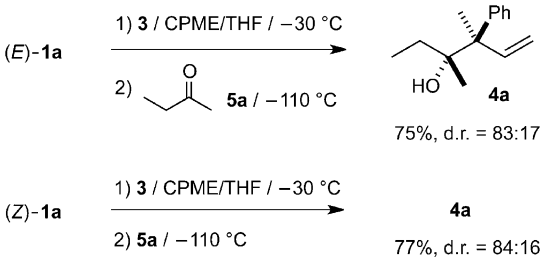


Scheme 2. Stereoselective reaction of (*E*)- and (*Z*)-3-phenyl-2-butenyl sulfides [(*E*)- and (*Z*)-**1a**] with ethyl methyl ketone (**5a**).

of both the stereoisomers of 3-phenyl-2-butenyl phenyl sulfide [(*E*)- and (*Z*)-**1a**] with the titanocene(II) 1-butene complex **3** at −30 °C, reacted with ethyl methyl ketone (**5a**) at −110 °C (using an ethanol slush bath) to produce the same diastereomer **4a** as a major product with almost the same diastereoselectivity (Scheme 2). The stereochemistry of the major isomer **4a** is assumed to be *anti* in analogy with the reaction of γ-monosubstituted allyl sulfides with ketones.

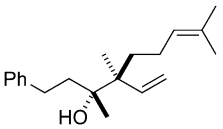
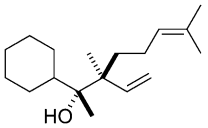
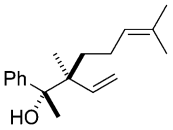
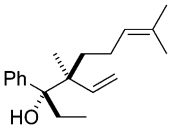
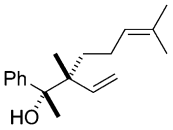
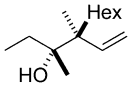
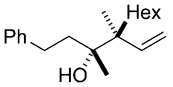
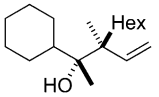
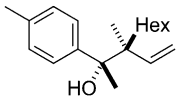
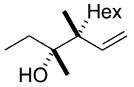
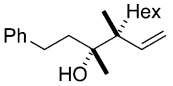
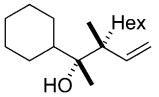
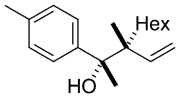
The reaction of allyltitanocene generated from geranyl phenyl sulfide [(*E*)-**1b**] reacted with 4-phenyl-2-butanone (**5b**) at −110 °C to produce the *anti*-alcohol **4b** with good diastereomeric ratio. A slight decrease of selectivity was observed when the reaction was carried out at −78 °C (Table 1, entry 1). The reactions of (*E*)-**1b** with methyl ketones having a bulky substituent, **5c** and **5d**, at −78 °C gave the *anti*-alcohols **4c** and **4d**, respectively, with almost perfect diastereoselectivity (entries 2 and 3). The use of cyclopentyl methyl ether (CPME) as a cosolvent is indispensable for good yield and diastereoselectivity (entry 3). Propiophenone (**5e**) also reacted with (*E*)-**1b** with comparable selectivity (entry 4).

In contrast to the reaction of (*E*)-**1b**, the *syn* isomer **4f** was exclusively produced by the reaction of neryl phenyl sulfide [(*Z*)-**1b**] with acetophenone (**5d**; Table 1, entry 5). These results are completely different from the reaction of γ-monosubstituted allyl sulfides. Stereochemistry of the reaction was further investigated using both the stereoisomers of the allyl sulfide **1c** bearing methyl and hexyl groups. As shown in entries 6–13, the *anti-tert*-homoallylic alcohols **4g–j** and their *syn*-isomers **4k–n** were obtained in good to high yields by the reaction of (*E*)- and (*Z*)-**1c**, respectively. The reaction was completely stereospecific and the diastereomeric excess of homoallyl alcohols was only dependent on ketones employed regardless of the geometry of allylic sulfides.

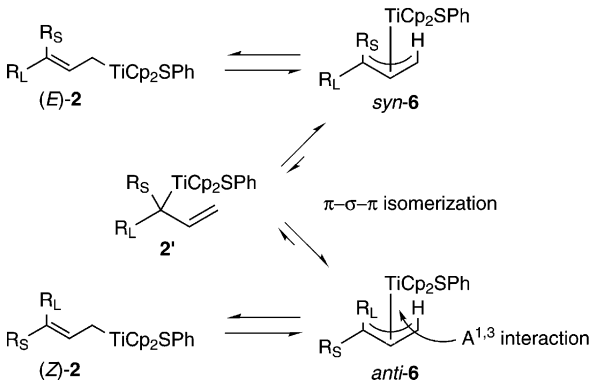
All these results indicate that the desulfurizative titanation of the highly substituted allyl sulfides **1** proceeds with retention of configuration with certain exceptions such as the cinnamyl sulfide (*Z*)-**1a**. The resulting allyltitanocenes **2** are conformationally stable enough to afford the homoallylic alcohols with high stereospecificity by their reaction with ketones via the chairlike six-membered transition state, in which the more bulky substituent of the ketone occupies a pseudoequatorial position,[13] similar to the reaction of γ-monosubstituted allyltitanocenes with ketones.[6c]

The retention of configuration observed in the desulfurizative titanation of allylic sulfides **1** is explained by the steric influence of γ substituents. It is reasonable to assume that the inversion of configuration of the allyltitanocenes **2** proceeds via the π-allyltitanium complexes **6** which exist in equilibrium with the σ-allyl complexes **2** (Scheme 3). In the case of the

Table 1: Titanocene(II)-promoted stereospecific reaction of allyl sulfides **1** with ketones **5**.[a]

Entry	**1**	**5**	**4**[b]	Yield [%][c] (d.r.)[d]
1	(*E*)-**1b**	**5b**	 **4b**	87 (86:14)[e] 89 (83:17)
2	(*E*)-**1b**	**5c**	 **4c**	79 (99:1)[f]
3	(*E*)-**1b**	**5d**	 **4d**	79 (98:2) 64 (94:6)[g]
4	(*E*)-**1b**	**5e**	 **4e**	89 (97:3)[f]
5	(*Z*)-**1b**	**5d**	 **4f**	80 (95:5)
6	(*E*)-**1c**	**5a**	 **4g**	73 (83:17)[e] 68 (75:25)
7	(*E*)-**1c**	**5b**	 **4h**	91 (87:13)[e] 92 (84:16)
8	(*E*)-**1c**	**5c**	 **4i**	80 (98:2)[f]
9	(*E*)-**1c**	**5f**	 **4j**	91 (99:1)[f]
10	(*Z*)-**1c**	**5a**	 **4k**	74 (82:18)[e] 70 (76:24)
11	(*Z*)-**1c**	**5b**	 **4l**	87 (86:14)[e] 91 (83:17)
12	(*Z*)-**1c**	**5c**	 **4m**	84 (98:2)[f]
13	(*Z*)-**1c**	**5f**	 **4n**	90 (96:4)[f]

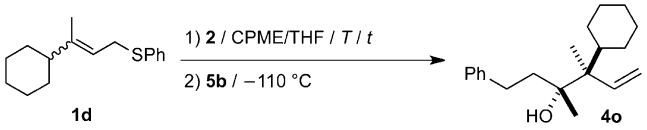
[a] All the reactions of **2** with **5** were carried out at −78 °C, unless otherwise noted. [b] For the relative configuration of **4**, see Ref. [12]. [c] Yield of isolated product. [d] Determined by NMR analysis. [e] The reaction of **2** with **5** was carried out at −110 °C. [f] Determined by GC analysis. [g] All the steps were carried out in THF.



Scheme 3. Inversion of the configuration of the allyltitanocenes **2** by π–σ–π isomerization.

allyltitanocenes bearing alkyl groups at the γ position, the π–σ–π isomerization between *syn*-**6** and *anti*-**6** is negligible under the reaction conditions because the intermediary α,α-disubstituted allyltitanocenes **2'** are largely destabilized by steric repulsion between the susbtituents and titanocene moiety. A similar conformational stability of γ,γ-disubstituted allylchromium(II) species observed in the allylation of aldehydes was reported by Knochel and co-workers.[14] In the case of the cinnamyl sulfide (*Z*)-**1a**, by contrast, complete inversion of configuration of *anti*-**6**, destabilized by an $A^{1,3}$ interaction, to the more stable *syn*-**6** takes place since the highly substituted allyltitanocene **2'** is stabilized with the adjacent electron-withdrawing phenyl group. Hence the *anti* selectivity was observed in the reactions of (*Z*)-**1a** with ethyl methyl ketone (**5a**).

The above speculation was supported by the fact that little to good stereoselectivity was observed in the reaction of a 1:1 stereoisomeric mixture of 3-cyclohexyl-2-butenyl phenyl sulfide (**1d**) depending on the temperature at which the desulfurizative titanation of **1d** was performed (Scheme 4). The reaction of (*E*)-**1d** (*E*/*Z* = 96:4) with **5b** produced the *anti*-homoallylic alcohol **4o** with 90% diastereoselectivity whereas the reaction using a 1:1 stereoisomeric mixture of **1d** showed little *anti* selectivity (d.r. = 58:42) when the desulfurizative titanation was carried out at −30 °C. The latter result implies that only little isomerization of *anti*-**6** to *syn*-**6** proceeded in these reactions. By contrast, good diastereoselectivity was observed when the desulfurizative titanation of a stereoisomeric mixture of **1d** was carried out at a higher temperature.



E/*Z*	*T* [°C]	*t* [h]	Yield [%]	d.r.
96:4	−30	6	69	90:10
50:50	−30	6	68	58:42
50:50	0	0.75	65	79:21

Scheme 4. Reaction of 3-cyclohexyl-2-butenyl phenyl sulfide (**1d**) with 4-phenyl-2-butanone (**5b**).

In conclusion, we have first realized the highly diastereoselective addition of γ,γ-disubstituted allylmetal species to aliphatic as well as aromatic ketones. Since the stereochemically defined γ,γ-disubstituted allyl sulfides are readily available from the corresponding allylic alcohols, the present reaction provides a highly practical way for the construction of a variety of acyclic systems having two adjacent quaternary carbon centers. Detailed study on stereochemistry of the reaction and the further extension of this methodology to the stereoselective construction of a variety of acyclic systems bearing multiple stereogenic centers is now under investigation.

Experimental Section

A 1.62 M *n*-hexane solution of BuLi (3.1 mL, 5.0 mmol) was added to a CPME (8 mL) suspension of [Cp_2TiCl_2] (623 mg, 2.50 mmol) was added over a 10 min period at −78 °C under argon. After 1 h, a THF (2 mL) solution of (*E*)-**1b** (308 mg, 1.25 mmol) was added dropwise over a 5 min period to the mixture in the dark, and stirring was continued for 15 min at the same temperature and then at −30 °C for 6 h. After stirring the reaction mixture at −78 °C for 15 min, **5d** (120 mg, 1.00 mmol) in THF (4 mL) was added over a 10 min period, and the reaction mixture was stirred for 18 h. The reaction was quenched by addition of 1 M NaOH (20 mL) and insoluble materials were filtered off through Celite and washed with diethyl ether. The organic materials were extracted with diethyl ether and dried over K_2CO_3. After removal of the solvent under reduced pressure, the residue was purified by silica gel PTLC (*n*-hexane/AcOEt 9:1, v/v) to give **4d** (204 mg, 79%).

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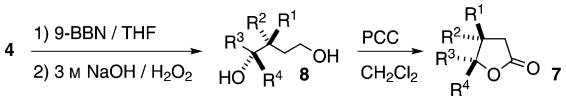
[12] The relative configuration of the the *anti*-alcohols **4g**,**h**,**j** and their *syn* counterparts **4k**,**l**,**n** was assigned based on NOESY experiments after transformation into the lactones **7** by hydroboration (9-BBN/THF/reflux/2 h)-oxidation (3 M $NaOH/H_2O_2$/25 °C/18 h) and subsequent PCC oxidation (PCC/CH_2Cl_2/25 °C/18 h) of the resulting diols **8** (see the Supporting Information). The stereochemistry of other alcohols **4** was deduced from the above results.



[13] A Zimmerman–Traxler transition state, in which the bulky group in the carbonyl compounds is in a pseudoaxial position, was proposed for the reaction of γ,γ-disubstituted allylzinc species with aldehydes. See: a) N. Gilboa, H. Wang, K. N. Houk, I. Marek, *Chem. Eur. J.* **2011**, *17*, 8000; b) T. Mejuch, M. Botoshansky, I. Marek, *Org. Lett.* **2011**, *13*, 3604.

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