Titanium Alkoxide-Based Method for Stereoselective Synthesis of Functionalized Conjugated Dienes

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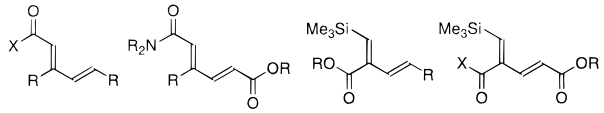
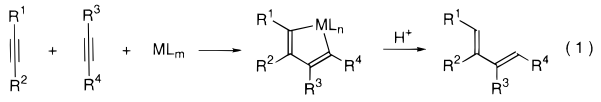
Abstract: Treatment of an internal acetylene such as 1-silyl-1-octyne (**3**) with a low-valent titanium reagent, (η^2-propene)Ti(O-*i*-Pr)$_2$ (**1**) readily prepared from Ti(O-*i*-Pr)$_4$ and *i*-PrMgCl in situ, generates an acetylene−titanium complex. This complex was allowed to react with a terminal acetylene, 4-(benzyloxy)-1-butyne (**5**), to give the intermediate titanacyclopentadiene (**6**) which, upon hydrolysis, deuteriolysis, or iodinolysis, gave diene **8**, or its bis-deuterated (>99% d_2) and bis-iodinated counterparts (**9** and **10**), in good yields and with high selectivities. This reaction is applicable to the cross-coupling reaction of functionalized acetylenes such as 2-alkynoates and 2-alkynamides **12**−**18** and a variety of terminal acetylenes **24**−**28** to give dienes **36**−**50** in good yields. A terminal acetylene **28** carrying an olefinic bond at the other terminus reacted with a silylpropiolate to afford the expected diene **42** without any complication.

Introduction

Stereoselective preparation of functionalized, conjugated dienes is an important synthetic transformation, because such dienes are frequently found as a partial structure of naturally occurring products[1] and are also useful intermediates in organic synthesis,[2] as has been amply demonstrated in the Diels−Alder and related reactions.[3] When regio- and stereoselective alignment of the substituent(s) and functional group(s) on the diene skeleton is considered, their synthesis is not necessarily a facile process and, rather, often requires a multistep procedure.[4] In this respect, group 4 metal (Ti or Zr) complex-assisted assembly of acetylenes to furnish conjugated dienes as formulated in eq 1 (M = metal, L = ligand) is an attractive method.[5,6] However, the synthesis of *functionalized* dienes such as those in Chart 1 (R = alkyl groups, X = OR or NR$_2$) by this method via a cross-coupling of different types of acetylenes *involving an* α,β*-acetylenic ester or amide* has remained undeveloped.[7] We report herein that a low-valent titanium reagent, (η^2-propene)Ti(O-*i*-Pr)$_2$ (**1**) readily prepared from Ti(O-*i*-Pr)$_4$ and *i*-PrMgCl in situ,[8−11] could realize the above process to give dienes of the general structures shown in Chart 1 in addition to other relevant 1,3-dienes.

Chart 1





(1)

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(3) Desimoni, G.; Tacconi, G.; Barco, A.; Pollini, G. P. *Natural Products Synthesis through Pericyclic Reactions*; American Chemical Society: Washington, DC, 1983. Fringuelli, F.; Taticchi, A. *Dienes in the Diels−Alder Reaction*; Wiley: New York, 1990. Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1990. Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, p 315. Weinreb, S. M. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, p 401. Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, p 513.

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(6) For the preparation of 1,3-dienes via a group 4 metal complex-mediated intermolecular coupling of acetylenes, see: (a) Buchwald, S. L.; Watson, B. T.; Huffman, J. C. *J. Am. Chem. Soc.* **1987**, *109*, 2544. (b) Buchwald, S. L.; Nielsen, R. B. *J. Am. Chem. Soc.* **1989**, *111*, 2870. (c) Hill, J. E.; Balaich, G.; Fanwick, P. E.; Rothwell, I. P. *Organometallics* **1993**, *12*, 2911. (d) Takahashi, T.; Kageyama, M.; Denisov, V.; Hara, R.; Negishi, E. *Tetrahedron Lett.* **1993**, *34*, 687. (e) Xi, Z.; Hara, R.; Takahashi, T. *J. Org. Chem.* **1995**, *60*, 4444.

(7) As functionalized acetylenes, alkynyl ether and sulfide have been reported to give the corresponding diene. Nugent, W. A.; Thorn D. L.; Harlow, R. L. *J. Am. Chem. Soc.* **1987**, *109*, 2788. Van Wagenen, B. C.; Livinghouse, T. *Tetrahedron Lett.* **1889**, *30*, 3495. Homo-coupling of dimethyl acetylenedicarboxylate with Cp$_2$Ti(CO)$_2$ was documented. Demerseman, B.; Dixneuf, P. H. *J. Chem. Soc., Chem. Commun.* **1981**, 665.

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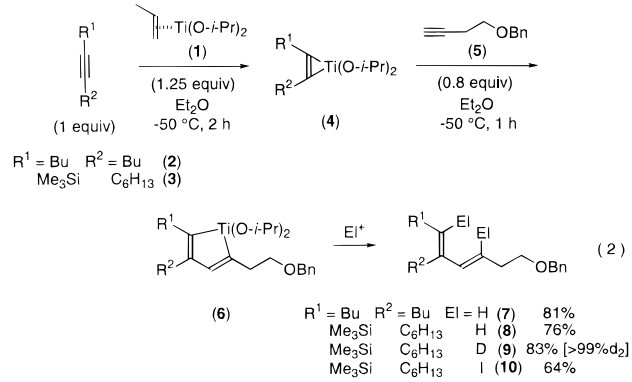
Results and Discussion

Treatment of an internal acetylene such as 5-decyne (**2**) or 1-silyl-1-octyne (**3**) with the above titanium complex **1** generates the acetylene−titanium complex (**4**),[12] which was allowed to react with a terminal acetylene, 4-(benzyloxy)-1-butyne (**5**), as the second component as shown in eq 2. The intermediate titanacyclopentadiene (**6**) was hydrolyzed, or intercepted with D^+ or I_2, to give the diene **7** or **8**, or its bis-deuterated (**9**) or bis-iodinated counterpart (**10**) in good yields. If an excess amount of **5** is used, the yield of **8** (based on **3**) decreases. The carbon−carbon bond formation occurred exclusively at the carbon β to the silyl group of **3** and at the terminal carbon of **5**. Other regio- and stereoisomers were not identified. In addition, under these reaction conditions, the amount of homo-coupling products resulting from **3** or **5** was kept to less than a trace amount. The present cross-coupling method between internal and terminal acetylenes appears to be operationally simple as compared to other methods using a group 4 metal complex.[13]

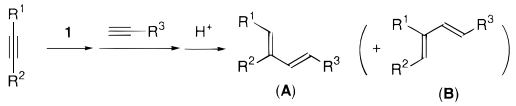


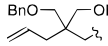
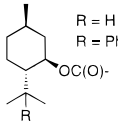
(2)

The preparation of other conjugated dienes according to eq 2 is shown in Table 1. An acetal moiety at the propargylic position of internal acetylene **11** does not hamper the reaction (entry 6). A few functional groups in the side chain of terminal acetylenes **19**, **20**, and **23**, which include carbonic and carboxylic esters or silyl ether at a remote position from the reacting center, can tolerate the reaction to give the corresponding dienes **29**, **30**, and **35** (entries 2, 3, and 6). The silylated propargyl alcohol derivatives **21** and **22** similarly participated in the reaction (entries 4−5), but these substrates led to the formation of a mixture of regioisomers **31** + **32** or **33** + **34**.

More importantly, we were pleased to find that the present method is nicely applicable to the cross-coupling reaction of functionalized acetylenes such as 2-alkynoates and 2-alkynamides, which is otherwise difficult to achieve as described above. The results are summarized in entries 7−19 in Table 1. It should be emphasized that the successful preparation of functionalized dienes **36**−**50** is, at the outset, dependent on the clean generation of a *functionalized* alkyne−titanium complex from acetylenes **12**−**18**. For representative cases, the presence of the complexes **51** and **52** (Chart 2), which have not yet been reported elsewhere, has been separately verified by the isolation of (*Z*)-olefins **53** and **54** upon hydrolytic workup (77 and 89% yields, respectively) and by the exclusive deuterium uptake after deuteriolysis (Chart 2). The coupling reaction of internal acetylenes **12**−**18** with terminal acetylenes **24**−**28** proceeded again in a highly regio- and stereoselective manner. The new carbon−carbon bond formation took place selectively at the carbon β to the ester group in the case of (nonsilylated) 2-alkynoate **12** (entries 7−8), but the silylpropiolates **13**−**16** reversed this preference (entries 9−15) where the reaction took place exclusively at the β position to the silyl group consistent with the observation for other silylalkynes **3** and **11** shown in entries 1−6. The intermediate titanacycle such as **55** in Chart 2 (to give **39** upon hydrolysis) has been confirmed by deuteration to give bis-deuterated **56** (in place of **39**). These functionalized titanacycles would be useful intermediates for further carbon−carbon bond formation and functionalization,[9] which will be

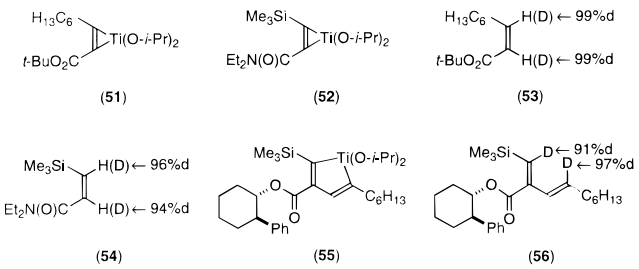
Table 1. Preparation of Functionalized Dienes via Cross-Coupling Reaction[a]



Entry	Internal Acetylene R^1	R^2		Terminal Acetylene R^3		Yield (%)[b] of Product(s) A	A + B [Ratio]
1	Me_3Si	C_6H_{13}	(**3**)	$BnO(CH_2)_2$-	(**5**)	76	(**8**)
2	"	"		$EtOC(O)O(CH_2)_2$-	(**19**)	67	(**29**)
3	"	"		$EtOC(O)(CH_2)_3$-	(**20**)	54	(**30**)
4	"	"		$TBSOCH_2$-	(**21**)		53 [80:20](**31**+**32**)
5	"	"		$Me_2CHCH_2CH(OTBS)$-	(**22**)		67 [84:16](**33**+**34**)
6	Me_3Si	$CH(OEt)_2$	(**11**)	$TBSO(CH_2)_2$-	(**23**)	88	(**35**)
7	CO_2Bu-*t*	C_6H_{13}	(**12**)	C_6H_{13}	(**24**)	(60[c])	(**36**)
8	CO_2Bu-*t*	C_6H_{13}	(**12**)	*t*-BuC(O)O$(CH_2)_4$-	(**25**)	57	(**37**)
9	Me_3Si	CO_2Bu-*t*	(**13**)	C_6H_{13}	(**24**)	77	(**38**)
10	Me_3Si		(**14**)	C_6H_{13}	(**24**)	78	(**39**)
11	"	"		Me_3Si	(**26**)	93	(**40**)
12	"	"		CO_2Bu-*t*	(**27**)	47	(**41**)
13	"	"			(**28**)	78	(**42**)
14	Me_3Si	 R = H	(**15**)	C_6H_{13}	(**24**)	65	(**43**)
15	Me_3Si	R = Ph	(**16**)	C_6H_{13}	(**24**)	71	(**44**)
16	$C(O)NEt_2$	C_6H_{13}	(**17**)	C_6H_{13}	(**24**)	65	(**45**)
17	$C(O)NEt_2$	C_6H_{13}	(**17**)	CO_2Bu-*t*	(**27**)	59	(**46**)
18	Me_3Si	$C(O)NEt_2$	(**18**)	C_6H_{13}	(**24**)		66 [60:40](**47**+**48**)
19	$C(O)NEt_2$	Me_3Si	(**18**)	CO_2Bu-*t*	(**27**)		64 [90:10](**49**+**50**)

[a] See eq 2 and Experimental Section. [b] Isolated yields. [c] Yield determined by ^1H NMR is shown, because the separation of diene **36** from **53** was unsuccessful at our hands.

Chart 2



(9) For intramolecular coupling of (nonfunctionalized) diynes with **1**, see: Urabe, H.; Hata, T.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 4261. Urabe, H.; Sato, F. *J. Org. Chem.* **1996**, *61*, 6756. Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 1245.

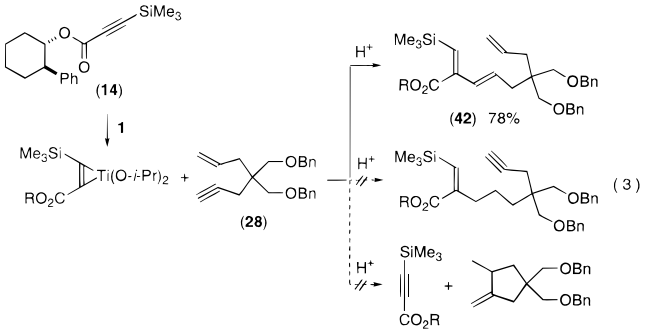
(10) For homo-coupling of (nonfunctionalized) acetylenes with **1**, see: Yamaguchi, S.; Jin, R.-Z.; Tamao, K.; Sato, F. *J. Org. Chem.* **1998**, *63*, 10060. Launay, V.; Beaudet, I.; Quintard, J.-P. *Synlett* **1997**, 821.

(11) For intramolecular cyclization of functionalized enynes with **1**, see: Suzuki, K.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **1996**, *118*, 8729. Urabe, H.; Suzuki, K.; Sato, F. *J. Am. Chem. Soc.* **1997**, *119*, 10014.

(12) Harada, K.; Urabe, H.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 3203. Takayanagi, Y.; Yamashita, K.; Yoshida, Y.; Sato, F. *Chem. Commun.* **1996**, 1725.

(13) The cross-coupling of terminal and internal acetylenes with the zirconocene-based reagent requires the hydrozirconation of the former (with Schwartz's reagent, $Cp_2ZrCl(H)$) prior to the coupling reaction (refs 6a and b). More recently, a terminal acetylene such as PhC≡CH was reported to give cross-coupling products with internal acetylenes via the ligand exchange reaction of zirconacyclopentene (ref 6e).

reported in due course. The 2-alkynamide **17** showed the same tendency as the corresponding ester **12** (entries 16−17), but the silylpropynamide **18** afforded a mixture of regioisomers with a varying ratio dependent on the coupling partners (entries 18−19). This phenomenon could show that the amide group is a more potent regiocontrolling element than the aforementioned ester group and is parallel to or exceeds the effect of the silyl group. Another interesting point is that a terminal acetylene **28** carrying an olefinic bond at the other terminus did not complicate the reaction (i.e., via the coupling reaction at its olefinic position or its own cyclization) as shown in eq 3 and in entry 13, Table 1. Thus, the preparation of substrates ready for an intramolecular Diels−Alder reaction like **42** is also encouraged by this method.



Conclusion

Preparation of certain kinds of functionalized dienes is readily achieved by the low-valent titanium alkoxide-mediated cross-coupling of alkynes. The functionalized titanacyclopentadienes as well as the intermediate alkyne−titanium complexes would be also a useful species for further synthetic transformation. In practice, the use of very inexpensive reagents such as Ti(O-*i*-Pr)$_4$ and a Grignard reagent, the simple operation, and the easy isolation of the products (in contrast to other group 4 metallocene-mediated reactions, the metal portion used herein goes to an aqueous solution upon workup, thus avoiding contamination of the organic products) are advantageous features of the present method. A study on the asymmetric Diels−Alder reaction taking advantage of the optically active dienes prepared herein[14] is now in progress.

Experimental Section

General. See Supporting Information.

Representative Procedure for the Preparation of Functionalized Dienes. (1*RS*,2*SR*)-2-Phenyl-1-cyclohexyl (3*E*)-2-[(*Z*)-(Trimethylsilyl)methylene]-3-decenoate (39). To a stirred solution of (1*RS*,2*SR*)-2-phenyl-1-cyclohexyl 3-(trimethylsilyl)propiolate (**14**) (500 mg, 1.66 mmol) and Ti(O-*i*-Pr)$_4$ (0.614 mL, 2.08 mmol) in 25 mL of Et_2O was added a 1.43 M solution of *i*-PrMgCl in ether (2.91 mL, 4.16 mmol) at −78 °C under argon to give a yellow homogeneous solution. The solution was warmed to −50 °C over 30 min, during which period its color turned red. After the solution was stirred at −50 °C for an additional 5 h, 1-octyne (**24**) (0.196 mL, 1.33 mmol) was introduced to the reaction mixture at −50 °C, and the solution was stirred at −50 °C for 3 h. The reaction was terminated by the addition of 1 N HCl, and the organic products were extracted with ether. The combined organic layers were washed with an aqueous solution of $NaHCO_3$, dried over Na_2SO_4, and concentrated in vacuo to give a crude oil, which was chromatographed on silica gel (hexanes−ether) to afford the title compound (429 mg, 78%). Even after careful ^{1}H NMR analysis, other isomers of this compound could not be identified.^{1}H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 9 H), 0.88 (t, J = 7.1 Hz, 3 H), 1.16−1.44 (m, 8 H), 1.44−1.62 (m, 4 H), 1.72−2.00 (m, 5 H), 2.28 (symmetric m, 1 H), 2.76 (d/t, J = 4.5, 10.8 Hz, 1 H), 5.09 (d/t, J = 15.6, 6.9 Hz, 1 H), 5.18 (d/t, J = 4.5, 10.8 Hz, 1 H), 5.76 (d, J = 15.6 Hz, 1 H), 5.84 (s, 1 H), 7.13−7.32 (m, 5 H). Irradiation of the proton at δ 0.04 ppm (Me_3Si) showed 6% nOe enhancement to the peak at δ 5.84 ppm (Me_3SiC<u>H</u>=C). Irradiation of the proton at δ 5.84 ppm (Me_3SiC<u>H</u>=C) showed 5% nOe enhancement to the peak at δ 5.09 ppm (CH=C<u>H</u>C<u>H</u>$_2$). Thus, the regiochemistry as well as the olefinic stereochemistry has been fully confirmed. ^{13}C NMR (75 MHz, $CDCl_3$) δ −0.70, 14.00, 22.51, 24.71, 25.68, 28.65, 28.85, 31.63, 32.34, 32.87, 34.56, 49.69, 76.87, 126.58, 127.68, 128.52, 129.41, 134.26, 136.89, 143.40, 146.80, 168.23; IR (neat) 3075, 3035, 2930, 2860, 1720 (C=O), 1465, 1450, 1250, 1205, 1140, 1120, 1015, 960, 860, 845, 755, 700 cm^{-1}. Anal. Calcd for $C_{26}H_{40}O_2Si$: C, 75.67; H, 9.77. Found: C, 75.38; H, 10.15.

Acknowledgment. We thank the Ministry of Education, Science, Sports and Culture (Japan) for financial support.

Supporting Information Available: Procedures for the preparation of key starting materials **14**−**16** and dienes **8**, **35**, and **44**, and characterization data for the starting materials and products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) To the best of our knowledge, the utility of 1,3-dienes like **39**−**44** having an optically active ester at its 2-position has not been examined in asymmetric Diels−Alder reaction, see: Whitesell, J. K. *Chem. Rev.* **1992**, *92*, 953. Waldmann, H. *Synthesis* **1994**, 535. Jones, G. B.; Chapman, B. J. *Synthesis* **1995**, 475. Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; Wiley: New York, 1995; p 513. As a preliminary result, we found that the following Diels−Alder reaction of **44** proceeds in a highly diastereoselective manner.