



Preparation of 1,4-dienes by the reaction of titanocene cycloalkenylidenes with 1-alkenes



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ARTICLE INFO

Article history:

Received 23 March 2015

Revised 23 April 2015

Accepted 28 April 2015

Available online 6 May 2015

Keywords:

1,4-Dienes

Chloro sulfides

Titanocene(II)

Titanium carbene complexes

1-Alkenes

ABSTRACT

Titanocene cycloalkenylidenes, generated by the reductive titination of 3-(aryltio)-1-chloro-1-cycloalkenes with titanocene(II)-triethyl phosphite complex, reacted with styrene derivatives to produce (*E*)-1,4-dienes. Their reaction with vinyl-borane and -silane also produced 1-boryl- and silyl-1,4-dienes, which were transformed into 1-substituted 1,4-dienes through the palladium(0)-catalyzed or copper(I)-promoted reaction with organic halides.

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We have studied the preparation of alkenylcarbene complexes **1** by the reductive titination of β,γ -unsaturated thioacetals,¹ 1,3-bis(phenylthio)-1-propene derivatives,² or 1-chloro-3-(phenylthio)-1-propene derivatives.³ The organometallic reagents **1** are useful for the preparation of di-² and trienes,⁴ and alkenylcyclopropanes.² The synthetic application of alkenylcarbene complexes **1**, however, is largely restricted by the fact that they exist in equilibrium with their valence tautomers, titanacyclobutenes **2** (Scheme 1). The position of equilibrium depends on their substitution pattern,³ and the highly substituted titanium alkenylcarbene complexes are difficult to utilize as synthetic intermediates.

Since titanocene cycloalkenylidenes exist only as alkenylcarbene complexes due to their fixed *cisoid* conformation, we have studied their reactivity toward multiple bond compounds. Here we describe the preparation of **1** by the reductive titination of 3-(aryltio)-1-chloro-1-cycloalkenes **3** with titanocene(II)-triethyl phosphite complex **4** and application of these species for the regio- and stereoselective preparation of 1,4-dienes **5** by their reaction with terminal olefins **6** (Scheme 2).

The treatment of 1-chloro-3-(phenylthio)-1-cyclohexene (**3a**) with the low-valent titanium species **4** (3 equiv) in the presence of styrene (**6a**) (4 equiv) at 50 °C for 1 h produced a mixture of the (*E*)-1,4-diene **5a** and 1,3-diene **7a** (**5a**:**7a** = 87:13) in 76% yield (Table 1, entry 1). The formation of two dienes is well explained by the intermediary regioisomeric titanacyclobutanes **8a** and **8b**, in



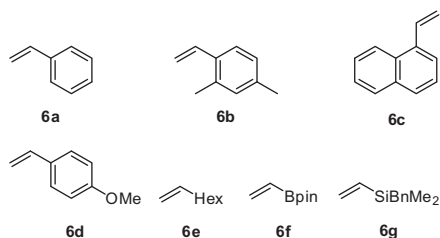
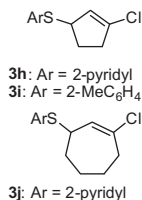
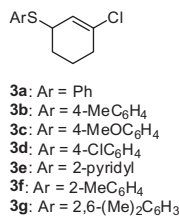
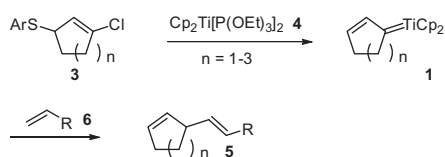
Scheme 1. Equilibrium between alkenylcarbene complexes **1** and titanacyclobutenes **2**.

which **8a** predominates due to the favorable formation of stable benzylic carbon–titanium bond (Scheme 3). The following β -hydride elimination with the opening of four-membered metallacycles and reductive elimination of the resulting allyltitanium species **9** afford the unconjugated and conjugated dienes **5a** and **7a**, respectively. Unlike the reaction of **3a**, the predominant formation of unconjugated dienes was observed in a similar reaction of 1,3-disubstituted 1-chloro-3-(phenylthio)-1-propenes, acyclic counterparts of **3a**, with styrene.³ The reason for such difference in product selectivity is not clear at present.

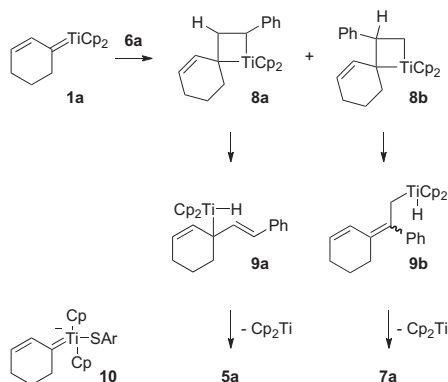
Skipped dienes are important motifs in natural products and much effort has been devoted to establish efficient routes to these substructures.⁵ The major routes include the allylation of alkenylmetals^{5b,e,f,i,l,p,s,w-z} and hydrovinylation of 1,3-dienes.^{5a,g,h,m,n,r} There are, however, limited accesses to such compounds containing a cycloalkene moiety.⁶ Then we further investigated the reaction of titanocene cycloalkenylidenes **1** with terminal olefins **6** to establish a new route to 1,4-dienes. For the selective formation of **5a**, the influence of leaving group on the mode of reaction was examined. The results of the reaction of 1-chlorocyclohexenes having a 4-substituted phenylthio group **3b-d**

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Scheme 2. Preparation of 1,4-dienes **5** by the reaction of titanocene cycloalkenylienes **1** with 1-alkenes **6**.

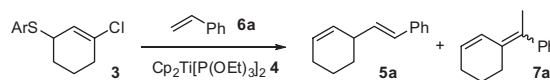


Scheme 3. Formation of 1,4- and 1,3-dienes **5a** and **7a** by the reaction of titanocene cyclohexenyliene (**1a**) with styrene (**6a**).

indicated that both the electron-donating and electron-withdrawing groups had little effect on the mode of the reaction (entries 2–4). Although the use of 2-pyridylthio group substituted chloro sulfide **3e** improved the yield of dienes, the selectivity for the formation of unconjugated diene **5a** slightly decreased (entry 5). What is striking is that the reaction of **3f** having an *o*-tolylthio group selectively furnished the diene **5a** (entry 6). In contrast, the selectivity was not improved when the sulfide bearing a 2,6-dimethylphenylthio group **3g** was employed (entry 7). Although the reason for the arylthio group-dependence of selectivity observed in the reaction of chloro sulfides **3** with **6a** is not clear at present, we assume that it would be attributable to the formation of the arylthio group coordinated titanate **10**.

Next the scope of the formation of unconjugated dienes **5** was examined using the *o*-tolylthio group-containing chloro sulfide **3f** and its five-membered congener **3i**, and various terminal olefins **6** (Table 2). Although the reaction of **3f** with sterically demanding 2,4-dimethylstyrene (**6b**) and 1-vinylnaphthalene (**6c**) produced the (*E*)-unconjugated dienes **5b** and **5c** as sole products (entries

Table 1
Reaction of 3-(arylthio)-1-chloro-1-cyclohexenes **3a–g** with styrene (**6a**)^a



Entry	3	Yield ^b (%)	5a:7a ^c
1	3a	76	87:13
2	3b	83	88:12
3	3c	74	91:9
4	3d	70	87:13
5	3e	88	78:22
6	3f	80	99:1
7	3g	81	90:10

^a Carried out at 50 °C for 1 h in THF using chloro sulfide **3** (0.3 mmol), Cp₂Ti[P(OEt)₃]₂ **4** (0.9 mmol), and **6a** (1.2 mmol).

^b Isolated yield based on **3** used.

^c Determined by NMR spectroscopy.

2 and 3), a substantial amount of the 1,3-diene **7b** was formed when 4-methoxystyrene (**6d**) was employed (entry 4). Furthermore, no selectivity was observed in the reaction of **3f** with 1-octene (**6e**) (entry 5). Similarly to the six-membered congener, the reaction of five-membered carbene complex generated from **3i** with styrene (**6a**) selectively produced the (*E*)-1,4-diene **5f** (entry 6).

To overcome the limitation of the above reaction that the highly selective formation of skipped dienes **5** is observed only in the reaction of particular substrates, we next examined a diversity-oriented access to **5** which consists of the reaction of carbene complexes **1** with vinylboranes or vinylsilanes and the cross-coupling between the resulting 1-boryl or silyl-1,4-dienes and organic halides. As was expected from the results described above, the reaction of titanocene cyclohexenyliene (**1a**), generated from **3f**, with sterically demanding vinylboronic acid pinacol ester (vinylBpin) (**6f**) and benzyltrimethylsilyl silane (**6g**) produced the

Table 2
Reaction of 1-chloro-3-(*o*-tolylthio)-1-cycloalkenes **3** with terminal olefins **6**^a

Entry	3	6	Products	Yield ^b (%) (5:7) ^c
1 ^d	3f	6a	5a , 7a	80 (99:1)
2 ^e	3f	6b	5b	80
3 ^e	3f	6c	5c	87
4 ^e	3f	6d	5d , 7b	81 (92:8)
5 ^d	3f	6e	5e , 7c	85 (50:50) ^f
6 ^d	3i	6a	5f	69

^a Carried out at 50 °C for 1 h in THF using chloro sulfide **3** (0.3 mmol) and Cp₂Ti[P(OEt)₃]₂ **4** (0.9 mmol).

^b Isolated yield based on **3** used.

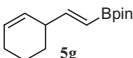
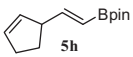
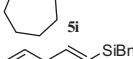
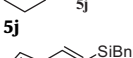
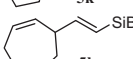
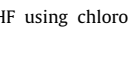
^c Determined by NMR spectroscopy.

^d Olefin **6** (1.2 mmol) were used.

^e Olefin **6** (0.36 mmol) were used.

^f ¹H NMR spectrum of the products contained unidentified signals.

Table 3
Preparation of 1-boryl- and 1-silyl-1,4-dienes^a

Entry	3	6	5	Yield ^b (%)
1 ^c	3f	6f		80
2 ^c	3e	6f	5g	87
3 ^c	3h	6f		64
4 ^c	3j	6f		69
5 ^d	3f	6g		60 ^e
6 ^d	3e	6g	5j	75 ^e
7 ^d	3h	6g		65
8 ^d	3j	6g		74 ^e

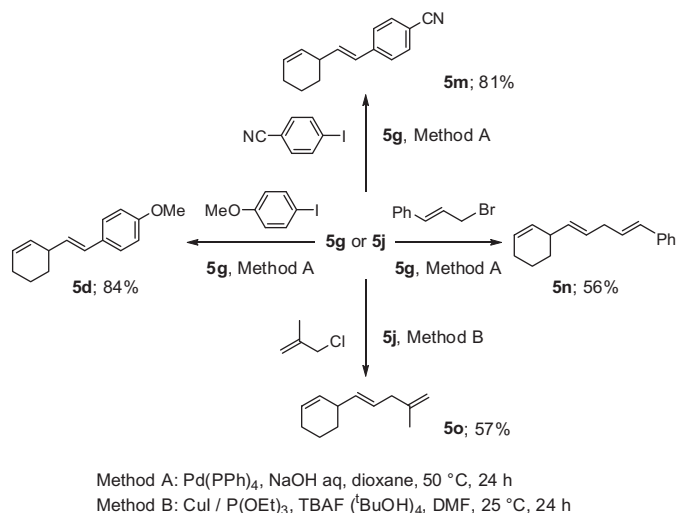
^a Carried out at 35 °C for 1 h in THF using chloro sulfide **3** (0.3 mmol) and Cp₂Ti[P(OEt)₃]₂ **4** (0.9 mmol).

^b Isolated yield based on **3** used.

^c Olefin **6** (1.2 mmol) were used.

^d Olefin **6** (0.36 mmol) were used.

^e ¹H NMR spectrum of the product contained unidentified signals.



Scheme 4. Cross-coupling of 1-boryl- and 1-silyl-1,4-dienes **5g** and **5j** with organic halides.

(*E*)-1,4-dienes **5g** and **5j** with complete regio and stereoselectivity (Table 3, entries 1 and 5). The yields of the products were increased by using the 2-pyridylthio group-containing chloro sulfide **3e** (entries 2 and 6). In a similar fashion, five- and seven-membered homologues were obtained in good yields with perfect selectivity (entries 3, 4, 7, and 8).

The alkenylboranes **5g–i** thus formed were good substrates for the Suzuki–Miyaura cross-coupling reaction.⁷ Likewise 1,4-dienes **5j–l** bearing a benzyltrimethylsilyl group are expected to react with

aryl halides through the Pd(0)-catalyzed process.⁸ These alkenylsilanes are also potential substrates for the copper(I)-promoted cross-coupling with alkyl and allyl halides.^{5x} The advantage of this approach is clearly shown in Scheme 4; 3-(4-methoxystyryl)-1-cyclohexene (**5d**) was obtained as a sole product by the two-step process. The stereoselective preparation of 1,4,7-triene **5n** was achieved by the cinnamylation of **5g**. The copper(I) iodide-promoted cross-coupling between the alkenylbenzyltrimethylsilane **5j** and methylallyl chloride also furnished the 1,4,7-triene **5o** in good yield. All these results clearly show the potential utility of **5g–l** for diversity-oriented approach to skipped dienes.

In summary, we have developed a new method for the preparation of skipped dienes bearing a cycloalkene moiety. It is expected that the diversity-oriented approach via dienyboranes and dieny-silanes described here will become a useful tool for the construction of highly unsaturated systems.

Supplementary data

Supplementary data (experimental procedures and full characterization of chloro sulfides and all products) associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2015.04.124>.

References and notes

- Horikawa, Y.; Watanabe, M.; Fujiwara, T.; Takeda, T. *J. Am. Chem. Soc.* **1997**, *119*, 1127.
- Horikawa, Y.; Nomura, T.; Watanabe, M.; Fujiwara, T.; Takeda, T. *J. Org. Chem.* **1997**, *62*, 3678.
- Shono, T.; Kurashige, R.; Mukaiyama, R.; Tsubouchi, A.; Takeda, T. *Chem. Eur. J.* **2007**, *13*, 4074.
- Takeda, T.; Fukada, T.; Tsubouchi, A. *Tetrahedron Lett.* **2014**, *55*, 1434.
- For recent examples, see: (a) Zhang, A.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2006**, *128*, 54; (b) Kabalka, G. W.; Al-Masum, M. *Org. Lett.* **2006**, *8*, 11; (c) Hilt, G.; Treutwein, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 8500; (d) Kolundzic, F.; Micalizio, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 15112; (e) Lee, Y.; Akiyama, K.; Gillingham, D. G.; Brown, M. K.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 446; (f) Dey, R.; Chattopadhyay, K.; Ranu, B. C. *J. Org. Chem.* **2008**, *73*, 9461; (g) Shimp, H. L.; Hare, A.; McLaughlin, M.; Micalizio, G. C. *Tetrahedron* **2008**, *64*, 3437; (h) Moreau, B.; Wu, J. Y.; Ritter, T. *Org. Lett.* **2009**, *11*, 337; (i) Alacid, E.; Nájera, C. *J. Org. Chem.* **2009**, *74*, 2321; (j) Hilt, G.; Treutwein, J. *Chem. Commun.* **2009**, 1395; (k) He, H.; Liu, W.-B.; Dai, L.-X.; You, S.-L. *J. Am. Chem. Soc.* **2009**, *131*, 8346; (l) Akiyama, K.; Gao, F.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 419; (m) Sharma, R. K.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2010**, *132*, 3295; (n) Arndt, M.; Reinhold, A.; Hilt, G. *J. Org. Chem.* **2010**, *75*, 5203; (o) Liu, W.-B.; He, H.; Dai, L.-X.; You, S.-L. *Chem. Eur. J.* **2010**, *16*, 7376; (p) Gao, F.; McGrath, K. P.; Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 14315; (q) Macklin, T. K.; Micalizio, G. C. *Nature Chem.* **2010**, *2*, 638; (r) Arndt, M.; Dindaroğlu, M.; Schmalz, H.-G.; Hilt, G. *Org. Lett.* **2011**, *13*, 6184; (s) Jung, B.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2012**, *134*, 1490; (t) Stokes, B. J.; Opra, S. M.; Sigman, M. S. *J. Am. Chem. Soc.* **2012**, *134*, 11408; (u) Hamilton, J. Y.; Sarlah, D.; Carreira, E. M. *J. Am. Chem. Soc.* **2013**, *135*, 994; (v) Ma, X.-T.; Wang, Y.; Dai, R.-H.; Liu, C.-R.; Tian, S.-K. *J. Org. Chem.* **2013**, *78*, 11071; (w) Tsubouchi, A.; Muramatsu, D.; Takeda, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 12719; (x) Takeda, T.; Matsumura, R.; Wasa, H.; Tsubouchi, A. *Asian J. Org. Chem.* **2014**, *3*, 838; (y) Gao, F.; Carr, J. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2014**, *136*, 2149; (z) Takeda, T.; Obata, R.; Muramatsu, D.; Takeda, Y.; Tsubouchi, A. *Chem. Commun.* **2014**, 15156.
- (a) Larock, R. C.; Gong, W. H. *J. Org. Chem.* **1989**, *54*, 2047; (b) Luparia, M.; Vadalà, A.; Zanon, G.; Vidari, G. *Org. Lett.* **2006**, *8*, 2147; (c) Nakao, Y.; Ebata, S.; Chen, J.; Imanaka, H.; Hiyama, T. *Chem. Lett.* **2007**, 36, 606; (d) Lysenko, I. L.; Kim, K.; Lee, H. G.; Cha, J. K. *J. Am. Chem. Soc.* **2008**, *130*, 15997; (e) Nishimoto, Y.; Kajioka, M.; Saito, T.; Yasuda, M.; Baba, A. *Chem. Commun.* **2008**, 6496; (f) Yue, H.; Wei, W.; Li, M.; Yang, Y.; Ji, J. *Adv. Synth. Catal.* **2011**, *353*, 3139.
- Miyaura, N.; Suzuki, M. *Chem. Rev.* **1995**, *95*, 2457.
- Trost, B. M.; Machacek, M. R.; Ball, Z. T. *Org. Lett.* **2003**, *5*, 1895.