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Doctoral Dissertation

Studies on Palladium-Catalyzed Reactions of Functionalized 2-Bromo-1,3-dienes

(官能基化2-ブロモ-1,3-ジエン類のパラジウム触媒反応に関する研究)

Chen Yen-Chou

陳 彦洲

Graduate School of Life Science, Hokkaido University

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Abbreviations

Me	methyl
Et	ethyl
ⁿ Bu	<i>normal</i> -butyl
^t Bu	<i>tert</i> -butyl
ⁱ Pr	isopropyl
Ph	phenyl
Bn	benzyl
Ar	aryl
TMS	trimethylsilyl
TBS	<i>tert</i> -butyldimethylsilyl
boc	<i>tert</i> -butyloxycarbonyl
Ts	<i>p</i> -toluenesulfonyl
BDT	benzodithiole tetraoxide
r.t.	room temperature
cat.	catalyst
L	ligand
DMF	<i>N,N'</i> -dimethylformamide
THF	tetrahydrofuran
DCM	dichloromethane
dppb	2,2'-bis(diphenylphosphino)-1,1'-biphenyl
dppe	1,2-bis(diphenylphosphino)ethane
dppb	1,4-bis(diphenylphosphino)butane
dppf	1,1'-ferrocenediyl-bis(diphenylphosphine)
DPEphos	(oxydi-2,1-phenylene)bis(diphenylphosphine)
Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
binap	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
segphos	4,4'-bi-1,3-benzodioxole-5,5'-diylbis(diphenylphosphane)
DTBMsegphos	5,5'-bis[di(3,5-di- <i>tert</i> -butyl-4-methoxyphenyl)phosphino]-4,4'-bi-1,3-benzodioxole

DeBuPhos	(7,7'-di- <i>tert</i> -butyl-[4,4'-bibenzodioxole]-5,5'-diyl)bis(bis(3,5-di- <i>tert</i> -butyl-4-methoxyphenyl)phosphane)
^t Bu-segphos	(7,7'-di- <i>tert</i> -butyl-[4,4'-bibenzodioxole]-5,5'-diyl)bis(diphenylphosphane)
ee	enantiomeric excess
de	diastereomeric excess
eq. or equiv	equivalent
concd.	concentrated
TLC	thin layer chromatography
GPC	gel permeation chromatography
NMR	nuclear magnetic resonance
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrum
s	singlet
d	doublet
t	triplet
q	quartet
quint	quintet
m	multiplet
br	broad

Chapter I

General Introduction

Section 1.

Axially Chiral Allenes

Allenenes, a class of compounds characterized by two cumulated carbon-carbon double bonds, are unique building blocks in organic chemistry.^[1,2] The two C=C bonds in a propadiene unit are perpendicular to each other, and the four atoms/substituents in an allenic framework are arranged in an elongated tetrahedral fashion. Substituted allenenes become chiral when $R^1 \neq R^2$ and $R^3 \neq R^4$ (Figure 1-1). Whereas the rotation barrier of the allenic C=C=C axis is generally high,^[3] enantiomeric pairs of axially chiral allenenes can be separable as persistent isomers under usual conditions. The allenic chirality is referred to as "**axial chirality**".

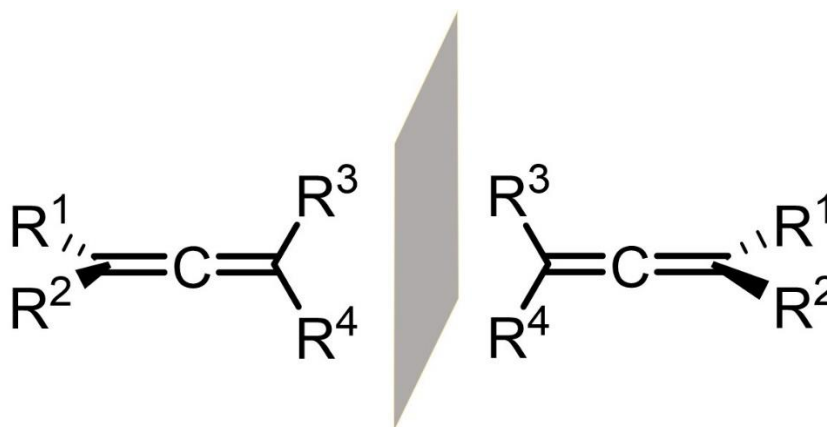


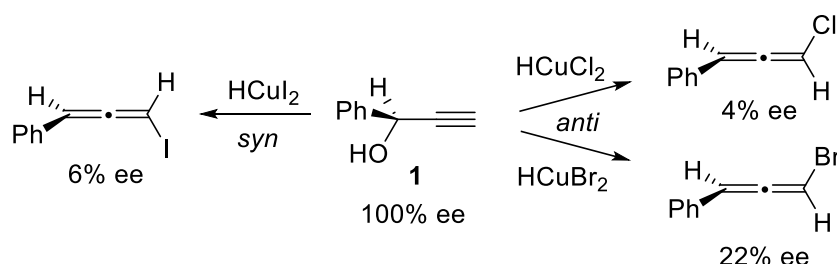
Figure 1-1. Enantiomeric Pair of Axially Chiral Allene

Section 2.

Applications of Axially Chiral Allenes

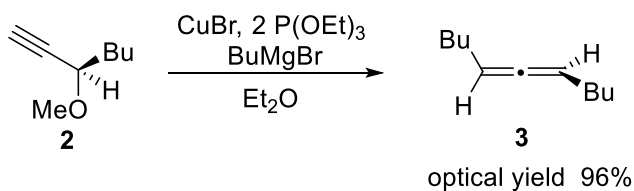
The methods of preparing optically active forms of such axially chiral allenes have been developed over a half-century. Most of the reported methods for preparing scalemic axially chiral allenes require stoichiometric chiral sources as either substrates or reagents.^[4] For instance, as shown in Schemes 1-1 and 1-2, the preparation of the non-racemic axially chiral allenes from chiral propargyl compound **1** by copper-mediated reactions has been reported, but the chirality in **1** did not transfer to the corresponding axially chiral allenes (Scheme 1-1). On the other hand, the formation of axially chiral allene **3** from chiral propargyl compound **2** with good retention of chirality could be realized by using a Grignard reagent in the presence of CuBr and P(OEt)₃, however, a stoichiometric amount of the organometallic reagent is necessary (Scheme 1-2).^[4d,4e]

Scheme 1-1. *syn/anti*-Stereoselectivities for the Formation of Haloallenes.^[4d]

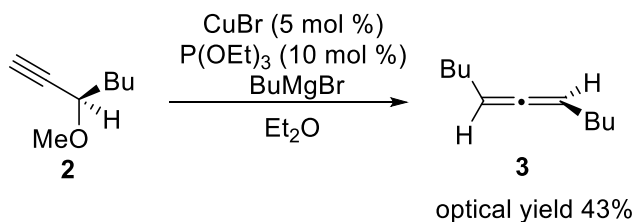


Scheme 1-2. Copper-Mediated Reaction of Propargyl Ether **2**.^[4e]

stoichiometric amount of transition metal reagents

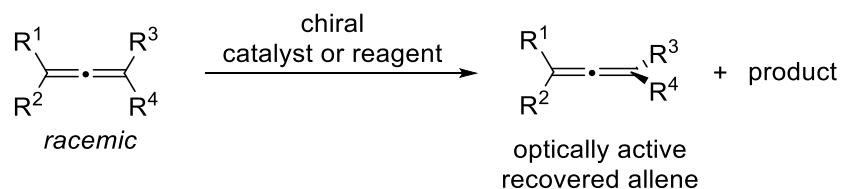


catalytic amount of transition metal reagents



Resolution of racemic axially chiral allenes is still a valuable method, which involves fractional crystallization, the chiral stationary phase column chromatography, and kinetic resolutions. However, these methods still show limitation: resolution of racemic allenes by crystallization is limited to the substrates bearing a specific functional group such as carboxylic acid; the chromatographic resolution of simple chiral allenes does not seem suitable for the resolution of a large quantity of racemic allenes; the kinetic resolution needs an appropriate chiral reagent or catalyst (Scheme 1-3).^[5]

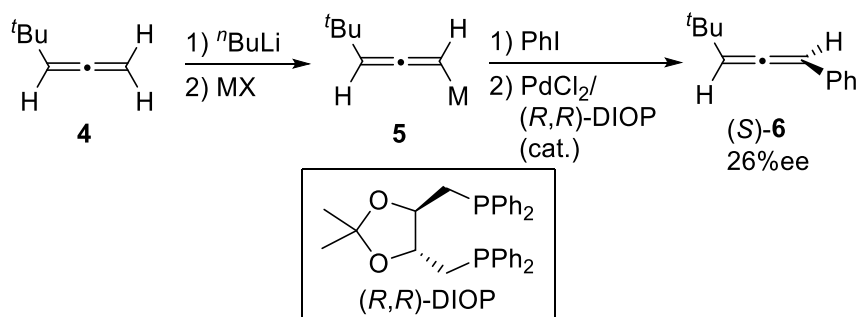
Scheme 1-3. Kinetic Resolution of Racemic Allenes.



The more efficient approaches to scalemic axially chiral allenes are *catalytic enantioselective syntheses* which have been developed recently. The catalytic

asymmetric synthesis of allenes was first achieved by Elsevier et al. in 1989 (Scheme 1-4).^[6] Lithiation of 4,4-dimethyl-1,2-pentadiene (**4**) takes place highly regioselectively at the terminal position, and various metalated allenes **5** are generated in situ from the lithiated species by appropriate metal exchanges. Metalated allenes **5** undergo the cross-coupling reaction with iodobenzene in the presence of a palladium species coordinated with chiral ligand (*R,R*)-DIOP to give axially chiral allene **6** with modest enantioselectivity. Among the chiral ligands examined, bidentate bisphosphine (*R,R*)-DIOP shows the highest enantioselectivity for the reaction with the zinc reagent (M = ZnI in **5**) giving (*S*)-**6** of 26% ee. Treatment of **4** with various organometallic reagents (M = MgCl, Cu) under the same conditions provide a reversal of the configuration in allenic product (*R*)-**6** with a low enantiopurity (3-10% ee).

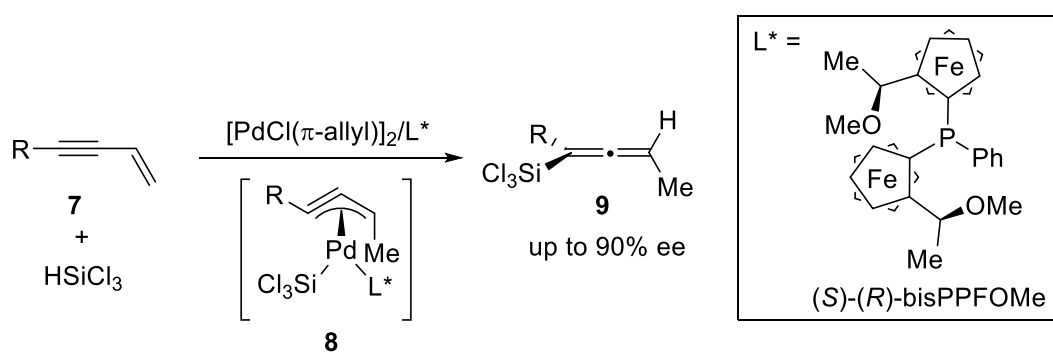
Scheme 1-4. Palladium-Catalyzed Cross-Coupling of Metalated Allenes.



Enantioselective syntheses of axially chiral allenes under transition metal catalysis have been developed so far, and these methods have provided axially chiral allenes in high enantioselectivities.^[7] For example, an asymmetric hydrosilylation of preparing axially chiral allenes with excellent enantioselectivities was reported by Hayashi et al, which was catalyzed by a chiral palladium complex (Scheme 1-5),^[7a]. The asymmetric hydrosilylation of enynes **7**, which is with a bulky substituent (R = *t*Bu, mesityl, or TBS), with trichlorosilane was catalyzed by the palladium complex generated from

$[\text{PdCl}(\pi\text{-allyl})]_2$ (1 mol %) and (+)-(*S*)-(*R*)-bisPPFOMe (2.2 mol %) to give allenylsilanes **9** in good to high yields with up to 90% ee. The palladium-catalyzed hydrosilylation of 1,3-enynes **7** with trichlorosilane proceeds via a 1,4-addition process, and gives axially chiral allenylsilanes **9** in high enantioselectivities, which is probably due to a contribution of π -propargyl(silyl)palladium intermediate **8**.

Scheme 1-5. Palladium-Catalyzed Asymmetric Hydrosilylation of Enynes **7** Forming Allenylsilanes **9**.



Since the methods of preparing allenes have been developed so far, the applications of allenic compounds have also been found in pharmaceutical field (Figure 1-2).^[1d] For instance, Enprostil (**13**), a prostaglandin E₂ derivative having an allenic structure, is a medicine for human beings, which was found as a highly potent inhibitor of gastric HCl secretion. In addition, over 150 natural products comprising an allenic or a related cumulenenic structure have been discovered (Figure 1-2), some of which have further applications in pharmaceutical field.^[1d] Because allenic compounds have large numbers of applications in medicine, the method of preparing allenes is still essential in organic/pharmaceutical synthesis.

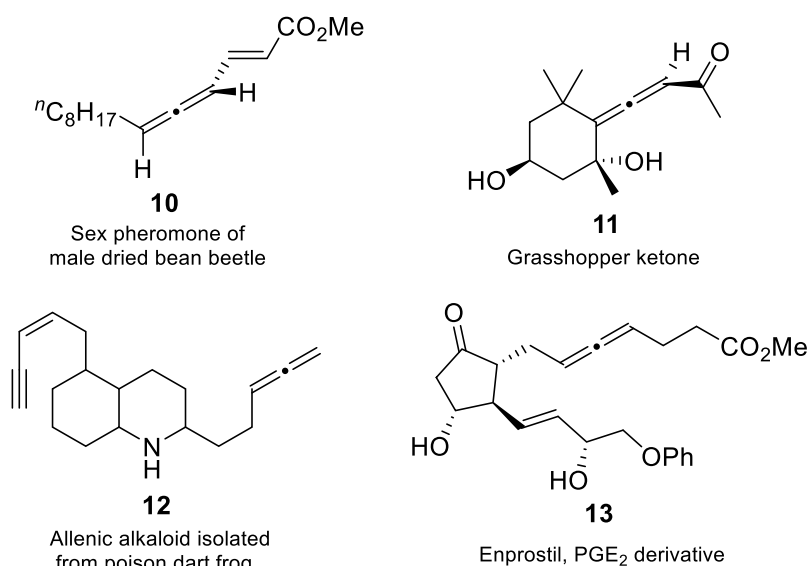
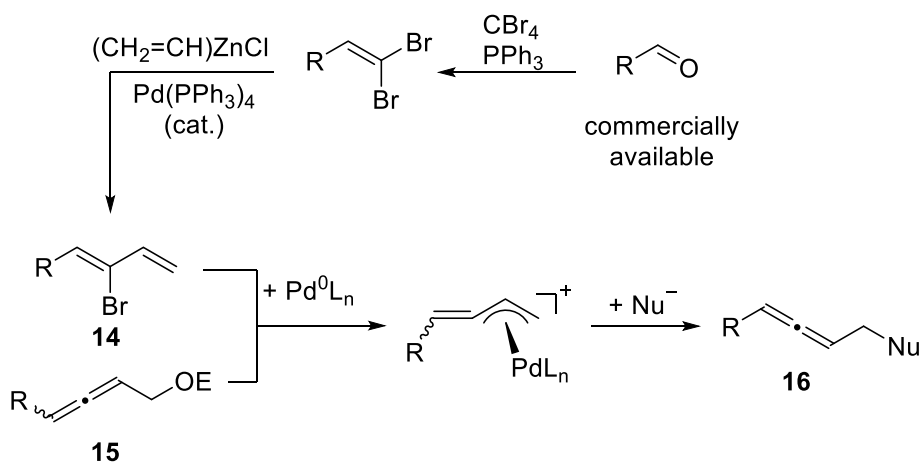


Figure 1-2. Allenic Natural Products and Pharmaceuticals

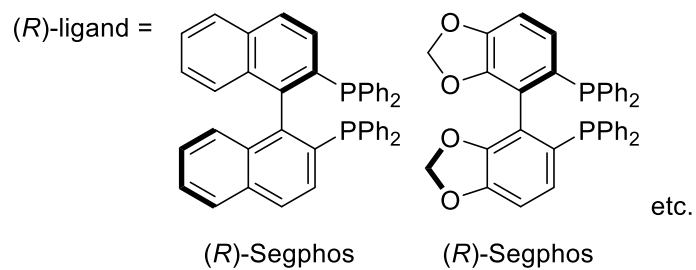
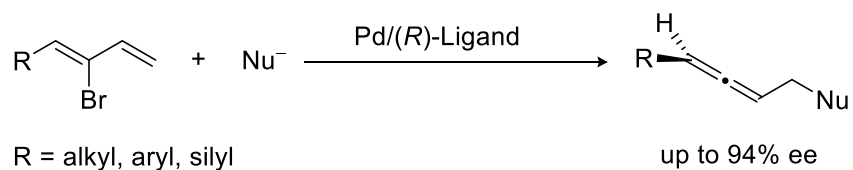
In the last few decades, our research group has developed a palladium-catalyzed reaction of preparing functionalized allenes **16** starting with 2-halo-1,3-dienes **14** and appropriate soft nucleophiles (Scheme 1-6).^[8] The reaction proceeds via an (alkylidene- π -allyl)palladium intermediate. An analogous palladium species can be generated by the oxidative addition of allenylmethyl ester **15** to a zero-valent palladium species, and its reaction with a soft nucleophile also provides comparable allenic product **16** (Scheme 1-6, bottom).^[9] It should be mentioned that the key substrates, 2-bromo-1,3-dienes **14**, are readily/efficiently prepared from the commercially available aldehyde via two-step synthesis.

Scheme 1-6. Palladium-Catalyzed Nucleophilic Substitution on 2-Bromo-1,3-dienes and Allenylmethyl Esters.



This reaction is an ideal prototype for catalytic asymmetric synthesis of axially chiral allenes, which is catalyzed by a palladium species coordinated with a chiral bisphosphine ligand. And indeed, it has showed the good to excellent enantioselectivities (Scheme 1-7).^[10]

Scheme 1-7. Palladium-Catalyzed Asymmetric Synthesis of Axially Chiral Allenes.



Section 3.

Outline of This Thesis

Recently, the Ogasawara's group has developed various synthetic methods for preparing various allenic derivatives including optically active allenes by the Pd-catalyzed reaction. In this thesis, I have been interested in examining the reactivities and further applications of functionalized 2-bromo-1,3-dienes in our Pd-catalyzed reaction (Figure 1-3, middle). In my doctoral study, I have focused on two key areas; (1) synthesis of the monomeric allenes (chapters II and III) and (2) synthesis of allenic polymers (chapters IV and V).

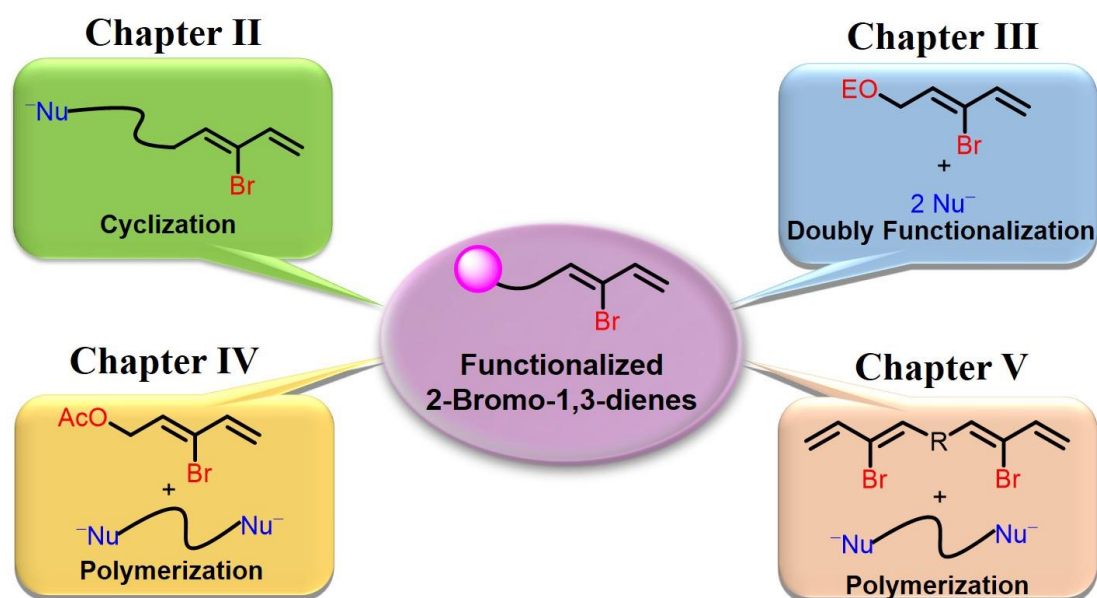


Figure 1-3. Outline of This Thesis

In Chapter II, I would like to discuss the palladium-catalyzed cyclizations of nucleophile-tethered 2-bromo-1,3-dienes. A palladium-catalyzed reaction for preparing various endocyclic allenes was developed, and the 2-bromo-1,3-dienyl substrates for the palladium-catalyzed reaction were readily prepared. As widely recognized, medium-membered carbocycles are difficult to construct and are provided in low yields

in typical cyclization reactions. On the other hand, my method could provide medium- to large-membered carbocycle in relatively high yields (up to 67%). Additionally, the method of preparing endocyclic allenes was extended into an asymmetric counterpart by the use of a chiral Pd catalyst, and enantiomerically enriched axially chiral endocyclic allenes were obtained in up to 70% ee.

In chapter III, I will discuss the palladium-catalyzed nucleophilic substitution on 3-bromopenta-2,4-dienyl esters. In 2012, our research group demonstrated that 3-bromopenta-2,4-dienyl acetate was an excellent precursor to prepare doubly functionalized allenes by the twofold palladium-catalyzed substitution reaction.^[9d] In this chapter, I have investigated approaches to preparing various allenic derivatives via the palladium-catalyzed nucleophilic substitution reaction between the newly prepared 3-bromopenta-2,4-dienyl esters (benzoate and phosphate) and soft nucleophiles. The reaction has been extended to the asymmetric counterparts using appropriate chiral palladium catalysts to give the axially chiral allenes in enantiomerically enriched forms, and the details will be described.

In chapter IV, I will describe the application of the palladium-catalyzed reaction in polymer chemistry. Since the palladium-catalyzed reaction between 3-bromopenta-2,4-dienyl acetate and 2 equivalents soft nucleophile provides the corresponding C_2 -symmetric allenes with excellent regioselectivity, I have envisioned that the use of an appropriate bifunctional nucleophile in the palladium-catalyzed reaction might produce oligomeric/polymeric products, which possess allenic scaffolds as a repeating unit in their main chains. The palladium-catalyzed polymerization between 3-bromopenta-2,4-dienyl acetate and appropriate bifunctional nucleophiles provided allenic polymers in up to 82% yield and the M_n values reached up to 13700. Asymmetric synthesis of axially

chiral allenic polymers was examined by the use of chiral palladium catalysts in the reaction. I have also developed a new method of determining the *R/S* distribution (enantio-regularity) of axially chiral allenic polymers.

In chapter V, I have examined bis(2-bromo-1,3-diene) as a new bifunctional electrophile monomer in my palladium-catalyzed polymerization instead of using 3-bromopenta-2,4-dienyl acetate as a substrate. The asymmetric synthesis of corresponding axially chiral allenic polymers by the enantioselective palladium-catalyzed reaction will be described in detail.

[1] (a) Patai, S.(Ed.), *The Chemistry of Ketenes, Allenes, and Related Compounds*, Wiley, Chichester, 1980. (b) Landor, S. R. (Ed.), *The Chemistry of the Allenes*, Academic Press, London, 1982. (c) Coppola, G. M.; Schuster, H. F., *Allenenes in Organic Synthesis*, Wiley, New York, 1984. (d) Krause, N.; Hashmi, A. S. K. (Eds.), *Modern Allene Chemistry*, Wiley-VCH, Weinheim, 2004. (e) Krause, N. (Ed.), *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations Vol. 44: Cumulenes and Allenes*, Thieme, Stuttgart, 2008.

[2] (a) Marshall, J. A. *Chem. Rev.* **1996**, 96, 31. (b) Wang, K. K. *Chem. Rev.* **1996**, 96, 207. (c) Yamamoto, Y.; Radhakrishnan, U. *Chem. Soc. Rev.* **1999**, 28, 199. (d) Hashmi, A. S. K. *Angew. Chem.* **2000**, 112, 3737; *Angew. Chem. Int. Ed.* **2000**, 39, 3590. (e) Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, 100, 3067. (f) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, 34, 535. (g) Ma, S.; Li, L. *Synlett* **2001**, 1206. (h) Tius, M. A. *Acc. Chem. Res.* **2003**, 36, 284. (i) Ma, S. *Acc. Chem. Res.* **2003**, 36, 701. (j) Sydnes, L. K. *Chem. Rev.* **2003**, 103, 1133. (k) Ma, S. *Eur. J. Org. Chem.* **2004**, 1175. (l) Brandsma, L.; Nedolya, N. A. *Synthesis* **2004**, 735. (m) Ma, S. *Chem. Rev.* **2005**, 105, 2829. (n) Brummond, K. M.; DeForrest, J. E. *Synthesis* **2007**, 795. (o) Yu, S.; Ma, S. *Chem. Commun.* **2011**, 47, 5384.

[3] Roth, W. R.; Ruf, G.; Ford, P. W. *Chem. Ber.* **1974**, 107, 48.

[4] General reviews for the preparation of optically active allenenes; see: (a) Rossi, R.; Diversi, P. *Synthesis* **1973**, 25. (b) Elsevier, C. J. In *Houben-Weyl Series Methods of Organic Chemistry*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1995; Vol. E21a, p. 537. (c) Ohno, H.; Nagaoka, Y.; Tomioka, K. In *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, 2004; p. 141. (d) Elsevier, C. J.; Vermeer, P. *J. Org. Chem.* **1984**, 49, 1649. (e) I. Marek,

- P. Mangeney, A. Alexakis, J. F. Normant, *Tetrahedron Lett.* **1986**, 27, 5499.
- [5] For transition metal-catalyzed kinetic resolutions of racemic allenes, see: (a) Noguchi, Y.; Takiyama, H.; Katsuki, T. *Synlett* **1998**, 543. (b) Sweeney, Z. K.; Salsman, J. L.; Andersen, R. A.; Bergman, R. G. *Angew. Chem. Int. Ed.* **2000**, 39, 2339. For transition metal-catalyzed dynamic kinetic resolutions of racemic allenes, see: (c) Imada, Y.; Ueno, K.; Kutsuwa, K.; Murahashi, S. *Chem. Lett.* **2002**, 140. (d) Trost, B. M.; Fandrick, D. R.; Dinh, D. C. *J. Am. Chem. Soc.* **2005**, 127, 14186. (e) Imada, Y.; Nishida, M.; Kutsuwa, K.; Murahashi, S.; Naota, T. *Org. Lett.* **2005**, 7, 5837.
- [6] de Graaf, W.; Boersma, J.; van Koten, G.; Elsevier, C. J. *J. Organomet. Chem.* **1989**, 378, 115.
- [7] (a) Matsumoto, Y.; Naito, M.; Uozumi, Y.; Hayashi, T. *J. Chem. Soc., Chem. Commun.* **1993**, 1468. (b) Tillack, A.; Michalik, D.; Koy, C.; Michalik, M. *Tetrahedron Lett.* **1999**, 40, 6567. (c) Tillack, A.; Koy, C.; Michalik, D.; Fischer, C. *J. Organomet. Chem.* **2000**, 603, 116. (d) Han, J. W.; Tokunaga, N.; Hayashi, T. *J. Am. Chem. Soc.* **2001**, 123, 12915. (e) Hayashi, T.; Tokunaga, N.; Inoue, K. *Org. Lett.* **2004**, 6, 305.
- [8] (a) Ogasawara, M.; Ikeda, H.; Hayashi, T. *Angew. Chem. Int. Ed.* **2000**, 39, 1042. (b) Ogasawara, M.; Murakami, H.; Furukawa, T.; Takahashi, T.; Shibata, N. *Chem. Commun.* **2009**, 7366. (c) Ogasawara, M.; Okada, A.; Subbarayan, V.; Sörgel, S.; Takahashi, T. *Org. Lett.* **2010**, 12, 5736. (d) Ogasawara, M.; Suzuki, M.; Takahashi, T. *J. Org. Chem.* **2012**, 77, 5406. and references cited therein.
- [9] (a) Djahanbini, D.; Cazes, B.; Goré, J. *Tetrahedron Lett.* **1984**, 25, 203. (b) Kleijn, H.; Westmijze, H.; Meijer, J.; Vermeer, P. *Recl. Trav. Chim. Pays-Bas* **1983**, 102, 378.
- [10] (a) Ogasawara, M.; Ikeda, H.; Nagano, T.; Hayashi, T. *J. Am. Chem. Soc.* **2001**, 123, 2089. (b) Ogasawara, M.; Ueyama, K.; Nagano, T.; Mizuhata, Y.; Hayashi, T. *Org.*

Lett. **2003**, *5*, 217. (c) Ogasawara, M.; Nagano, T.; Hayashi, T. *J. Org. Chem.* **2005**, *70*, 5764. and references cited therein.

Chapter II

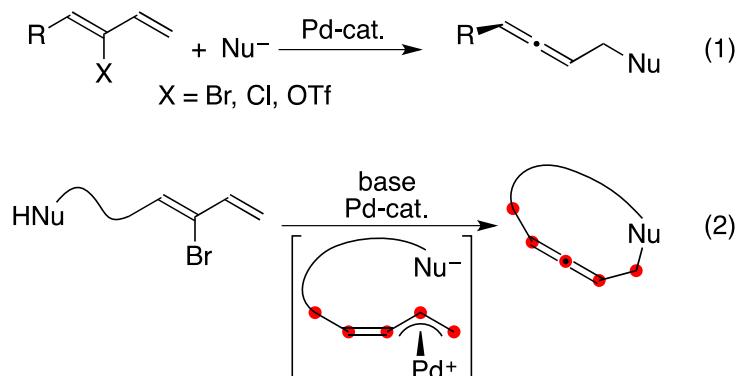
Palladium-Catalyzed S_N2'-Cyclization of Ambivalent (Bromoalkadienyl)malonates: Preparation of Medium- to Large- Membered Endocyclic Allenes

Section 1.

Introduction for Chapter II

Allenes are a class of compounds characterized by two cumulated carbon-carbon double bonds. Due to the propadiene structures, they show distinctive steric and electronic properties and have emerged as highly interesting target molecules in organic synthesis.^[1,2] Incorporation of an allenic substructure into a carbocycle creates a peculiar topological property.^[3] Although various endocyclic allenes have been prepared and reported so far, most of their synthetic methods construct an allenic motif within a preformed carbocycle precursor.^[4-6] Two of the most widely applicable methods in the synthesis of endocyclic allenes, namely the ring enlargement of cycloalkenes via the corresponding *gem*-dibromobicyclo[*n*.1.0]alkenes by the Doering-Moore-Skattebøl reaction^[4] and dehydrohalogenation of 1-halocycloalkenes,^[5] are also classified to this category. Another approach to the endocyclic allenes is cyclization of preformed acyclic allenes.^[7] This approach, however, is not applicable to the synthesis of relatively smaller-ring cyclic allenes. The third category of the endocyclic allene synthesis is simultaneous construction of both allenic and cyclic structures by a single process, but the reported examples in this category are very rare.^[8] Recently, Prof. Ogasawara's group has developed a palladium-catalyzed reaction of preparing functionalized allenes starting with 2-halo-1,3-dienes and appropriate soft nucleophiles (eq 1 in Scheme 2-1).^[9] The reaction was extended into an asymmetric counterpart by the use of a chiral Pd catalyst, and enantiomerically enriched axially chiral allenes were obtained in up to 94% ee.^[10] They also demonstrated that the palladium-catalyzed reaction could be used for the synthesis of a series of endocyclic allenes starting with cycloalkenones.^[9e]

Scheme 2-1. Palladium-Catalyzed Reaction of 2-Halo-1,3-dienes with Soft Nucleophile



In this report, I would like to describe a novel method of preparing various endocyclic allenes utilizing the Pd-catalyzed reaction. The two reactants of the palladium-catalyzed reaction, namely a 2-bromo-1,3-diene and a soft nucleophile, are incorporated into a single molecule and the $\text{S}_{\text{N}}2'$ -cyclization of the "ambivalent" substrates proceeds primarily intramolecularly to afford various endocyclic allenes in fair yields.

The allenic substructure, which is with two cumulated orthogonal carbon-carbon double bonds, suppresses the relative motion among the five consecutive atoms (marked in red; eq 2 in Scheme 2-1). Similarly, the relative orientation of the five atoms is fastened in the (alkylidene- π -allyl)palladium intermediate of the palladium-catalyzed reaction.^[11] These rigid substructures in the palladium-intermediates as well as in the allenic products may lead to the unusual preference/selectivity in the present cyclization reactions. Indeed, the cyclization process could provide various medium- to large-carbocycles in reasonable yields. It should be mentioned that formation of five- to seven-membered carbocycles, which are easy to be assembled in typical cyclization processes, are impractical by the present method, because thermodynamically stable

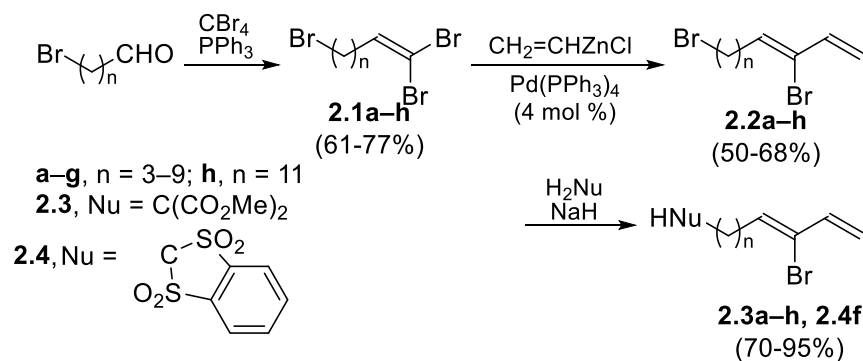
endo-carbocyclic allenes are usually nine-membered or larger.^[12] Although a few kinetically stabilized eight-membered carbocyclic allenes were reported to be isolable,^[13] endocyclic allenes with a seven-membered or a smaller carbocycle exist only as transient reactive intermediates.

Section 2.

Preparation of Pronucleophile-Tethered 3-Bromo-1,3-diene Derivatives

The substrates for my endocyclic allene synthesis are pronucleophile-tethered 3-bromo-1,3-dienes (**2.3a-h** and **2.4f**), and they are prepared from ω -bromoalkanal by the simple three-step sequence as depicted in Scheme 2-2. Readily available ω -bromoalkanal were converted into the corresponding 1,1, ω -tribromoalkenes **2.1a-i** in 61-77% yields by the standard Wittig dibromoolefination.^[14] The palladium-catalyzed cross-coupling of **2.1** with vinylzinc chloride proceeded at the sterically less congested alkenyl-Br (i.e., C=CBr *trans* to the ω -bromoalkyl group) selectively to give the corresponding (Z)-3, ω -dibromo-1,3-dienes **2.2a-h** in 50-68% yields.^[15] Alkylation of dimethyl malonate or benzodithiole tetraoxide (BDT) with **2.2** furnished designed substrates **2.3a-h** and **2.4f** in pure form (70-95%).

Scheme 2-2. Preparation of Pronucleophile-Tethered 3-Bromo-1,3-dienes



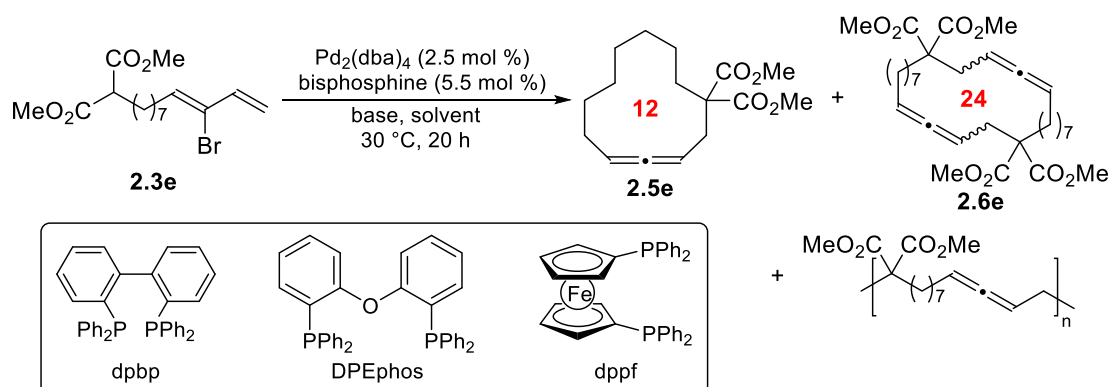
Section 3.

Palladium-Catalyzed Reactions of Pronucleophile-Tethered 3-Bromo-1,3-diene Derivatives

Substrates **2.3** and **2.4** prepared as in Scheme 2-2 were subjected to the palladium-catalyzed reaction. At the outset, the conditions for the palladium-catalyzed reaction were optimized using **2.3e** ($n = 7$) as a model substrate, and the results of the optimization studies are summarized in Table 2-1. The reaction of **2.3e** was efficiently catalyzed by 5 mol % of a palladium complex generated in situ from $\text{Pd}_2(\text{dba})_4$ and $\text{dppb}^{[16]}$ (1.1 equiv to Pd) in THF in the presence of potassium *tert*-butoxide (1.1 equiv to **2.3e**). Under the rather standard conditions, i.e. with the initial concentration of substrate **2.3e** being 1.4×10^{-2} mol/L, **2.3e** was completely consumed within 20 h at 30 °C. However, to my disappointment, yield of desired 12-membered endocyclic allene **2.5e** was only 9% (entry 1). Complete consumption of **2.3e** and the low yield of **2.5e** indicated that intermolecular processes giving oligomeric/polymeric products competed with the unimolecular cyclization reaction. Indeed, reactions under dilution conditions facilitated the desired intramolecular pathway leading to the higher yields of **2.5e** (entries 2 and 3). When the initial concentration of **2.3e** was 1.4×10^{-3} mol/L, **2.5e** was isolated in 31% yield (entry 3). It should be mentioned that the reactions in entries 1-3 produced dimeric endocyclic bis-allene **2.6e** in 11-19% yields together with **2.5e**. Endocyclic bis-allene **2.6e** was obtained as a mixture of *dl*- and *meso*-diastereomers with respect to the allenic axial chirality; two allenic central sp-C signals were detected at δ 205.8 and 205.9 in the ^{13}C -NMR spectrum (see Experimental Section).^[17] THF was the best solvent examined so far. Reactions in DMF, toluene, or dichloromethane gave **2.5e** in much lower yields ranging 0-8% (entries 4-6). The choice of a proper base drastically influence the yield of **2.5e**; while the reactions with KO^tBu or NaOMe

afforded the monomeric endocyclic allene in 31% yield (entries 3 and 7), the yield of **2.5e** declined to 16% by the use of CsO^tBu (entry 8), and the reaction using Cs₂CO₃ did not provide **2.5e** at all (entry 9). On the other hand, the effects of the bisphosphine ancillary ligands were minor, and the reactions with DPEphos^[18] (1.1 equiv to Pd) or dppf gave **2.5e** in 23% and 25% yields, respectively (entries 10 and 11).

Table 2-1. Optimization of Reaction Conditions for Palladium-Catalyzed S_N2' -Cyclization of **2.3e**.^a

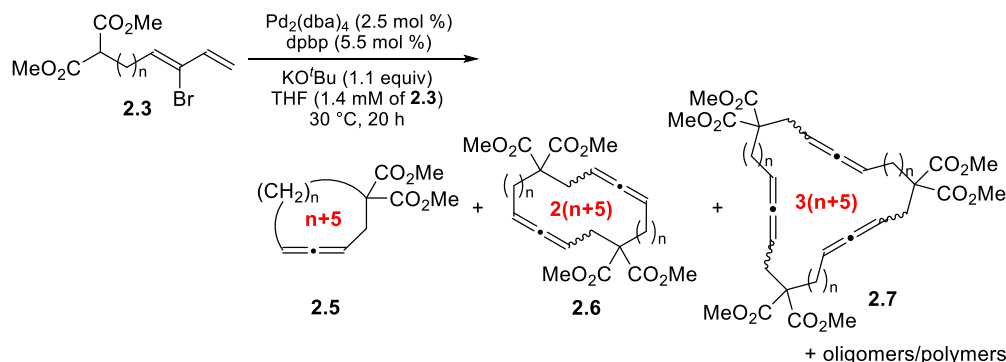


entry	solvent	base	ligand	conc. of 2.3e (mol/L)	yield of 2.5e (%)	yield of 2.6e (%)
1	THF	KO ^t Bu	dpbp	1.4×10^{-2}	9 ^b	13 ^b
2	THF	KO ^t Bu	dpbp	1.4×10^{-2}	22 ^b	11 ^b
3	THF	KO ^t Bu	dpbp	1.4×10^{-3}	31 ^b	19 ^b
4	DMF	KO ^t Bu	dpbp	1.4×10^{-3}	8 ^c	n.d. ^d
5	toluene	KO ^t Bu	dpbp	1.4×10^{-3}	7 ^c	n.d. ^d
6	CH ₂ Cl ₂	KO ^t Bu	dpbp	1.4×10^{-3}	0 ^c	n.d. ^d
7	THF	NaOMe	dpbp	1.4×10^{-3}	31 ^b	15 ^b
8	THF	CsO ^t Bu	dpbp	1.4×10^{-3}	16 ^c	n.d. ^d
9	THF	Cs ₂ CO ₃	dpbp	1.4×10^{-3}	0	n.d. ^d
10	THF	NaOMe	DPEphos	1.4×10^{-3}	23	n.d. ^d
11	THF	NaOMe	dppf	1.4×10^{-3}	25	n.d. ^d

^a The reaction was carried out with **2.3e** (140 μmol) and a base (154 μmol) in the given solvent at 30 °C for 20 h in the presence of a palladium catalyst (5 mol %) generated from $\text{Pd}_2(\text{dba})_4$ and a bisphosphine ligand. ^b Isolated yield by recycle HPLC. ^c Determined by GC analysis. ^d Not determined.

The reaction conditions shown in entry 3 of Table 2-1 were selected as "optimized conditions" and they were applied to the other substrates in the same way. The results of the palladium-catalyzed reaction are summarized in Table 2-2.

While the substrates with more than three methylene units (i.e., **2.3b** and the longer ones) afforded the corresponding monomeric endocyclic allenes **2.5b-h** in moderate yields by the palladium-catalyzed reaction, the reaction of **2.3a** did not provide eight-membered endocyclic allene **2.5a** (entry 1). The highest yield of **2.5** was achieved for the reaction of **2.3f** giving thirteen-membered monomeric endocyclic allene **2.5f** in 52% yield (entry 6). With a longer polymethylene chain in **2.3g** ($n = 9$) and **2.3h** ($n = 11$), the yields of **2.5g** (42%) and **2.5h** (33%) were slightly declined (entries 7 and 8). Likewise, shorter substrates **2.3b-e** afforded the corresponding monomeric endocyclic allenes **2.5b-e** in lower yields ranging 11% to 31% (entries 2-5). In all the cases including the reaction of **2.3a**, substrates **2.3** were completely consumed under these conditions, and the formation of dimeric endocyclic bis-allenes **2.6**, which were isolated in 10-30% yields by the HPLC separation, was observed. Homologous trimeric endocyclic tris-allenes **2.7a**, **2.7c**, and **2.7d** were also isolated in 10%, 7%, and 9% yields, respectively, in the reactions giving **2.6** in relatively higher yields (entries 1, 3, and 4). Since bis-allenes **2.6** and tris-allenes **2.7** possess multiple allenic axially chiral elements, they were obtained as diastereomeric mixtures.

Table 2-2. Influences of Ring Size in Palladium-Catalyzed S_N2'-Cyclization of **2.3**.^a

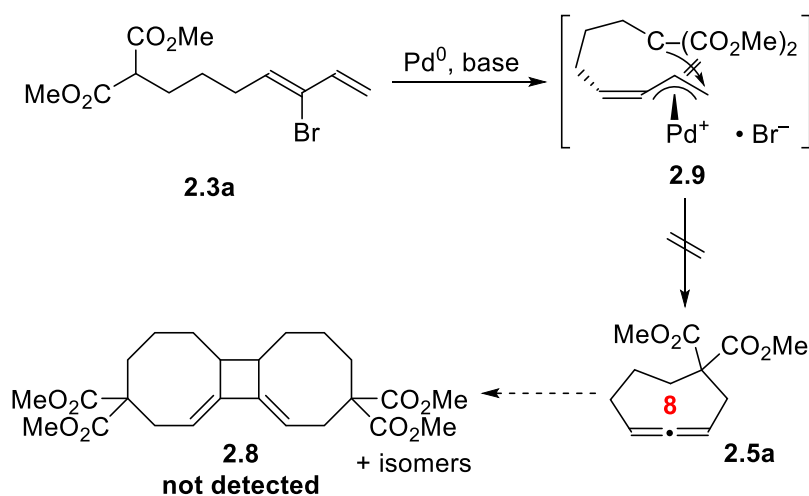
entry	substrate 2.3	yield of 2.5 (%) ^b	yield of 2.6 (%) ^{b-d}	yield of 2.7 (%) ^{b-d}
1	2.3a (n = 3)	0 (2.5a)	30 (2.6a)	10 (2.7a)
2	2.3b (n = 4)	23 (2.5b)	16 (2.6b)	<i>e</i>
3	2.3c (n = 5)	11 (2.5c)	24 (2.6c)	7 (2.7c)
4	2.3d (n = 6)	18 (2.5d)	27 (2.6d)	9 (2.7d)
5	2.3e (n = 7)	31 (2.5e)	19 (2.6e)	<i>e</i>
6	2.3f (n = 8)	52 (2.5f)	14 (2.6f)	<i>e</i>
7	2.3g (n = 9)	42 (2.5g)	21 (2.6g)	<i>e</i>
8	2.3h (n = 11)	33 (2.5h)	10 (2.6g)	<i>e</i>

^a The reaction was carried out with **2.3** (350 μmol) and a base (385 μmol) in THF (250 mL) at 30 °C for 20 h in the presence of a palladium catalyst (5 mol %) generated from Pd₂(dba)₄ and dpbp. ^b Isolated yield by recycle HPLC. ^c Calculated based on **2.3**. ^d Obtained as diastereomeric mixtures. ^e Not determined or <5% yield.

Whereas eight-membered endo-carbocyclic allenes are generally too reactive to be isolated without appropriate kinetically stabilizing bulky substituents,^[3a,e,13] it was rational that **2.5a** was not detected in the reaction of **2.3a**. However, the undetection of **2.5a** should not be ascribed to its high reactivity. Once highly reactive **2.5a** was generated in situ, it was expected to undergo [2+2]cycloaddition^[19] giving an isomeric mixture of homodimers such as **2.8**, but **2.8** and/or related isomeric species were not detected in the reaction mixture. The key intermediate of the palladium-catalyzed

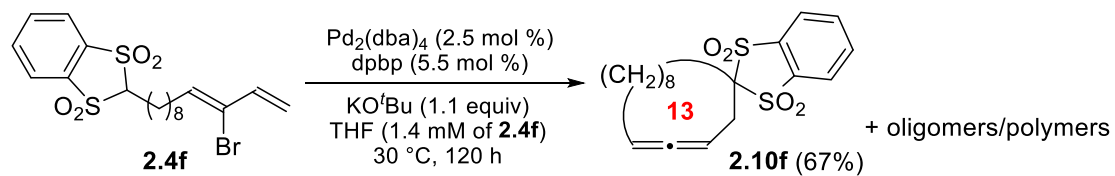
reaction of **2.3a** is (alkylidene- π -allyl)palladium species **2.9**. Due to the short trimethylene chain in **2.9**, the nucleophilic malonate moiety is not capable of attacking the CH₂ π -allyl terminus intramolecularly, and thus the formation of **2.5a** could not be realized (Scheme 2-3).

Scheme 2-3.



The cyclization reaction of **2.4f** was also examined. Substrate **2.4f** possesses a benzo[1,3]dithiole tetraoxide (BDT) substructure as a pronucleophilic moiety. The palladium-catalyzed reaction of **2.4f** was conducted essentially in the same way as in Table 2-2 except for the reaction time. Due probably to the lower nucleophilicity of BDT, the reaction took longer time (120 h) for completion, and monomeric endocyclic allene **2.10f** was obtained in the highest yield of 67% (Scheme 2-4). The formation of the corresponding endocyclic dimeric bis-allene and trimeric tris-allene was minor (<5%) in this reaction. The BDT moiety in **2.4f** is sterically more compact than the malonate moiety in **2.3f**, which may facilitate the intramolecular cyclization in the palladium-catalyzed process.

Scheme 2-4. Palladium-Catalyzed S_N2'-Cyclization of BDT-Tethered Substrate **2.4f**.

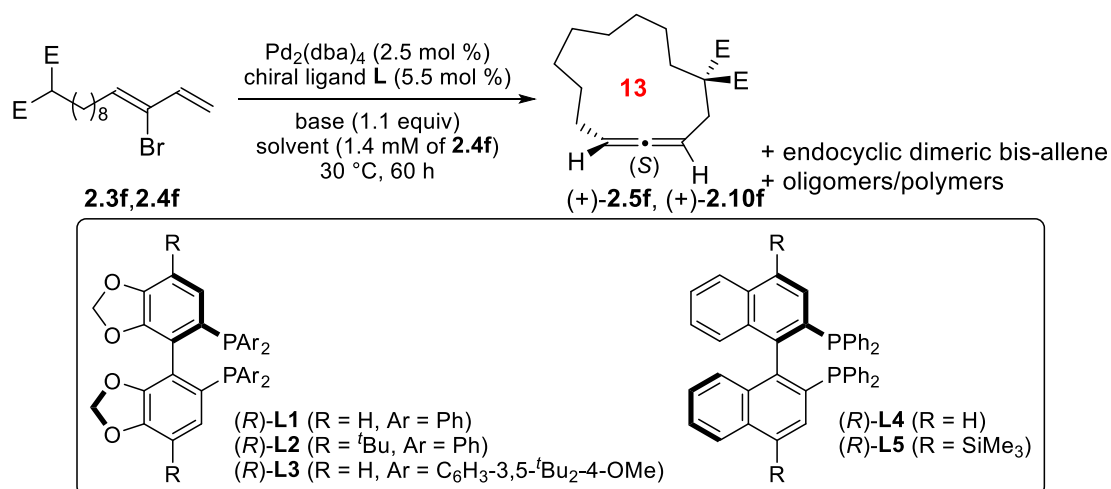


Section 4.

Palladium-Catalyzed Asymmetric Synthesis of Axially Chiral Endocyclic Allenes

Endocyclic allenes **2.5** and **2.10** obtained as in Table 2-2 and Scheme 2-4 are axially chiral but racemic. Using **2.3f** as a representative substrate, palladium-catalyzed enantioselective synthesis of **2.5f** was examined according to our previous studies.^[10] That is, with a palladium catalyst (5 mol %) generated from Pd₂(dba)₄ and (*R*)-segphos ((*R*)-**L1**) in THF at 30 °C in the presence of KO^tBu, (+)-**2.5f** was obtained in 50% yield with 65% ee (Table 2-3, entry 1). Among the various solvents and bases examined, the combination of THF and KO^tBu showed the highest yield and the highest enantioselectivity for the reaction of **2.3f** (entries 1-5). While (*R*)-**L2**, (*R*)-**L4**, and (*R*)-**L5** showed lower enantioselectivity than (*R*)-**L1** with 45-55% ee (entries 6, 8, and 9), the enantioselectivity was improved to 70% ee by the use of (*R*)-**L3** although the chemical yield of (+)-**2.5f** was considerably lower (entry 7). The enantioselective reaction of **2.4f** was conducted as in entry 7 and (+)-**2.10f** was obtained in 51% ee and 29% yield (entry 10). The absolute configurations of dextrorotatory (+)-**2.5f** and (+)-**2.10f** were deduced to be (*S*) by the Lowe-Brewster rule.^[20]

Table 2-3. Palladium-Catalyzed Asymmetric Synthesis of Axially Chiral Endocyclic Allenes **2.5f/2.10f**.^a



entry	substrate	chiral ligand	base	solvent	yield (%) ^b	% ee (config) ^{c,d}
1	2.3f	(<i>R</i>)- L1	KO ^t Bu	THF	50 (2.5f)	65 (<i>S</i>)
2	2.3f	(<i>R</i>)- L1	KO ^t Bu	dioxane	5 (2.5f)	11 (<i>S</i>)
3	2.3f	(<i>R</i>)- L1	KO ^t Bu	CH ₂ Cl ₂	n.d. ^e	—
4	2.3f	(<i>R</i>)- L1	NaOMe	THF	13 (2.5f)	59 (<i>S</i>)
5	2.3f	(<i>R</i>)- L1	CsO ^t Bu	THF	35 (2.5f)	55 (<i>S</i>)
6	2.3f	(<i>R</i>)- L2	KO ^t Bu	THF	42 (2.5f)	45 (<i>S</i>)
7	2.3f	(<i>R</i>)- L3	KO ^t Bu	THF	25 (2.5f)	70 (<i>S</i>)
8	2.3f	(<i>R</i>)- L4	KO ^t Bu	THF	34 (2.5f)	55 (<i>S</i>)
9	2.3f	(<i>R</i>)- L5	KO ^t Bu	THF	54 (2.5f)	50 (<i>S</i>)
10	2.4f	(<i>R</i>)- L3	KO ^t Bu	THF	29 (2.10f)	51 (<i>S</i>)

^a The reaction was carried out with **2.3f** or **2.4f** (100 μmol) and a base (110 μmol) in a given solvent (70 mL) at 30 °C for 60 h in the presence of a palladium catalyst (5 mol %) generated from $\text{Pd}_2(\text{dba})_4$ and a chiral ligand **L**. ^b Isolated yield by recycle HPLC. ^c Determined by chiral HPLC analysis (see Experimental Section for details). ^d The absolute configurations were deduced by the Lowe-Brewster rule (ref 20). ^e Not determined.

Conclusions for Chapter II

In summary, I have developed a general method of preparing various endocyclic allenes of a nine- to sixteen-membered carbocycle utilizing the palladium-catalyzed reaction. Readily available ω -(pronucleophile-tethered)-3-bromo-1,3-alkadienes **2.3** and **2.4** undergo the unimolecular S_N2'-cyclization in the presence of an appropriate palladium catalyst to give the corresponding endocyclic allenes **2.5/2.10** in fair yields together with the dimeric endocyclic bis-allenes and higher oligomers/polymers. The highest yield of 67% was achieved for the preparation of the thirteen-membered cyclic allene. Due probably to the rigid substructures in the allenic C=C=C products as well as in the (alkylidene- π -allyl)palladium intermediates, the medium- to large-membered carbocyclic compounds are accessible in reasonable yields by the present cyclization reaction. By the use of a chiral palladium-catalyst, axially chiral endocyclic allenes were obtained in up to 70% ee.

Experimental Section for Chapter II

General. All anaerobic and/or moisture sensitive manipulations were carried out with standard Schlenk techniques under predried nitrogen or with glovebox techniques under prepurified argon. ^1H NMR (at 400 MHz) and ^{13}C NMR (at 100 MHz) chemical shifts are reported in ppm downfield of internal tetramethylsilane. Tetrahydrofuran (from benzophenone-ketyl) and dichloromethane (from CaH_2) were distilled under nitrogen prior to use. $\text{Pd}(\text{PPh}_3)_4$,^[21] $\text{Pd}_2(\text{dba})_4$,^[22] dpbp ,^[16] (*R*)-**L1**,^[23] (*R*)-**L2**,^[24] (*R*)-**L4**,^[25] (*R*)-**L5**,^[26] and 1,3-benzodithiole-1,1,3,3-tetraoxide (BDT)^[27] were prepared according to the reported methods. All the other chemicals were obtained from commercial sources and used as received unless otherwise noted.

Preparation of ω -bromoalkanals.

The ω -bromoalkanals were prepared from the corresponding commercially available ω -bromo-1-alkanols according to the reported procedure,^[28] in which the preparation of 8-bromooctanal ($n = 7$ in Scheme 2-2) was described in detail. All the ω -bromoalkanals used in this study are known compounds and were characterized by comparison of their NMR spectra with those reported previously ($n = 3$,^[29] $n = 4$,^[29] $n = 5$,^[30] $n = 6$,^[31] $n = 7$,^[28] $n = 8$,^[32] $n = 9$,^[32] $n = 11$ ^[33]).

Preparation of 1,1, ω -Tribromo-1-alkenes (2.1a-h). To a CH_2Cl_2 (40 mL) solution of CBr_4 (12.3 g, 37.0 mmol) was added PPh_3 (20.0 g, 76.2 mmol) portionwise at 0 °C, and the solution was kept stirring at this temperature for 20 min. A solution of ω -bromoalkanal (22.0 mmol) in CH_2Cl_2 (10 mL) was added dropwise at 0 °C, and the mixture was stirred at the same temperature for 10 min. After quenching the reaction mixture with a small amount of water (ca. 1 mL), the mixture was concentrated under

reduced pressure. Addition of hexane (ca. 100 mL) to the concentrated solution precipitated triphenylphosphine oxide as pale yellow solid, which was removed by filtration. The filtrate was evaporated, and the residue was purified by silica gel column chromatography (with hexane) to give the title compound as colorless oil. The characterization data of **2.1a-h** are given below.

1,1,5-Tribromo-1-pentene (2.1a; n = 3). Yield: 63%. ^1H NMR (CDCl_3): δ 1.96-2.03 (m, 2H), 2.25-2.31 (m, 2H), 3.42 (t, J = 6.6 Hz, 2H), 6.40 (t, J = 7.3 Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ 30.8, 31.7, 32.5, 90.5, 136.7. EI-HRMS Calcd for $\text{C}_5\text{H}_7\text{Br}_3$: 303.8098. Found: 303.8101.

1,1,6-Tribromo-1-hexene (2.1b; n = 4). Yield: 5.78 g (61%) starting with 5-bromopentanal (4.90 g). ^1H NMR (CDCl_3): δ 1.56-1.64 (m, 2H), 1.86-1.93 (m, 2H), 2.12-2.17 (m, 2H), 3.42 (t, J = 6.7 Hz, 2H), 6.39 (t, J = 7.2 Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ 26.3, 31.9, 32.1, 33.3, 89.5, 137.9. EI-HRMS Calcd for $\text{C}_6\text{H}_9\text{Br}_3$: 317.8254. Found: 317.8251.

1,1,7-Tribromo-1-heptene (2.1c; n = 5). Yield: 65%. ^1H NMR (CDCl_3): δ 1.41-1.52 (m, 4H), 1.84-1.91 (m, 2H), 2.09-2.14 (m, 2H), 3.41 (t, J = 6.8 Hz, 2H), 6.39 (t, J = 7.3 Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ 27.0, 27.6, 32.5, 32.8, 33.6, 89.1, 138.3. EI-HRMS Calcd for $\text{C}_7\text{H}_{11}\text{Br}_3$: 331.8411. Found: 331.8405.

1,1,8-Tribromo-1-octene (2.1d; n = 6). Yield: 1.78 g (61%) starting with 7-bromoheptanal (1.62 g). ^1H NMR (CDCl_3): δ 1.31-1.38 (m, 2H), 1.41-1.49 (m, 4H), 1.83-1.90 (m, 2H), 2.07-2.13 (m, 2H), 3.41 (t, J = 6.8 Hz, 2H), 6.38 (t, J = 7.3 Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ 27.6, 27.9, 28.2, 32.7, 32.9, 33.9, 88.8, 138.6. EI-HRMS Calcd for $\text{C}_8\text{H}_{13}\text{Br}_3$: 345.8567. Found: 345.8570.

1,1,9-Tribromo-1-nonene (2.1e; n = 7). Yield: 77%. ^1H NMR (CDCl_3): δ 1.31-1.47 (m, 8H), 1.82-1.89 (m, 2H), 2.07-2.12 (m, 2H), 3.41 (t, $J = 6.8$ Hz, 2H), 6.38 (t, $J = 7.2$ Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ 27.7, 28.1, 28.5, 28.8, 32.7, 32.9, 34.0, 88.7, 138.7. EI-HRMS Calcd for $\text{C}_9\text{H}_{15}\text{Br}_3$: 359.8724. Found: 359.8718.

1,1,10-Tribromo-1-decene (2.1f; n = 8). Yield: 63%. ^1H NMR (CDCl_3): δ 1.28-1.47 (m, 10H), 1.82-1.89 (m, 2H), 2.06-2.12 (m, 2H), 3.41 (t, $J = 6.8$ Hz, 2H), 6.39 (t, $J = 7.3$ Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ 27.8, 28.1, 28.7, 28.9, 29.2, 32.8, 33.0, 34.1, 88.6, 138.9. EI-HRMS Calcd for $\text{C}_{10}\text{H}_{17}\text{Br}_3$: 373.8880. Found: 373.8881.

1,1,11-Tribromo-1-undecene (2.1g; n = 9). Yield: 66%. ^1H NMR (CDCl_3): δ 1.26-1.43 (m, 12H), 1.82-1.89 (m, 2H), 2.06-2.12 (m, 2H), 3.41 (t, $J = 6.9$ Hz, 2H), 6.38 (t, $J = 7.2$ Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ 27.8, 28.1, 28.7, 29.0, 29.2, 29.3, 32.8, 33.0, 34.1, 88.5, 138.9. EI-HRMS Calcd for $\text{C}_{11}\text{H}_{19}\text{Br}_3$: 387.9037. Found: 387.9037.

1,1,13-Tribromo-1-tridecene (2.1h; n = 11). Yield: 68%. ^1H NMR (CDCl_3): δ 1.26-1.46 (m, 16H), 1.82-1.89 (m, 2H), 2.06-2.11 (m, 2H), 3.41 (t, $J = 6.9$ Hz, 2H), 6.38 (t, $J = 7.2$ Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ 27.8, 28.2, 28.8, 29.1, 29.3, 29.4, 29.49, 29.50, 32.9, 33.0, 34.1, 88.5, 138.9. EI-HRMS Calcd for $\text{C}_{13}\text{H}_{23}\text{Br}_3$: 415.9350. Found: 415.9356.

Preparation of (Z)-3, ω -Dibromo-1,3-alkadienes (2.2a-h). To a suspension of $(\text{CH}_2=\text{CH})\text{ZnCl}$ in THF, prepared from dry ZnCl_2 (28 mmol) and vinylmagnesium chloride (2.0 M THF solution; 12 mL; 24 mmol), was added a solution of 1,1, ω -tribromo-1-alkene **2.1** (8.0 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (0.20 mmol) in THF (16 mL) at 0 °C. After stirring the mixture for 4.5 h at room temperature, the reaction mixture was diluted with hexane, filtered, and evaporated to dryness. The residue was purified by silica gel chromatography (with hexane), and further purified by recycle HPLC to

give the title compound as colorless oil. The characterization data of **2.2a-h** are given below.

(Z)-3,7-Dibromo-1,3-heptadiene (2.2a; n = 3). Yield: 54%. ^1H NMR (CDCl_3): δ 1.99-2.06 (m, 2H), 2.46-2.52 (m, 2H), 3.43 (t, $J = 6.8$ Hz, 2H), 5.20 (d, $J = 10.4$ Hz, 1H), 5.56 (d, $J = 16.3$ Hz, 1H), 5.98 (t, $J = 7.2$ Hz, 1H), 6.32 (dd, $J = 16.3$ and 10.4 Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ 30.3, 31.5, 32.9, 118.2, 127.4, 132.7, 135.7. EI-HRMS Calcd for $\text{C}_7\text{H}_{10}\text{Br}_2$: 251.9149. Found: 251.9144.

(Z)-3,8-Dibromo-1,3-octadiene (2.2b; n = 4). Yield: 54%. ^1H NMR (CDCl_3): δ 1.58-1.66 (m, 2H), 1.87-1.94 (m, 2H), 2.34-2.39 (m, 2H), 3.43 (t, $J = 6.7$ Hz, 2H), 5.19 (d, $J = 10.5$ Hz, 1H), 5.55 (d, $J = 16.3$ Hz, 1H), 5.97 (t, $J = 7.1$ Hz, 1H), 6.31 (dd, $J = 16.3$ and 10.5 Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ 26.9, 30.6, 32.2, 33.6, 117.7, 126.6, 134.0, 135.7. EI-HRMS Calcd for $\text{C}_8\text{H}_{12}\text{Br}_2$: 265.9306. Found: 265.9303.

(Z)-3,9-Dibromo-1,3-nonadiene (2.2c; n = 5). Yield: 52%. ^1H NMR (CDCl_3): δ 1.47-1.50 (m, 4H), 1.85-1.92 (m, 2H), 2.31-2.36 (m, 2H), 3.41 (t, $J = 6.8$ Hz, 2H), 5.17 (d, $J = 10.5$ Hz, 1H), 5.54 (d, $J = 16.3$ Hz, 1H), 5.98 (t, $J = 7.2$ Hz, 1H), 6.31 (dd, $J = 16.3$ and 10.5 Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ 27.5, 27.8, 31.3, 32.6, 33.7, 117.5, 126.2, 134.5, 135.8. EI-HRMS Calcd for $\text{C}_9\text{H}_{14}\text{Br}_2$: 279.9462. Found: 279.9467.

(Z)-3,10-Dibromo-1,3-decadiene (2.2d; n = 6). Yield: 51%. ^1H NMR (CDCl_3): δ 1.32-1.51 (m, 6H), 1.83-1.90 (m, 2H), 2.30-2.35 (m, 2H), 3.41 (t, $J = 6.9$ Hz, 2H), 5.17 (d, $J = 10.5$ Hz, 1H), 5.53 (d, $J = 16.3$ Hz, 1H), 5.97 (t, $J = 7.1$ Hz, 1H), 6.31 (dd, $J = 16.3$ and 10.5 Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ 28.0, 28.2, 28.4, 31.4, 32.7, 34.0, 117.3, 126.1, 134.9, 135.8. EI-HRMS Calcd for $\text{C}_{10}\text{H}_{16}\text{Br}_2$: 293.9619. Found: 293.9617.

(Z)-3,11-Dibromo-1,3-undecadiene (2.2e; n = 7). Yield: 63%. ^1H NMR (CDCl_3): δ 1.31-1.49 (m, 8H), 1.82-1.89 (m, 2H), 2.29-2.34 (m, 2H), 3.41 (t, $J = 6.9$ Hz, 2H), 5.16

(d, $J = 10.5$ Hz, 1H), 5.53 (d, $J = 16.3$ Hz, 1H), 5.98 (t, $J = 7.1$ Hz, 1H), 6.31 (dd, $J = 16.3$ and 10.5 Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ 28.1, 28.2, 28.6, 29.0, 31.5, 32.8, 34.0, 117.2, 126.0, 135.0, 135.8. EI-HRMS Calcd for $\text{C}_{11}\text{H}_{18}\text{Br}_2$: 307.9775. Found: 307.9777.

(Z)-3,12-Dibromo-1,3-dodecadiene (2.2f; n = 8). Yield: 50%. ^1H NMR (CDCl_3): δ 1.26-1.46 (m, 10H), 1.82-1.89 (m, 2H), 2.28-2.34 (m, 2H), 3.41 (t, $J = 6.8$ Hz, 2H), 5.16 (d, $J = 10.5$ Hz, 1H), 5.53 (d, $J = 16.3$ Hz, 1H), 5.98 (t, $J = 7.1$ Hz, 1H), 6.31 (dd, $J = 16.3$ and 10.5 Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ 28.2, 28.3, 28.7, 29.15, 29.24, 31.5, 32.8, 34.1, 117.2, 125.9, 135.2, 135.9. EI-HRMS Calcd for $\text{C}_{12}\text{H}_{20}\text{Br}_2$: 321.9932. Found: 321.9931.

(Z)-3,13-Dibromo-1,3-tridecadiene (2.2g; n = 9). Yield: 68%. ^1H NMR (CDCl_3): δ 1.30-1.34 (m, 8H), 1.39-1.46 (m, 4H), 1.82-1.89 (m, 2H), 2.28-2.34 (m, 2H), 3.41 (t, $J = 6.9$ Hz, 2H), 5.16 (d, $J = 10.5$ Hz, 1H), 5.53 (d, $J = 16.3$ Hz, 1H), 5.98 (t, $J = 7.1$ Hz, 1H), 6.31 (dd, $J = 16.3$ and 10.5 Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ 28.1, 28.3, 28.7, 29.2, 29.28, 29.32, 31.5, 32.8, 34.1, 117.1, 125.8, 135.2, 135.9. EI-HRMS Calcd for $\text{C}_{13}\text{H}_{22}\text{Br}_2$: 336.0088. Found: 336.0091.

(Z)-3,15-Dibromo-1,3-pentadecadiene (2.2h; n = 11). Yield: 56%. ^1H NMR (CDCl_3): δ 1.28-1.47 (m, 16H), 1.82-1.89 (m, 2H), 2.28-2.34 (m, 2H), 3.41 (t, $J = 6.9$ Hz, 2H), 5.15 (d, $J = 10.5$ Hz, 1H), 5.52 (d, $J = 16.3$ Hz, 1H), 5.98 (t, $J = 7.1$ Hz, 1H), 6.31 (dd, $J = 16.3$ and 10.5 Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ 28.2, 28.4, 28.8, 29.3, 29.450, 29.455, 29.53 (2C), 31.6, 32.9, 34.1, 117.1, 125.8, 135.3, 135.9. EI-HRMS Calcd for $\text{C}_{15}\text{H}_{26}\text{Br}_2$: 364.0401. Found: 364.0404.

Preparation of Malonate-Tethered Bromodienes 2.3a-h. A general procedure is given below. To a solution of NaH (4.9 mmol) in DMF (10 mL) was added dimethyl

malonate (4.9 mmol) at 0 °C. After gas evolution was ceased, dibromoalkadiene **2.2** (4.0 mmol) was added to the solution by means of syringe under nitrogen. The mixture was stirred at room temperature for 20 h. After quenching with saturated $\text{NH}_4\text{Cl}_{aq}$, the reaction mixture was extracted with Et_2O twice and the combined organic layer was washed with H_2O and NaCl_{aq} , dried over MgSO_4 , filtered, and evaporated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate = 4/1) to afford the malonate-tethered bromodiene **2.3**. The characterization data of **2.3a-h** are given below.

Dimethyl 2-((Z)-5-Bromo-4,6-heptadienyl)-1,3-propanedioate (2.3a; n = 3). Yield: 70%. ^1H NMR (CDCl_3): δ 1.43-1.53 (m, 2H), 1.92-1.98 (m, 2H), 2.33-2.38 (m, 2H), 3.39 (t, J = 7.5 Hz, 1H), 3.74 (s, 6H), 5.18 (d, J = 10.4 Hz, 1H), 5.54 (d, J = 16.3 Hz, 1H), 5.96 (t, J = 7.1 Hz, 1H), 6.30 (dd, J = 16.3 and 10.4 Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ 26.1, 28.4, 31.1, 51.5, 52.6, 117.7, 126.6, 133.8, 135.7, 169.8. Anal. Calcd for $\text{C}_{12}\text{H}_{17}\text{BrO}_4$: C, 47.23; H, 5.61. Found: C, 47.23; H, 5.57. ESI-HRMS Calcd for $\text{C}_{12}\text{H}_{17}\text{BrO}_4\text{Na}$: 327.0208 (M+Na). Found: 327.0220.

Dimethyl 2-((Z)-6-Bromo-5,7-octadienyl)-1,3-propanedioate (2.3b; n = 4). Yield: 80%. ^1H NMR (CDCl_3): δ 1.32-1.40 (m, 2H), 1.45-1.52 (m, 2H), 1.90-1.96 (m, 2H), 2.30-2.35 (m, 2H), 3.37 (t, J = 7.5 Hz, 1H), 3.74 (s, 6H), 5.17 (d, J = 10.5 Hz, 1H), 5.53 (d, J = 16.3 Hz, 1H), 5.96 (t, J = 7.3 Hz, 1H), 6.31 (dd, J = 16.3 and 10.5 Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ 27.0, 27.9, 28.7, 31.2, 51.6, 52.6, 117.5, 126.3, 134.5, 135.8, 169.9. Anal. Calcd for $\text{C}_{13}\text{H}_{19}\text{BrO}_4$: C, 48.92; H, 6.00. Found: C, 48.77; H, 5.97. EI-HRMS Calcd for $\text{C}_{13}\text{H}_{19}\text{BrO}_4$: 318.0467. Found: 318.0468.

Dimethyl 2-((Z)-7-Bromo-6,8-nonadienyl)-1,3-propanedioate (2.3c; n = 5). Yield: 75%. ^1H NMR (CDCl_3): δ 1.29-1.50 (m, 6H), 1.88-1.93 (m, 2H), 2.28-2.33 (m, 2H),

3.36 (t, $J = 7.6$ Hz, 1H), 3.74 (s, 6H), 5.16 (d, $J = 10.6$ Hz, 1H), 5.52 (d, $J = 16.3$ Hz, 1H), 5.96 (t, $J = 7.1$ Hz, 1H), 6.31 (dd, $J = 16.3$ and 10.6 Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ 27.1, 27.9, 28.69, 28.71, 31.3, 51.6, 52.4, 117.2, 126.0, 134.7, 135.8, 169.9. Anal. Calcd for $\text{C}_{14}\text{H}_{21}\text{BrO}_4$: C, 50.46; H, 6.35. Found: C, 50.37; H, 6.29. ESI-HRMS Calcd for $\text{C}_{14}\text{H}_{21}\text{BrO}_4\text{Na}$: 355.0515 ($\text{M}+\text{Na}$). Found: 355.0516.

Dimethyl 2-((Z)-8-Bromo-7,9-decadienyl)-1,3-propanedioate (2.3d; n = 6). Yield: 73%. ^1H NMR (CDCl_3): δ 1.29-1.34 (m, 6H), 1.40-1.47 (m, 2H), 1.87-1.93 (m, 2H), 2.28-2.33 (m, 2H), 3.36 (t, $J = 7.5$ Hz, 1H), 3.74 (s, 6H), 5.16 (d, $J = 10.3$ Hz, 1H), 5.53 (d, $J = 16.3$ Hz, 1H), 5.97 (t, $J = 7.2$ Hz, 1H), 6.31 (dd, $J = 16.3$ and 10.3 Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ 27.3, 28.2, 28.8, 28.9, 29.0, 31.5, 51.7, 52.5, 117.2, 126.0, 135.0, 135.9, 170.0. Anal. Calcd for $\text{C}_{15}\text{H}_{23}\text{BrO}_4$: C, 51.88; H, 6.68. Found: C, 51.72; H, 6.60. EI-HRMS Calcd for $\text{C}_{15}\text{H}_{23}\text{BrO}_4$: 346.0780. Found: 346.0781.

Dimethyl 2-((Z)-9-Bromo-8,10-undecadienyl)-1,3-propanedioate (2.3e; n = 7). Yield: 95%. ^1H NMR (CDCl_3): δ 1.26-1.32 (m, 8H), 1.39-1.47 (m, 2H), 1.87-1.92 (m, 2H), 2.28-2.33 (m, 2H), 3.36 (t, $J = 7.6$ Hz, 1H), 3.74 (s, 6H), 5.16 (d, $J = 10.4$ Hz, 1H), 5.53 (d, $J = 16.3$ Hz, 1H), 5.97 (t, $J = 7.1$ Hz, 1H), 6.31 (dd, $J = 16.3$ and 10.4 Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ 27.3, 28.3, 28.8, 29.09, 29.11 (2C), 31.5, 51.7, 52.5, 117.2, 125.9, 135.2, 135.9, 170.0. Anal. Calcd for $\text{C}_{16}\text{H}_{25}\text{BrO}_4$: C, 53.19; H, 6.97. Found: C, 52.66; H, 6.91. EI-HRMS Calcd for $\text{C}_{16}\text{H}_{25}\text{BrO}_4$: 360.0936. Found: 360.0936.

Dimethyl 2-((Z)-10-Bromo-9,11-dodecadienyl)-1,3-propanedioate (2.3f; n = 8). Yield: 80%. ^1H NMR (CDCl_3): δ 1.26-1.33 (m, 10H), 1.39-1.47 (m, 2H), 1.87-1.92 (m, 2H), 2.28-2.33 (m, 2H), 3.36 (t, $J = 7.6$ Hz, 1H), 3.74 (s, 6H), 5.16 (d, $J = 10.5$ Hz, 1H), 5.53 (d, $J = 16.4$ Hz, 1H), 5.98 (t, $J = 7.1$ Hz, 1H), 6.31 (dd, $J = 16.4$ and 10.5 Hz, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ 27.4, 28.3, 28.9, 29.18, 29.21, 29.22, 29.3, 31.5, 51.8, 52.5,

117.2, 125.9, 135.2, 135.9, 170.0. Anal. Calcd for $C_{17}H_{27}BrO_4$: C, 54.41; H, 7.25. Found: C, 54.48; H, 7.27. EI-HRMS Calcd for $C_{17}H_{27}BrO_4$: 374.1093. Found: 374.1093.

Dimethyl 2-((Z)-11-Bromo-10,12-tridecadienyl)-1,3-propanedioate (2.3g; n = 9).

Yield: 91%. ^1H NMR ($CDCl_3$): δ 1.28-1.33 (m, 12H), 1.40-1.47 (m, 2H), 1.87-1.92 (m, 2H), 2.28-2.33 (m, 2H), 3.36 (t, $J = 7.6$ Hz, 1H), 3.74 (s, 6H), 5.15 (d, $J = 10.4$ Hz, 1H), 5.52 (d, $J = 16.3$ Hz, 1H), 5.98 (t, $J = 7.3$ Hz, 1H), 6.31 (dd, $J = 16.3$ and 10.4 Hz, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 27.3, 28.3, 28.8, 29.16, 29.21, 29.25, 29.34, 29.38, 31.5, 51.7, 52.4, 117.1, 125.8, 135.2, 135.9, 170.0. Anal. Calcd for $C_{18}H_{29}BrO_4$: C, 55.53; H, 7.51. Found: C, 55.60; H, 7.39. EI-HRMS Calcd for $C_{18}H_{29}BrO_4$: 388.1249. Found: 388.1247.

Dimethyl 2-((Z)-13-Bromo-12,14-pentadecadienyl)-1,3-propanedioate (2.3h; n =

2.11). Yield: 77%. ^1H NMR ($CDCl_3$): δ 1.26-1.35 (m, 16H), 1.40-1.47 (m, 2H), 1.87-1.92 (m, 2H), 2.28-2.34 (m, 2H), 3.36 (t, $J = 7.6$ Hz, 1H), 3.74 (s, 6H), 5.15 (d, $J = 10.4$ Hz, 1H), 5.52 (d, $J = 16.3$ Hz, 1H), 5.98 (t, $J = 7.1$ Hz, 1H), 6.31 (dd, $J = 16.3$ and 10.4 Hz, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 27.4, 28.4, 28.9, 29.2, 29.29, 29.32, 29.4, 29.51, 29.54, 29.6, 31.6, 51.8, 52.5, 117.1, 125.8, 135.3, 135.9, 170.0. Anal. Calcd for $C_{20}H_{33}BrO_4$: C, 57.55; H, 7.97. Found: C, 57.69; H, 7.84. ESI-HRMS Calcd for $C_{20}H_{33}BrO_4Na$: 439.1454 (M+Na). Found: 439.1449.

2-((Z)-10-Bromo-9,11-dodecadienyl)-1,3-benzodithiole-1,1,3,3-tetraoxide (2.4f).

To a mixture of NaH (26 mg, 1.1 mmol) and BDT (240 mg, 1.1 mmol) in DMF (4.5 ml) was added dibromododecadiene **2.2f** (274 mg, 844 μ mol) by means of syringe under nitrogen. After stirring the mixture for 16 h at 80 $^{\circ}C$, the reaction mixture was extracted with ethyl acetate twice and the combined organic layer was washed with H_2O and $NaCl_{aq}$, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by recycle HPLC to afford **2.4f** (263 mg, 570 μ mol, 68%) as

a white solid. ^1H NMR (CDCl_3): δ 1.33-1.50 (m, 10H), 1.75-1.80 (m, 2H), 2.30-2.34 (m, 4H), 4.36 (t, $J = 7.1$ Hz, 1H), 5.16 (d, $J = 10.4$ Hz, 1H), 5.53 (d, $J = 16.3$ Hz, 1H), 5.99 (t, $J = 7.0$ Hz, 1H), 6.32 (dd, $J = 16.3$ and 10.4 Hz, 1H) 7.91-7.94 (m, 2H), 8.02-8.05 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ 22.1, 25.8, 28.2, 28.8, 29.00, 29.04, 29.1, 31.4, 73.7, 117.1, 122.5, 125.8, 135.1, 135.78, 135.79, 137.6. Anal. Calcd for $\text{C}_{19}\text{H}_{25}\text{BrO}_4\text{S}_2$: C, 49.46; H, 5.46. Found: C, 49.80; H, 5.40. EI-HRMS Calcd for $\text{C}_{19}\text{H}_{25}\text{BrO}_4\text{S}_2$: 460.0378. Found: 460.0367.

Palladium-Catalyzed Reaction of Malonate-Tethered Bromodienes 2.3a-h. A general procedure is given below. To a mixture of $\text{Pd}_2(\text{dba})_4$ (17.5 μmol), dpbp (19.2 μmol), and KO^tBu (385 μmol) in THF (250 mL) was added malonate-tethered bromodiene **2.3** (350 μmol , 1.4 mM) by means of syringe under nitrogen. After stirring the mixture for 20 h at 30 °C, the reaction mixture was concentrated, filtered through a short pad of silica gel, and evaporated to dryness. The crude product was purified by recycle HPLC to afford the corresponding endocyclic allenes **2.5**, **2.6**, and **2.7**. The characterization data of the cyclic allenic products (**5**, **6**, and **7**) are listed below.

Dimethyl 2,2-(2,3-Octadien-1,8-diyl)-1,3-propanedioate (2.5b; n = 4). ^1H NMR (CDCl_3): δ 1.42-1.58 (m, 4H), 1.93-2.06 (m, 3H), 2.36-2.46 (m, 1H), 2.57-2.63 (m, 1H), 2.81-2.87 (m, 1H), 3.71 (s, 3H), 3.72 (s, 3H), 4.94-5.01 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ 18.9, 24.1, 24.8, 28.4, 31.6, 52.5, 52.6, 57.0, 85.3, 87.4, 172.2, 172.6, 209.8. ESI-HRMS Calcd for $\text{C}_{13}\text{H}_{18}\text{O}_4\text{Na}$: 261.1103 (M+Na). Found: 261.1106.

Dimethyl 2,2-(2,3-Nonadien-1,9-diyl)-1,3-propanedioate (2.5c; n = 5). ^1H NMR (CDCl_3): δ 1.29-1.84 (m, 7H), 1.88-1.96 (m, 1H), 2.04-2.11 (m, 1H), 2.32-2.41 (m, 1H), 2.61-2.72 (m, 2H), 3.72 (s, 3H), 3.73 (s, 3H), 4.98-5.05 (m, 1H), 5.29-5.32 (m, 1H).

$^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ 20.0, 20.6, 28.3, 29.7, 29.8, 32.6, 52.5, 52.6, 55.5, 87.0, 92.9, 172.0, 172.7, 205.9. EI-HRMS Calcd for $\text{C}_{14}\text{H}_{20}\text{O}_4$: 252.1362. Found: 252.1363.

Dimethyl 2,2-(2,3-Decadien-1,10-diyl)-1,3-propanedioate (2.5d; n = 6). ^1H NMR (CDCl_3): δ 1.18-1.62 (m, 8H), 1.78-1.96 (m, 2H), 2.04-2.15 (m, 2H), 2.59 (dd, J = 14.1 and 11.6 Hz, 1H), 2.79 (dt, J = 14.1 and 4.4 Hz, 1H), 3.71 (s, 3H), 3.74 (s, 3H), 5.01-5.08 (m, 1H), 5.26-5.31 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ 20.4, 26.0, 26.1, 26.4, 26.8, 30.9, 34.0, 52.5, 52.6, 57.2, 87.4, 91.4, 171.8, 172.2, 206.0. EI-HRMS Calcd for $\text{C}_{15}\text{H}_{22}\text{O}_4$: 266.1518. Found: 266.1516.

Dimethyl 2,2-(2,3-Undecadien-1,11-diyl)-1,3-propanedioate (2.5e; n = 7). ^1H NMR (CDCl_3): δ 0.97-1.59 (m, 10H), 1.74-1.82 (m, 1H), 1.93-2.17 (m, 3H), 2.55 (dd, J = 13.9 and 11.6 Hz, 1H), 2.68-2.73 (m, 1H), 3.71 (s, 3H), 3.74 (s, 3H), 4.61-4.67 (m, 1H), 4.89-4.96 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ 19.1, 21.4, 22.3, 25.9, 26.48, 26.54, 27.3, 32.1, 52.5, 52.6, 56.8, 83.8, 89.2, 171.7, 171.8, 208.4. Anal. Calcd for $\text{C}_{16}\text{H}_{24}\text{O}_4$: C, 68.54; H, 8.63. Found: C, 68.28; H, 8.74. EI-HRMS Calcd for $\text{C}_{16}\text{H}_{24}\text{O}_4$: 280.1675. Found: 280.1675.

Dimethyl 2,2-(2,3-Dodecadien-1,12-diyl)-1,3-propanedioate (2.5f; n = 8). ^1H NMR (CDCl_3): δ 1.06-1.15 (m, 1H), 1.26-1.62 (m, 11H), 1.90-2.12 (m, 4H), 2.55 (dd, J = 14.6 and 11.4 Hz, 1H), 2.77 (dtd, J = 14.6, 4.4, and 1.2 Hz, 1H), 3.71 (s, 3H), 3.73 (s, 3H), 4.74-4.81 (m, 1H), 5.12-5.17 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ 21.7, 25.0, 26.1, 26.9, 27.2, 27.9, 28.6, 30.8, 31.7, 52.45, 52.51, 57.4, 85.7, 91.4, 171.8 (2C), 206.1. Anal. Calcd for $\text{C}_{17}\text{H}_{26}\text{O}_4$: C, 69.36; H, 8.90. Found: C, 69.28; H, 9.05. EI-HRMS Calcd for $\text{C}_{17}\text{H}_{26}\text{O}_4$: 294.1831. Found: 294.1824.

Dimethyl 2,2-(2,3-Tridecadien-1,13-diyl)-1,3-propanedioate (2.5g; n = 9). ^1H NMR (CDCl_3): δ 0.73-0.90 (m, 1H), 1.14-1.57 (m, 13H), 1.87-2.04 (m, 4H), 2.58 (dd, J =

14.5 and 11.6 Hz, 1H), 2.78 (dtd, $J = 14.5, 4.4,$ and 0.9 Hz, 1H), 3.72 (s, 3H), 3.73 (s, 3H), 4.63-4.70 (m, 1H), 5.02-5.08 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ 20.7, 23.2, 23.9, 26.0, 26.37, 26.40, 27.16, 27.18, 31.6, 32.4, 52.5, 52.6, 57.2, 84.5, 91.3, 171.8, 171.9, 206.1. Anal. Calcd for $\text{C}_{18}\text{H}_{28}\text{O}_4$: C, 70.10; H, 9.15. Found: C, 70.00; H, 9.11. EI-HRMS Calcd for $\text{C}_{18}\text{H}_{28}\text{O}_4$: 308.1988. Found: 308.1989.

Dimethyl 2,2-(2,3-Pentadecadien-1,15-diyl)-1,3-propanedioate (2.5h; $n = 11$). ^1H NMR (CDCl_3): δ 1.07-1.43 (m, 18H), 1.82-2.03 (m, 4H), 2.56 (dd, $J = 14.2$ and 9.8 Hz, 1H), 2.71 (ddd, $J = 14.2, 6.0,$ and 3.2 Hz, 1H), 3.72 (s, 3H), 3.73(s, 3H), 4.69-4.71 (m, 1H), 5.07-5.13 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ 23.6, 24.2, 24.4, 25.9, 26.0, 26.2, 26.3, 27.4, 27.5, 29.0, 31.9, 32.9, 52.41, 52.44, 57.3, 84.6, 91.2, 171.81, 171.84, 206.2. EI-HRMS Calcd for $\text{C}_{20}\text{H}_{32}\text{O}_4$: 336.2301. Found: 336.2302.

5,5,13,13-Tetra(methoxycarbonyl)cyclohexadeca-1,2,9,10-tetraene (2.6a; $n = 3$). Diastereomeric mixture (^{13}C NMR signals not completely resolved). ^1H NMR (CDCl_3): δ 1.02-1.10 (m, 1H), 1.17-1.41 (m, 3H), 1.79-2.12 (m, 8H), 2.49-2.55 (m, 2H), 2.66-2.72 (m, 2H), 3.70-3.72(s, 12H), 4.63-4.81 (m, 2H), 4.97-5.10 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ 23.9, 24.8, 29.7, 31.0, 31.1, 31.5, 31.8, 32.1, 52.5, 52.57, 52.64, 57.0, 84.3, 84.8, 90.5, 90.6, 171.51, 171.55, 171.60, 171.62, 205.7, 206.0. Anal. Calcd for $\text{C}_{24}\text{H}_{32}\text{O}_8$: C, 64.27; H, 7.19. Found: C, 64.08; H, 7.25. EI-HRMS Calcd for $\text{C}_{24}\text{H}_{32}\text{O}_8$: 448.2097. Found: 448.2098.

5,5,14,14-Tetra(methoxycarbonyl)cyclooctadeca-1,2,10,11-tetraene (2.6b; $n = 4$). Diastereomeric mixture (^{13}C NMR signals not completely resolved). ^1H NMR (CDCl_3): δ 0.94-1.70 (m, 8H), 1.82-2.08 (m, 8H), 2.50-2.57 (m, 2H), 2.68-2.73 (m, 2H), 3.72-3.75 (m, 12H), 4.65-4.80 (m, 2H), 5.04-5.15 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ 23.7, 24.1, 28.4, 29.0, 30.2, 30.8, 31.7, 31.9, 32.6, 32.9, 52.50, 52.54, 52.6, 57.0, 57.1, 84.6,

85.5, 90.7, 90.9, 171.6, 171.7, 205.7, 206.0. Anal. Calcd for $C_{26}H_{36}O_8$: C, 65.53; H, 7.61. Found: C, 65.81; H, 7.77. EI-HRMS Calcd for $C_{26}H_{36}O_8$: 476.2410. Found: 476.2414.

5,5,15,15-Tetra(methoxycarbonyl)cycloeicosa-1,2,11,12-tetraene (2.6c; n = 5).

Diastereomeric mixture (^{13}C NMR signals not completely resolved). ^1H NMR ($CDCl_3$): δ 0.96-1.12 (m, 2H), 1.16-1.45 (m, 10H), 1.82-2.07 (m, 8H), 2.51-2.56 (m, 2H), 2.68-2.72 (m, 2H), 3.72-3.73 (m, 12H), 4.65-4.75 (m, 2H), 5.01-5.09 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 24.0, 24.1, 29.3, 29.5, 29.8, 30.1, 30.6, 30.7, 31.6, 31.7, 32.18, 32.22, 52.55, 52.60, 57.1, 57.2, 84.4, 84.8, 90.8, 90.9, 171.7, 205.8, 205.9. Anal. Calcd for $C_{28}H_{40}O_8$: C, 66.65; H, 7.99. Found: C, 66.49; H, 8.12. EI-HRMS Calcd for $C_{28}H_{40}O_8$: 504.2723. Found: 504.2724.

5,5,16,16-Tetra(methoxycarbonyl)cyclodocosa-1,2,12,13-tetraene (2.6d; n = 6).

Diastereomeric mixture (^{13}C NMR signals not completely resolved). ^1H NMR ($CDCl_3$): δ 0.96-1.38 (m, 16H), 1.84-2.02 (m, 8H), 2.50-2.56 (m, 2H), 2.68-2.74 (m, 2H), 3.72-3.73 (m, 12H), 4.65-4.77 (m, 2H), 5.03-5.13 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 24.3, 24.4, 29.0, 29.6, 29.87, 29.92, 30.3, 30.4, 30.6, 31.9, 32.6, 32.7, 52.50, 52.54, 57.11, 57.13, 84.6, 85.0, 90.99, 91.04, 171.8, 205.78, 205.82. Anal. Calcd for $C_{30}H_{44}O_8$: C, 67.64; H, 8.33. Found: C, 67.44; H, 8.38. EI-HRMS Calcd for $C_{30}H_{44}O_8$: 532.3036. Found: 532.3037.

5,5,17,17-Tetra(methoxycarbonyl)cyclotetracos-1,2,13,14-tetraene (2.6e; n = 7).

Diastereomeric mixture (^{13}C NMR signals not completely resolved). ^1H NMR ($CDCl_3$): δ 0.97-1.43 (m, 20H), 1.83-2.05 (m, 8H), 2.51-2.57 (m, 2H), 2.66-2.72 (m, 2H), 3.72 (s, 6H), 3.73(s, 6H), 4.66-4.75 (m, 2H), 5.02-5.10 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 24.1, 24.3, 29.4, 29.7, 29.75, 29.82, 29.9, 30.3, 30.38, 30.43, 30.8, 31.6, 31.7, 31.8, 32.3,

52.5, 52.6, 57.18, 57.23, 84.5, 84.6, 91.0, 91.1, 171.8, 205.8, 205.9. Anal. Calcd for $C_{32}H_{48}O_8$: C, 68.54; H, 8.63. Found: C, 68.78; H, 8.83. EI-HRMS Calcd for $C_{32}H_{48}O_8$: 560.3349. Found: 560.3353.

5,5,18,18-Tetra(methoxycarbonyl)cyclohexacosa-1,2,14,15-tetraene (2.6f; n = 8).

Diastereomeric mixture (^{13}C NMR signals not completely resolved). ^1H NMR ($CDCl_3$): δ 1.02-1.37 (m, 24H), 1.86-2.03 (m, 8H), 2.50-2.57 (m, 2H), 2.67-2.72 (m, 2H), 3.71-3.73 (m, 12H), 4.68-4.76 (m, 2H), 5.04-5.11 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 24.2, 24.3, 29.2, 29.6, 29.8, 30.0, 30.17, 30.21, 30.3, 30.4, 30.5, 30.6, 31.9, 32.6, 52.49, 52.52, 57.2, 84.6, 84.8, 91.1, 171.8, 205.8. Anal. Calcd for $C_{34}H_{52}O_8$: C, 69.36; H, 8.90. Found: C, 69.30; H, 9.09. EI-HRMS Calcd for $C_{34}H_{52}O_8$: 588.3662. Found: 588.3658.

5,5,19,19-Tetra(methoxycarbonyl)cyclooctacosa-1,2,15,16-tetraene (2.6g; n = 9).

Diastereomeric mixture (^{13}C NMR signals not completely resolved). ^1H NMR ($CDCl_3$): δ 1.01-1.37 (m, 28H), 1.86-2.05 (m, 8H), 2.56 (dd, $J = 14.3$ and 9.8 Hz, 2H), 2.68 (ddd, $J = 14.3$, 6.1 , and 3.3 Hz, 2H), 3.71 (s, 6H), 3.72 (s, 6H), 4.68-4.76 (m, 2H), 5.04-5.10 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 24.0, 24.1, 29.3, 29.5, 29.67, 29.72, 29.8, 29.97, 30.03, 30.1, 30.2, 30.3, 30.5, 31.8, 32.4, 52.5, 57.2, 84.58, 84.64, 91.1, 171.8, 205.8. Anal. Calcd for $C_{36}H_{56}O_8$: C, 70.10; H, 9.15. Found: C, 70.08; H, 9.01. EI-HRMS Calcd for $C_{36}H_{56}O_8$: 616.3975. Found: 616.3978.

5,5,21,21-Tetra(methoxycarbonyl)cyclodotriaconta-1,2,17,18-tetraene (2.6h; n = 11).

Diastereomeric mixture (^{13}C NMR signals not completely resolved). ^1H NMR ($CDCl_3$): δ 1.04-1.41 (m, 36H), 1.86-2.05 (m, 8H), 2.55 (ddd, $J = 14.3$, 9.6 , and 1.2 Hz, 2H), 2.67 (ddd, $J = 14.3$, 6.2 , and 3.3 Hz, 2H), 3.71 (s, 6H), 3.72 (s, 6H), 4.70-4.78 (m, 2H), 5.04-5.10 (m, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 24.0, 29.20, 29.24, 29.57, 29.63, 29.7, 29.8, 29.85, 29.94, 30.02, 30.07, 30.2, 30.3, 31.8, 32.4, 52.5, 57.3, 84.7, 91.1,

171.9, 205.8. Anal. Calcd for C₄₀H₆₄O₈: C, 71.39; H, 9.59. Found: C, 70.96; H, 9.56.

EI-HRMS Calcd for C₄₀H₆₄O₈: 672.4601. Found: 672.4602.

5,5,13,13,21,21-Hexa(methoxycarbonyl)cyclotetracos-1,2,9,10,17,18-hexaene

(2.7a; n = 3). Diastereomeric mixture (¹³C NMR signals not completely resolved). ¹H NMR (CDCl₃): δ 1.19-1.35 (m, 6H), 1.86-2.08 (m, 12H), 2.56-2.67 (m, 6H), 3.71-3.74 (m, 18H), 4.79-4.871 (m, 3H), 4.98-5.06 (m, 3H). ¹³C{¹H} NMR (CDCl₃): δ 23.9, 29.4, 31.4, 32.6, 52.5, 57.3, 84.8, 90.3, 171.6, 205.8, 205.9, 206.0. EI-HRMS Calcd for C₃₆H₄₈O₁₂: 672.3146. Found: 672.3148.

5,5,15,15,25,25-Hexa(methoxycarbonyl)cyclotriacont-1,2,11,12,21,22-hexaene

(2.7c; n = 5). Diastereomeric mixture (¹³C NMR signals not completely resolved). ¹H NMR (CDCl₃): δ 1.11-1.43 (m, 18H), 1.86-1.98 (m, 12H), 2.55-2.66 (m, 6H), 3.71-3.72 (m, 18H), 4.78-4.85 (m, 3H), 5.03-5.08 (m, 3H). ¹³C{¹H} NMR (CDCl₃): δ 23.6, 28.7, 28.9, 29.2, 31.8, 32.5, 52.5, 57.5, 84.9, 90.8, 171.8, 205.8. EI-HRMS Calcd for C₄₂H₆₀O₁₂: 756.4085. Found: 756.4085.

5,5,16,16,27,27-Hexa(methoxycarbonyl)cyclotritriacont-1,2,12,13,23,24-hexaene

(2.7d; n = 6). Diastereomeric mixture (¹³C NMR signals not completely resolved). ¹H NMR (CDCl₃): δ 1.10-1.41 (m, 24H), 1.86-1.98 (m, 12H), 2.55-2.66 (m 6H), 3.715 (s, 9H), 3.718 (s, 9H), 4.79-4.86 (m, 3H), 5.03-5.09 (m, 3H). ¹³C{¹H} NMR (CDCl₃): δ 23.8, 28.7, 28.8, 29.1, 29.6, 31.9, 32.5, 52.5, 57.5, 84.9, 90.9, 171.8, 205.8. EI-HRMS Calcd for C₄₅H₆₆O₁₂: 798.4554. Found: 798.4552.

2,2-(Dodecadien-1,12-diyl)-1,3-benzodithiole-1,1,3,3-tetraoxide (2.10f). To a mixture of Pd₂(dba)₄ (5.5 mg, 11 μmol), dpbp (6.0mg, 12 μol), KO^tBu (23.6 mg, 210 μmol) in THF (150 ml) was added **2.4f** (96.9 mg, 210 μmol, 1.4 mM) by means of syringe under nitrogen. After stirring the mixture for 120 h at 30 °C, the reaction

mixture was concentrated, filtered through a short pad of silica gel, and evaporated to dryness. The crude product was purified by recycle HPLC to afford **2.10f** (53.2 mg, 140 μ mol, 67%). ^1H NMR (CDCl_3): δ 1.21-1.86 (m, 12H), 2.02-2.15 (m, 2H), 2.26-2.38 (m, 2H), 2.88 (dt, $J = 15.3$ and 4.3 Hz, 1H), 2.99 (dd, $J = 15.3$ and 10.6 Hz, 1H), 5.22-5.28 (m, 1H), 5.43-5.50 (m, 1H) 7.88-7.93 (m, 2H), 7.98-8.04 (m, 2H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3): δ 21.1, 25.3, 25.7, 26.1, 26.6, 26.7, 27.5, 29.0, 29.7, 79.5, 83.4, 92.6, 123.1, 123.2, 135.1, 135.2, 135.8, 136.3, 207.1. Anal. Calcd for $\text{C}_{19}\text{H}_{24}\text{O}_4\text{S}_2$: C, 59.97; H, 6.36. Found: C, 60.04; H, 6.36. EI-HRMS Calcd for $\text{C}_{19}\text{H}_{24}\text{O}_4\text{S}_2$: 380.1116. Found: 380.1121.

Palladium-Catalyzed Asymmetric Synthesis of Axially Chiral 2.5f and 2.10f. The asymmetric reactions were conducted in the same way as with the non-asymmetric reaction described above except for using a chiral ligand instead of achiral dpbp (see Table 2-3 for details). **(S)-2.5f** (entry 7, Table 2-3): $[\alpha]^{25}_{\text{D}} = +93.1$ (c 0.73, CHCl_3 for the sample of (*S*)-70% ee). Chiral HPLC Analysis Conditions: Chiralpak IC; eluent, hexane/*i*PrOH = 200/1; flow rate, 1.0 mL/min; t_1 [(*R*)-enantiomer] = 20.8 min, t_2 [(*S*)-enantiomer] = 40.7 min. **(S)-2.10f** (entry 10, Table 2-3): $[\alpha]^{25}_{\text{D}} = +56.9$ (c 0.37, CHCl_3 for the sample of (*S*)-51% ee). Chiral HPLC Analysis Conditions: Chiralpak IC; eluent, hexane/*i*PrOH = 9/1; flow rate, 1.0 mL/min; ; t_1 [(*S*)-enantiomer] = 20.0 min, t_2 [(*R*)-enantiomer] = 31.9 min.

- [1] (a) Taylor, D. R. *Chem. Rev.* **1967**, 67, 317. (b) Pasto, D. J. *Tetrahedron* **1984**, 40, 2805. (c) Patai, S., Ed. *The Chemistry of Ketenes, Allenes, and Related Compounds*; Wiley: Chichester, 1980. (d) Landor, S. R., Ed. *The Chemistry of the Allenes*; Academic Press: London, 1982. (e) Coppola, G. M.; Schuster, H. F. *Allenenes in Organic Synthesis*; Wiley: New York, 1984. (f) Krause, N.; Hashmi, A. S. K., Eds. *Modern Allene Chemistry*; Wiley-VCH: Weinheim, 2004.
- [2] (a) Krause, N., Ed. *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Georg Thieme Verlag: Stuttgart, 2008; Volume 44 (Cumulenes and Allenes). (b) Brummond, K. M.; DeForrest, J. E. *Synthesis* **2007**, 795. (c) Ogasawara, M. *Tetrahedron: Asymmetry* **2009**, 20, 259. (d) Yu, S.; Ma, S. *Chem. Commun.* **2011**, 47, 5384. (e) Yu, S.; Ma, S. *Angew. Chem. Int. Ed.* **2012**, 51, 3074. (f) Ye, J.; Ma, S. *Org. Chem. Front.* **2014**, 1, 1210.
- [3] (a) Johnson, R. P. *Chem. Rev.* **1989**, 89, 1111. (b) Hopf, H. In *The Chemistry of Ketenes, Allenes, and Related Compounds*; Patai, S., Ed.; Wiley: Chichester, 1980; p 823. (c) Coppola, G. M.; Schuster, H. F. *Allenenes in Organic Synthesis*; Wiley: New York, 1984; p 38. (d) Christl, M. In *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, 2004; p 243. (e) Kawase, T. In *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Krause, N., Ed.; Georg Thieme Verlag: Stuttgart, 2008; Volume 44 (Cumulenes and Allenes), Chapter 44.3, p 395.
- [4] (a) Skattebøl, L. *Tetrahedron Lett.* **1961**, 167. (b) Moore, W. R.; Ward, H. R. *J. Org. Chem.* **1962**, 27, 4179. (c) Untch, K. G.; Martin, D. J.; Castellucci, N. T. *J. Org. Chem.* **1965**, 30, 3572.
- [5] (a) Ball, W. J.; Landor, S. R. *J. Chem. Soc.* **1962**, 2298. (b) Moore, W. R.; Bertelson, R. C. *J. Org. Chem.* **1962**, 27, 4182.

- [6] Zelder, C; Krause, N. *Eur. J. Org. Chem.* **2004**, 3968.
- [7] Janßen, C. E.; Krause, N. *Eur. J. Org. Chem.* **2005**, 2322.
- [8] (a) Brody, M. S.; Williams, R. M.; Finn, M. G. *J. Am. Chem. Soc.* **1997**, *119*, 3429.
[b] Kulyk, S.; Dougherty, Jr., W. G.; Kassel, W. S.; Fleming, S. A.; Sieburth, S. M. *Org. Lett.* **2010**, *12*, 3296. (c) Mömming, C. M.; Kehr, G.; Wibbeling, B.; Fröhlich, R.; Schirmer, B.; Grimme, S.; Erker, G. *Angew. Chem. Int. Ed.* **2010**, *49*, 2414.
- [9] (a) Ogasawara, M.; Ikeda, H.; Hayashi, T. *Angew. Chem. Int. Ed.* **2000**, *39*, 1042.
(b) Ogasawara, M.; Ikeda, H.; Nagano, T.; Hayashi, T. *Org. Lett.* **2001**, *3*, 2615. (c) Ogasawara, M.; Ge, Y.; Uetake, K.; Fan, L.; Takahashi, T. *J. Org. Chem.* **2005**, *70*, 3871. (d) Ogasawara, M.; Ge, Y.; Uetake, K.; Takahashi, T. *Org. Lett.* **2005**, *7*, 5697.
(e) Ogasawara, M.; Okada, A.; Nakajima, K.; Takahashi, T. *Org. Lett.* **2009**, *11*, 177.
(f) Ogasawara, M.; Murakami, H.; Furukawa, T.; Takahashi, T.; Shibata, N. *Chem. Commun.* **2009**, 7366. (g) Ogasawara, M.; Suzuki, M.; Takahashi, T. *J. Org. Chem.* **2012**, *77*, 5406.
- [10] (a) Ogasawara, M.; Ikeda, H.; Nagano, T.; Hayashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 2089. (b) Ogasawara, M.; Ueyama, K.; Nagano, T.; Mizuhata, Y.; Hayashi, T. *Org. Lett.* **2003**, *5*, 217. (c) Ogasawara, M.; Nagano, T.; Hayashi, T. *J. Org. Chem.* **2005**, *70*, 5764. (d) Ogasawara, M.; Okada, A.; Subbarayan, V.; Sörgel, S.; Takahashi, T. *Org. Lett.* **2010**, *12*, 5736.
- [11] Ogasawara, M.; Okada, A.; Watanabe, S.; Fan, L.; Uetake, K.; Nakajima, K.; Takahashi, T. *Organometallics* **2007**, *26*, 5025.
- [12] Daoust, K. J.; Hernandez, S. M.; Konrad, K. M.; Mackie, I. D.; Winstanley, Jr., J.; Johnson, R. P. *J. Org. Chem.* **2006**, *71*, 5708.
- [13] Price, J. D.; Johnson, R. P. *Tetrahedron Lett.* **1986**, *27*, 4679.

- [14] (a) Ramirez, F.; Desai, N. B.; McKelvie, N. *J. Am. Chem. Soc.* **1962**, *84*, 1745. (b) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *36*, 3769.
- [15] For palladium-catalyzed selective substitutions of one of the two halides in 1,1-dihalo-1-alkenes, see: (a) Minato, A.; Suzuki, K.; Tamao, K. *J. Am. Chem. Soc.* **1987**, *109*, 1257. (b) Roush, W. R.; Moriarty, K. J.; Brown, B. B. *Tetrahedron Lett.* **1990**, *31*, 6509. (c) Minato, A. *J. Org. Chem.* **1991**, *56*, 4052. (d) Baldwin, J. E.; Chesworth, R.; Paker, J. S.; Russell, A. T. *Tetrahedron Lett.* **1995**, *36*, 9551. (e) Roush, W. R.; Koyama, K.; Curtin, M. L.; Moriarty, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 7502. (f) Uenishi, J.; Kawahama, R.; Yonemitsu, O.; Tsuji, J. *J. Org. Chem.* **1996**, *61*, 5716. (g) Uenishi, J.; Kawahama, R.; Shiga, Y.; Yonemitsu, O.; Tsuji, J. *Tetrahedron Lett.* **1996**, *37*, 6759. (h) Panek, J. S.; Hu, T. *J. Org. Chem.* **1997**, *62*, 4912. (i) Shen, W.; Wang, L. *J. Org. Chem.* **1999**, *64*, 8873. (j) Zeng, X.; Hu, Q.; Qian, M.; Negishi, E. *J. Am. Chem. Soc.* **2003**, *125*, 13636.
- [16] dpbp = 2,2'-bis(diphenylphosphino)-1,1'-biphenyl. See, Ogasawara, M.; Yoshida, K.; Hayashi, T. *Organometallics* **2000**, *19*, 1567, and references cited therein.
- [17] The dl/meso-diastereomeric ratios could not be determined due to the incomplete separation of their NMR signals.
- [18] DPEphos = bis[2-(diphenylphosphino)phenyl]ether. See, Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Goubitz, K.; Fraanje, J. *Organometallics* **1995**, *14*, 3081.
- [19] Jacobs, T. L.; McClenon, J. R.; Muscio, O. J., Jr. *J. Am. Chem. Soc.* **1969**, *91*, 6038.
- [20] (a) Lowe, G. *Chem. Commun.* **1965**, 411. (b) Brewster, J. H. *Topics in Stereochemistry* **1967**, *2*, 1.
- [21] Coulson, D. R. *Inorg. Synth.* **1972**, *13*, 121.

- [22] Ukai, T.; Kawazura, H.; Ishii, Y.; Bonnet, J. J.; Ibers, J. A. *J. Organomet. Chem.* **1974**, *65*, 253.
- [23] Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2001**, *343*, 264.
- [24] Hu, A.; Ogasawara, M.; Sakamoto, T.; Okada, A.; Nakajima, K.; Takahashi, T.; Lin, W. *Adv. Synth. Catal.* **2006**, *348*, 2051.
- [25] Cai, D.; Payack, J. F.; Bender, D. R.; Hughes, D. L.; Verhoeven, T. R.; Reider, P. *J. J. Org. Chem.* **1994**, *59*, 7180.
- [26] Hu, A.; Ngo, H. L.; Lin, W. *Angew. Chem. Int. Ed.* **2004**, *43*, 2501.
- [27] Kündig, E. P.; Cunningham, A. F. *Tetrahedron* **1988**, *44*, 6855.
- [28] Clyne, D. S.; Weiler, L. *Tetrahedron* **1999**, *55*, 13659.
- [29] Somekawa, K.; Okuhira, H.; Sendayama, M.; Suishu, T.; Shimo, T. *J. Org. Chem.* **1992**, *57*, 5708.
- [30] LeBorgne, J.-F. *J. Organomet. Chem.* **1976**, *122*, 123.
- [31] Zakrzewski, J.; Grodner, J.; Bobbitt, J. M.; Karpinska, M. *Synthesis* **2007**, *16*, 2491.
- [32] Bestmann, H. J.; Kellermann, W. *Synthesis* **1994**, 1257.
- [33] Porter, N. A.; Chang, V. H.-T.; Magnin, D. R.; Wright, B. T. *J. Am. Chem. Soc.* **1988**, *110*, 3554.

Chapter III

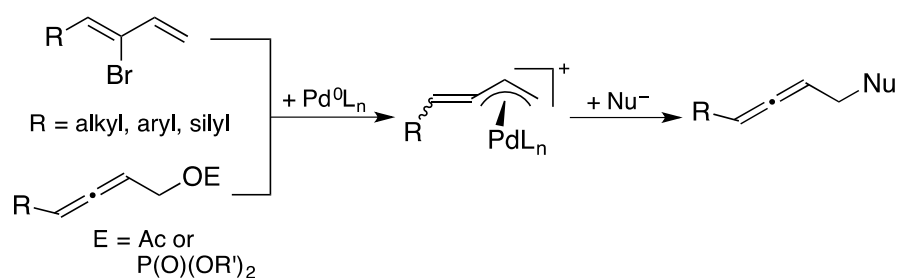
Palladium-Catalyzed Twofold Sequential Nucleophilic Substitution on 3-Bromopenta-2,4-dienyl Phosphate: Preparation of C_1 - and C_2 - Symmetric Doubly Functionalized Allenes

Section 1.

Introduction for Chapter III

Development of novel and efficient methods of preparing allenic compounds has been an important subject due to synthetic usefulness of allenes in organic chemistry.^[1] In 2000, Prof. Ogasawara's group reported a palladium-catalyzed reaction for preparing various functionalized allenes starting with an easily accessible 1-hydrocarbyl- or 1-silyl-2-bromo-1,3-diene and a soft nucleophile (Scheme 3-1, top).^[2] By the use of an appropriate chiral palladium species as a precatalyst, the reaction could provide enantiomerically enriched axially chiral allenes in up to 94% ee.^[3] A key intermediate of the palladium-catalyzed process is an (alkylidene- π -allyl)palladium species,^[4] that is somewhat similar to the widely accepted intermediates in the Tsuji-Trost reaction.^[5] Addition of an allenylmethyl ester to a zero-valent palladium species also provides an analogous (alkylidene- π -allyl)palladium species,^[6] and its reaction with soft nucleophiles gives comparable allenic products (Scheme 3-1, bottom).^[7] As shown in Scheme 3-1, the two Pd-catalyzed processes are closely related to each other.

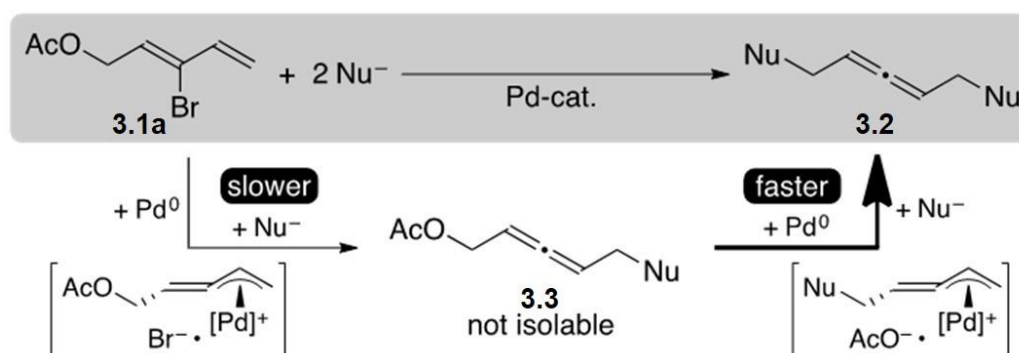
Scheme 3-1. Palladium-Catalyzed Nucleophilic Substitution on 2-Bromo-1,3-dienes and Allenylmethyl Esters.



In 2012, Prof. Ogasawara's group introduced 3-bromopenta-2,4-dienyl acetate (**3.1a**) as a unique bifunctional electrophile in the palladium-catalyzed reaction.^[8] Compound **3.1a** possesses properties and substructures of both 2-bromo-1,3-dienes and allylic acetates, and it undergoes the "twofold Pd-catalyzed nucleophilic substitution"

to give doubly functionalized C_2 -symmetric allenes **3.2** in high yields with excellent regioselectivity. The vinylic C-Br bond in **3.1a** is more reactive than the allylic acetate moiety in the addition to Pd(0), and thus the primal intermediary product was suggested to be allenylmethyl acetate **3.3**. Whereas monosubstituted intermediate **3.3** is more reactive than **3.1a** in the palladium-catalyzed reaction, generated **3.3** is consumed faster than **3.1a**. Accordingly, **3.3** is *not* isolable nor detectable, and C_2 -symmetric doubly substituted allene **3.2** was obtained preferentially even in the presence of remaining **3.1a** (Scheme 3-2). In other words, stepwise introduction of two different Nu-groups in the doubly substituted allenes is *not* possible by the palladium-catalyzed reaction of **3.1a**.

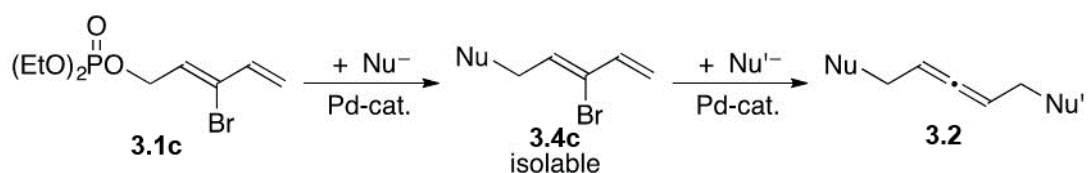
Scheme 3-2. Palladium-Catalyzed Double Nucleophilic Substitution on 3-Bromo-2,4-pentadienyl Acetate **3.1a**.



In this chapter, I report the effects of acyl groups in 3-bromopenta-2,4-dienyl esters in the palladium-catalyzed reaction. It is found that the reactivity of 3-bromopenta-2,4-dienyl diethyl phosphate (**3.1c**) is different from that of the corresponding carboxylates. The allylic phosphate moiety is the better leaving group than the vinylic bromide in **3.1c**, and the monosubstituted intermediates, bromodienes **3.4**, can be isolated starting with **3.1c**. That is, stepwise introduction of two different Nu groups is realized starting

with **3.1c** leading to various doubly substituted unsymmetric (C_1 -symmetric) allenic products **3.2** (Scheme 3-3).

Scheme 3-3. Palladium-Catalyzed "Sequential" Double Nucleophilic Substitution on 3-Bromo-2,4-pentadienyl Diethyl Phosphate **3.1c**.



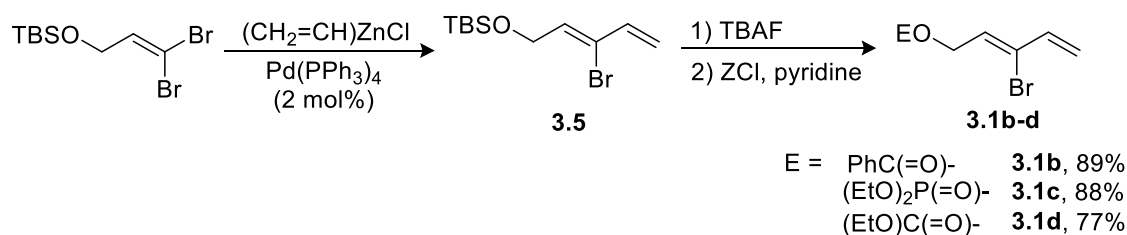
Section 2.

Palladium-Catalyzed Twofold Sequential Nucleophilic Substitution on 3-Bromopenta-2,4-dienyl Esters

3-2-1. Preparation of 3-Bromopenta-2,4-dienyl Esters

The substrates for this study, 3-bromopenta-2,4-dienyl benzoate (**3.1b**), phosphate (**3.1c**), and carbonate (**3.1d**), were prepared as depicted in Scheme 3-4 starting with TBS-protected (Z)-3-bromopenta-2,4-dienol (**3.5**).^[9] The fluoride-induced deprotection of **3.5** followed by reactions with benzoyl chloride, diethyl chlorophosphate, or ethyl chlorocarbonate afforded (Z)-**3.1b-d** in 77-89% yields. Whereas unprotected 3-bromopenta-2,4-dienol was susceptible to polymerization, it was applied to the esterification without extensive purification/isolation. Among the three bromopentadienyl esters, carbonate **3.1d** was found to be unstable and polymerize easily under the ambient conditions. Accordingly, **3.1d** was eliminated from further studies, and **3.1b** and **3.1c** were examined in the palladium-catalyzed reactions (vide infra).

Scheme 3-4. Preparation of 3-Bromopenta-2,4-dienyl Esters (**3.1b-d**).



3-2-2. Preparation of C₂-Symmetric Allenes by Palladium-Catalyzed Nucleophilic Double Substitution of 3.1

At the outset, substrates **3.1a-c** were applied in the Pd-catalyzed reaction in the presence of excess (2.5 equiv with respect to **3.1**) prototypical malonate pronucleophiles **3.6a** or **3.6b** (Table 3-1). All the three substrates reacted with **3.6a** smoothly with a palladium catalyst (2.0 mol %) generated in situ from [PdCl(π-allyl)]₂ and dpbp. The substrates were consumed completely within 12 hours and doubly functionalized C₂-symmetric allene **3.2aa** was isolated in 83-89% yields (entries 1-3). Under the similar conditions, the reactions with phenylmalonate **3.6b** provided the corresponding C₂-symmetric allene **3.2bb** in good yields ranging 81% to 86% irrespective of the choice of the substrates (entries 4-6).

Table 3-1. Palladium-Catalyzed Reactions of **3.1a-c** with Excess Pronucleophile **3.6a** or **3.6b**.^a

$\text{EO-CH}_2\text{CH}(\text{Br})\text{CH}=\text{CH}_2$ (**3.1a-c**) + Nu-H (**3.6**, 2.5 equiv) $\xrightarrow[\text{base, THF, 40 } ^\circ\text{C, 12 h}]{[\text{Pd}(\pi\text{-allyl})\text{Cl}]_2 (1.0 \text{ mol } \%), \text{ dpbp } (2.2 \text{ mol } \%)}$ Nu-CH₂-CH=C-CH₂-Nu (**3.2**)

3.6a: CHMe(CO₂Me)₂ **3.6b:** CHPh(CO₂Et)₂ dpbp =

entry	substrate 3.1	Nu-H 3.6	base	yield of 3.2 (%) ^b
1 ^c	3.1a	3.6a	NaH	83 (3.2aa)
2	3.1b	3.6a	NaH	89 (3.2aa)
3	3.1c	3.6a	NaH	87 (3.2aa)
4 ^c	3.1a	3.6b	^t BuOK	84 (3.2bb)
5	3.1b	3.6b	^t BuOK	81 (3.2bb)
6	3.1c	3.6b	^t BuOK	86 (3.2bb)

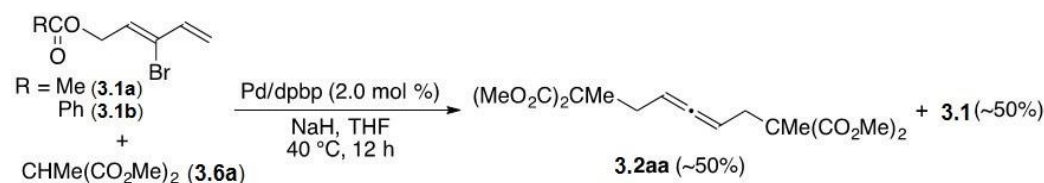
^a The reaction was carried out with **3.1** (0.50 mmol) and **3.6** (1.25 mmol) in THF in the presence of an appropriate base and a Pd-catalyst (2 mol %) generated from [PdCl(π-allyl)]₂ and dpbp. ^b Isolated yield by silica gel chromatography. ^c Taken from ref. 8.

3-2-3. Palladium-Catalyzed Nucleophilic Single Substitution of **3.1c**.

While all three substrates **3.1a-c** showed the similar results in the palladium-catalyzed reaction with an excess (2.5 equiv. to **3.1**) soft nucleophile (Table 3-1), the carboxylates and the phosphate exhibited different reactivities in the reaction with a stoichiometric soft nucleophile.

Treatment of the carboxylate, **3.1a** or **3.1b**, with an equimolar mixture of **3.6a** and NaH (1 equiv with respect to **3.1**) in THF in the presence of the Pd/dpbp catalyst (2 mol %) afforded *C*₂-symmetric allene **3.2aa** in ca. 50% yield together with ca. 50% unreacted **3.1** (Scheme 3-5).^[8] This result indicated that presumed intermediate **3.3** was more reactive than **3.1a** and **3.1b** in the palladium-catalyzed nucleophilic substitution (see Scheme 3-2).

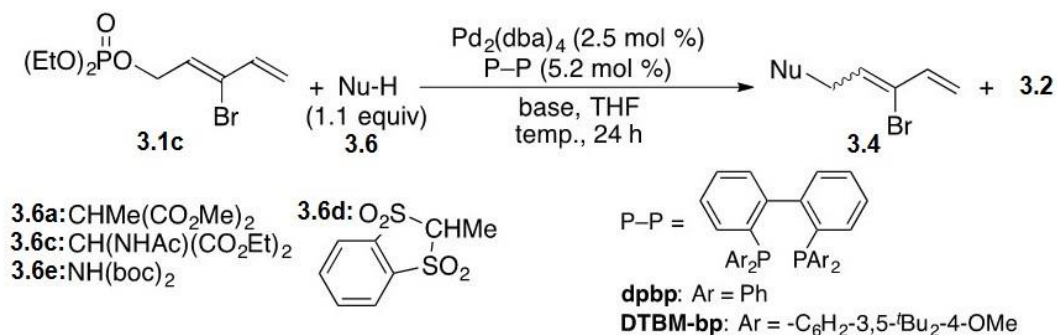
Scheme 3-5. Preparation of 3-Bromopenta-2,4-dienyl Esters (**3.1b-d**).



On the other hand, the palladium-catalyzed reactions of phosphate **3.1c** with equimolar soft nucleophiles provided the corresponding "single substitution" products, nucleophile-substituted 3-bromopenta-2,4-dienes **3.4**, predominantly. The results of the nucleophilic single substitution of **3.1c** are listed in Table 3-2 with the detailed reaction conditions. The reactions of **3.1c** with methylmalonate (**3.6a**) or acetoamidemalonate (**3.6c**) were conducted using the Pd/dpbp precatalyst (5 mol %). The reactions proceeded with good selectivity under the optimized conditions, and the corresponding single substitution products **3.4a** and **3.4c** were obtained in 88% and 83% yields,

respectively (entries 1 and 2). In both cases, the formation of the double substitution products, C_2 -symmetric allenes **3.2**, was minor. On the other hand, the reaction with bis-sulfone pronucleophile **3.6d** was much less selective in the presence of the Pd/dpbp precatalyst irrespective of the bases (entries 3 and 4). Although expected single-substitution product **3.4d** was obtained in modest yields, the concomitant formation of allene **3.2** was detected together with unreacted **3.1c**. It was found that the palladium precatalyst coordinated with a bulkier bis(triarylphosphine) ligand (DTBM-bp) showed the much better selectivity of the mono-substitution, and **3.4d** was obtained in up to 88% selectivity under the optimized conditions (entries 5 and 6). The relatively low isolated yield (50%) of **3.4d** was ascribed to the instability of the compound that polymerized/oligomerized slowly during silica gel chromatography. The reaction with *N*-pronucleophile **3.6e** also took place in excellent selectivity with the Pd/dpbp precatalyst, and the corresponding (boc)₂N-substituted bromodiene **3.4e** was isolated in 91% yield (entry 7). All the 5-Nu-3-bromopenta-1,3-dienes **3.4** were obtained as mixtures of the two geometric isomers with the *E*-isomers predominant in 82-88%.

Table 3-2. Palladium-Catalyzed Reactions of **3.1c** with Equimolar Pronucleophiles **3.6**.^a



entry	Nu-H	base	temp.	P-P	3.1c/3.4/3.2 ^b	yield of 3.4 ^c	<i>E/Z</i> in 3.4 ^b
1	3.6a	NaH	0 °C	dpbp	7/90/3	88% (3.4a)	84/16
2	3.6c	KO ^t Bu	23 °C	dpbp	4/84/12	83% (3.4c)	82/18
3	3.6d	NaH	23 °C	dpbp	70/19/11	—	—
4	3.6d	LiCH ₂ SiMe ₃	40 °C	dpbp	18/48/34	—	—
5	3.6d	LiCH ₂ SiMe ₃	40 °C	DTBM-bp	48/49/3	—	—
6	3.6d	LiCH ₂ SiMe ₃	60 °C	DTBM-bp	12/88/0	50% (3.4d)	88/12
7	3.6e	KO ^t Bu	40 °C	dpbp	6/94/0	91% (3.4e)	88/12

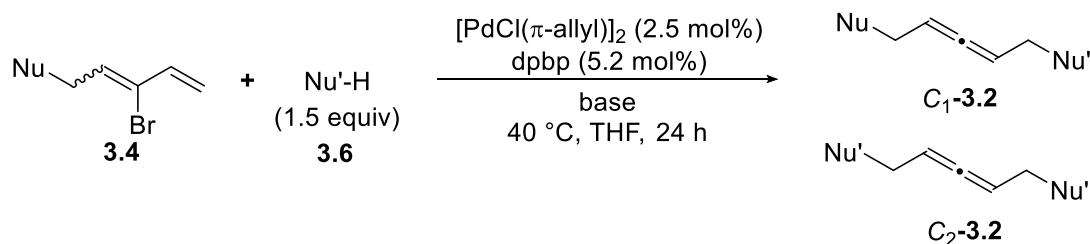
^a The reaction was carried out with **3.1c** (0.20 mmol) and **3.6** (0.22 mmol) in THF in the presence of an appropriate base (0.22 mmol) and a Pd-catalyst (5 mol %) generated from Pd₂(dba)₄ and a bisphosphine. ^b Determined by the ¹H-NMR measurements. ^c Isolated yield by silica gel chromatography.

Section 3.

Palladium-Catalyzed Synthesis of C_1 -Symmetric Allenes **3.2**

Single substitution products **3.4**, obtained from **3.1c** and a soft nucleophile Nu^- as in Table 3-2, were excellent substrates in the palladium-catalyzed "second" nucleophilic substitution to give doubly functionalized allenes **3.2**. When a nucleophile Nu^- in the second palladium-catalyzed reaction was different from a Nu group in **3.4**, doubly substituted unsymmetric (C_1 -symmetric) allenes **3.2** were obtained selectively (except for the reactions of **3.4e**; vide infra). These C_1 -symmetric allenes **3.2** could not be prepared starting with acetate **3.1a** or benzoate **3.1b** (see Schemes 3-2 and 3-5). The results of preparing the C_1 -symmetric allenes are listed in Table 3-3. Both methylmalonate- or acetoamidomalonate-tethered bromodienes **3.4a** and **3.4c** were equally reactive and the treatments with an appropriate **3.6** gave the corresponding C_1 -symmetric allenes in high yields ranging 72–94% (entries 1-6). Allenes **3.2ad** and **3.2cd**, which possess a malonate and a bissulfone moieties within the molecules, were also accessed by the reverse introduction of the two functional groups. That is, the reactions of bissulfone-tethered **3.4d** with a malonate pronucleophile **3.6a** or **3.6c** provided **3.2ad** or **3.2cd** in 84% and 77% yields, respectively (entries 7 and 8). While the palladium-catalyzed reactions of **3.4a**, **3.4c**, and **3.4d** proceeded with excellent chemoselectivity to give the corresponding C_1 -symmetric allenes exclusively, the products from **3.4e** comprised of the two allenic species. For example, the reaction between **3.4e** and **3.6a** afforded C_1 -symmetric allene **3.2ae** in 21% yield together with C_2 -symmetric allene **3.2aa** in 46% yield (entry 9). The reactions of **3.4e** with the other pronucleophile showed a similar trend (entries 10 and 11).

Table 3-3. Palladium-Catalyzed Synthesis of C_1 -Symmetric Doubly Functionalized Allenes **3.2** from **3.4**.^a



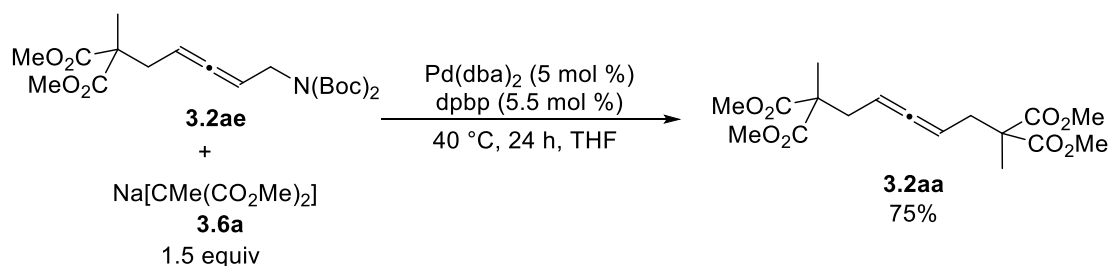
entry	bromodiene 3.4	Nu' -H 3.6	base	yield of C_1 - 3.2 (%) ^b	yield of C_2 - 3.2 (%) ^b
1	3.4a	3.6c	^t BuOK	87 (3.2ac)	—
2		3.6d	NaH	91 (3.2ad)	—
3		3.6e	^t BuOK	78 (3.2ae)	—
4	3.4c	3.6a	NaH	94 (3.2ac)	—
5		3.6d	NaH	72 (3.2cd)	—
6		3.6e	^t BuOK	93 (3.2ce)	—
7	3.4d	3.6a	NaH	84 (3.2ad)	—
8		3.6c	^t BuOK	77 (3.2cd)	—
9	3.4e	3.6a	NaH	21 (3.2ae)	46 (3.2aa)
10		3.6c	^t BuOK	15 (3.2ce)	44 (3.2cc)
11		3.6d	NaH	33 (3.2de)	59 (3.2dd)

^a The reaction was carried out with **3.4** (0.10 mmol) and **3.6** (0.15 mmol) in THF in the presence of an appropriate base and a Pd-catalyst (5 mol %) generated from $[PdCl(\pi\text{-allyl})]_2$ and dpbp. ^b Isolated yield by silica gel chromatography.

The C_2 -symmetric allenes obtained from (boc)₂N-tethered **3.4e** do not possess the (boc)₂N group. These observations implied that the (boc)₂N moieties in **3.2ae**, **3.2ce**, and **3.2de** functioned as leaving groups under the palladium catalysis. Indeed, this possibility was confirmed by the reaction of **3.2ae** with excess **3.6a** in the presence of the Pd/dpdp species, which provided **3.2aa** in 75% yield (Scheme 3-6). The results in Table 3-3 and Scheme 3-6 clearly indicated that the (boc)₂N group needed to be

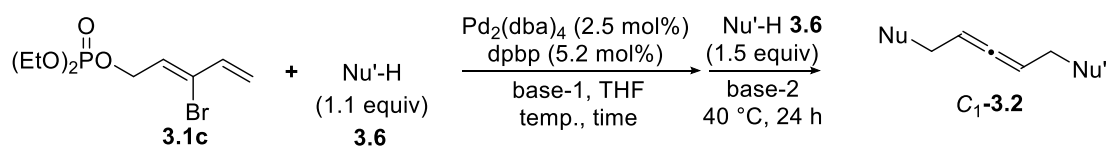
introduced at the second step in the preparation of mono-N(boc)₂ C₁-symmetric allenes such as **3.2ae** and **3.2ce**.

Scheme 3-6. Palladium-Catalyzed Substitution of N(boc)₂ Moiety in **3.2ae**.



The C₁-symmetric doubly functionalized allenes could be prepared by the "one-pot" procedure directly from **3.1c** as outlined in Table 3-4. After the treatment of **3.1c** with slight excess pronucleophile **3.6** and an appropriate base (1.1 equiv. to **3.1c**) in the presence of the Pd/dpbp precatalyst until the total consumption of **3.1c** (checked by TLC), a second nucleophile, which was generated from **3.6** (typically different from the first one) and a base, was added to the reaction mixture without an additional palladium catalyst. Stirring the reaction mixtures for 24 h at 40 °C gave the corresponding C₁-symmetric allenes in 60-81% yields. Although the yields by the one-pot procedure are competitive with or slightly lower than the combined yields from the two step sequence via **3.4**, the operational simplicity of the procedure provided easier access to doubly substituted unsymmetric allenes **3.2**.

Table 3-4. Preparation of *C*₁-Symmetric Allenes **3.2** from **3.1c** by "One-Pot" Procedure.^a



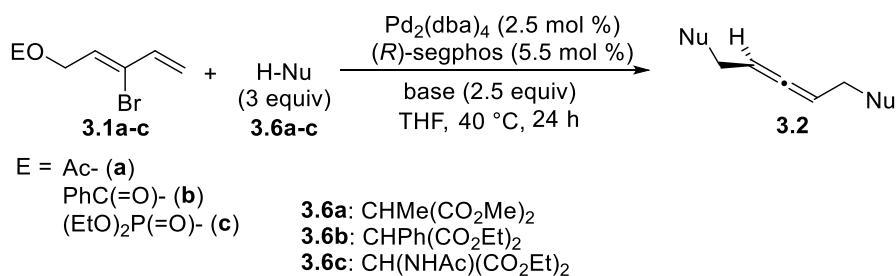
entry	Nu-H 3.6	base-1	temp	time	Nu'-H 3.6	base-2	yield of 3.2 (%) ^b
1	3.6a	NaH	0 °C	48 h	3.6c	<i>t</i> BuOK	60 (3.2ac)
2					3.6d	NaH	76 (3.2ad)
3					3.6e	<i>t</i> BuOK	81 (3.2ae)
4	3.6c	<i>t</i> BuOK	23 °C	24 h	3.6a	NaH	62 (3.2ac)
5					3.6d	NaH	64 (3.2cd)
6					3.6e	<i>t</i> BuOK	60 (3.2ce)

^a The reaction was carried out starting with **3.1c** (0.20 mmol) in THF in the presence of a Pd-catalyst (5 mol %) generated from Pd₂(dba)₄ and dpbp. ^b Isolated yield by silica gel chromatography.

Section 4.

Palladium-Catalyzed Asymmetric Synthesis of Axially Chiral Allenes **3.2**.

Allenenes **3.2** obtained in this study are axially chiral, and application of an appropriate chiral palladium species to the reaction may furnish **3.2** in enantiomerically enriched forms. Three malonate pronucleophiles **3.6a-c** were chosen, and their asymmetric reactions with bromopentadienyl esters **3.1a-c** were examined using a palladium precatalyst (5 mol %) generated from Pd₂(dba)₄ and (*R*)-segphos according to our previous studies (Table 3-5).^[3] The enantioselective reactions of **3.6a** provided axially chiral allene **3.2aa** in excellent yields ranging 87% to 92% irrespective of the choice of substrates **3.1a-c**, and the highest enantioselectivity of 88% ee was observed in the reaction of phosphate **3.1c** (entries 1-3). The best result in the asymmetric synthesis of **3.2bb** was obtained in the reaction of **3.1b** in 99% yield and 85% ee (entry 5). Among the three pronucleophiles examined, **3.6c** showed the highest enantioselectivity (entries 7-9). The highest enantioselectivity of 95% ee was recorded in the reaction between **3.1b** and **3.6c** using ^tBuOCs as a base (entry 8). All the axially chiral allenenes obtained in Table 3-5 were levorotatory and their absolute configurations were deduced to be (*R*) by the Lowe-Brewster rule.^[10]

Table 3-5. Palladium-Catalyzed Asymmetric Synthesis of Axially Chiral Allenes **3.2**.^a

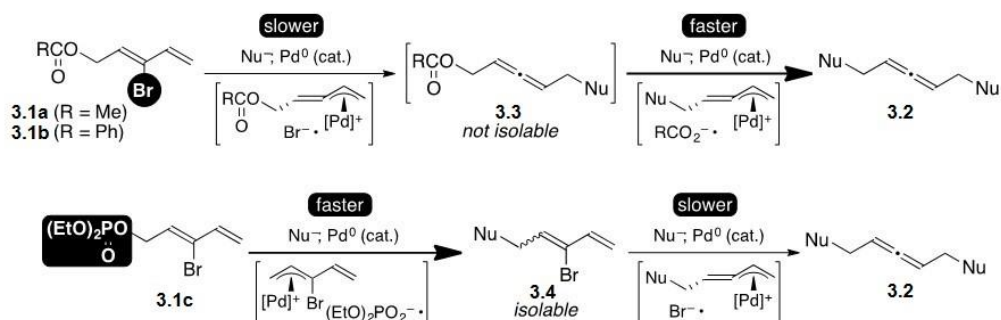
entry	3.1	Nu-H 3.6	base	yield of 3.2 (%) ^b	ee of 3.2 (%) ^c
1	3.1a	3.6a	NaH	87 (3.2aa)	79
2	3.1b			92 (3.2aa)	61
3	3.1c			91 (3.2aa)	88
4	3.1a	3.6b	^t BuOCs	79 (3.2bb)	80
5	3.1b			99 (3.2bb)	85
6	3.1c			77 (3.2bb)	81
7	3.1a	3.6c	^t BuOCs	72 (3.2cc)	81
8	3.1b			74 (3.2cc)	95
9	3.1c			77 (3.2cc)	86

^a The reaction was carried out with **3.1** (0.20 mmol) and **3.6** (0.60 mmol) at 40 °C for 24 h in THF (1.5 mL) in the presence of an appropriate base and a chiral Pd-catalyst (5 mol %) generated from Pd₂(dba)₄ and (*R*)-segphos. ^b Isolated yield by alumina chromatography ^c Determined by chiral HPLC analysis.

Section 5.

Consideration to Relative Reactivity between Carboxylate, Phosphate, and Bromide in 3.1

Scheme 3-7. Proposed Reaction Pathways from 3.1 to 3.2.



Substrates **3.1a-c** possess two different sites susceptible to activation with palladium catalysis, and the carboxylates and the phosphate show different reactivity toward the palladium-catalyzed nucleophilic substitution. Because the bromo substituents are more reactive than the carboxylate moieties in **3.1a** and **3.1b**, the initially formed monosubstitution intermediates should be **3.3**. The carboxylate moieties in **3.3** are more reactive than the bromide substituents in **3.1a** and **3.1b**, and intermediates **3.3** are consumed faster than **3.1** (Scheme 3-7, top). Accordingly, **3.3** are not isolable and *C*₂-symmetric allenes **3.2** are preferentially obtained even in the presence of remaining **3.1a** and **3.1b**.^[8] On the other hand, the phosphate substituent is more reactive than the C-Br moiety in **3.1c**. Accordingly, the initial products from **3.1c** are bromodienes **3.4** which are less reactive than **3.1c**. Therefore, monosubstitution products **3.4** are isolable, and the introduction of two different Nu groups in allenes **3.2** is realized starting from **3.1c** under the controlled reaction conditions (Scheme 3-7, bottom).

Conclusions for Chapter III

In summary, we have demonstrated that readily available 3-bromopenta-2,4-dienyl esters **3.1a-c** are excellent precursors to a variety of doubly functionalized allenes **3.2**. The reaction of **3.1** and soft nucleophile **3.6** is catalyzed by the Pd/dpbp complex, and **3.1** undergoes the twofold nucleophilic substitution via formal S_N2' and S_N2 processes to give the allenic products in high yields. Stepwise introduction of two different Nu groups can be realized by the reaction starting with phosphate **3.1c** leading to the C₁-symmetric allenes, which are not accessible from carboxylates **3.1a** and **3.1b**. By the use of a chiral palladium catalyst, axially chiral doubly functionalized allenes were obtained in up to 95% ee.

Experimental Section for Chapter III

General. All anaerobic and/or moisture-sensitive manipulations were carried out with standard Schlenk techniques under predried nitrogen or with glovebox techniques under prepurified argon. ^1H NMR (at 400 MHz) and ^{13}C NMR (at 101 MHz) chemical shifts are reported in ppm downfield of internal tetramethylsilane. ^{31}P NMR (at 162 MHz) chemical shifts are externally referenced to 85% H_3PO_4 . Tetrahydrofuran was distilled from benzophenone–ketyl under nitrogen prior to use. Dichloromethane was distilled from CaH_2 under nitrogen prior to use. *O*-TBS-protected (*Z*)-3-bromopenta-2,4-dienol (**3.5**),^[9] 1,3-benzodithiole-1,1,3,3-tetraoxide,^[11] dpbp,^[12] chlorobis(3,5-di-*tert*-butyl-4-methoxyphenyl),^[13] and (*R*)-segphos^[14] were prepared as reported. All other chemicals were obtained from commercial sources and used without additional purification.

(*Z*)-3-Bromopenta-2,4-dienyl Benzoate (3.1b). To a stirred solution of **3.5** (3.00 g, 10.8 mmol) in THF (40 mL) was added a solution of tetrabutylammonium fluoride (1.0 M in THF, 10.8 mL, 10.8 mmol) dropwise at 0 °C. After stirring the solution for 30 min at room temperature, the reaction mixture was quenched with saturated $\text{NH}_4\text{Cl}_{aq}$ (100 mL). The organic layer was separated, and the aqueous layer was extracted with ether three times. The combined organic layer was washed with brine, dried over MgSO_4 , then concentrated under reduced pressure. The residue, crude (*Z*)-3-bromopenta-2,4-dienol, was dissolved in dichloromethane (40 mL), and to this were added pyridine (2.14 g, 27.1 mmol) and benzoyl chloride (3.04 g, 21.6 mmol) at 0 °C. The solution was allowed to warm to room temperature and kept stirred for 1 h. The solution was diluted with dichloromethane (40 mL) and washed successively with water, saturated

CuSO_{4aq} twice, water, and brine. The organic layer was dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate = 20/1) followed by vacuum transfer to give **3.1b** as a pale-yellow oil. Yield: 2.59 g (89%). ¹H NMR (CDCl₃): δ 5.10 (d, *J* = 6.0 Hz, 2H), 5.34 (d, *J* = 10.4 Hz, 1H), 5.69 (d, *J* = 16.3 Hz, 1H), 6.28 (t, *J* = 6.0 Hz, 1H), 6.37 (dd, *J* = 16.3 and 10.4 Hz, 1H), 7.41-7.49 (m, 2H), 7.53-7.62 (m, 1H), 8.03-8.10 (m, 2H). ¹³C NMR (CDCl₃): δ 64.4, 120.3, 128.25, 128.28, 128.6, 129.8, 130.0, 133.3, 135.1, 166.5. ESI-HRMS Calcd for C₁₂H₁₁BrO₂Na (M + Na): 288.9840. Found: 288.9849.

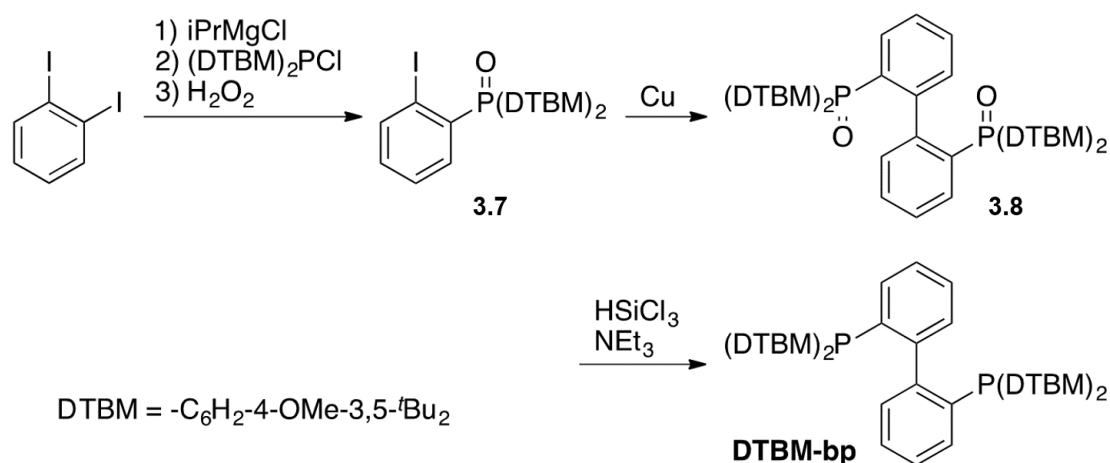
(Z)-3-Bromopenta-2,4-dienyl Diethyl Phosphate (3.1c). This compound was prepared essentially in the same way of the synthesis of **3.1c** using diethyl phosphoryl chloride (3.73 g, 21.6 mmol) instead of benzoyl chloride. The crude product was purified by silica gel chromatography (benzene/EtOAc/Et₃N = 75/25/1) followed by vacuum transfer to give **3.1c** as a pale-yellow oil. Yield: 2.86 g (88%). ¹H NMR (CDCl₃): δ 1.31-1.40 (m, 6H), 4.08-4.20 (m, 4H), 4.81 (dd, *J* = 8.6, 5.9 Hz, 2H), 5.33 (d, *J* = 10.4 Hz, 1H), 5.67 (d, *J* = 16.3 Hz, 1H), 6.21 (t, *J* = 5.9 Hz, 1H), 6.34 (dd, *J* = 16.3 and 10.4 Hz, 1H). ¹³C NMR (CDCl₃): δ 16.3 (d, *J*_{CP} = 6.4 Hz), 64.2 (d, *J* = 5.7 Hz), 66.6 (d, *J*_{CP} = 5.2 Hz), 120.5, 127.5, 128.8 (d, *J*_{CP} = 7.5 Hz), 134.9. ³¹P NMR (CDCl₃): δ -0.28. EI-HRMS Calcd for C₉H₁₆BrO₄PNa (M + Na): 320.9867. Found: 320.9875.

(Z)-3-Bromopenta-2,4-dienyl Ethyl Carbonate (3.1d). This compound was prepared essentially in the same way of the synthesis of **3.1d** using ethyl chloroformate (2.35 g, 21.6 mmol) instead of benzoyl chloride. The crude product was purified by silica gel chromatography (hexane/CHCl₃ = 3/1) followed by vacuum transfer to give **3.1d** as a pale-yellow oil. Yield: 1.95 g (77%). ¹H NMR (CDCl₃): δ 1.32 (t, *J* = 7.1 Hz, 3H), 4.22 (q, *J* = 7.1 Hz, 2H), 4.90 (d, *J* = 6.1 Hz, 2H), 5.33 (d, *J* = 10.5 Hz, 1H), 5.67 (d, *J* = 16.2

Hz, 1H), 6.17 (t, $J = 6.1$ Hz, 1H), 6.34 (dd, $J = 16.2$ and 10.5 Hz, 1H). ^{13}C NMR (CDCl_3): δ 14.4, 64.5, 66.9, 120.5, 127.7, 128.2, 135.0, 155.1. EI-HRMS Calcd for $\text{C}_8\text{H}_{11}\text{BrO}_3\text{Na}$ ($\text{M} + \text{Na}$): 256.9789. Found: 256.9783.

2-Methyl-1,3-benzodithiole 1,1,3,3-Tetraoxide (3.6d). To a suspension of 1,3-benzodithiole-1,1,3,3-tetraoxide (3.00 g, 13.8 mmol) and NaH (0.40 g, 16.5 mmol) in THF (30 mL) was added a THF solution (20 mL) of iodomethane (2.34 g, 16.5 mmol) at room temperature under nitrogen, and then the mixture was refluxed overnight. The mixture was filtered through a short pad of silica gel to remove precipitated inorganic salts. The silica gel pad was washed with a small amount of CHCl_3 three times, and the combined solution was evaporated to dryness under reduced pressure. The residue was purified by column chromatography on silica gel ($\text{CHCl}_3/\text{hexane}/\text{benzene}/\text{Et}_2\text{O} = 9/2/2/1$) to give the title compound as a white solid. Yield: 2.95 g (92%). ^1H NMR (CDCl_3): δ 1.87 (d, $J = 6.8$ Hz, 3H), 4.47 (q, $J = 6.8$ Hz, 1H), 7.90-7.98 (m, 2H), 8.01-8.07 (m, 2H). ^{13}C NMR (CDCl_3): δ 6.9, 70.3, 122.9, 135.4, 137.7. ESI-HRMS Calcd for $\text{C}_8\text{H}_8\text{O}_4\text{S}_2\text{Na}$ ($\text{M} + \text{Na}$): 254.9762. Found: 254.9752.

2,2'-Bis[bis(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-1,1'-biphenyl (DTBM-bp). This compound was reported previously,^[15] however, no characterization data were given. The synthesis was attained by the three-step sequence as outlined below.^[16]



To a solution of 1,2-diiodobenzene (3.60 g, 10.9 mmol) in THF (25 mL) was added isopropylmagnesium chloride (2.0 M solution in THF, 5.45 mL; 10.9 mmol) dropwise at $-30\text{ }^{\circ}\text{C}$, then the resulting orange mixture was warmed to $-20\text{ }^{\circ}\text{C}$ over a period of 20 min. The reaction progress was monitored by gas chromatography. A solution of chlorobis(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphine (5.50 g, 10.9 mmol) in THF (15 mL) was added dropwise via a cannula at $-20\text{ }^{\circ}\text{C}$. The mixture was allowed to warm up to room temperature and stirred overnight. After an addition of a small amount of water, the mixture was concentrated under reduced pressure. The residue was then partitioned between ethyl acetate and water. The solution of the crude phosphine was oxidized using aqueous H₂O₂ (30%; monitored by TLC). The mixture was extracted with chloroform, and the combined organic layer was washed with water three times and brine. The organic layer was dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/Et₂O = 1/5) to give **3.7** as a pale-yellow solid. Yield: 5.43 g (72%). ¹H NMR (CDCl₃): δ 1.37

(s, 36H), 3.71 (s, 6H), 7.10-7.21 (m, 2H), 7.37-7.46 (m, 1H), 7.48-7.60 (m, 5H), 7.98-8.06 (m, 1H). ^{13}C NMR (CDCl_3): δ 31.9, 36.0, 64.5, 99.4 (d, $J_{\text{CP}} = 6.5$ Hz), 124.8 (d, $J_{\text{CP}} = 110.7$ Hz), 127.5 (d, $J_{\text{CP}} = 10.9$ Hz), 131.2 (d, $J_{\text{CP}} = 11.6$ Hz), 132.7, 135.68, 136.8 (d, $J_{\text{CP}} = 103.7$ Hz), 142.0 (d, $J_{\text{CP}} = 8.7$ Hz), 144.0 (d, $J_{\text{CP}} = 12.6$ Hz), 162.8 (d, $J_{\text{CP}} = 3.2$ Hz). ^{31}P NMR (CDCl_3): δ 35.2. ESI-HRMS Calcd for $\text{C}_{36}\text{H}_{50}\text{IO}_3\text{PNa}$ ($\text{M} + \text{Na}$): 711.2440. Found: 711.2417.

A mixture of **7** (6.40 g, 9.30 mmol) and activated bronze^[17] (1.77 g, 27.9 mmol) was suspended in dry DMF (40 mL), and the mixture was stirred at 140 °C for 2 h. Volatiles were removed under reduced pressure at 70 °C, and the residue was extracted with warm dichloromethane. The combined organic layer was washed with saturated $\text{NH}_4\text{Cl}_{\text{aq}}$ twice, dried over MgSO_4 , and evaporated dryness under reduced pressure at 70 °C. The crude residue was purified by silica gel column chromatography (hexane/ $\text{Et}_2\text{O} = 1/3$) to give **3.8** as a pale-yellow solid. Yield: 2.59 g (50%). ^1H NMR (CDCl_3): δ 1.34 (s, 36H), 1.36 (s, 36H), 3.69 (s, 6H), 3.69 (s, 6H), 6.69-6.77 (m, 2H), 7.07-7.15 (m, 2H), 7.17-7.28 (m, 4H), 7.41 (s, 2H), 7.44 (s, 2H), 7.68 (s, 2H), 7.71 (s, 2H). ^{13}C NMR (CDCl_3): δ 32.10, 32.11, 36.0, 36.1, 64.4, 64.5, 126.2 (d, $J_{\text{CP}} = 12.2$ Hz), 128.62 (d, $J_{\text{CP}} = 215.2$ Hz), 128.64 (d, $J_{\text{CP}} = 1.5$ Hz), 129.4 (d, $J_{\text{CP}} = 2.8$ Hz), 130.8 (d, $J_{\text{CP}} = 11.0$ Hz), 131.2 (d, $J_{\text{CP}} = 9.5$ Hz), 132.0 (d, $J_{\text{CP}} = 11.5$ Hz), 132.58 (d, $J_{\text{CP}} = 13.0$ Hz), 132.64 (d, $J_{\text{CP}} = 102.4$ Hz), 143.2 (d, $J_{\text{CP}} = 12.0$ Hz), 143.3 (d, $J_{\text{CP}} = 11.7$ Hz), 145.7 (dd, $J_{\text{CP}} = 6.9$

and 4.1 Hz), 162.0 (d, $J_{\text{CP}} = 3.0$ Hz), 162.1 (d, $J_{\text{CP}} = 3.0$ Hz). ^{31}P NMR (CDCl_3): δ 29.8.

ESI-HRMS Calcd for $\text{C}_{72}\text{H}_{100}\text{O}_6\text{P}_2\text{Na}$ ($\text{M} + \text{Na}$): 1145.6893. Found: 1145.6909.

To a solution of **3.8** (2.80 g, 2.5 mmol) and NEt_3 (3.53 g, 34.9 mmol) in degassed xylene (25 mL) was added HSiCl_3 (3.38 g, 24.9 mmol) at 0 °C. The reaction mixture was then heated at 130 °C for 12 h. After cooling to 0 °C, a degassed saturated NaHCO_3 (2 mL) was added. The mixture was filtered through a pad of MgSO_4 under a nitrogen atmosphere, and the MgSO_4 pad was washed with degassed Et_2O . The combined solution was evaporated to dryness under reduced pressure at 70 °C. The residue was purified by silica gel column chromatography (Et_2O) to give DTBM-bp as a white amorphous solid. Yield: 2.43 g (89%). ^1H NMR (CDCl_3): δ 1.29 (s, 36H), 1.32 (s, 36H), 3.63 (s, 6H), 3.68 (s, 6H), 6.98-7.02 (m, 4H), 7.02-7.07 (m, 4H), 7.15-7.22 (m, 2H), 7.28-7.34 (m, 4H). ^{13}C NMR (CDCl_3): δ 32.2, 32.3, 35.8, 36.0, 64.3, 64.4, 127.2, 127.6, 130.5 (t, $J_{\text{CP}} = 4.3$ Hz), 131.6 (t, $J_{\text{CP}} = 4.1$ Hz), 132.2 (dd, $J_{\text{CP}} = 6.4$ and 5.3 Hz), 132.4 (t, $J_{\text{CP}} = 11.5$ Hz), 133.0 (t, $J_{\text{CP}} = 11.5$ Hz), 133.1, 139.1 (dd, $J_{\text{CP}} = 5.4$ and 4.1 Hz), 142.8 (t, $J_{\text{CP}} = 3.6$ Hz), 143.0 (t, $J_{\text{CP}} = 3.1$ Hz), 147.1 (d, $J_{\text{CP}} = 17.5$ Hz), 159.6, 160.0. ^{31}P NMR (CDCl_3): δ -12.4. ESI-HRMS Calcd for $\text{C}_{72}\text{H}_{100}\text{O}_4\text{P}_2\text{Na}$ ($\text{M} + \text{Na}$): 1113.6995. Found: 1113.6965.

Preparation of C_2 -Symmetric Allenes **3.2 by Palladium-Catalyzed Double Substitution of **3.1**.** The reactions were conducted according to a reported procedure.⁸

The reaction conditions and the results are summarized in Table 3-1. A mixture of $[\text{PdCl}(\pi\text{-allyl})]_2$ (1.8 mg, 10 $\mu\text{mol}/\text{Pd}$), dpbp (5.7 mg, 11 μmol), and **3.1** (0.50 mmol) was dissolved in THF (5 mL) and the solution was added to a mixture of **3.6** (1.25 mmol) and base (1.25 mmol) via cannula under nitrogen. The mixture was stirred for 12 h at 40 °C, then filtered through a short pad of silica gel to remove precipitated inorganic salts. The silica gel pad was washed with a small amount of Et_2O three times and the combined solution was evaporated to dryness under reduced pressure. The yellow residue was chromatographed on silica gel to give allene **3.2** in pure form. The ^1H - and ^{13}C -NMR spectra of **3.2aa** and **3.2bb** were consistent with those reported previously.⁸

Palladium-Catalyzed Nucleophilic Single Substitution of 3.1c. The reaction conditions and the results are summarized in Table 3-2. A mixture of $\text{Pd}(\text{dba})_2$ (5.8 mg, 10 μmol), a bisphosphine ligand (10.5 μmol), and **3.1c** (60 mg, 0.20 mmol) was dissolved in THF (2 mL), and the solution was added to a mixture of **3.6** (0.22 mmol) and an appropriate base (0.22 mmol) via a cannula under nitrogen. The mixture was stirred for 24 h, and then filtered through a short pad of silica gel to remove precipitated inorganic salts. The silica gel pad was washed with a small amount of EtOAc three times, and the combined solution was evaporated to dryness under reduced pressure. The yellow residue was chromatographed on silica gel to give bromodiene **3.4** in pure form. The characterization data of bromodiene products **3.6** are listed below.

Dimethyl 2-(3-Bromopenta-2,4-dienyl)-2-methylmalonate (3.4a). Colorless oil. Yield: 52 mg (88%) starting with **3.1c** (60 mg; 0.20 mmol). $E/Z = 84/16$. (*E*)-**3.4a**: ^1H NMR (CDCl_3): δ 1.45 (s, 3H), 2.92 (d, $J = 7.2$ Hz, 2H), 3.74 (s, 6H), 5.23 (d, $J = 10.4$ Hz, 1H), 5.57 (d, $J = 16.3$ Hz, 1H), 5.92 (t, $J = 7.2$ Hz, 1H), 6.31 (dd, $J = 16.3$ and 10.4 Hz, 1H). ^{13}C NMR (CDCl_3): δ 20.4, 37.9, 52.9, 53.7, 118.8, 128.9, 129.0, 135.8, 172.2.

(*Z*)-**3.4a**: ^1H (CDCl_3): δ 1.44 (s, 1H), 2.80 (d, $J = 8.4$ Hz), 3.73 (s, 6H), 5.38 (d, $J = 10.8$ Hz), 5.69 (d, $J = 16.4$ Hz), 6.00 (t, $J = 8.4$ Hz), 6.58 (dd, $J = 16.4$ and 10.8 Hz). ESI-HRMS Calcd for $\text{C}_{11}\text{H}_{15}\text{BrO}_4\text{Na}$ ($\text{M} + \text{Na}$): 313.0051. Found: 313.0062.

Diethyl 2-Acetamido-2-(3-bromopenta-2,4-dienyl)malonate (3.4c). Pale-yellow oil.

Yield: 60 mg (83%) starting with **3.1c** (60 mg; 0.20 mmol). $E/Z = 82/18$. (*E*)-**3.4b**: ^1H NMR (CDCl_3): δ 1.26 (t, $J = 7.1$ Hz, 6H), 2.04 (s, 3H), 3.39 (d, $J = 7.4$ Hz, 2H), 4.26 (q, $J = 7.2$ Hz, 4H), 5.23 (d, $J = 10.4$ Hz, 1H), 5.57 (d, $J = 16.3$ Hz, 1H), 5.81 (t, $J = 7.4$ Hz, 1H), 6.29 (dd, $J = 16.3$ and 10.4 Hz, 1H), 6.78 (s, 1H). ^{13}C NMR (CDCl_3): δ 14.1, 23.2, 35.5, 63.0, 65.6, 119.2, 127.4, 129.3, 135.7, 167.6, 169.3. (*Z*)-**3.4b**: ^1H NMR (CDCl_3): δ 1.26 (t, $J = 7.2$ Hz, 6H), 2.02 (s, 3H), 3.29 (d, $J = 8.8$ Hz, 2H), 4.25 (qd, $J = 7.1$ and 1.2 Hz, 5H), 5.37 (d, $J = 10.8$ Hz, 1H), 5.67 (d, $J = 16.0$ Hz, 1H), 5.84 (t, $J = 8.8$ Hz, 1H), 6.53 (ddd, $J = 16.0$, 10.8, and 0.8 Hz, 1H), 6.78 (s, 1H). ^{13}C NMR (CDCl_3): δ 14.1, 23.1, 32.7, 63.1, 65.9, 122.1, 126.5, 128.0, 129.7, 167.3, 169.5. ESI-HRMS Calcd for $\text{C}_{14}\text{H}_{20}\text{BrNO}_5\text{Na}$ ($\text{M} + \text{Na}$): 384.0423. Found: 384.0431.

2-(3-Bromopenta-2,4-dienyl)-2-methylbenzodithiole 1,1,3,3-Tetraoxide (3.4d).

White solid. Yield: 38 mg (50%) starting with **3.1c** (60 mg; 0.20 mmol). $E/Z = 88/12$. (*E*)-**3.4d**: ^1H NMR (CDCl_3): δ 1.76 (s, 3H), 3.35 (d, $J = 7.2$ Hz, 2H), 5.36 (d, $J = 10.4$ Hz, 1H), 5.68 (d, $J = 16.3$ Hz, 1H), 6.19 (t, $J = 6.9$ Hz, 1H), 6.43 (dd, $J = 16.3$ and 10.4 Hz, 1H), 7.90-7.97 (m, 2H), 8.00-8.08 (m, 2H). ^{13}C NMR (CDCl_3): δ 16.7, 31.6, 76.3, 120.6, 123.4, 124.0, 132.0, 135.3, 135.5, 135.8. (*Z*)-**3.4d**: ^1H NMR (CDCl_3): δ 1.76 (s, 3H), 3.18 (d, $J = 8.4$ Hz, 2H), 5.51 (d, $J = 10.4$ Hz, 1H), 5.80 (d, $J = 16.0$ Hz, 1H), 6.19 (t, $J = 6.9$ Hz, 1H), 6.66 (d, $J = 16.0$ and 10.4 Hz, 1H), 7.90-7.97 (m, 2H), 8.00-8.08 (m, 2H). ESI-HRMS Calcd for $\text{C}_{13}\text{H}_{13}\text{BrO}_4\text{S}_2\text{Na}$ ($\text{M} + \text{Na}$): 398.9336. Found: 398.9350.

***N,N*-Di(*tert*-butoxycarbonyl)-*N*-(3-bromopenta-2,4-dienyl)amine (3.4e).** Pale-yellow oil. Yield: 66 mg (91%) starting with **3.1c** (60 mg; 0.20 mmol). *E/Z* = 88/12. (*E*)-**3.4e**: ¹H NMR (CDCl₃): δ 1.50 (s, 18H), 4.46 (d, *J* = 5.6 Hz, 2H), 5.24 (d, *J* = 10.4 Hz, 1H), 5.59 (d, *J* = 16.4 Hz, 1H), 5.99 (t, *J* = 5.6 Hz, 1H), 6.31 (dd, *J* = 16.4 and 10.4 Hz, 1H). ¹³C NMR (CDCl₃): δ 28.2, 47.8, 82.9, 118.9, 125.7, 131.3, 135.2, 152.3. (*Z*)-**3.4e**: ¹H NMR (CDCl₃): δ 1.50 (s, 18H), 4.35 (d, *J* = 7.3 Hz, 2H), 5.40 (d, *J* = 10.6 Hz, 1H), 5.69 (d, *J* = 16.1 Hz, 1H), 6.12 (t, *J* = 6.7 Hz, 1H), 6.31 (dd, *J* = 16.2 and 10.5 Hz, 1H). ESI-HRMS Calcd for C₁₅H₂₄BrNO₄Na (M + Na): 384.0786. Found: 384.0775.

Preparation of C₁-Symmetric Allenes **2 by Palladium-Catalyzed Substitution of **3.4**.** The reaction conditions and the results are summarized in Table 3-3. A mixture of [PdCl(π-allyl)]₂ (1.0 mg, 2.5 μmol), dpbp (2.9 mg, 5.5 μmol), and **3.4** (0.10 mmol) was dissolved in THF (1 mL), and the solution was added to a mixture of **3.6** (0.15 mmol) and an appropriate base (0.15 mmol) via a cannula under nitrogen. The mixture was stirred for 24 h, and then filtered through a short pad of silica gel to remove precipitated inorganic salts. The silica gel pad was washed with a small amount of EtOAc three times, and the combined solution was evaporated to dryness under reduced pressure. The yellow residue was chromatographed on silica gel to give allene **3.2** in pure form. The characterization data of C₁-symmetric allenes **3.2** are listed below.

Dimethyl 2-[6-Acetamido-6,6-di(ethoxycarbonyl)hexa-2,3-dienyl]-2-methylmalonate (3.2ac). ¹H NMR (CDCl₃): δ 1.26 (t, *J* = 7.1 Hz, 6H), 1.42 (s, 3H), 2.04 (s, 3H), 2.52 (dd, *J* = 7.9 and 2.3 Hz, 2H), 2.82-3.09 (m, 2H), 3.72 (d, *J* = 2.7 Hz, 6H), 4.22-4.26 (m, 4H), 4.85-5.00 (m, 2H), 6.81 (s, 1H). ¹³C NMR (CDCl₃): δ 14.1, 19.9, 23.0, 32.6, 35.8, 52.7, 53.8, 62.7, 66.4, 84.1, 85.6, 167.6, 169.1, 172.2, 207.7. ESI-HRMS Calcd for C₂₀H₂₉NO₉Na (M + Na): 450.1740. Found: 450.1745.

2-[6,6-Di(methoxycarbonyl)hepta-2,3-dienyl]-2-methylbenzodithiole 1,1,3,3-Tetraoxide (3.2ad). ¹H NMR (CDCl₃): δ 1.45 (s, 3H), 1.77 (s, 3H), 2.62 (dd, *J* = 7.8 and 2.3 Hz, 2H), 2.94 (dd, *J* = 7.8 and 2.1 Hz, 2H), 3.74 (s, 6H), 5.13-5.27 (m, 2H), 7.88-7.96 (m, 2H), 7.98-8.05 (m, 2H). ¹³C NMR (CDCl₃): δ 16.8, 20.0, 29.9, 35.4, 52.75, 52.78, 53.9, 76.2, 82.2, 87.1, 123.25, 123.26, 135.32, 135.33, 136.08, 136.10, 172.12, 172.15, 208.8. ESI-HRMS Calcd for C₁₉H₂₂O₈S₂Na (M + Na): 465.0654. Found: 465.0654.

Dimethyl 2-[5-{*N,N*-Di(*tert*-butoxycarbonyl)amino}penta-2,3-dienyl]-2-methylmalonate (3.2ae). ¹H NMR (CDCl₃): δ 1.44 (s, 3H), 1.50 (s, 18H), 2.58 (dd, *J* = 7.8 and 2.3 Hz, 2H), 3.72 (d, *J* = 2.1 Hz, 6H), 4.01-4.25 (m, 2H), 4.98-5.23 (m, 2H). ¹³C NMR (CDCl₃): δ 19.9, 28.2, 35.8, 45.0, 52.6, 52.7, 53.9, 82.5, 87.5, 88.3, 152.3, 172.2, 172.3, 206.2. ESI-HRMS Calcd for C₂₁H₃₃NO₈Na (M + Na): 450.2104. Found: 450.2096.

2-[6-Acetamido-6,6-di(ethoxycarbonyl)hexa-2,3-dienyl]-2-methylbenzodithiole 1,1,3,3-Tetraoxide (3.2cd). ¹H NMR (CDCl₃): δ 1.26 (t, *J* = 7.2 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.75 (s, 3H), 2.05 (s, 3H), 2.81-2.99 (m, 2H), 2.99-3.14 (m, 2H), 4.01-4.41 (m, 4H), 4.92-5.11 (m, 1H), 5.11-5.32 (m, 1H), 7.87-7.96 (m, 2H), 7.98-8.05 (m, 2H). ¹³C NMR (CDCl₃): δ 14.11, 14.13, 16.7, 23.1, 29.8, 32.4, 62.85, 62.89, 66.35, 76.1, 82.5, 86.0, 123.26, 123.29, 135.3, 135.4, 136.05, 136.12, 167.5, 167.6, 169.2, 208.8. ESI-HRMS Calcd for C₂₂H₂₇NO₉S₂Na (M + Na): 536.1025. Found: 536.1037.

Diethyl 2-Acetamido-2-[5-{*N,N*-di(*tert*-butoxycarbonyl)amino}penta-2,3-dienyl]malonate (3.2ce). ¹H NMR (CDCl₃): δ 1.25 (t, *J* = 7.2 Hz, 3H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.51 (s, 18H), 2.05 (s, 3H), 2.94-3.11 (m, 2H), 4.05-4.16 (m, 2H), 4.16-4.30 (m, 4H), 4.98-5.01 (m, 1H), 5.14-5.17 (m, 1H), 6.89 (s, 1H). ¹³C NMR (CDCl₃): δ 14.10,

14.11, 23.0, 28.2, 32.5, 45.1, 62.6, 62.7, 66.5, 82.6, 86.2, 88.6, 152.4, 167.6, 167.7, 169.3, 206.2. ESI-HRMS Calcd for C₂₄H₃₈N₂O₉Na (M + Na): 521.2475. Found: 521.2468.

2-[5-{*N,N*-Di(*tert*-butoxycarbonyl)amino}penta-2,3-dienyl]-2-

methylbenzodithiole 1,1,3,3-Tetraoxide (3.2de). ¹H NMR (CDCl₃): δ 1.51 (s, 18H), 1.79 (s, 3H), 2.86-3.05 (m, 2H), 4.09-4.27 (m, 2H), 5.26-5.42 (m, 2H), 7.87-7.94 (m, 2H), 7.97-8.05 (m, 2H). ¹³C NMR (CDCl₃): δ 16.7, 28.2, 30.0, 44.6, 76.3, 82.8, 84.6, 89.9, 123.26, 123.28, 135.29, 135.31, 136.11, 136.14, 152.3, 207.2. ESI-HRMS Calcd for C₂₃H₃₁NO₈S₂Na (M + Na): 536.1389. Found: 536.1389.

Palladium-Catalyzed Substitution of N(boc)₂ Moiety in 3.2ae with Malonate. A mixture of [PdCl(π-allyl)]₂ (0.73 mg, 2.0 μmol), dpbp (2.3 mg, 4.4 μmol), and **3.2ae** (34.0 mg, 79.5 μmol) was dissolved in THF (1 mL), and the solution was added to a mixture of **3.6a** (20 mg, 0.12 mmol) and NaH (3.0 mg, 0.13 mmol) via a cannula under nitrogen. The mixture was stirred at 40 °C for 24 h and then filtered through a short pad of silica gel to remove precipitated inorganic salts. The silica gel pad was washed with a small amount of EtOAc three times, and the combined solution was evaporated to dryness under reduced pressure. The yellow residue was chromatographed on silica gel to give allene **3.2aa** (21 mg; 75% yield).

Palladium-Catalyzed "One-Pot" Synthesis of C₁-Symmetric Allenes 3.2. The reaction conditions and the results are summarized in Table 3-4. A mixture of Pd(dba)₂ (5.8 mg, 10 μmol), dpbp (5.8 mg, 11 μmol), and **3.1c** (60 mg, 0.20 mmol) was dissolved in THF (2 mL), and the solution was added to a mixture of first pronucleophile **3.4** (0.22 mmol) and an appropriate base (0.22 mmol) via a cannula under nitrogen. The reaction progress was monitored by TLC. When **3.1c** was consumed completely, a solution of

second pronucleophile **3.2** (0.30 mmol) and an appropriate base (0.30 mmol) in THF (1.5 mL) was added to the reaction mixture via a cannula under nitrogen. The mixture was stirred for 24 h at 40 °C, and then filtered through a short pad of silica gel to remove precipitated inorganic salts. The silica gel pad was washed with a small amount of EtOAc three times, and the combined solution was evaporated to dryness under reduced pressure. The yellow residue was chromatographed on silica gel to give allene **3.2** in pure form. The ¹H- and ¹³C-NMR analyses clarified that the allenic products obtained here were identical with those prepared from **3.4** (see Table 3-3).

Pd-Catalyzed Asymmetric Synthesis of (*R*)-(-)-3.2**.** To a mixture of Pd₂(dba)₄ (5.8 mg, 5.0 μmol), (*R*)-segphos (6.7 mg, 11 μmol), **3.6** (0.60 mmol), and an appropriate base (0.50 mmol) in THF (3 mL) was added **3.1** (0.20 mmol) by means of syringe under nitrogen. After stirring the mixture for 24 h at 40 °C, the mixture was filtered through a short pad of Al₂O₃ to remove precipitated inorganic salts. The Al₂O₃ pad was washed with a small amount of a hexane/EtOAc (1:1) mixture, and the combined organic solution was evaporated to dryness under reduced pressure. The residue was purified by chromatography on Al₂O₃ to give (*R*)-(-)-**3.2** in pure form. The absolute configurations were deduced to be (*R*) by the Lowe-Brewster rule^[10] from the signs of optical rotation. Axially chiral allenes **3.2aa**, **3.2bb**, and **3.2cc** were reported previously as racemates.^[8] The conditions for the chiral HPLC analyses are listed below. (*R*)-(-)-**3.2aa**: [α]_D²⁹ = -21.5 (*c* 3.03, CHCl₃ for the sample of 88% ee). Chiral HPLC Analysis Conditions: Chiralpak OZ-H; eluent, hexane/*i*PrOH = 10/1; flow rate: 0.5 mL/min; *t*₁ [(*S*)-enantiomer] = 18.7 min, *t*₂ [(*R*)-enantiomer] = 20.4 min. (*R*)-(-)-**3.2bb**: [α]_D³¹ = -22.5 (*c* 4.77, CHCl₃ for the sample of 85% ee). Chiral HPLC Analysis Conditions: Chiralpak AD-H; eluent, hexane/*i*PrOH = 20/1; flow rate, 0.8 mL/min; *t*₁ [(*R*)-

enantiomer] = 34.2 min, t_2 [(*S*)-enantiomer] = 42.9 min. (*R*)-(-)-**3.2cc**: $[\alpha]^{21}_{\text{D}} = -51.8$
(*c* 0.49, CHCl₃ for the sample of 95% ee)^[8]. Chiral HPLC Analysis Conditions:
Chiralpak AD-H; eluent, hexane/^{*i*}PrOH = 5/1; flow rate, 0.8 mL/min; t_1 [(*S*)-enantiomer]
= 19.6 min, t_2 [(*R*)-enantiomer] = 21.4 min.

- [1] (a) Krause, N., Ed. *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Georg Thieme Verlag: Stuttgart, 2008; Volume 44 (Cumulenes and Allenes). (b) Brummond, K. M.; DeForrest, J. E. *Synthesis* **2007**, 795. (c) Ogasawara, M. *Tetrahedron: Asymmetry* **2009**, 20, 259. (d) Yu, S.; Ma, S. *Chem. Commun.* **2011**, 47, 5384. (e) Yu, S.; Ma, S. *Angew. Chem. Int. Ed.* **2012**, 51, 3074. (f) Ye, J.; Ma, S. *Org. Chem. Front.* **2014**, 1, 1210.
- [2] (a) Ogasawara, M.; Ikeda, H.; Hayashi, T. *Angew. Chem., Int. Ed.* **2000**, 39, 1042. (b) Ogasawara, M.; Ge, Y.; Uetake, K.; Fan, L.; Takahashi, T. *J. Org. Chem.* **2005**, 70, 3871. (c) Ogasawara, M.; Okada, A.; Nakajima, K.; Takahashi, T. *Org. Lett.* **2009**, 11, 177. (d) Ogasawara, M.; Murakami, H.; Furukawa, T.; Takahashi, T.; Shibata, N. *Chem. Commun.* **2009**, 7366.
- [3] (a) Ogasawara, M.; Ikeda, H.; Nagano, T.; Hayashi, T. *J. Am. Chem. Soc.* **2001**, 123, 2089. (b) Ogasawara, M.; Ueyama, K.; Nagano, T.; Mizuhata, Y.; Hayashi, T. *Org. Lett.* **2003**, 5, 217. (c) Ogasawara, M.; Nagano, T.; Hayashi, T. *J. Org. Chem.* **2005**, 70, 5764. (d) Ogasawara, M.; Okada, A.; Subbarayan, V.; Sörgel, S.; Takahashi, T. *Org. Lett.* **2010**, 12, 5736.
- [4] (a) Ogasawara, M.; Okada, A.; Watanabe, S.; Fan, L.; Uetake, K.; Nakajima, K.; Takahashi, T. *Organometallics* **2007**, 26, 5025. (b) Zeng, X.; Hu, Q.; Qian, M.; Negishi, E. *J. Am. Chem. Soc.*, **2003**, 125, 13636.
- [5] (a) Tsuji, J. *Acc. Chem. Res.* **1969**, 2, 144. (b) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, 96, 395. (c) Trost, B. M.; Chulbom, L. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; VCH: New York, 2000; p 593. (d) Consiglio, G.; Waymouth, M. *Chem. Rev.* **1989**, 89, 257.

- [6] (a) Benyunes, S. A.; Brandt, L.; Fries, A.; Green, M.; Mahon, M. F.; Papworth, T. M. T. *J. Chem. Soc., Dalton Trans.* **1993**, 3785. (b) Kleijn, H.; Westmijze, H.; Meijer, J.; Vermeer, P. *Recl. Trav. Chim. Pays-Bas* **1983**, 102, 378. (c) Djahanbini, D.; Cazes, B., Goré, J. *Tetrahedron* **1985**, 41, 867. (d) Nokami, J.; Maihara, A.; Tsuji, J. *Tetrahedron Lett.* **1990**, 31, 5629. (e) Piotti, M. E.; Alper, H. *J. Org. Chem.* **1994**, 59, 1956.
- [7] (a) Djahanbini, D.; Cazes, B., Goré, J. *Tetrahedron Lett.* **1984**, 25, 203. (b) Trost, B. M.; Tour, J. M. *J. Org. Chem.* **1989**, 54, 484. (c) Imada, Y.; Ueno, K.; Kutsuwa, K.; Murahashi, S. *Chem. Lett.* **2002**, 140. (d) Trost, B. M.; Fandrick, D. R.; Dinh, D. C. *J. Am. Chem. Soc.* **2005**, 127, 14186.
- [8] Ogasawara, M.; Suzuki, M.; Takahashi, T. *J. Org. Chem.* **2012**, 77, 5406.
- [9] (a) Cayzer, T. N.; Wong, L. S.-M.; Turner, P.; Paddon-Row, M. N.; Sherburn, M. S. *Chem. Eur. J.* **2002**, 8, 739. (b) Miller, N. A.; Willis, A. C.; Sherburn, M. S. *Chem. Commun.* **2008**, 1226.
- [10] (a) Lowe, G. *Chem. Commun.* **1965**, 411. (b) Brewster, J. H. *Top. Stereochem.* **1967**, 2, 1.
- [11] Kündig, E. P.; Cunningham, Jr., A. F. *Tetrahedron* **1988**, 44, 6855.
- [12] dpbp = 2,2'-bis(diphenylphosphino)-1,1'-biphenyl. See: Ogasawara, M.; Yoshida, K.; Hayashi, T. *Organometallics* **2000**, 19, 1567 and references cited therein.
- [13] Sawano, T.; Ou, K.; Nishimura, T.; Hayashi, T. *J. Org. Chem.* **2013**, 78, 8986.
- [14] Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2001**, 343, 264.
- [15] Mikami, K.; Aikawa, K.; Korenaga, T. *Org. Lett.* **2001**, 3, 243.
- [16] Desponds, O.; Schlosser, M. *J. Organomet. Chem.* **1996**, 507, 257.

[17] Fuson, R. C; Cleveland, E. A. *Org. Synth.* **1940**, 20, 45.

Chapter IV

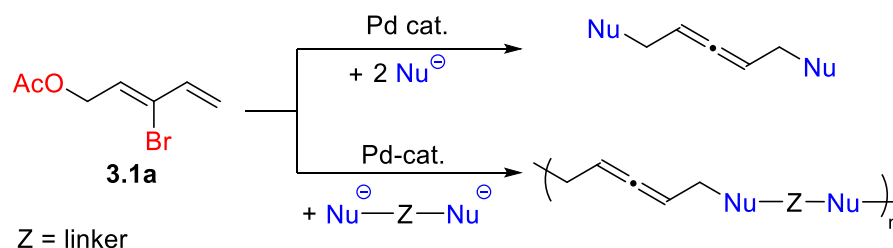
Palladium-Catalyzed Preparation of Optically Active Allenic Polymers from 3-Bromopenta-2,4-dienyl Acetate

Section 1.

Introduction for Chapter IV.

In 2012, Prof. Ogasawara's group demonstrated that the palladium-catalyzed reactions between 3-bromopenta-2,4-dienyl acetate **3.1a** and soft nucleophiles (2 equiv to **3.1a**) provided the corresponding C_2 -symmetric allenes in high yields with excellent regioselectivity (Scheme 4-1-1, top). Whereas compound **3.1a** can be seen as a bifunctional electrophile, I have envisioned that the use of an appropriate bifunctional nucleophile in the palladium-catalyzed reaction might produce oligomeric/polymeric products, which possess allenic scaffolds as a repeating unit in their main chains (Scheme 4-1-1, bottom).

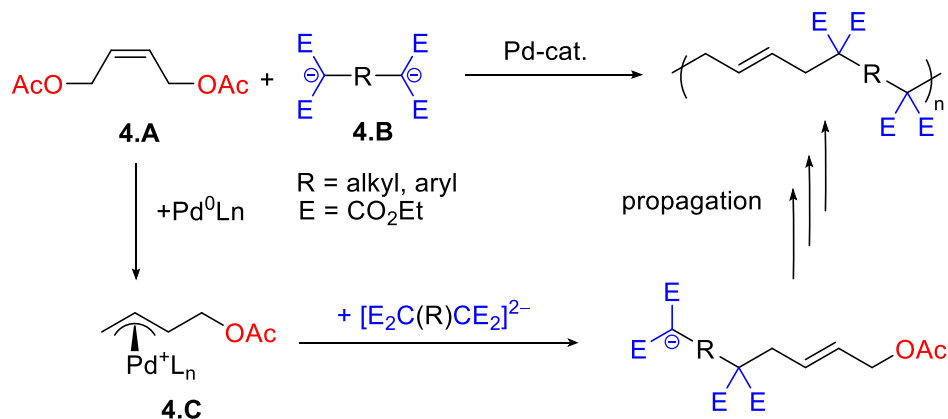
Scheme 4-1-1. Applications of 3-Bromopenta-2,4-dienyl Acetate in Palladium-Catalyzed Reaction.



Allylic substitution reactions catalyzed by an organometallic complex are powerful methods for creating carbon–carbon and carbon–hetero atom bonds.^[1] In polymer synthesis, the polycondensation reactions by repeating allylic substitutions have been reported.^[2] For instance, Nomura and co-workers reported the polymerization of bifunctional monomers **4.A** and **4.B** by the allylic substitutions catalyzed by a palladium complex (Scheme 4-1-2).^[3] The reaction proceeds via an $(\pi\text{-allyl})$ palladium intermediate **4.C** that is a widely accepted intermediate in the Tsuji–Trost reaction, and the formation of polymers tolerates various backbones in the main chain. However, the reports of asymmetric polymerization reactions catalyzed by chiral transition metal

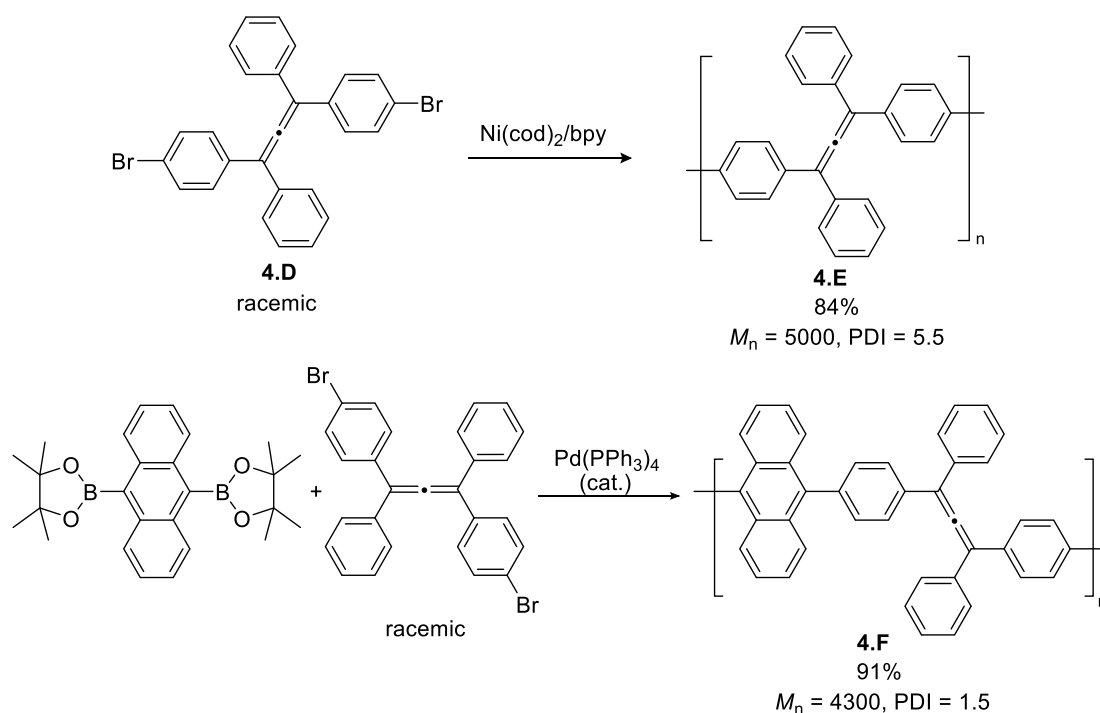
catalysts via asymmetric allylic substitution are rare.^[4]

Scheme 4-1-2. Polymerization via Tsuji-Trost Reaction Process.



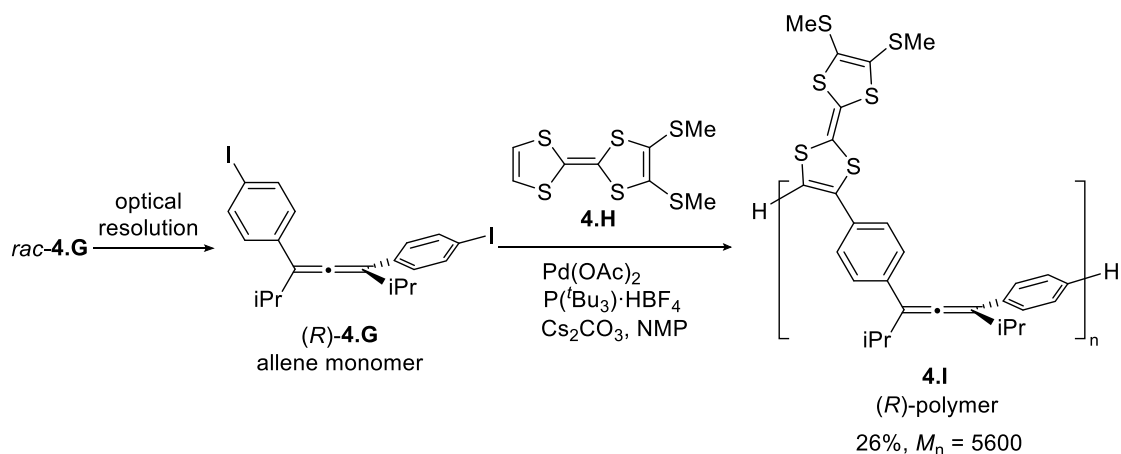
The first allenic polymer was reported by Kijima et al.^[5] Dehalogenative polycondensation of bromoarene **4.D** with a racemic allenic junction was conducted in the presence of a stoichiometric amount of $\text{Ni}(\text{cod})_2$ (Scheme 4-1-3, top). The corresponding allenic polymer **4.E**, purified by a precipitation process, was provided in 84% yield and M_n reached to 5000 and $\text{PDI} = 5.5$. On the other hand, the preparation of similar allenic copolymer **4.F** was reported by same group, the arene-arene coupling reaction catalyzed by $\text{Pd}(\text{PPh}_3)_4$ proceeds via the Suzuki cross-coupling reaction (Scheme 4-1-3, bottom).^[6]

Scheme 4-1-3. Preparations of Allenic Polymers by Arene-Arene Coupling Reactions.



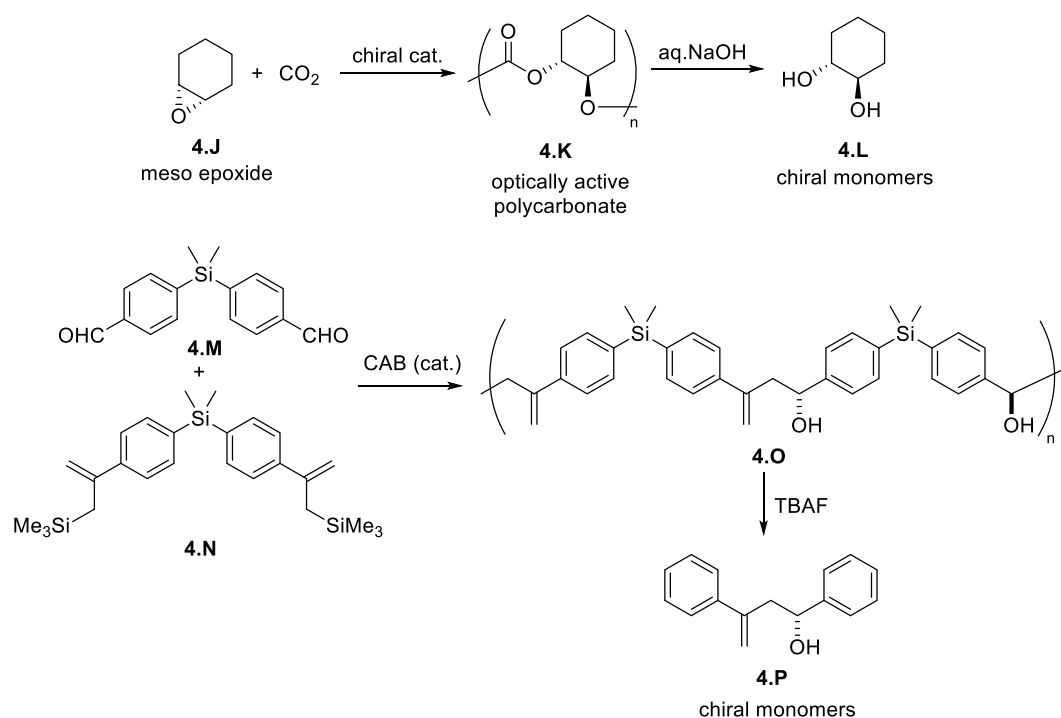
Polymerization reactions for preparing allenic polymers by an arene-arene coupling reaction could be extended to a further application of preparing optically active allenic polymers, which was to utilize haloarene **4.G** with an enantiomerically enriched axially chiral allene junction for the reaction (Scheme 4-1-4).^[7] Axially chiral allenyl iodoarene (*R*)-**4.G** and olefin **4.H** were used for the palladium-catalyzed Mizoroki-Heck reaction to give optically active allenic polymer **4.I** with a single configuration in allenic frameworks. However, optical resolution of racemic **4.G** prior to the polymerization is necessary.

Scheme 4-1-4. Preparation of Optically Active Allenic Polymer.



Although the optical rotation and CD (circular dichroism) measurements indicated the formation of the optically active polymers, the determination of the enantiomeric purity of chiral polymers by direct analysis was impossible. Few reports provided methods to unambiguously determine the degree of asymmetric induction (Scheme 4-1-5).^[8,9] The methods of degradation of chiral polymers have been developed by Nozaki and Itsuno. Nozaki reported asymmetric copolymerization of preparing optically active polycarbonate **4.K** from meso epoxide **4.J** with CO₂ initiated by a chiral Zn catalyst. Treatment of optically active polycarbonate with aqueous NaOH provided corresponding chiral cyclohexane-1,2-diols **4.L** for a chiral HPLC analysis (Scheme 4-1-5, top).^[8] Another method was developed by Itsuno, monomers **4.M** and **4.N** containing silicon-phenyl linkage catalyzed by chiral (acyloxy)borane (CAB) catalyst provided the corresponding optically active polymer **4.O**. Treatment of chiral polymer **4.O** with TBAF cleaved silicon-phenyl bonds readily to afford chiral monomers **4.P** for a chiral HPLC analysis (Scheme 4-1-5, bottom).^[9]

Scheme 4-1-5. Degradation of Chiral Polymers.



To the best of my knowledge, without a pre-existed allenic framework in monomer, a method of directly generating allenic structure in the polymer's main chains has not been reported yet. In this chapter, I have provided a method of preparing the allenic polymer by means of the palladium-catalyzed reaction between 3-bromopenta-2,4-dienyl acetate **3.1a** and bifunctional nucleophiles. The asymmetric polymerizations have been examined by using chiral palladium complexes generated from $\text{Pd}(\text{dba})_2$ and various chiral bisphosphine ligands. Moreover, I have developed a method to determine enantioselectivity (*R/S* distribution) in the axially chiral allenic polymers by the degradation of the axially chiral allenic polymers (Figure 4-1). I have also demonstrated the validity of the method which was not discussed in the reports depicted in Scheme 4-1-5.

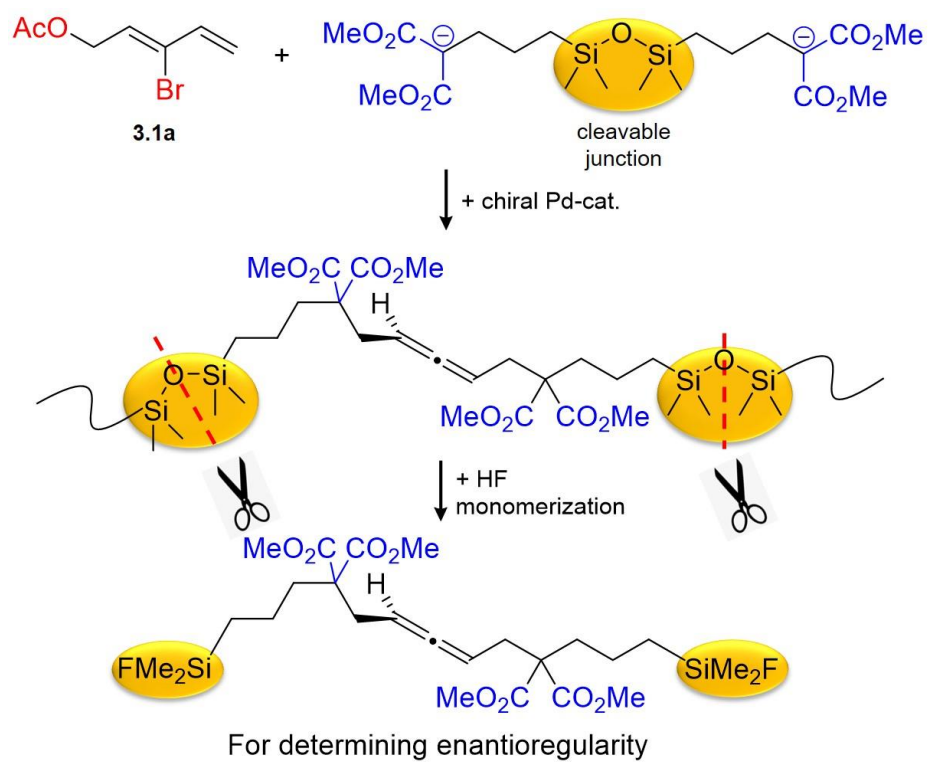


Figure 4-1. Degradation of the Axially Chiral Allenic Polymers

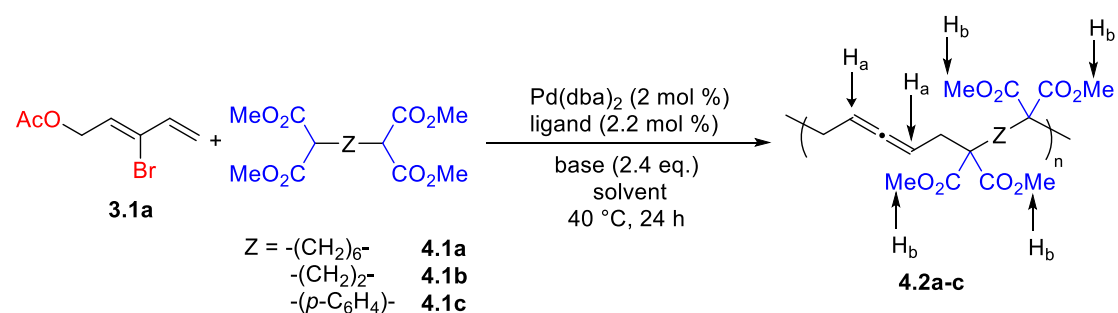
Section 2.

Palladium-Catalyzed Polymerization of 3-Bromopenta-2,4-dienyl Acetate with Bifunctional Nucleophiles

4-2-1. Optimization of Palladium-Catalyzed Polymerization

At the outset, the conditions for the reaction were optimized using bis-malonate **4.1a** and **3.1a** as model substrates, and the results of the optimization studies are summarized in Table 4-1. The reaction of **3.1a** with **4.1a** was catalyzed by 2 mol % of a palladium complex generated in situ from Pd(dba)₂ and dpbp (1.1 equiv to Pd) in THF in the presence of NaH (2.4 equiv to **4.1a**). The substrates were consumed within 24 h at 40 °C, and crude polymer **4.2a** was obtained quantitatively (entry 1). The ¹H NMR spectral analysis may offer valuable information about the degree of polymerization. I used the ¹H NMR spectral method for analyzing the degree of polymerization by comparing integrations between H_a and H_b in the crude product (H_a = integration of alkenic protons; H_b = integration of protons of methoxy groups on the malonate; H_b/H_a ≅ 6 indicates that the polymer may be provided in high degree of polymerization). The polymer obtained under the conditions (as shown in entry 1) was determined by the ¹H NMR spectral method for its degree of polymerization (H_b/H_a = 7.36). Whereas the three terminal moieties (the bromodienyl group and the acetoxy group are from **3.1a**; the malonate group is from **4.1a**) were observed in the ¹H NMR spectrum of the polymer, the calculation of the average molecular weight based on the terminal moiety was not applicable. Other bases were applied in the polymerization. The reaction with KO^tBu consumed **3.1a** but remained the unreacted **4.1a** (entry 3). THF was the best solvent examined so far. Reactions in 1,4-dioxane or DMF gave **4.2a** in comparable H_a/H_b ratio (entries 4 and 5). Dichloromethane was not suitable for the reaction, and the substrates were only consumed partly (entry 6). Next, the effects of the bisphosphine ancillary

ligands were examined, and the reactions with dppb (1.1 equiv to Pd) gave **4.2a** in the lowest $H_b/H_a = 6.90$ (entries 7-11). While slightly decreasing the amount of base in the palladium-catalyzed reaction, the better degree of polymerization was provided ($H_b/H_a = 6.77$, entry 12). To the best of my knowledge, prolonged reaction time may improve the degree of polymerization. The reactions using dppb or dpbp were conducted for 5 days to give **4.2a** in 67% and 72% yields after purification by precipitation from $CHCl_3$ /hexane (1/3). The SEC analysis indicated the reaction using dppb offered a better $M_n = 6900$, and $PDI = 1.98$ (entries 13 and 14). The reaction conditions with dpbp and dppb were also applied for examining bismalonate **4.1b-c** in the palladium-catalyzed reaction. The reactions of bismalonate **4.1b**, which was with a ethylene linker, provided polymer **4.2b** in 75% and 58% yields but with lower $M_n = 1300-1600$ (entries 15 and 16). Bismalonate **4.1c**, which was with a phenylene linker, was also a reactive pronucleophile to give **4.2c**, but a higher reaction temperature (60 °C) was necessary to improve the solubility of **4.1c** in the reaction. The reaction of **4.1c** with dppb did not afford the polymeric product and showed unreacted substrates remaining (entry 17). On the other hand, the reaction of **4.1c** using dpbp provided **4.2c** in 70% yield and $M_n = 6700$ but a higher base loading (2.4 equiv) was necessary to assist the palladium-catalyzed reaction completed. The use of 2.1 equiv of NaH led the incomplete reaction (unreacted **4.1c** was observed) in 5 days. (entry 18).

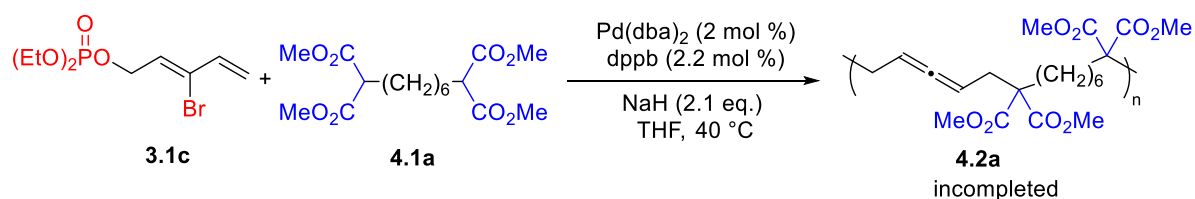
Table 4-1. Optimization of Palladium-Catalyzed Polymerization ^a

entry	Nu	ligand	base	solvent	yield (%) ^b	H _b /H _a ^c	M _n ^d	PDI ^{d,e}
1	4.1a	dpbp	NaH	THF	-	7.36	-	
2	4.1a	dpbp	NaOMe	THF	-	8.66	-	
3	4.1a	dpbp	KO ^t Bu	THF	-	14.22	-	
4	4.1a	dpbp	NaH	1,4-dioxane	-	7.61	-	
5	4.1a	dpbp	NaH	DMF	-	10.66	-	
6	4.1a	dpbp	NaH	CH ₂ Cl ₂	-	-	-	
7	4.1a	dppe	NaH	THF	-	8.96	-	
8	4.1a	dppb	NaH	THF	-	6.90	-	
9	4.1a	dppf	NaH	THF	-	7.57	-	
10	4.1a	DPEphos	NaH	THF	-	7.68	-	
11	4.1a	Xantphos	NaH	THF	-	10.64	-	
12 ^g	4.1a	dppb	NaH	THF	-	6.77	-	
13 ^{f,g}	4.1a	dppb	NaH	THF	67%	6.45	6900	1.98
14 ^{f,g}	4.1a	dpbp	NaH	THF	72%	6.32	6100	4.59
15 ^{f,g}	4.1b	dppb	NaH	THF	75%	7.88	1600	8.54
16 ^{f,g}	4.1b	dpbp	NaH	THF	58%	7.96	1300	1.28
17 ^{f,h}	4.1c	dppb	NaH	THF	trace	-	-	-
18 ^{f,h}	4.1c	dpbp	NaH	THF	70%	6.39	6700	3.34

^a The reaction was carried out with **3.1a** (0.25 mmol) and **4.1** (0.25 mmol) in a given solvent (1.5 mL) at 40 °C for 24 h in the presence of a given base (2.4 equiv to **4.1**) and a Pd catalyst (2 mol %) generated from Pd(dba)₂ and a given ligand. ^b Precipitated from CHCl₃/hexane = 1/3. ^c Determined by ¹H NMR. ^d Estimated by SEC (CHCl₃, polystyrene standard). ^e Polydispersity index, M_w/M_n. ^f 5 days. ^g NaH (2.1 equiv to **4.1**). ^h 60 °C.

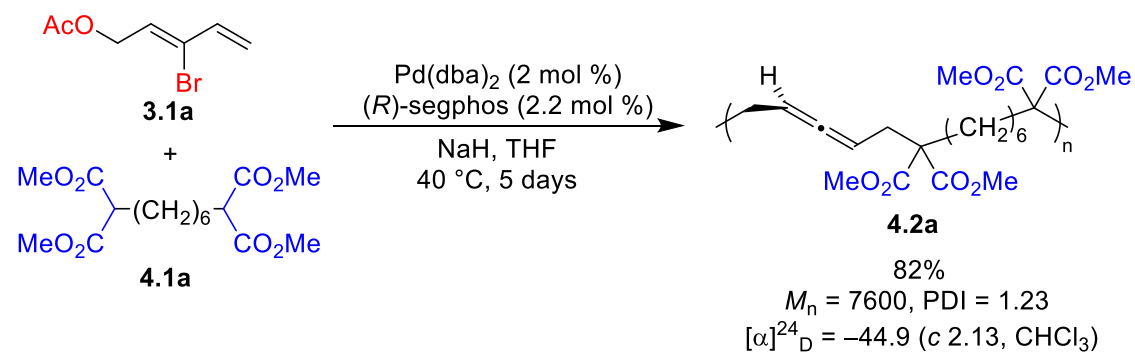
In the previous chapter, I have demonstrated that phosphate **3.1c** is also an excellent precursor to prepare the C_2 -symmetric allenes by the palladium-catalyzed reaction. Herein, I have applied **3.1c** with **4.1a** for the palladium-catalyzed polymerization (Scheme 4-2-1). However, within 6 hours, uncharacterized insoluble materials were precipitated and the reaction was not complete.

Scheme 4-2-1. The Palladium-Catalyzed Polymerization of **3.1c** with **4.1a**



Allenic polymer **4.2a** is with the axially chiral units in the main chains, and application of an appropriate chiral palladium species to the reaction may furnish allenic polymer **4.2a** in enantiomerically enriched forms. The asymmetric extension was explored for a reaction of **3.1a** with **4.1a**, and the result is shown in Scheme 4-2-2. The asymmetric reaction catalyzed by a chiral palladium species generated from Pd(dba)_2 and (*R*)-segphos provided allenic polymer in 82% yield and $M_n = 7600$. The stereochemistry of the main-chain structure was evaluated by the optical rotation measurement. Resulting polymer **4.2a** in Scheme 4-2-2 exhibited the optical rotational value of $[\alpha]^{24}_D = -44.9$, which indicated the axially chiral allenic polymer was optically active.

Scheme 4-2-2. Palladium-Catalyzed Synthesis of Axially Chiral Allenic Polymer



Section 3.

Palladium-Catalyzed Asymmetric Polymerization of 3-Bromopenta-2,4-dienyl Acetate with Cleavable Bifunctional Nucleophiles

4-3-1. Strategy of Determining Enantioselectivity in Axially Chiral Allenic Polymers

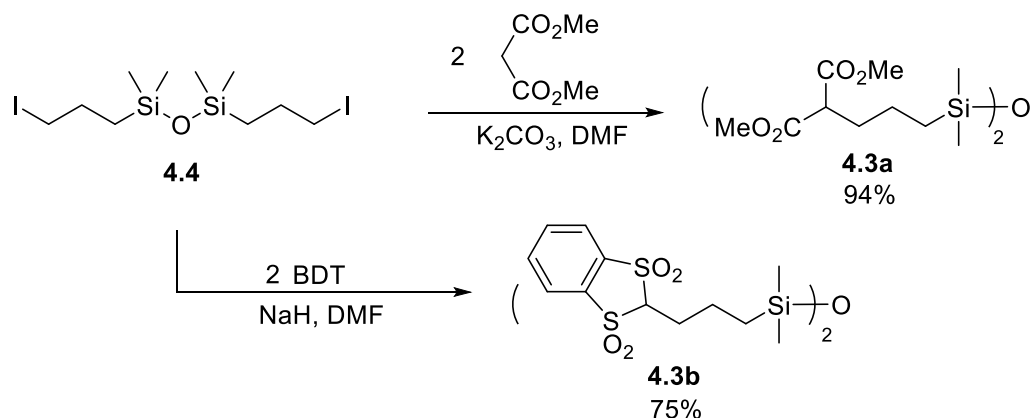
Although the optical rotation measurements could indicate that axially chiral allenic polymer **4.2a** in Scheme 4-2-2 was optically active, the direct determination of the enantiomeric purity (*R/S* distribution) of axially chiral allenic polymers was impossible. A persuasive and reliable method to determine the asymmetric induction (enantioselectivity) is the analysis for single-component chiral compounds derived from degradation of the chiral polymer.^[9]

In order to determine enantioselectivity of the axially chiral allenic polymers, I have designed a new monomer with a suitable structure for the degradation analysis. I report herein the preparation of new monomers possessing Si-O-Si linkages (chapter 4-3-2) and their asymmetric polymerization (chapter 4-3-3). The obtained optically active polymers were broken into the single-component chiral compound, which was analyzed by the chiral HPLC to evaluate the enantioselectivity. The corresponding model reactions have been studied as well (chapter 4-3-5).

4-3-2. Preparation of Bifunctional Nucleophiles with Disiloxy Linker

It is well known that the bond between Si and O can be cleaved easily by treatment with fluoride anion. On the other hand, treatment of the Si-O-Si group with hydrofluoric acid can provide two equivalents of the SiF groups.^[10] I have prepared new monomers **4.3a-c** containing a Si-O-Si substructure as shown in Schemes 4-3-1 and 4-3-2. After the asymmetric polymerization, the Si-O-Si linkages in the main chain of the axially chiral allenic polymer may be cleaved cleanly. The structures of new monomers with a disiloxane linkage for the Pd-catalyzed asymmetric polymerization are depicted as **4.3a-c**, and they were prepared from corresponding silyl/disiloxy halides by the simple one- or two-step sequence as depicted in Schemes 4-3-1 and 4-3-2. Readily available 1,3-bis(3-iodopropyl)tetramethyldisiloxane **4.4**^[11] were converted into **4.3a-b** in 94% and 75% yields by alkylations of dimethyl malonate or benzodithiole tetraoxide (BDT) as shown in Scheme 4-3-1.

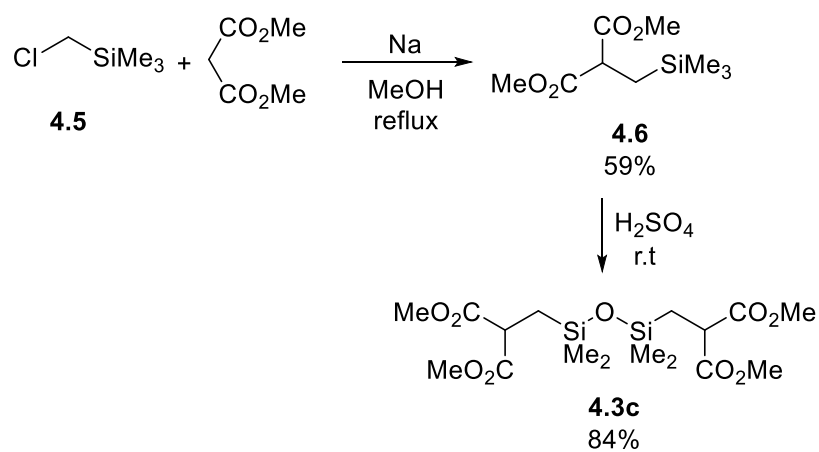
Scheme 4-3-1. Preparation of Bifunctional Nucleophiles **4.3a-b**.



Monomer **4.3c** with a shorter disiloxane linkage was prepared from commercially available (trimethylsilyl)methyl chloride **4.5** by the two-step sequence (Scheme 4-3-2). Alkylation of **4.5** with dimethyl malonate provides **4.6** in 59% yield. Treatment of

malonate-tethered trimethylsilane **4.6** with concentrated sulfuric acid selectively cleaved one methyl group from the trimethylsilyl moiety to provide disiloxy product **4.3c** in pure form (84% yield).

Scheme 4-3-2. Preparation of Bifunctional Nucleophile **4.3c**.

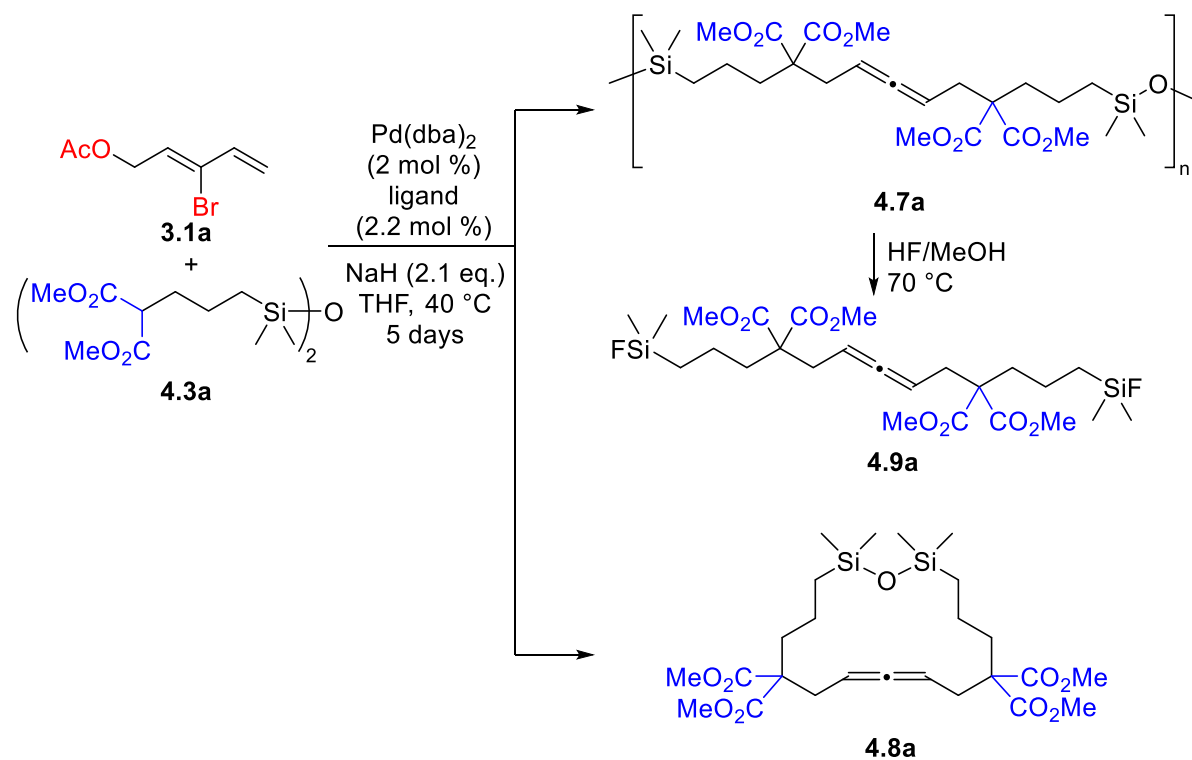


4-3-3. Palladium-Catalyzed Asymmetric Polymerization of 3-Bromopenta-2,4-dienyl Acetate and Cleavable Bifunctional Nucleophiles

The asymmetric polymerizations of **3.1a** with **4.3a-c** were catalyzed by 2 mol % of chiral palladium complexes generated from Pd(dba)₂ and chiral bisphosphine ligands at 40 °C in THF for 5 days in the presence of NaH (2.1 equiv to **4.3a**). The results of the palladium-catalyzed asymmetric polymerization of bismalonate-tethered disiloxane **4.3a** with **3.1a** are summarized in Table 4-2. At the outset, the reactions with dppb or dpbp provided the racemic axially chiral allenic polymers **4.7a** in 43% and 40 % yields, and *M_n* reached up to 13700 (entries 1 and 2). The ¹H NMR analysis of the crude reaction mixture revealed the concomitant formation of cyclic allene **4.8a** as a side product. The Pd-catalyzed asymmetric reactions with chiral Pd complexes generated from Pd(dba)₂ and corresponding chiral bisphosphine ligands provided the polymers in 43-62% yield with *M_n* ranging from 3600 to 5100, and the cyclic products were also observed in a comparable ratio (entries 3-6). In order to evaluate the enantioselectivity of axially chiral allenic polymers **4.7a** in entries 3-6, its selective degradation was examined. Treatment of **4.7a**, which were prepared from **3.1a** and **4.3a** using a Pd/(*R*)-(biaryl-bisphosphine) catalyst, with excess aqueous hydrofluoric acid at 70 °C in MeOH cleaved the disiloxane junction cleanly to give the corresponding monomerized allene **4.9a** quantitatively, of which enantiomeric excess value could be determined by the standard chiral HPLC analysis. The results of the chiral HPLC analysis of axially chiral allenic monomer **4.9a** are summarized in Table 4-2. While (*R*)-binap and (*R*)-DTBMsegphos showed lower enantioselectivity than (*R*)-segphos with 45-68% ee (entries 3-5), the enantioselectivity was improved to 73% ee by the use of (*S*)-^{*t*}Bu-segphos (entry 6). The Pd-catalyzed asymmetric polymerization with (*R*)-segphos provided the optically active allenic polymer (–)-**4.7a** with [α]_D²⁴ = –14.5 (*c* 0.44,

CHCl₃). Due to the concomitant formation of monomeric cyclic allenes **4.8b**, the modest yields of allenic polymers **4.7a** were reasonable. The enantioselectivities of cyclic allenes **4.8a** were also determined by chiral HPLC analysis, and no obvious correlation was observed between the %ee values of monomerized allene **4.9a** and cyclic allene **4.8a**.

Table 4-2. Palladium-Catalyzed Asymmetric Polymerization of **3.1a** with **4.3a**.^a

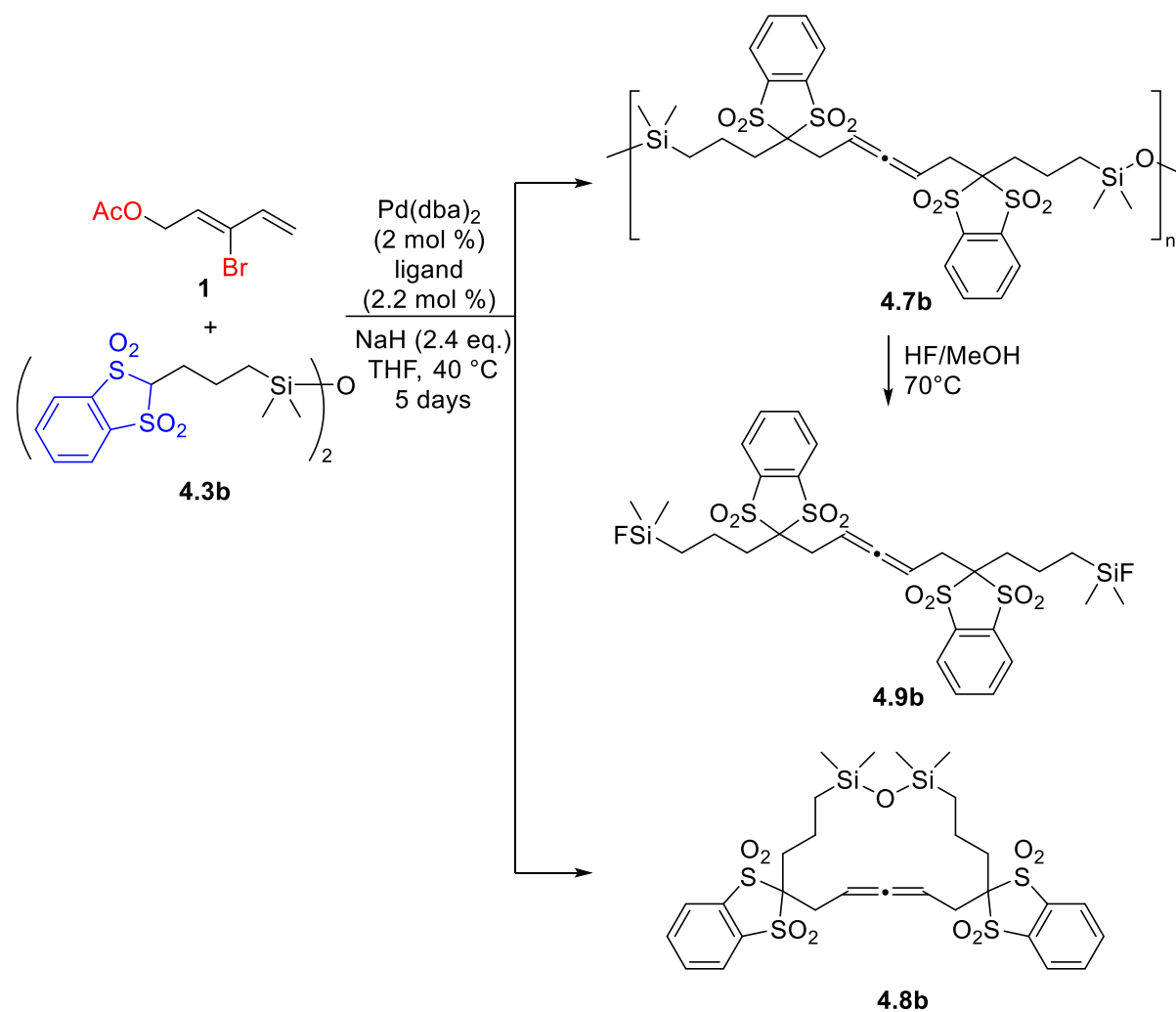


entry	ligand	4.7a : 4.8a ^b	yield (%) ^c	M_n ^d	PDI ^{d, e}	ee of 4.9a (%) ^f	ee of 4.8a (%) ^f
1	dppb	78 : 22	43%	3830	1.59	-	-
2	dpbp	75 : 25	40%	13700	1.23	-	-
3	(<i>R</i>)-binap	81 : 19	47%	3600	1.50	52(−)	46(+)
4	(<i>R</i>)-segphos	79 : 21	45%	4700	3.32	71(−)	81(+)
5	(<i>R</i>)-DTBMsegphos	81 : 19	43%	5100	2.53	68(−)	63(+)
6	(<i>S</i>)- ^{<i>t</i>} Bu-segphos	81 : 19	62%	4200	1.85	73(+)	80(−)

^a The reaction was carried out with **3.1a** (0.250 mmol), **4.3a** (0.250 mmol) and NaH (0.525 mmol) at 40 °C for 5 days in THF (1.5 mL) in the presence of a Pd catalyst (2 mol %) generated from Pd(dba)_2 and a given ligand. ^b Determined by ^1H NMR. ^c Precipitated from CHCl_3 /hexane = 1/3. ^d Estimated by SEC (CHCl_3 , polystyrene standard). ^e Polydispersity index, M_w/M_n . ^f Determined by chiral HPLC analysis.

The BDT moiety in **4.3b** is sterically more compact than the malonate moiety in **4.3a**, which was utilized for the palladium-catalyzed asymmetric polymerization as shown in Table 4-3. The use of dppb ligand for the palladium-catalyzed reaction provided the corresponding polymer **4.7b** in a low 18% yield due to a 66% formation of cyclic allene **4.8b**, which was determined by the NMR measurement of the crude reaction mixture (entry 1). The reaction with dpbp ligand provided **4.7b** in a higher 43% yield with $M_n = 8600$ and a narrow dispersity (PDI = 1.12) (entry 2). The palladium-catalyzed asymmetric polymerizations with chiral Pd complexes generated from Pd(dba)₂ and chiral biaryl bisphosphine ligands were examined in the same way, and polymers **4.7b** were obtained in 23-48% yields and M_n ranging from 7100 to 8200. A trend of a ratio between **4.7b** and **4.8b** in the reactions was observed. While using bulky ligands, which are with DTBM groups on the phosphorus atoms, improved the ratio of polymer in the reaction mixture (entries 4-7). The determination of enantioselectivity of axially chiral allenic polymers **4.7b** was conducted by the method as shown in Table 4-3, and the highest ee value for monomerized allenes **4.9b** was provided by the use of (*R*)- or (*S*)-DeBuPhos in the palladium-catalyzed asymmetric reaction (90% ee, entries 6 and 7). The optical rotation values for optically active allenic polymer (–)-**4.7** prepared using the (*R*)-DeBuPhos was determined to be $[\alpha]^{25}_D = -64.0$ (*c* 0.18, CHCl₃) (entry 6).

Table 4-3. Palladium-Catalyzed Asymmetric Polymerization of **3.1a** with **4.3b**.^a



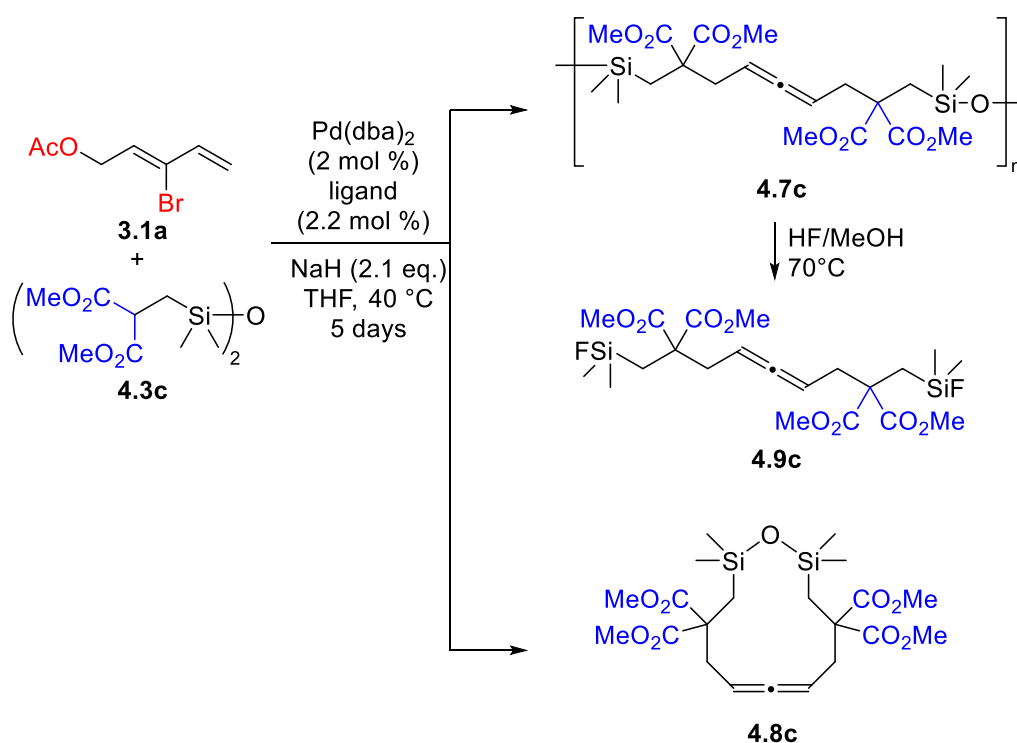
entry	ligand	4.7b : 4.8b ^b	Yield (%) ^c	M_n^d	PDI ^e	ee of 4.9b (%) ^f	ee of 4.8b (%) ^f
1	dppb	44 : 66	18%	9300	1.14	-	-
2	dpbp	59 : 41	43%	8600	1.12	-	-
3	(<i>R</i>)-binap	52 : 48	23%	7300	1.10	58(–)	60(–)
4	(<i>R</i>)-segphos	61 : 39	45%	8200	1.12	78(–)	53(–)
5	(<i>R</i>)-DTBMsegphos	64 : 36	41%	7100	1.09	71(–)	45(–)
6	(<i>R</i>)-DeBuPhos	69 : 31	45%	7400	1.09	90(–)	68(–)
7	(<i>S</i>)-DeBuPhos	71 : 29	48%	7700	1.10	90(+)	74(+)

^a The reaction was carried out with **3.1a** (0.25 mmol), **4.3b** (0.25 mmol) and NaH (0.6

mmol) at 40 °C for 5 days in THF (1.5 mL) in the presence of a Pd catalyst (2 mol %) generated from Pd(dba)₂ and a given ligand. ^b Determined by ¹H NMR. ^c Precipitated from CHCl₃/hexane = 1/1. ^d Estimated by SEC (CHCl₃, polystyrene standard). ^e Polydispersity index, M_w/M_n . ^f Determined by chiral HPLC analysis.

Bismalonate **4.3c**, which is with a shorter disiloxane linkage, was also used in the palladium-catalyzed asymmetric polymerization as shown in Table 4-4. The palladium-catalyzed polymerization of **4.3c** with **3.1a** showed the formations of polymer **4.7c** and cyclic allene **4.8c** in a good ratio of ca. 9/1 irrespective of the choice of the ligands. The polymers in Table 4-4 were provided in 40-57% yields with M_n = 6100-7700 (entries 1-6). While (*R*)-binap and (*S*)-*t*Bu-segphos showed lower enantioselectivity of **4.9c** than (*R*)-segphos with 36-68% ee (entries 3,4, and 6), the enantioselectivity was improved to 80% ee by the use of (*R*)-DTBMsegphos (entry 5). Optically active allenic polymer (+)-**4.7c** afforded from the (*R*)-DTBMsegphos showed the optical rotation of $[\alpha]^{22}_D = +32.6$ (*c* 0.31, CHCl₃) (entry 5).

Table 4-4. Palladium-Catalyzed Asymmetric Polymerization of **3.1a** with **4.3c**.^a



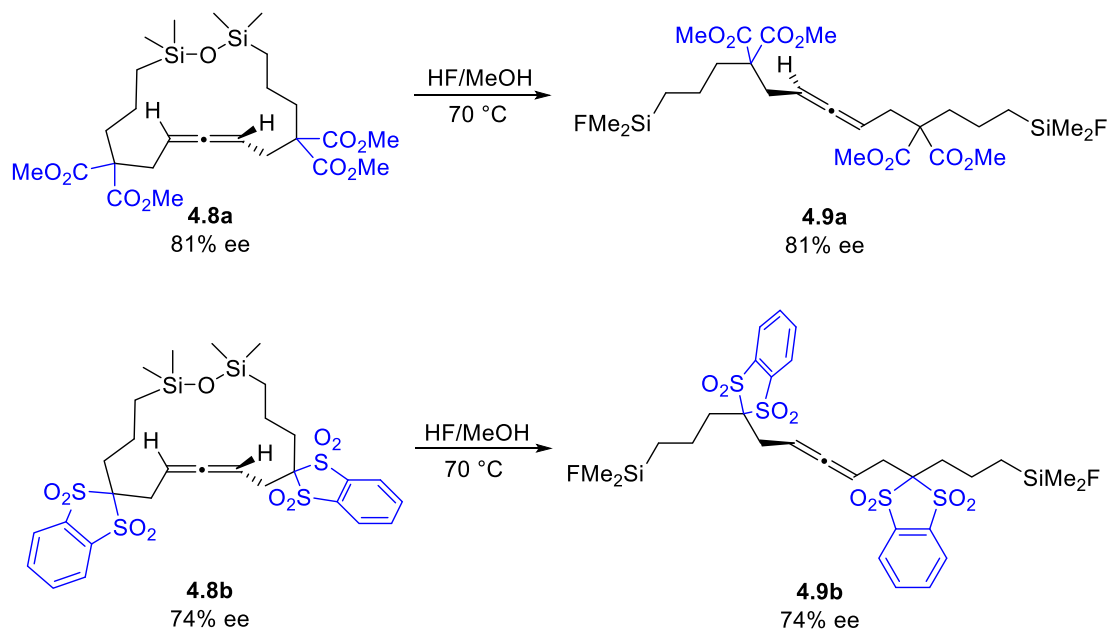
entry	ligand	4.7c : 4.8c ^b	Yield (%) ^c	M_n ^d	PDI ^{d, e}	ee of 4.9c (%) ^f	ee of 4.8c (%) ^f
1	dppb	97 : 3	54%	7200	1.27	-	-
2	dpbp	90 : 10	52%	6100	1.29	-	-
3	(<i>R</i>)-binap	90 : 10	50%	6400	1.25	36(+)	46(+)
4	(<i>R</i>)-segphos	89 : 11	56%	7600	1.53	72(+)	80(+)
5	(<i>R</i>)-DTBMsegphos	93 : 7	57%	7700	1.43	80(+)	70(+)
6	(<i>S</i>)- ^{<i>t</i>} Bu-Segphos	91 : 9	40%	7300	2.15	68(-)	80(-)

^a The reaction was carried out with **3.1a** (0.250 mmol), **4.3c** (0.250 mmol) and NaH (0.525 mmol) at 40 °C for 5 days in THF (1.5 mL) in the presence of a Pd catalyst (2 mol %) generated from Pd(dba)_2 and a given ligand. ^b Determined by ^1H NMR. ^c Precipitated from CHCl_3 /hexane = 1/3. ^d Estimated by SEC (CHCl_3 , polystyrene standard). ^e Polydispersity index, M_w/M_n . ^f Determined by chiral HPLC analysis.

4-3-4. Validity of the Method to Determine the Enantioselectivity of Axially Chiral Allenic Polymers

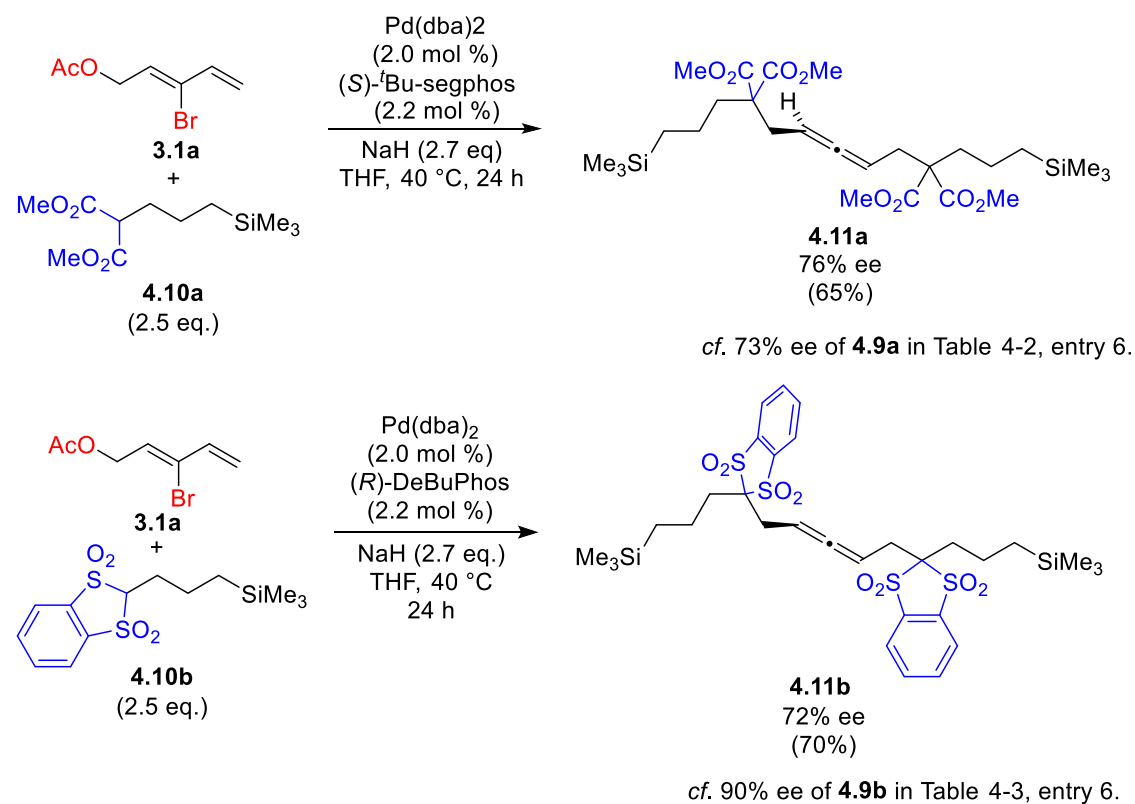
Due to the concomitant formation of monomeric cyclic allenes **4.8**, the yields of allenic polymers **4.7** were remained modest. However, the side products, **4.8**, were utilized to confirm the validity of my method of determining the enantioselectivity in **4.7**. The ee values of monomeric **4.8** could be determined by the conventional chiral HPLC analyses. Treatment of **4.8a**, which was prepared from **3.1a** and **4.3a** using a Pd/(*R*)-segphos catalyst, with aqueous hydrofluoric acid provided monomeric acyclic **4.9a**, of which enantiomeric purity was also determined by the chiral HPLC. Comparison of the two ee values in **4.8a** and **4.9a** showed the retention of the axial chirality (no racemization) in the allenic framework at the hydrofluoric acid treatment (Scheme 4-3-3, top). Likewise, cyclic **4.8b**, which was prepared from **3.1a** and **4.3** using a Pd/(*S*)-DeBuPhos catalyst, was treated in the same way to afford acyclic **4.9b** without racemization. According to these experiments, I could claim that my method of determining enantio-regularity in axially chiral allenic polymers was reliable.

Scheme 4-3-3. Ring-Opening Process of Cyclic **4.8a-b**.



4-3-5. Substrate Control of Palladium-Catalyzed Asymmetric Reaction

Scheme 4-3-4. Enantioselective Palladium-Catalyzed Reaction of **4.10** with **3.1a**



In order to estimate the degree of asymmetric induction during the polymerization, I investigated the enantioselective palladium-catalyzed reaction of **4.10a-b**, which has the same substructure with **4.3a-b** (Scheme 4-3-4). Firstly, the reaction of **4.10a** with **3.1a** was catalyzed by a chiral Pd complex generated from Pd(dba)₂ and (S)-^tBu-segphos, which provided the highest enantioselectivity in asymmetric polymerization in Table 4-2, entry 6. The monomeric allene **4.11a** was obtained in 65% yield with 76% ee, which showed similar enantioselectivity in Pd-catalyzed asymmetric polymerization (Scheme 4-3-4, top). However, while the reaction of **4.10b** was catalyzed by a chiral palladium complex generated from Pd(dba)₂ and (R)-DeBuPhos, which provided the highest enantioselectivity in asymmetric polymerization in Table 4-3, entry 6, the **4.11b** was obtained in 72% ee in 70% yield. The ee value of **4.11b** is

considerably lower than monomerized allene **4.9b** of 90% ee generated from the polymer **4.7b** using the same chiral catalytic system. This could be explained that the propagation intermediate with **4.3b**, of which main chain contains a multiple axially chiral units, provided a positive correlation in the diastereomeric fashion at the asymmetric polymerization, and thus, the ee value of **4.9b** generated from axially chiral allenic polymer (Table 4-3, entry 6) was higher than **4.11b** under the same catalytic conditions (Table 4-3, entry 6).^[13]

Section 4.

Proposed Mechanism of Palladium-Catalyzed Polymerization of 3-Bromopenta-2,4-dienyl Acetate with Bifunctional Nucleophile

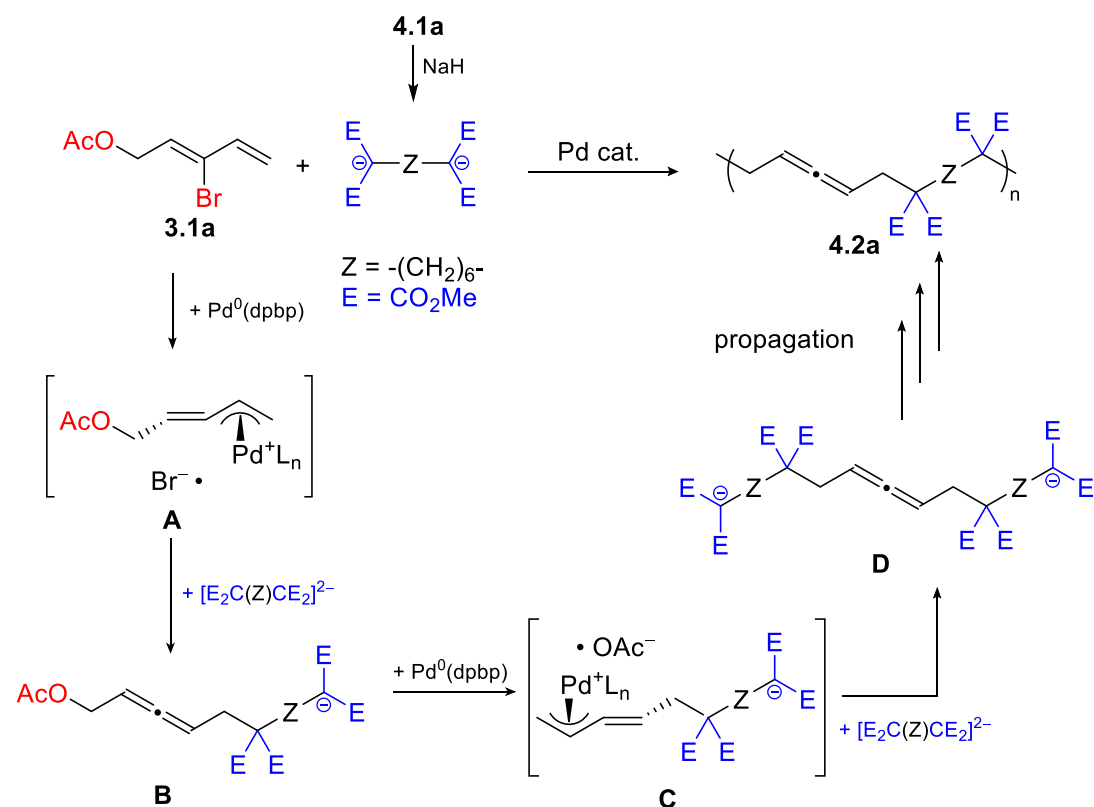


Figure 4-2. Proposed Mechanism of Palladium-Catalyzed Polymerization.

The proposed mechanism of palladium-catalyzed polymerization of **3.1a** and bifunctional nucleophile **4.1a** is shown in Figure 4-2. Substrate **3.1a** possesses two different sites (marked in red) susceptible to activation with palladium catalysis. According to my previous studies on the reactivity of **3.1a** in the palladium-catalyzed reaction (chapter III), treatment of **3.1a** with a nucleophile generated from **4.1a** and NaH in THF in the presence of the Pd/dpbp catalyst preferentially afforded monosubstituted intermediate **B** proceeding via an (alkylidene-π-allyl)palladium intermediate **A**, which was generated by the oxidative addition of the vinylic C-Br to Pd(0). The oxidative addition of the allylic acetate in monosubstituted intermediate **B** to Pd(0) provided intermediate **C**, and a repetitive propagation process would afford the

polymer **4.2a** proceeding via intermediate **D**.

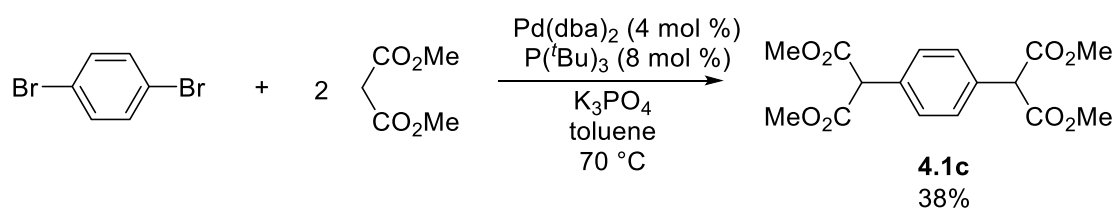
Conclusions for Chapter IV

In this chapter, I have developed an efficient and enantioselective method of preparing various axially chiral allenic polymers with optically active properties. Bifunctional electrophilic substrate **3.1a** has been demonstrated an excellent precursor not only to the doubly functionalized C_2 -symmetric allenes but also to the allenic polymers. The reaction was effectively catalyzed by an appropriate palladium complex, and **3.1a** and bifunctional nucleophile generated from **4.1** or **4.3** underwent the repetitive nucleophilic substitution via formal S_N2' and S_N2 processes to give the allenic polymers in good to high yields with comparable M_n . By the use of a chiral palladium catalyst, axially chiral allenic polymers were obtained and they were optically active. I have developed a reliable method of determining the enantioselectivity of my axially chiral allenic polymer. These chiral polymers generated from cleavable **4.3a-c** could be monomerized readily by the treatment with aqueous hydrofluoric acid to give the corresponding enantioenriched **4.9a-c**. Chiral HPLC analysis of the axially chiral allenyl dimethylfluorosilane **4.9a-c** revealed that the asymmetric polymerization took place with a high level of asymmetric induction, and the **4.9a-c** were obtained in up to 90% ee.

Experimental Section for Chapter IV

General. All anaerobic and/or moisture sensitive manipulations were carried out with standard Schlenk techniques under predried nitrogen or with glovebox techniques under prepurified argon. ^1H NMR (400 MHz), ^{13}C NMR (101 MHz), and ^{19}F NMR (376 MHz) chemical shifts are reported in ppm downfield of internal tetramethylsilane. Tetrahydrofuran and 1,4-dioxane were distilled from benzophenone-ketyl under nitrogen prior to use. Dichloromethane and DMF were distilled from CaH_2 under nitrogen prior to use. Methanol was distilled from Mg metal under nitrogen prior to use. The following compounds were prepared according to the reported methods: tetramethyl octane-1,1,8,8-tetracarboxylate (**4.1a**),^[15] tetramethyl butane-1,1,4,4-tetracarboxylate (**4.1b**),^[16] 1,3-Bis(3-iodopropyl)-1,1,3,3-tetramethyldisiloxane (**4.4**),^[11] BDT,^[14] (3-iodopropyl) trimethylsilane^[19] All the other chemicals were obtained from commercial sources and used as received unless otherwise noted. The absolute configurations of axially chiral allenes were deduced by the Lowe–Brewster rule.^[20]

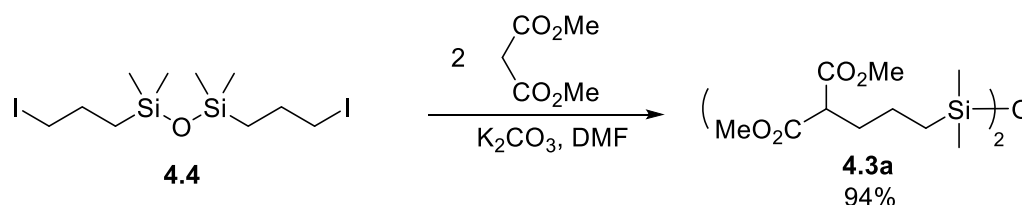
Synthesis of Tetramethyl 2,2'-(1,4-Phenylene)dimalonate (**4.1c**)



The procedure of preparation of **4.1c** was consulted with the palladium-catalyzed alkylation of malonates reported by Hartwig.^[17] To a 300 mL Schlenk flask containing dimethyl malonate (17.58 g, 133.1 mmol) and *p*-dibromobenzene (14.27 g, 60.5 mmol) were added $\text{P}(\text{tBu})_3$ (980 mg, 4.84 mmol), $\text{Pd}(\text{dba})_2$ (1390 mg, 2.42 mmol), and K_3PO_4 (77.05 g, 363.0 mmol) followed by toluene (120 mL). The heterogeneous reaction mixture was stirred at $70\text{ }^\circ\text{C}$ and monitored by TLC. After complete conversion of the

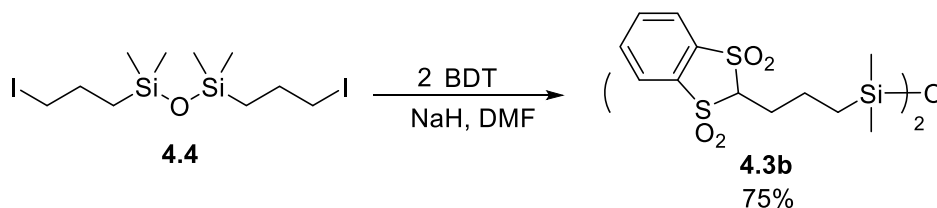
p-dibromobenzene, the crude reaction was filtered through a plug of Celite 545[®] and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (hexane/EtOAc = 3/2) followed by recrystallization from benzene to give the **4.1c** (7.81 g, 38% yield) as a white solid. ¹H NMR (CDCl₃): δ 3.76 (s, 12H), 4.65 (s, 2H), 7.41 (s, 4H). ¹³C NMR (CDCl₃): δ 53.1, 57.3, 129.7, 132.7, 168.4. ESI-HRMS Calcd for C₁₆H₁₈O₈Na (M + Na): 361.0899. Found: 361.0896.

Synthesis of 1,3-Bis(4,4-dimethoxycarbonylbutyl)-1,1,3,3-tetramethyldisiloxane (4.3a)



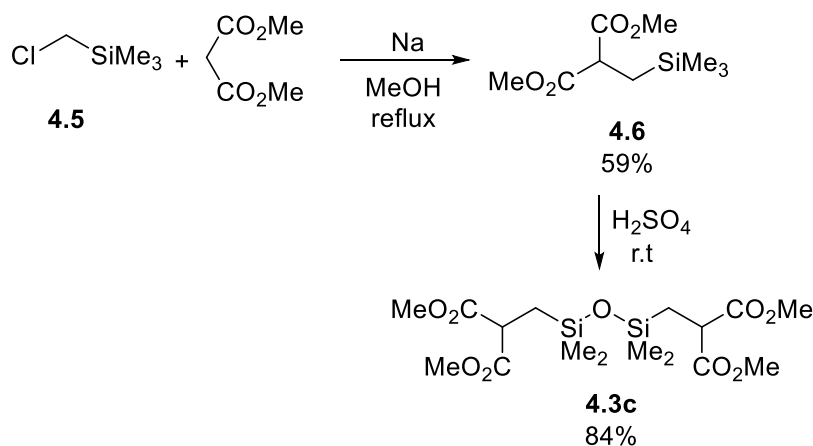
To a 300 mL Schlenk flask containing **4.4** (15.00 g, 31.9 mmol) was added dimethyl malonate (10.11 g, 76.6 mmol) and K₂CO₃ (10.58 g, 76.6 mmol) followed by DMF (60 mL). The reaction mixture was stirred at 100 °C and monitored by ¹H NMR. After complete conversion of **4.4**, the crude reaction was filtered through a plug of Celite 545[®], washed with EtOAc (3 x 50 mL). The mixture was washed with H₂O (3 x 100 mL), brine (100 mL), dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (hexane/Et₂O = 6/5) to give the **4.3a** (14.30 g, 94% yield) as a colorless oil. ¹H NMR (CDCl₃): δ 0.03 (s, 12H), 0.50-0.54 (m, 4H), 1.33-1.35 (m, 4H), 1.92 (q, *J* = 7.6 Hz, 4H), 3.40 (t, *J* = 7.6 Hz, 2H), 3.74 (s, 12H). ¹³C NMR (CDCl₃): δ 0.4, 18.1, 21.4, 32.4, 51.6, 52.6, 170.1. ESI-HRMS Calcd for C₂₀H₃₈O₉Si₂Na (M + Na): 501.1952. Found: 501.1951.

Synthesis of 2,2'-[(1,1,3,3-Tetramethyldisiloxane-1,3-diyl)bis(propane-1,3-diyl)]bis(-benzodithiole-1,1,3,3-tetraoxide) (4.3b)



To a 100 mL Schlenk flask containing **4.4** (2.94 g, 6.3 mmol) was added BDT (3.00 g, 13.8 mmol) and NaH (375 mg, 15.63 mmol) followed by DMF (20 mL). The reaction mixture was stirred at 80 °C and monitored by ^1H NMR. After complete conversion of **4.4**, the crude reaction was filtered through a plug of Celite 545[®], washed with CHCl_3 (3 x 50 mL). The mixture was washed with H_2O (3 x 100 mL), brine (100 mL), dried over MgSO_4 , and concentrated under reduced pressure. The residue was purified by chromatography on silica gel ($\text{CHCl}_3/\text{EtOAc} = 9/1$) followed by GPC separation to give the **4.3b** (3.04 g, 75% yield) as a white solid. ^1H NMR (CDCl_3): δ 0.12 (s, 12H), 0.70-0.74 (m, 4H), 1.84-1.86 (m, 4H), 2.36 (q, $J = 7.6$ Hz, 4H), 4.51 (t, $J = 7.2$ Hz, 2H), 7.87-7.90 (m, 4H), 8.01-8.03 (m, 4H). ^{13}C NMR(CDCl_3): δ 0.2, 18.2, 20.4, 25.7, 73.6, 122.7, 135.1, 138.0. ESI-HRMS Calcd for $\text{C}_{24}\text{H}_{34}\text{O}_9\text{S}_4\text{Si}_2\text{Na}$ ($\text{M} + \text{Na}$): 673.0522. Found: 673.0522.

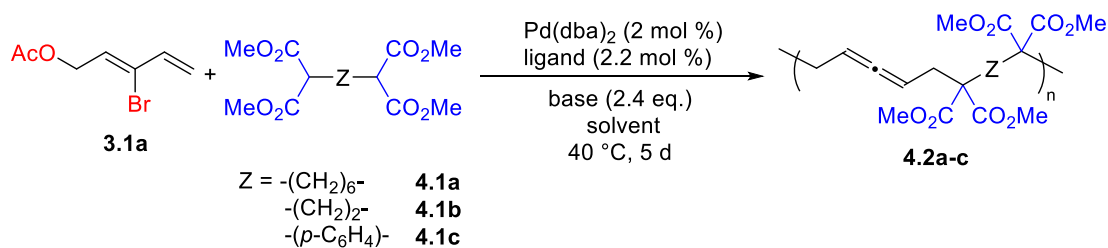
Synthesis of 1,3-Bis(2,2-dimethoxycarbonyl)ethyl-1,1,3,3-tetramethyldisiloxane (4.3c)



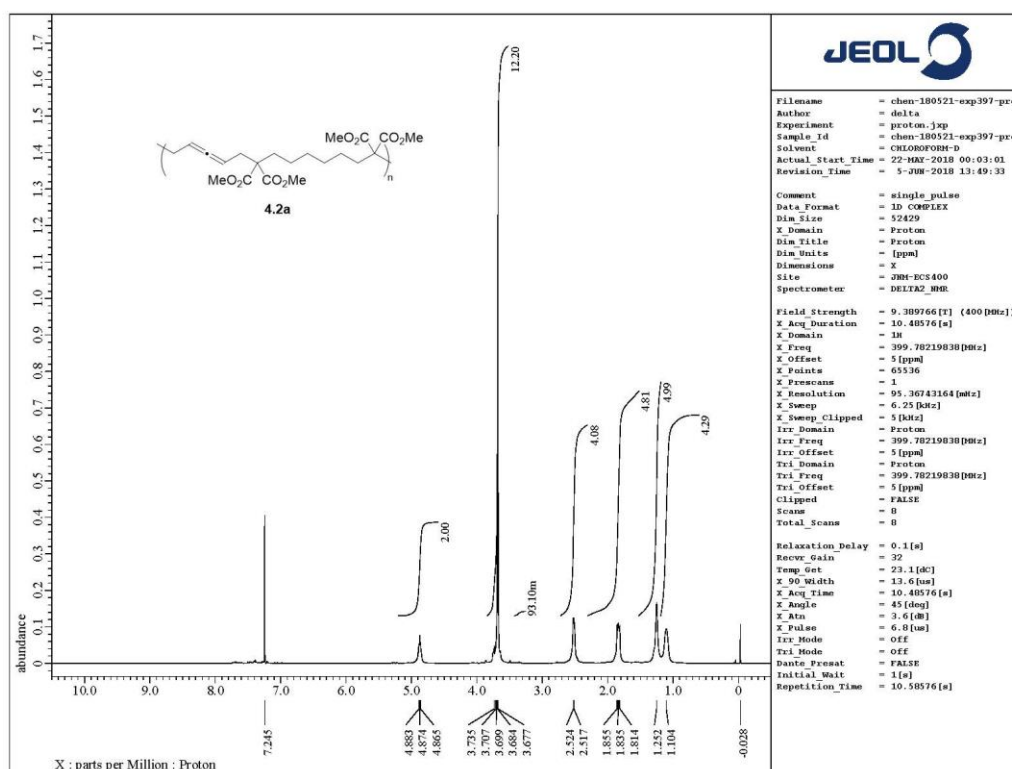
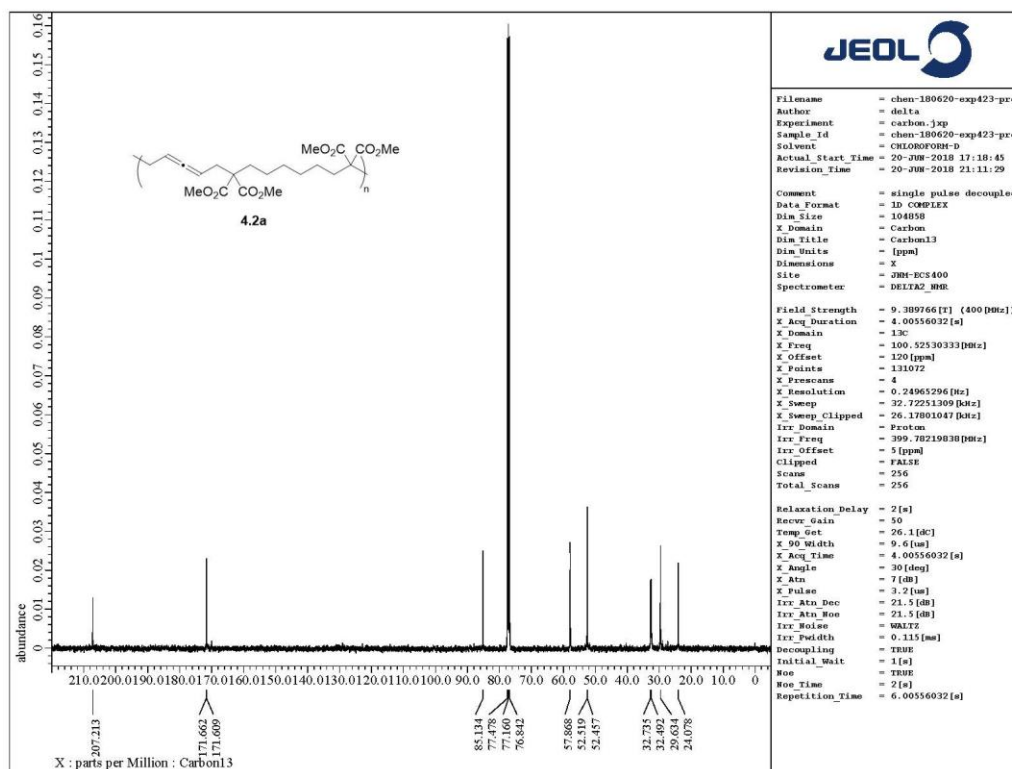
In a Schlenk flask fitted with a reflux condenser, metal sodium (2.01 g, 87.6 mmol) was dissolved in 60 mL of methanol at room temperature, and dimethyl malonate (12.15 g, 91.9 mmol) and (chloromethyl)trimethylsilane **4.5** (10.74 g, 87.6 mmol) was added by means of syringe under nitrogen. The mixture was heated for 24 hours at the temperature of boiling methanol. After cooled down to room temperature, the mixture was neutralized by 1 M HCl_{aq} until pH = 7–8, extracted with Et₂O (3 x 100 mL), washed with brine (100 mL), and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (hexane/Et₂O = 2/1) to give the **4.6** ^[18] (11.31 g, 59% yield). ¹H NMR (CDCl₃): δ 0.13 (s, 9H), 1.19 (d, *J* = 8.1 Hz, 2H), 3.40 (t, *J* = 8.1 Hz, 1H), 3.73 (s, 6H).

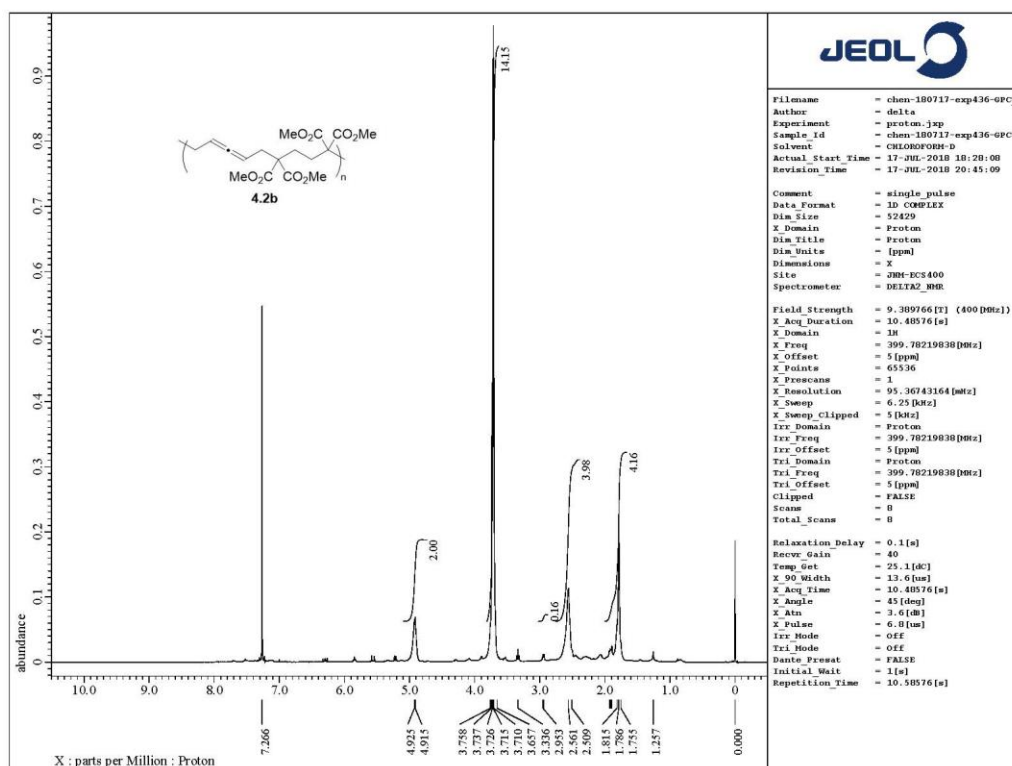
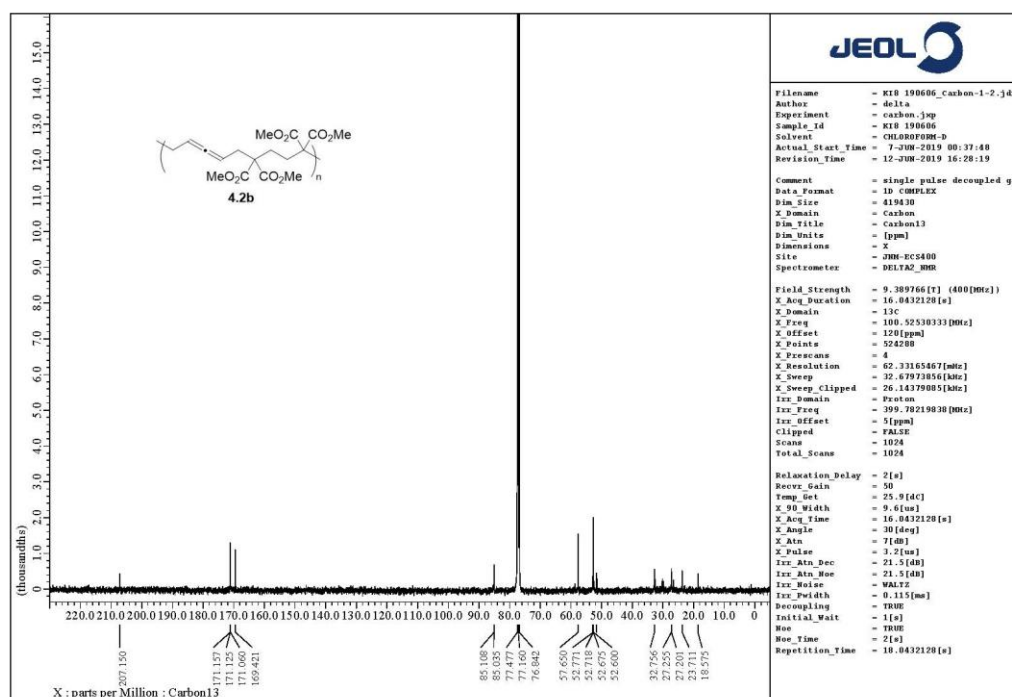
To a 100 mL Schlenk flask containing **4.6** (11.31 g, 51.8 mmol) was added concd. H₂SO₄ (40 mL). The reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with H₂O (100 mL), washed Et₂O (3 x 100 mL). The organic layers were combined and washed with saturated NaHCO_{3aq} (2 x 100 mL), brine (100 mL), and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (hexane/Et₂O = 1/1) to give **4.3c** (9.21 g, 84% yield) as a colorless oil. ¹H NMR(CDCl₃): δ 0.08, 1.20 (d, *J* = 8.0 Hz, 4H), 3.43 (t, *J* = 8.0 Hz, 2H), 3.73 (s, 12H). ¹³C NMR(CDCl₃): δ 0.7, 17.6, 47.0, 52.7, 171.04. ESI-HRMS Calcd for C₁₆H₃₀O₉Si₂Na (M + Na): 445.1326. Found: 445.1312.

Palladium-Catalyzed Polymerization of **3.1a** with **4.1a-c** (Table 4-1)

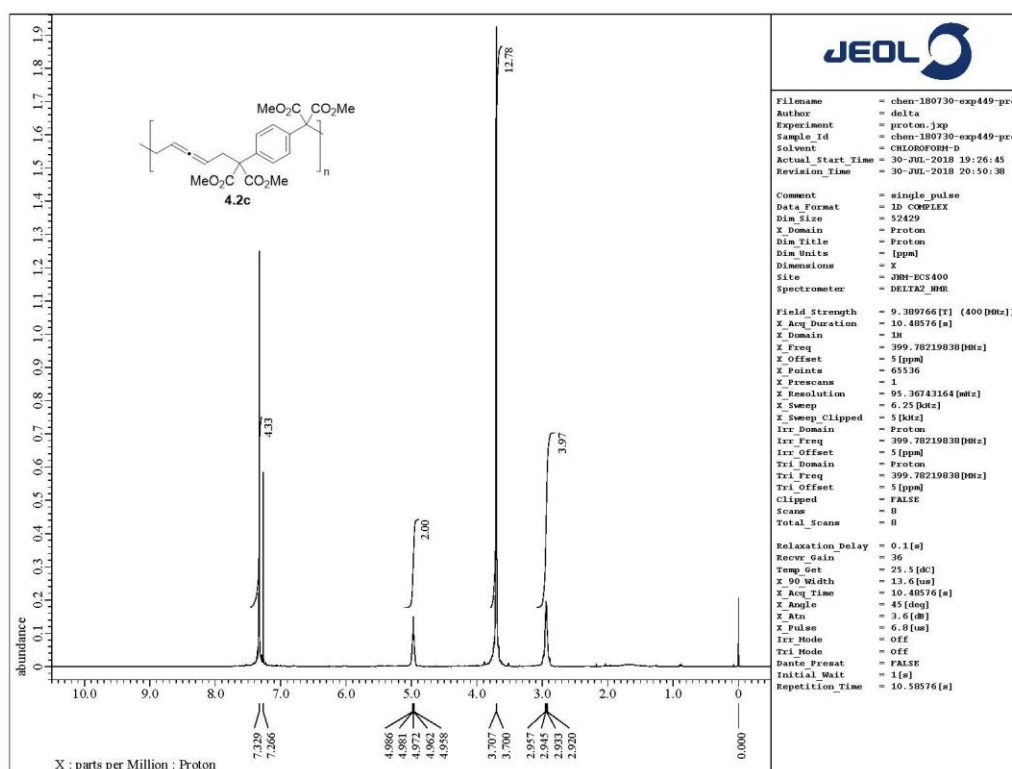


The reaction conditions and the results are summarized in Table 4-1. To a mixture of $\text{Pd}(\text{dba})_2$ (2.9 mg, 5 μmol), ligand (5.5 μmol), **4.1** (0.25 mmol), and an appropriate base (0.60 mmol) in THF (1.5 mL) was added **3.1a** (51 mg, 0.25 mmol) by means of syringe under nitrogen. After being stirred for 5 days at 40 °C, the mixture was added 3 mL of H_2O , and extracted with a small amount of CHCl_3 three times. The combined organic solution was dried over MgSO_4 and evaporated to dryness under reduced pressure. The residue was purified by precipitation from CHCl_3 and hexane to give corresponding polymer **4.2a-c**. The ^1H NMR and ^{13}C NMR charts of allenic polymer **4.2a-c** are listed below.

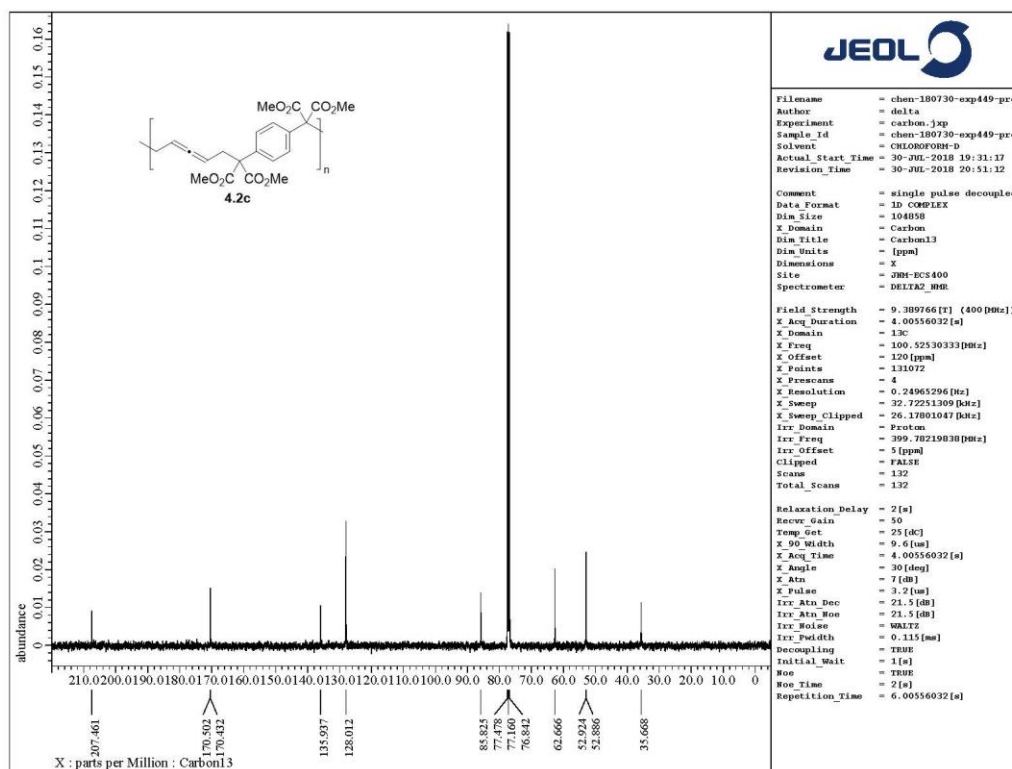
¹H NMR of polymer **4.2a** ^{13}C NMR of polymer **4.2a**

¹H NMR of polymer **4.2b** ^{13}C NMR of polymer **4.2b**

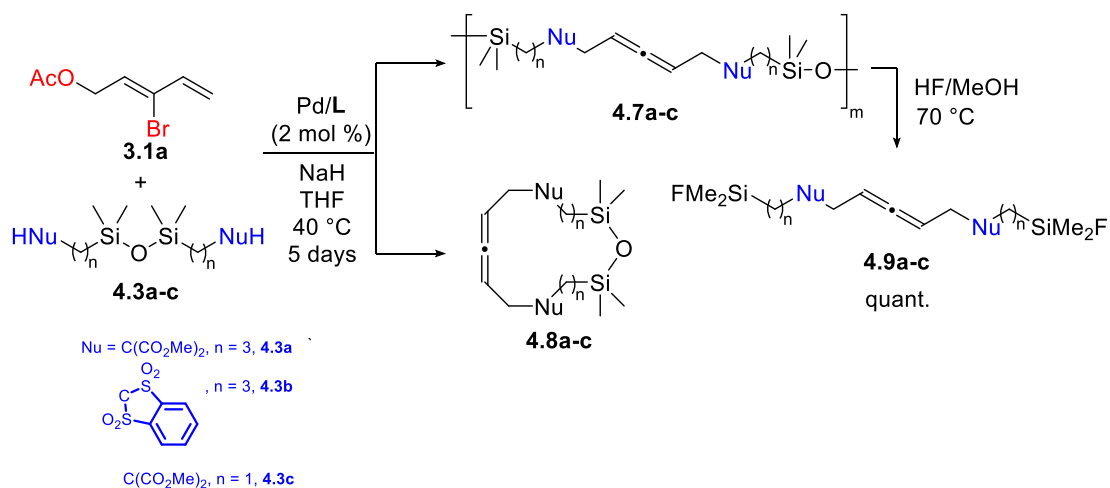
¹H NMR of polymer **4.2c**



¹³C NMR of polymer **4.2c**

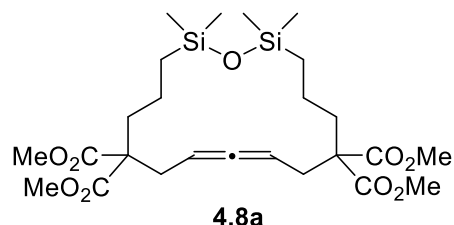


Palladium-Catalyzed Polymerization of **3.1a** with **4.3a-c** (Table 4-2, 4-3, 4-4)

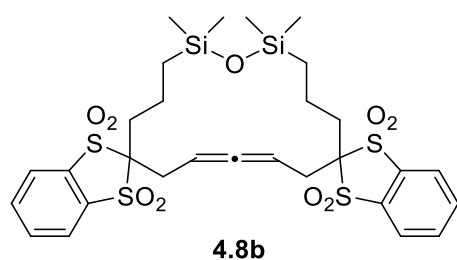


The reaction conditions and the results are summarized in Table 4-2, 4-3, 4-4. To a mixture of $\text{Pd}(\text{dba})_2$ (2.9 mg, 5 μmol), ligand (5.5 μmol), **4.3** (0.25 mmol), and an appropriate base (0.60 mmol) in THF (1.5 mL) was added **3.1a** (51 mg, 0.25 mmol) by means of syringe under nitrogen. After being stirred for 5 days at 40 °C, the mixture was added 3 mL of H_2O , and extracted with a small amount of CHCl_3 three times. The combined organic solution was dried over MgSO_4 and evaporated to dryness under reduced pressure. The residue was purified by precipitation from CHCl_3 and hexane to give corresponding polymer **4.7a-c**. The cyclic allene **4.8a-c** was separated from the corresponding mother liquor by chromatography on Al_2O_3 . The degradation of polymer **4.7a-c** was carried out as the procedure below. To a 20 mL polypropylene flask containing polymer **4.7** (50 μmol) was added a mixture of MeOH (3 mL) and aqueous hydrofluoric acid (0.5 mL, 55%). After being stirred for 3 h at 70 °C, the mixture was neutralized by saturated $\text{NaHCO}_{3\text{aq}}$, and extracted with EtOAc three times. The combined organic solution was dried over MgSO_4 and evaporated to dryness under reduced pressure. The residue was purified by recycle GPC separation to give corresponding polymer **4.9a-c** quantitatively. The characterization data, ^1H NMR and

^{13}C NMR charts of allenic polymer **4.7a-c**, cyclic allene **4.8a-c**, and dimethylfluorosilane **4.9a-c** are listed below.

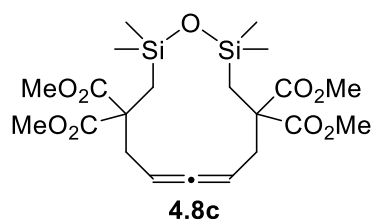


Tetramethyl (1,1,3,3-Tetramethyl-1,3-disila-2-oxa-9,10-cyclohexdecadiene)-7,7,13,13-tetracarboxylate (4.8a) ^1H NMR (CDCl_3): δ 0.02 (s, 6H), 0.04 (s, 6H), 0.48-0.54 (m, 4H), 1.20-1.26 (m, 4H), 1.94-1.99 (m, 4H), 2.58-2.72 (m, 4H), 3.71 (s, 6H), 3.72 (s, 6H), 4.80-4.85 (m, 2H). ^{13}C NMR (CDCl_3): δ 0.6, 0.7, 18.0, 18.7, 31.8, 35.2, 52.56, 52.65, 57.6, 85.5, 171.8, 171.9, 207.29. ESI-HRMS Calcd for $\text{C}_{25}\text{H}_{42}\text{O}_9\text{Si}_2\text{Na}$ ($\text{M} + \text{Na}$): 565.2265. Found: 565.2264. $[\alpha]_D^{25} = +16.3$ (c 0.20, CHCl_3 for the sample of (*S*)-81% ee). Chiral HPLC Analysis Conditions: Chiralpak OZ-H; eluent: hexane/*i*PrOH = 10/1; flow rate: 0.5 mL/min; wave length: 230 nm. t_1 [(*R*)-enantiomer] = 12.1 min, t_2 [(*S*)-enantiomer] = 14.5 min.

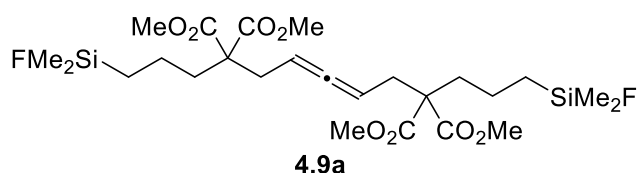


2,2'-[(1,1,3,3-Tetramethyldisiloxane-1,3-diyl)bis(propane-1,3-diyl)]-2,2'-(penta-2,3-diene-1,5-diyl)bis(-benzodithiole-1,1,3,3-tetraoxide) (4.8b) ^1H NMR (CDCl_3): δ 0.10 (s, 6H), 0.12 (s, 6H), 0.64-0.67 (m, 4H), 1.74-1.82 (m, 4H), 2.28-2.50 (m, 4H), 2.94-3.04 (m, 4H), 5.41-5.56 (m, 2H), 7.89-7.92 (m, 4H), 7.98-8.01 (m, 4H). ^{13}C NMR

(CDCl₃): δ 0.7, 1.0, 17.4, 18.7, 28.9, 30.9, 79.2, 84.4, 123.02, 123.03, 135.18, 135.23, 136.3, 136.5, 208.76. ESI-HRMS Calcd for C₂₉H₃₈O₉S₄Si₂Na (M + Na): 737.0835. Found: 737.0833. $[\alpha]^{25}_D = -32.9$ (*c* 0.69, CHCl₃ for the sample of (*R*)-68% ee). Chiral HPLC Analysis Conditions: Chiralpak IC; eluent: hexane/EtOAc = 5/1; flow rate: 0.8 mL/min; wave length: 254 nm. *t*₁ [(*R*)-enantiomer] = 20.1 min, *t*₂ [(*S*)-enantiomer] = 23.5 min.

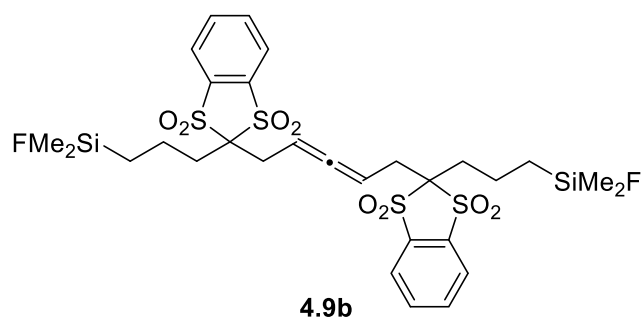


Tetramethyl (1,1,3,3-Tetramethyl-1,3-disila-2-oxa-7,8-cyclododecadiene)-5,5,11,11-tetracarboxylate (4.8c) ¹H NMR (CDCl₃): δ 0.02 (s, 6H), 0.10 (s, 6H), 1.54-1.58 (m, 4H), 2.71-2.85 (m, 4H), 3.70 (s, 6H), 3.72 (s, 6H), 4.68 (m, 2H). ¹³C NMR (CDCl₃): δ 0.8, 2.4, 22.1, 34.5, 52.6, 52.9, 55.4, 85.7, 172.5, 173.1, 208.271. ESI-HRMS Calcd for C₂₁H₃₄O₉Si₂Na (M + Na): 509.1639. Found: 509.1625. $[\alpha]^{25}_D = +32.3$ (*c* 0.41, CHCl₃ for the sample of (*S*)-80% ee). Chiral HPLC Analysis Conditions: Chiralpak OZ-H; eluent: hexane/*i*PrOH = 100/1; flow rate: 0.6 mL/min; wave length: 215 nm. *t*₁ [(*S*)-enantiomer] = 45.5 min, *t*₂ [(*R*)-enantiomer] = 59.2 min.

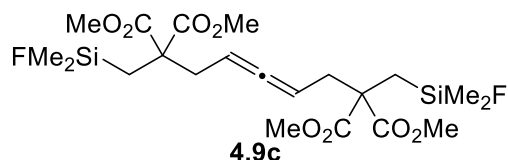


Tetramethyl 1,13-Bis(fluorodimethylsilyl)trideca-6,7-diene-4,4,10,10-tetracarboxylate (4.9a) ¹H NMR (CDCl₃): δ 0.20 (s, 6H), 0.22 (s, 6H), 0.65-0.71 (m,

4H), 1.26-1.30 (m, 4H), 1.91-1.95 (m, 4H), 2.50-2.59 (m, 4H), 3.71 (s, 6H), 3.72 (s, 6H), 4.90-4.93 (m, 2H). ^{13}C NMR (CDCl_3): δ -1.3, -1.2, 17.0 (d, $J_{\text{CF}} = 13.8$ Hz), 17.5, 32.8, 36.0, 52.56, 52.60, 57.8, 85.2, 171.56, 171.60, 207.3. ^{19}F NMR (CDCl_3): δ -161.9 (septet, $J_{\text{HF}} = 7.6$ Hz). ESI-HRMS Calcd for $\text{C}_{25}\text{H}_{42}\text{F}_2\text{O}_8\text{Si}_2\text{Na}$ ($\text{M} + \text{Na}$): 587.2284. Found: 587.2278. $[\alpha]^{25}_{\text{D}} = -8.5$ (c 0.10, CHCl_3 for the sample of (*R*)-71% ee). Chiral HPLC Analysis Conditions: Chiralpak OZ-H; eluent: hexane/*i*PrOH = 20/1; flow rate: 0.8 mL/min; wave length: 230 nm. t_1 [(*S*)-enantiomer] = 8.9 min, t_2 [(*R*)-enantiomer] = 10.4 min.

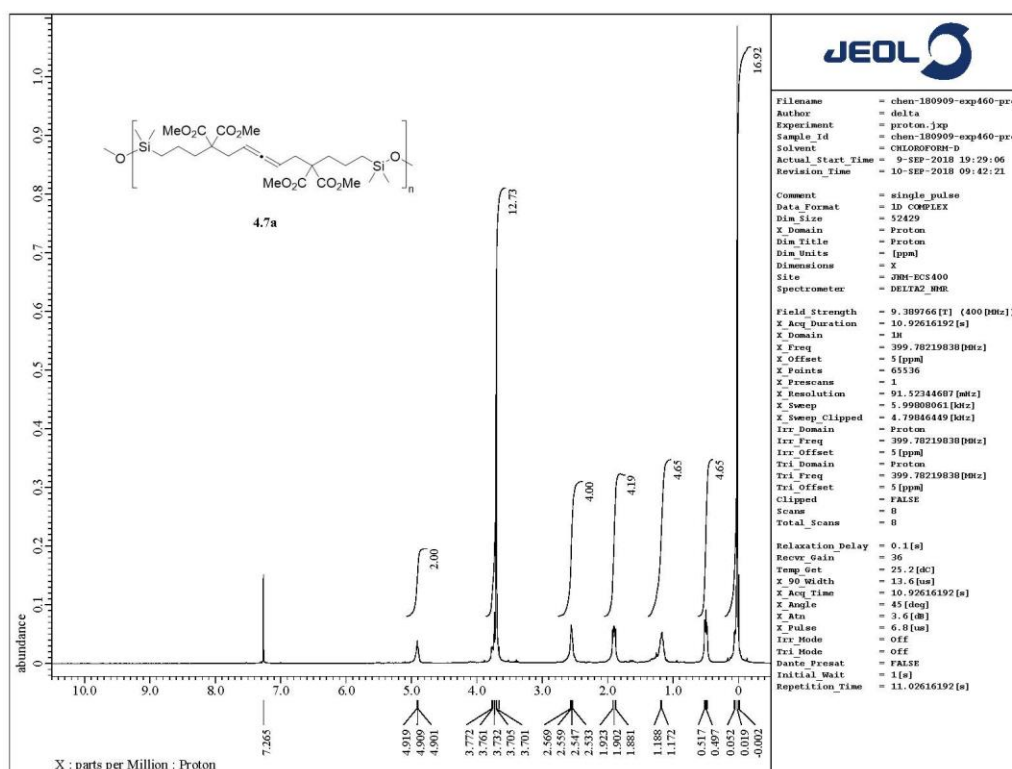
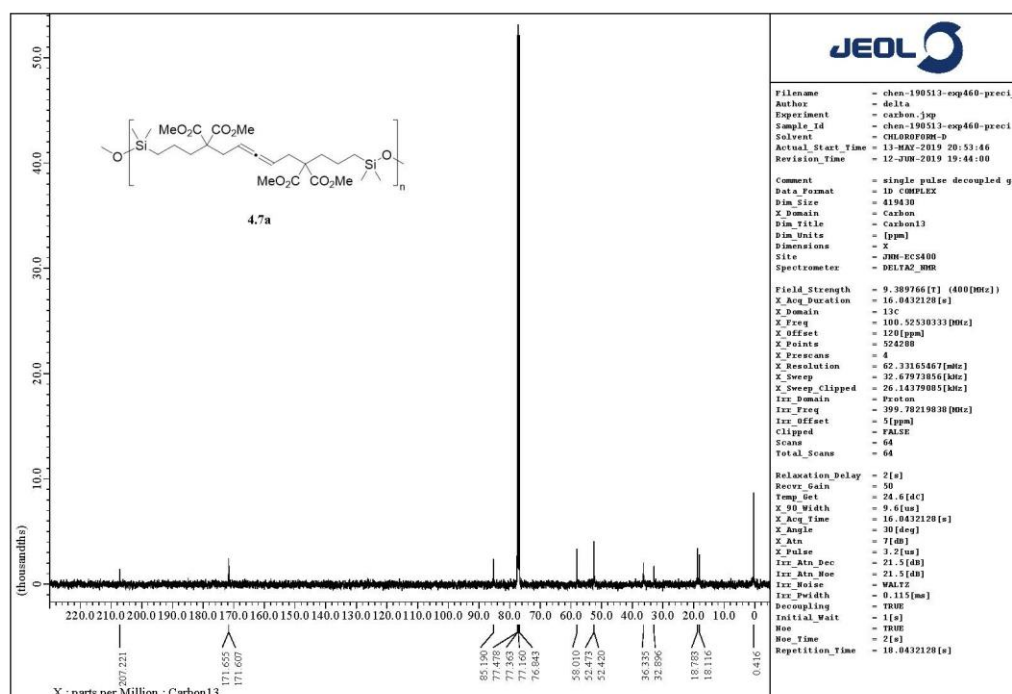


2,2'-(Penta-2,3-diene-1,5-diyl)bis[2-(3-(fluorodimethylsilyl)propyl)-benzodithiole-1,1,3,3-tetraoxide] (4.9b) ^1H NMR (CDCl_3): δ 0.22 (d, $J_{\text{HF}} = 2.0$ Hz, 6H), 0.23 (d, $J_{\text{HF}} = 2.0$ Hz, 6H), 1.58-1.69 (m, 4H), 2.20-2.38 (m, 4H), 2.90-2.93 (m, 4H), 5.23-5.27 (m, 2H), 7.88-7.94 (m, 4H), 7.98-8.01 (m, 4H). ^{13}C NMR (CDCl_3): δ -1.3, -1.2, 16.6, 17.2 (d, $J_{\text{CF}} = 14.2$ Hz), 29.9, 31.1, 78.7, 84.0, 122.92, 122.93, 135.4, 135.5, 136.7, 136.8, 209.14. ^{19}F NMR (CDCl_3): δ -156.6 (septet, $J_{\text{HF}} = 7.6$ Hz). ESI-HRMS Calcd for $\text{C}_{29}\text{H}_{38}\text{O}_8\text{S}_4\text{Si}_2\text{Na}$ ($\text{M} + \text{Na}$): 759.0854. Found: 759.0885. $[\alpha]^{25}_{\text{D}} = -45.1$ (c 0.41, CHCl_3 for the sample of (*R*)-90% ee). Chiral HPLC Analysis Conditions: Chiralpak IA; eluent: hexane/*i*PrOH = 10/1; flow rate: 0.8 mL/min; wave length: 254 nm. t_1 [(*S*)-enantiomer] = 117.6 min, t_2 [(*R*)-enantiomer] = 132.2 min.

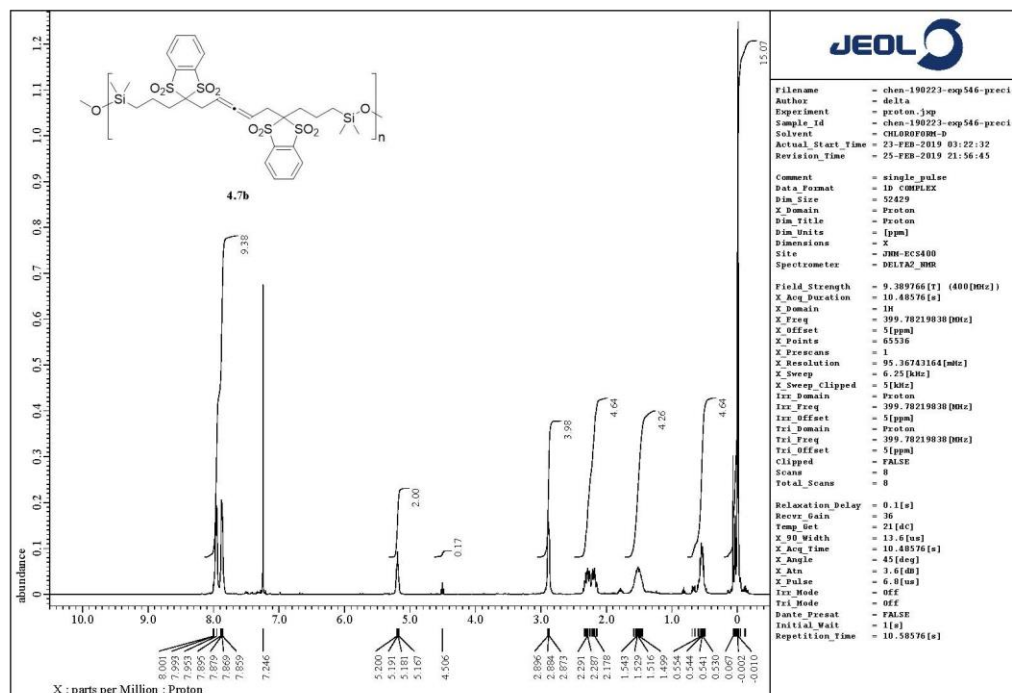


Tetramethyl 1,9-Bis(fluorodimethylsilyl)nona-4,5-diene-2,2,8,8-tetracarboxylate

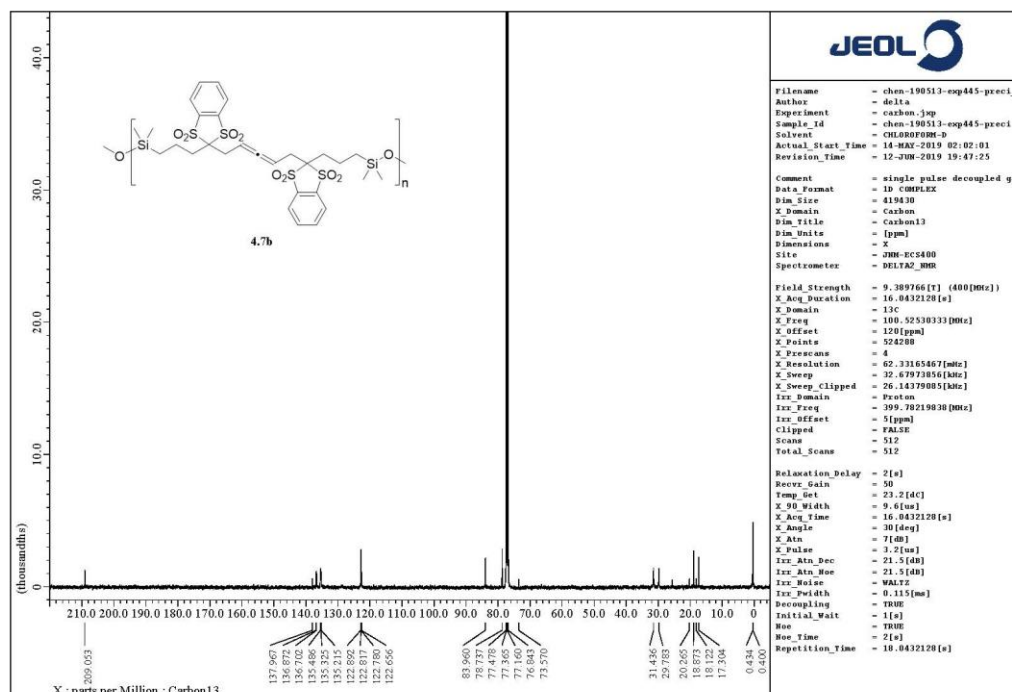
(4.9c) ^1H NMR (CDCl_3): δ 0.24 (s, 6H), 0.26 (s, 6H), 1.38 (d, $J_{\text{HF}} = 6.4$ Hz, 4H), 2.58–2.63 (m, 4H), 3.726 (s, 6H), 3.728 (s, 6H), 4.97–5.02 (m, 2H). ^{13}C NMR (CDCl_3): δ 0.01 (d, $J_{\text{CF}} = 2.0$ Hz), 0.16 (d, $J_{\text{CF}} = 2.1$ Hz), 22.41 (d, $J_{\text{CF}} = 15.1$ Hz), 36.73, 52.76, 52.79, 55.83 (d, $J_{\text{CF}} = 1.0$ Hz), 85.59, 172.18, 172.19, 207.95. ^{19}F NMR (CDCl_3): δ –156.62 (septet, $J_{\text{HF}} = 7.5$ Hz). EI-HRMS calcd for $\text{C}_{21}\text{H}_{34}\text{F}_2\text{O}_8\text{Si}_2\text{Na}$ 531.1658, found 531.1656. $[\alpha]_D^{25} = +38.3$ (c 0.29, CHCl_3 for the sample of (*S*)-80% ee). Chiral HPLC Analysis Conditions: Chiralpak OZ-H; eluent: hexane/*i*PrOH = 100/1; flow rate: 0.5 mL/min; wave length: 215 nm. t_1 [(*R*)-enantiomer] = 35.7 min, t_2 [(*S*)-enantiomer] = 53.9 min.

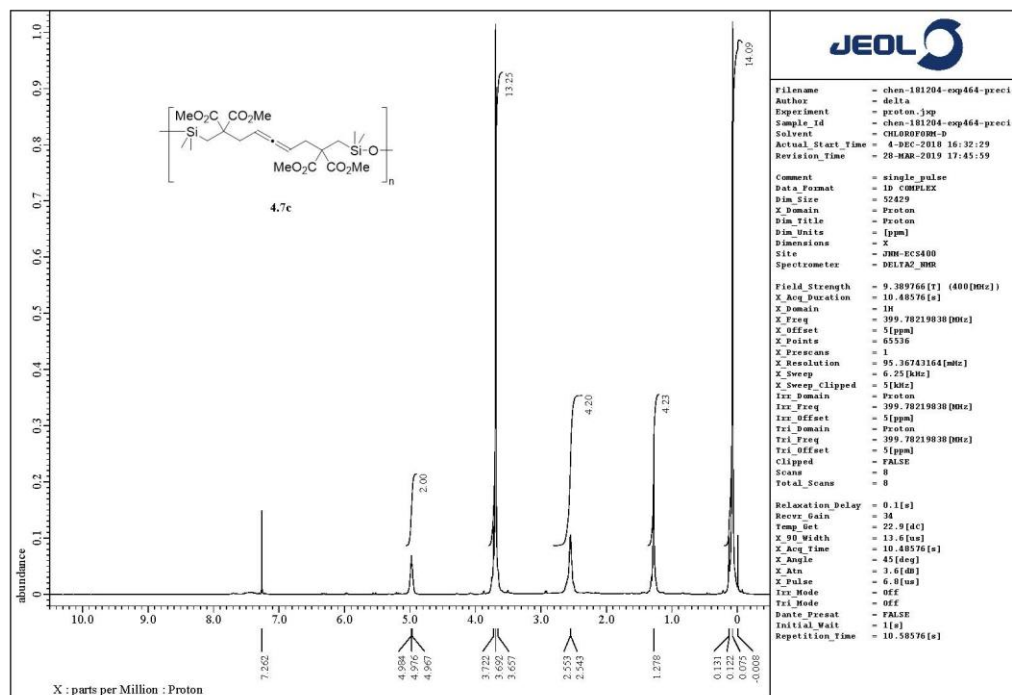
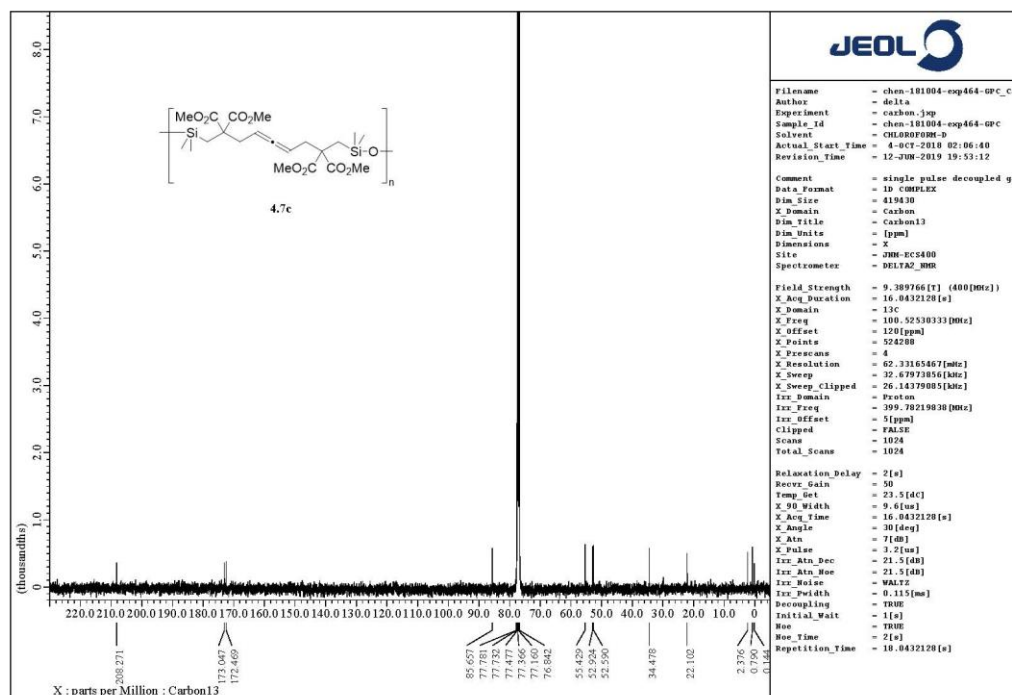
¹H NMR of polymer **4.7a** ^{13}C NMR of polymer **4.7a**

¹H NMR of polymer **4.7b**

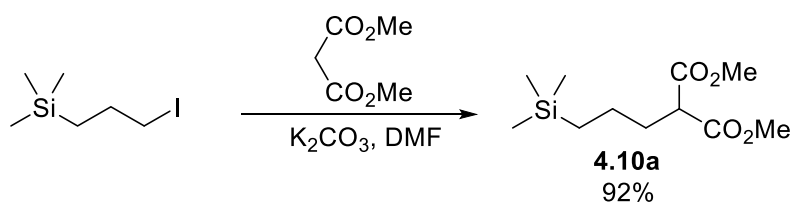


¹³C NMR of polymer **4.7b**



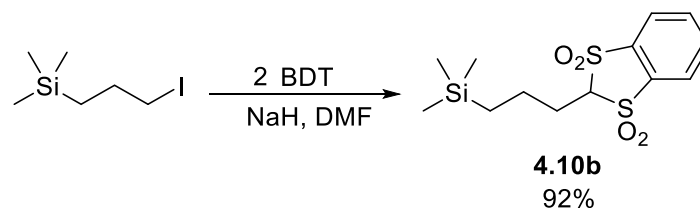
¹H NMR of polymer **4.7c** ^{13}C NMR of polymer **4.7c**

Synthesis of Dimethyl 2-[3-(Trimethylsilyl)propyl]malonate (**4.10a**)



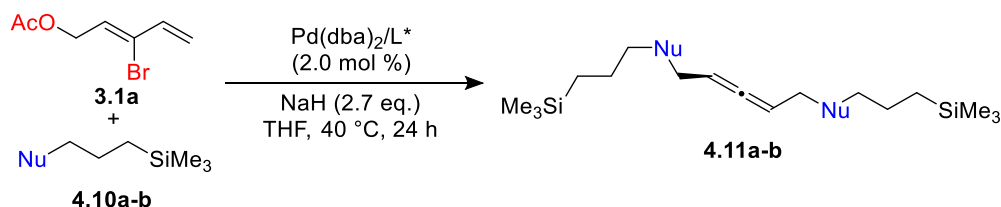
To a 100 mL Schlenk flask containing (3-iodopropyl)trimethylsilane (3.00 g, 12.4 mmol) were added dimethyl malonate (1.96 g, 14.9 mmol) and K₂CO₃ (2.07 g, 15.0 mmol) followed by DMF (20 mL). The reaction mixture was stirred at 100 °C and monitored by ¹H NMR. After complete conversion of (3-iodopropyl)trimethylsilane, the crude reaction was filtered through a plug of Celite 545[®], washed with EtOAc (3 x 50 mL). The mixture was washed with H₂O (3 x 100 mL), brine (100 mL), dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (hexane/EtOAc = 5/1) to give the **4.10a** (2.82 g, 92% yield) as a colorless oil. ¹H NMR (CDCl₃): δ -0.03 (s, 9H), 0.48-0.53 (m, 2H), 1.31-1.34 (m, 2H), 1.92 (q, *J* = 7.6 Hz, 2H), 3.39 (t, *J* = 7.5 Hz, 1H), 3.73 (s, 6H). ¹³C NMR (CDCl₃): δ -1.6, 16.4, 22.0, 32.6, 51.6, 52.6, 170.1. ESI-HRMS Calcd for C₁₁H₂₂O₄SiNa (M + Na): 269.1185. Found: 269.1183.

Synthesis of 2,2'-[(1,1,3,3-Tetramethyldisiloxane-1,3-diyl)bis(propane-1,3-diyl)]bis(-benzodithiole-1,1,3,3-tetraoxide) (4.10b**)**



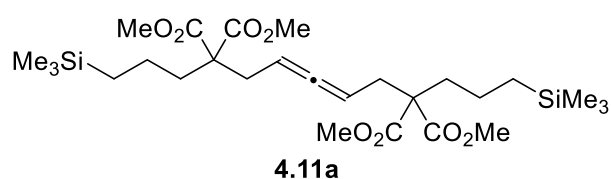
To a 100 mL Schlenk flask containing (3-iodopropyl)trimethylsilane (0.93 g, 3.8 mmol) was added BDT (1.00 g, 4.6 mmol) and NaH (110 mg, 4.6 mmol) followed by DMF (20 mL). The reaction mixture was stirred at 80 °C and monitored by ^1H NMR. After complete conversion of (3-iodopropyl)trimethylsilane, the crude reaction was filtered through a plug of Celite 545[®], washed with EtOAc (3 x 50 mL). The mixture was washed with sat. H_2O (3 x 100 mL), brine (100 mL), dried over MgSO_4 , and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (hexane/EtOAc = 3/2) to give the **4.10b** (1.17 g, 92% yield) as a white solid. ^1H NMR (CDCl_3): δ 0.04, (s, 9H), 0.65–0.70 (m, 2H), 1.78–1.81 (m, 2H), 2.34 (q, J = 7.2 Hz, 2H), 4.41 (t, J = 7.2 Hz), 7.91–7.93 (m, 2H), 8.02–8.04 (m, 2H). ^{13}C NMR(CDCl_3): δ –1.7, 16.6, 21.0, 25.8, 73.7, 122.7, 135.2, 138.1. ESI-HRMS Calcd for $\text{C}_{13}\text{H}_{20}\text{O}_4\text{S}_2\text{SiNa}$ ($\text{M} + \text{Na}$): 355.0470. Found: 355.0470.

Palladium-Catalyzed Asymmetric Reaction of Axially Chiral Monomeric Allene **4.10 with **3.1a****



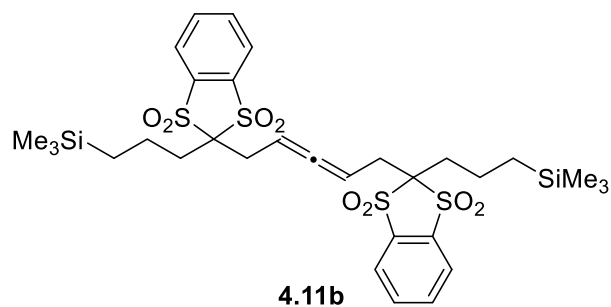
The reaction conditions and the results are summarized in Scheme 4-3-4. A mixture of $\text{Pd}(\text{dba})_2$ (2.8 mg, 5 μmol), ligand (5.5 μmol), and **3.1a** (51 mg, 0.25 mmol) was

dissolved in THF (2 mL), and the solution was added to a mixture of **4.10** (0.63 mmol) and an NaH (0.68 mmol) via cannula under nitrogen. The mixture was stirred at 40 °C. for 24 h, then added 3 mL of H₂O, and extracted with a small amount of CHCl₃ three times. The combined organic solution was dried over MgSO₄ and evaporated to dryness under reduced pressure. The residue was chromatographed on Al₂O₃ to give allene **4.11** in pure form. The characterization data of monomeric allene **4.11a-b** are listed below.



Tetramethyl 1,13-Bis(trimethylsilyl)trideca-6,7-diene-4,4,10,10-tetracarboxylate

(4.11a) Colorless oil. Yield: 88 mg (65%). ¹H NMR (CDCl₃): δ −0.44 (s, 18H), 0.48-0.50 (m, 4H), 1.13-1.17 (m, 4H), 1.88-1.92 (m, 4H), 2.49-2.61(m, 4H), 3.69 (s, 6H), 3.70 (s, 6H), 4.87-4.90(m, 2H). ¹³C NMR (CDCl₃): δ −1.5, 17.1, 18.6, 32.8, 36.4, 52.5, 52.5, 57.9, 85.2, 171.7, 171.8, 207.3. ESI-HRMS Calcd for C₂₇H₄₈O₈Si₂Na (M + Na): 579.2786. Found: 579.2788. [α]_D²⁴ = +47.1 (c 2.86, CHCl₃ for the sample of (*S*)-76% ee). Chiral HPLC Analysis Conditions: Chiralpak OZ-H; eluent: hexane/*i*PrOH = 100/1; flow rate: 0.8 mL/min; wave length: 230 nm. *t*₁ [(*S*)-enantiomer] = 13.8 min, *t*₂ [(*R*)-enantiomer] = 19.2 min.



2,2'-(Penta-2,3-diene-1,5-diyl)bis[2-{3-(trimethylsilyl)propyl}-benzodithiole

1,1,3,3-tetraoxide] (4.11b) White solid. Yield: 126 mg (69%). ^1H NMR (CDCl_3): δ – 0.03 (s, 18H), 0.53-0.57 (m, 4H), 1.52-1.54 (m, 4H), 2.20-2.29 (m, 4H), 2.89-2.92 (m, 2H), 5.23-5.26 (m, 2H), 7.88-7.90 (m, 4H), 7.96-7.98 (m, 4H). ^{13}C NMR (CDCl_3): δ – 1.6, 17.4, 17.9, 29.8, 31.6, 78.8, 84.0, 122.8, 122.9, 135.3, 135.4, 136.7, 136.8, 209.03. ESI-HRMS Calcd for $\text{C}_{31}\text{H}_{44}\text{O}_8\text{S}_4\text{Si}_2\text{Na}$ ($\text{M} + \text{Na}$): 751.1356 Found: 751.1349. $[\alpha]^{24}_{\text{D}} = -48.1$ (c 1.08, CHCl_3 for the sample of (*R*)-99% ee). Chiral HPLC Analysis Conditions: Chiralpak IC; eluent: hexane/*i*PrOH = 5/1; flow rate: 0.8 mL/min; wave length: 254 nm. t_1 [(*R*)-enantiomer] = 28.3 min, t_2 [(*S*)-enantiomer] = 35.8 min.

- [1] (a) Trost, B. M.; Machacek, M. R.; Aponick, A. *Acc. Chem. Res.* **2006**, *39*, 747. (b) Mohr, J. T.; Stoltz, B. M. *Chem.-Asian J.* **2007**, *2*, 1476. (c) Lu, Z.; Ma, S. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 258. (d) Trost, B. M.; Zhang, T.; Sieber, J. D. *Chem. Sci.* **2010**, *1*, 427. (e) Kazamaier, U. *Transition Metal Catalyzed Enantioselective Allylic Substitution in Organic Synthesis*; Springer: New York, 2011.
- [2] Kieseewetter, M. K.; Edward, J. A.; Kim, H.; Waymouth, R. M. *J. Am. Chem. Soc.* **2011**, *133*, 16390.
- [3] (a) Nomura, N.; Tsurugi, K.; Okada, M. *J. Am. Chem. Soc.* **1999**, *121*, 7268. (b) Nomura, N.; Tsurugi, K.; Okada, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 1932. (c) Tsurugi, K.; Nomura, N.; Aoi, K. *Tetrahedron Lett.* **2002**, *43*, 469. (d) Koizumi, T.; Sakamoto, J.; Gondo, Y.; Endo, T. *Macromolecules* **2002**, *35*, 2898. (e) Nomura, N.; Komiyama, S.; Kasugai, H.; Saba, M. *J. Am. Chem. Soc.* **2008**, *130*, 812.
- [4] (a) Kanbayashi, N.; Okamura, T.; Onitsuka, K. *Macromolecules* **2014**, *47*, 4178. (b) Kanbayashi, N.; Okamura, T.; Onitsuka, K. *Macromolecules* **2015**, *48*, 8437. (c) Kanbayashi, N.; Hosoda, K.; Okamura, T.; Aoshima, S.; Onitsuka, K. *Polym. Chem.*, **2016**, *7*, 3691.
- [5] (a) Kijima, M.; Kinoshita, I.; Shirakawa, H. *Synth. Met.* **1999**, *100*, 61. (b) Kijima, M.; Hiroki, K.; Shirakawa, H. *Macromol. Rapid Commun.* **2002**, *23*, 901.
- [6] Hiroki, K.; Kijima, M. *Chem. Lett.* **2005**, *34*, 942.
- [7] Hasegawa, M.; Endo, J.; Iwata, S.; Shimasaki, T.; Mazaki, Y. *Beilstein J. Org. Chem.* **2015**, *11*, 972.
- [8] (a) Nozaki, K.; Nakano, K.; Hiyama, T. *J. Am. Chem. Soc.* **1999**, *121*, 11008. (b) Nozaki, K.; Nakano, K.; Hiyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 5501. (c) Nakano, K.; Kosaka, N.; Hiyama, T.; Nozaki, K. *Dalton Trans.* **2003**, 4039.

- [9] (a) Kumagai, T.; Itsuno S. *Macromolecules* **2000**, *33*, 4995. (b) Kumagai, T.; Itsuno, S. *Macromolecules* **2001**, *34*, 7624. (c) Itsuno, S.; Kumagai, T. *Synthesis* **2002**, 941. (d) Itsuno, S. *Prog. Polym. Sci.* **2005**, *30*, 540.
- [10] (a) Eaborn, C. *J. Chem. Soc.* **1952**, 2840. (b) Eaborn, C. *J. Chem. Soc.* **1952**, 2846. (c) Eaborn, C. *Pure Appl. Chem.* **1969**, *19*, 375.
- [11] Perry, R. J.; O'Brien, M. J. *Energy Fuels* **2011**, *25*, 1906.
- [12] (a) Sommer, L. H.; Pioch, R. P.; Marans, N. S.; Goldberg, G. M.; Rockett J.; Kerlin, J. *J. Am. Chem. Soc.* **1953**, *75*, 2932. (b) Sommer, L. H.; Pioch, R. P. *J. Am. Chem. Soc.* **1953**, *75*, 6337. (c) Sommer, L. H.; English, W. D.; Ansul, G. R.; Vivona, D. N. *J. Am. Chem. Soc.* **1955**, *77*, 2485. (d) Sommer, L. H.; Masterson, J. M.; Steward, O. W.; Leitheiser, R. H. *J. Am. Chem. Soc.* **1956**, *78*, 2010.
- [13] Glueck, D. S. *Catal. Sci. Technol.* **2011**, *1*, 1099.
- [14] Kündig, E. P.; Cunningham Jr. A. F. *Tetrahedron* **1988**, *44*, 6855.
- [15] Newkome, G. R.; Baker, G. R.; Arai, S.; Saunders, M. J.; Russo, P. S.; Theriot, K. J.; Moorefield, C. N.; Rogers, L. E.; Miller, J. E.; Lieux, T. R.; Murray, M. E.; Phillips, B.; Pascal, L. *J. Am. Chem. Soc.* **1990**, *112*, 8458.
- [16] Marvel, S. C.; Vest, R. D. *J. Am. Chem. Soc.* **1959**, *81*, 984.
- [17] Beare, N. A.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 541.
- [18] Fleming, I.; Goldhill, J.; Perry, D.A. *J. Chem. Soc., Perkin Trans I* **1982**, *7*, 1563.
- [19] Kuwajima, I.; Urabe, H. *Org. Synth.* **1988**, *66*, 87.
- [20] (a) Lowe, G. *Chem. Commun.* **1965**, 411.; (b) Brewster, J. H. *Topics in Stereochemistry* **1967**, *2*, 1.

Chapter V

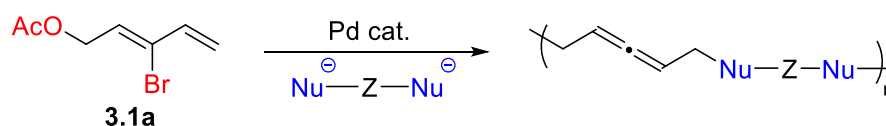
Palladium-Catalyzed Preparation of Allenic Polymers from Bis(2-bromo-1,3-diene)s

Section 1.

Introduction for Chapter V

I have demonstrated that the 3-bromopenta-2,4-dienyl esters are excellent precursors for constructing the doubly nucleophilic-substituted allenic derivatives, including the C_2 -symmetric allenes, C_1 -unsymmetric allenes, and allenic polymers. Herein, I have been interested in an extension of preparation of allenic polymers using bis(2-bromo-1,3-diene) **5.1a** as a bifunctional electrophilic monomer instead of 3-bromopenta-2,4-dienyl acetate (Figure 5-1).

Chapter IV



This Chapter

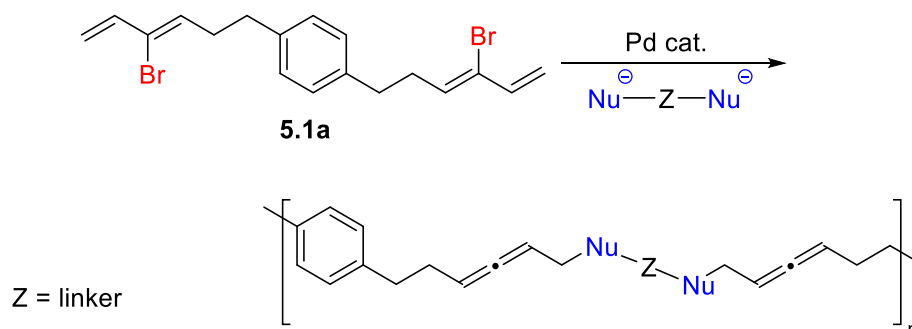


Figure 5-1. Polymerization of Bifunctional Electrophilic Substrates

The new axially chiral allenic polymers generated from the bis(2-bromo-1,3-diene)s possessing the two axially chiral allenic moieties (marked in green, Figure 5-2) in a repeating subunit might make the determination of enantioregularities more complicated by my method (i.e., the cleaved fragments from the repeating subunit become diastereomeric mixtures of bisallenes, as shown in Figure 5-2). In this chapter, I will discuss that the polymerization of monomers, bis(2-bromo-1,3-diene) and a bifunctional nucleophile (**4.1** or **4.3**), catalyzed by a palladium complex generated from

a palladium precursor and a bisphosphine ligand. Furthermore, a bis(2-bromo-1,3-diene) with a cleavable substructure was prepared for my palladium-catalyzed polymerization, which was used for the asymmetric extensions using chiral palladium complexes as catalysts in my polymerization.

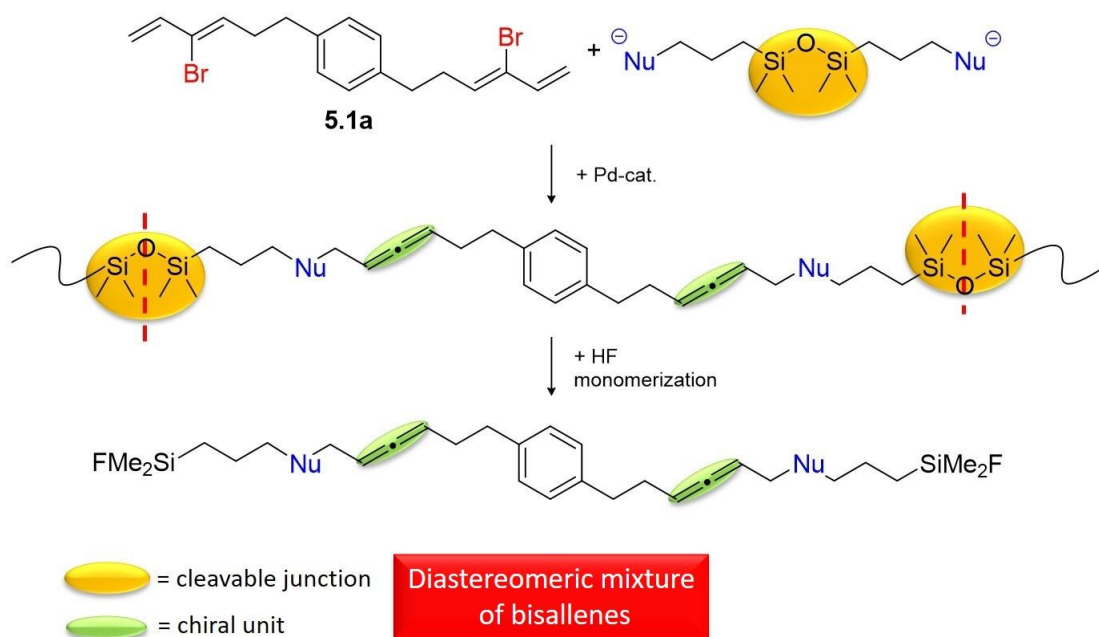


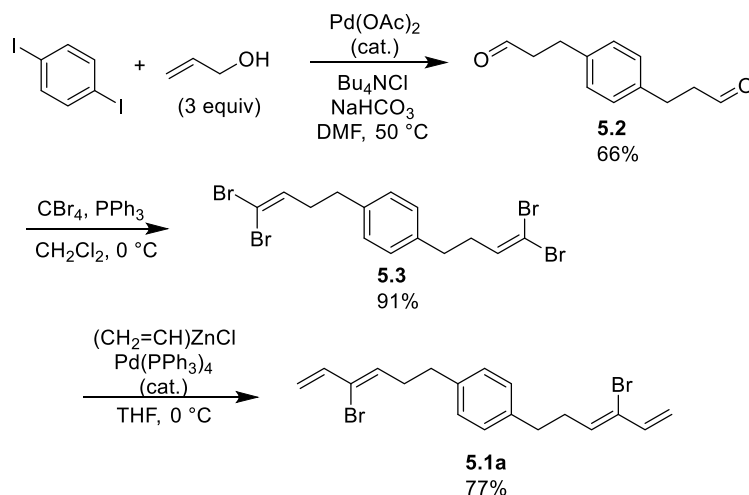
Figure 5-2. Degradation of Axially Chiral Allenic Polymer Providing Diastereomeric Bisallenes

Section 2.

Palladium-Catalyzed Polymerization of Bis(2-bromo-1,3-diene) with Bifunctional Nucleophiles

5-2-1. Preparation of Bis(2-bromo-1,3-diene)

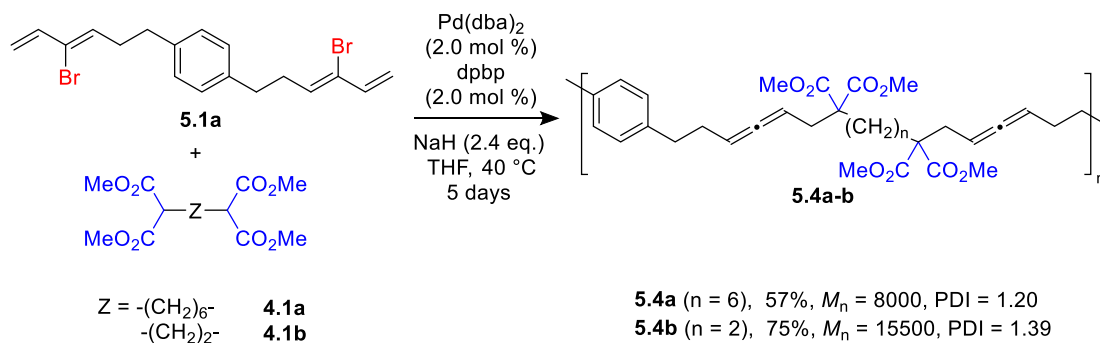
Scheme 5-1. Preparation of Bis(2-bromo-1,3-diene) **5.1a**.



The substrate for this study is bis(2-bromo-1,3-diene) **5.1a**, and it is prepared from *para*-diiodobenzene by the three-step sequence as depicted in Scheme 5-1. The preparation of *para*-phenylene-3,3-dipropanal **5.2** was followed by the palladium-catalyzed Mizoroki-Heck arylation of allylic alcohols as reported by Brückner.^[1b] The reaction of *para*-diiodobenzene with allyl alcohol catalyzed by $\text{Pd}(\text{PPh}_3)_4$ in the presence of sodium bicarbonate and *tetra-n*-butylammonium chloride provided dialdehyde **5.2** in 66% yield. Dialdehyde **5.2** was converted into 1,4-bis(4,4-dibromo-3-butenyl)benzene **5.3** by the standard Wittig dibromoolefination (Ramirez olefination).^[2] The palladium-catalyzed Negishi coupling of **5.3** with vinylzinc chloride proceeded with excellent regioselectivity to give bis(2-bromo-1,3-diene) **5.1a** in 77% yield exclusively.^[3]

5-2-2. Palladium-Catalyzed Polymerization of Bis(2-bromo-1,3-diene) with Bifunctional Nucleophiles

Scheme 5-2. Palladium-Catalyzed Polymerization of Bis(2-bromo-1,3-diene) **5.1a** with Bifunctional Nucleophiles.

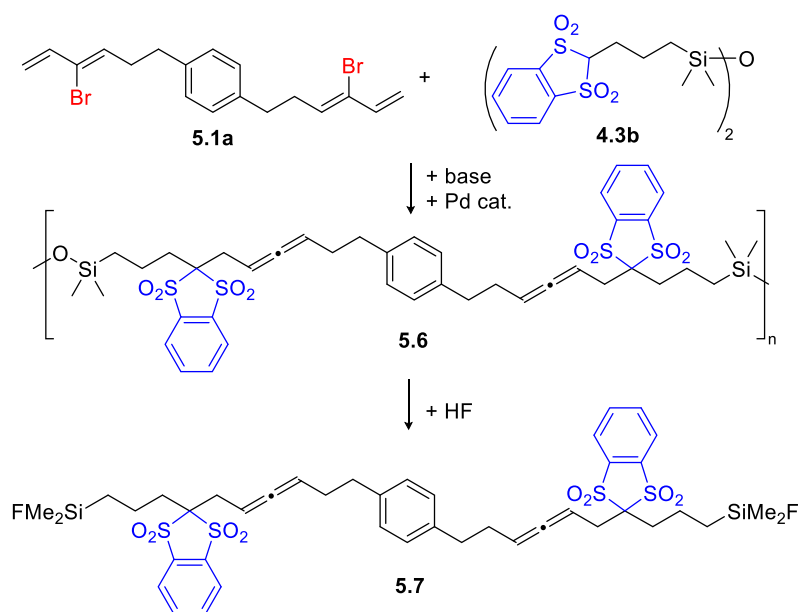


Monomers **5.1a**, which was prepared as depicted in Scheme 5-1, and **4.1a-b** were subjected to the palladium-catalyzed polymerization. The polymerizations of **5.1a** and **4.1a-b** catalyzed by a palladium complex (2 mol %) generated from $\text{Pd}(\text{dba})_2$ and dpdp at 40 °C for 5 days in THF in the presence of NaH (2.4 equiv to **4.1**) provided the corresponding allenic polymers **5.4a-b** in 57% and 75% yield after purification by a precipitation from CHCl_3 /hexane (1/3). The SEC analysis indicated polymers **5.4a-b** with comparable $M_n = 8000$ -15500, and with good dispersities (PDI = 1.20-1.39).

Whereas the palladium-catalyzed reaction of **5.1a** showed the good to excellent degree of polymerization irrespective of the choice of the substrates **4.1**, I would like to extend the reaction of bis(2-bromo-1,3-diene) **5.1a** with a cleavable monomer **4.3b** into an asymmetric counterpart by the use of the chiral palladium catalysts (Scheme 5-3). Axially chiral allenic polymer **5.6** should be obtained in enantiomerically enriched forms, and a degradation process of polymer **5.6** would provide the corresponding axially chiral bisallene **5.7**, of which diastereomeric excess value might be determined by the standard NMR analysis (Scheme 5-3). However, bisallene **5.7** generated from

the repeating subunits of the **5.6** contains two axially chiral allenic units, which would make the determination of enantioregularity difficult due to the presence of three stereoisomers ((*R,R*)-, (*S,S*)-, and *meso*-**5.7**).^[4]

Scheme 5-3. Palladium-Catalyzed Polymerization of **5.1a** with **4.3b**.



Section 3.

Palladium-Catalyzed Asymmetric Polymerization of Cleavable Bis(2-bromo-1,3-diene) with Cleavable Bifunctional Nucleophile

5-3-1. Strategy of Determining Enantioselectivity in Axially Chiral Allenic Polymers

In this section, I offer a method to overcome the difficulty of determining the enantioselectivity of the axially chiral allenic polymer generated from the bis(2-bromo-1,3-diene) and a cleavable nucleophile. The method is to design a *cleavable* bis(2-bromo-1,3-diene) as an electrophilic bifunctional monomer for the palladium-catalyzed reaction. The palladium-catalyzed reaction of cleavable **5.1b** and cleavable nucleophile would incorporate two cleavable junctions in a repeating subunit of axially chiral allenic polymer **5.8**, and the degradation of **5.8** would give the corresponding axially chiral allene **5.9**, which contains only one axially chiral allenic unit for a further chiral HPLC analysis (Figure 5-4).

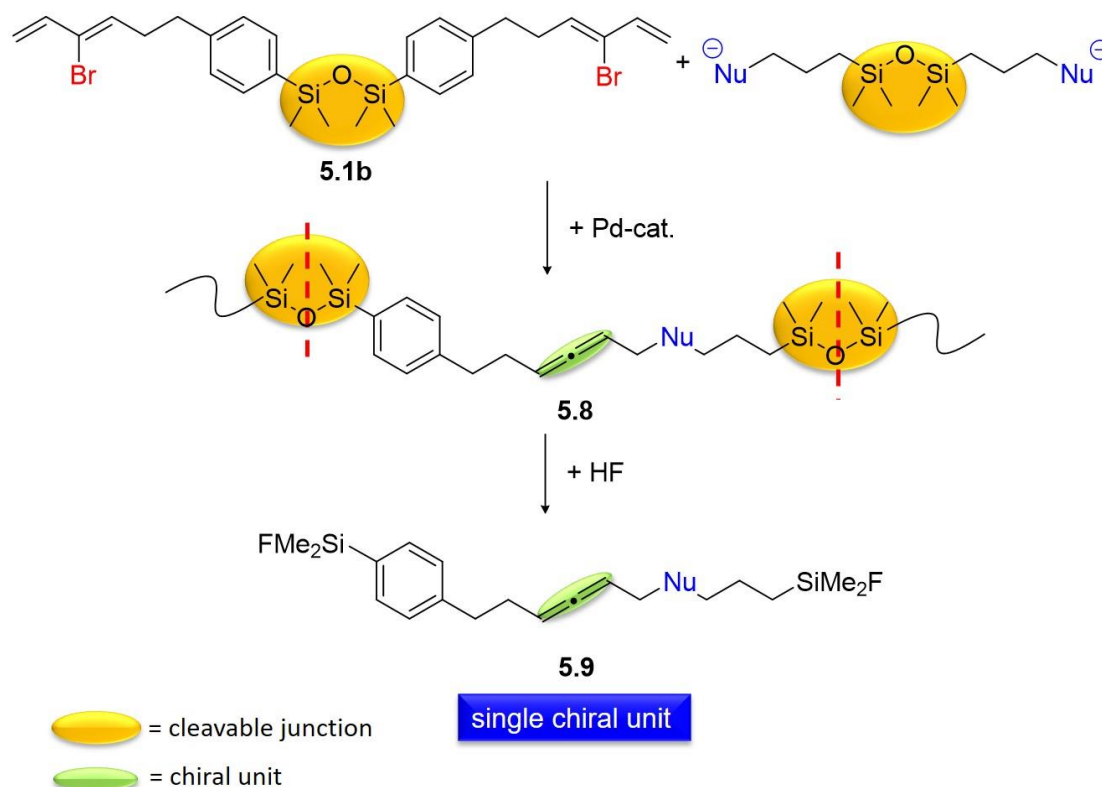
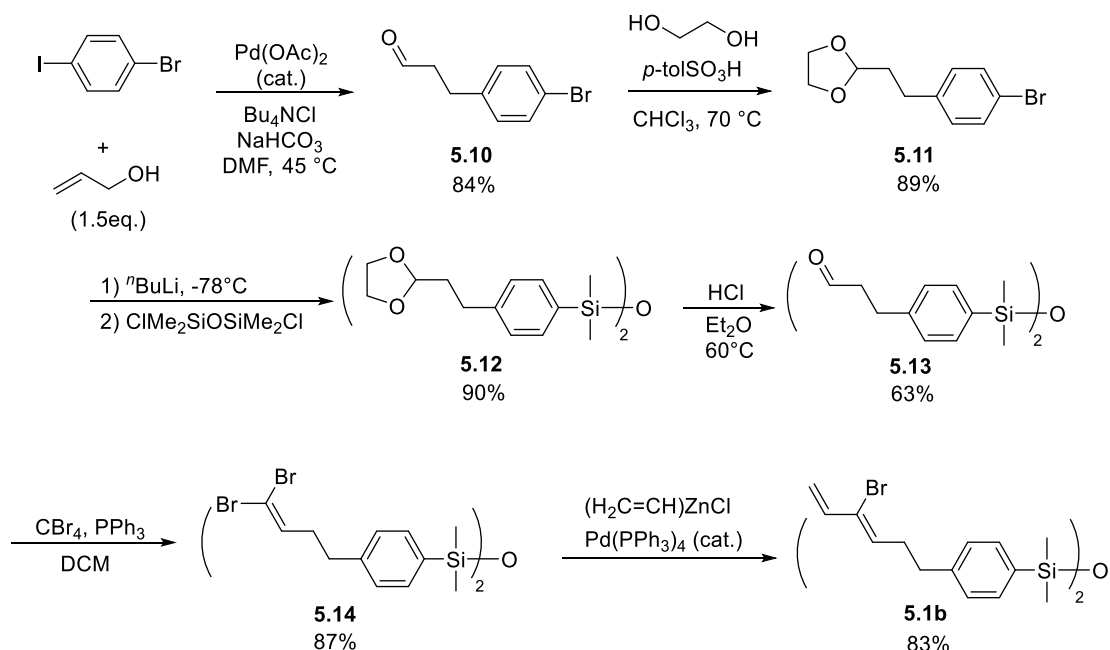


Figure 5-4. Degradation of Axially Chiral Allenic Polymer Providing Enantiomeric Allenes.

5-3-2. Preparation of Cleavable Bis(2-bromo-1,3-diene)

Scheme 5-4. Preparation of Cleavable Bis(2-bromo-1,3-diene) **5.1b**.



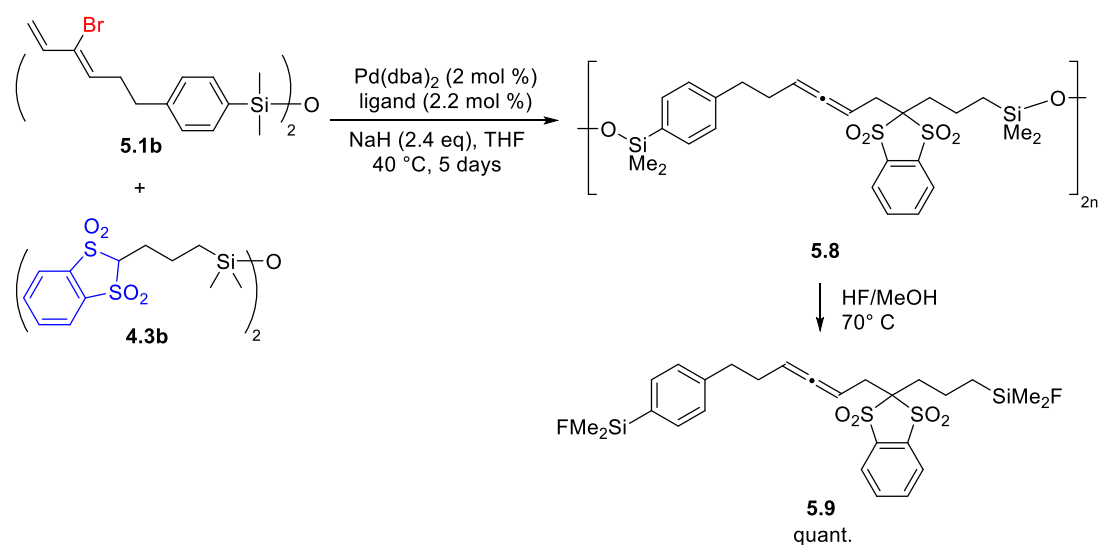
The monomer for asymmetric polymerization is **5.1b** having a similar substructure as **5.1a**, and it is prepared from *para*-bromoiodobenzene by the six-step sequence as depicted in Scheme 5-4. The preparation of 3-(4-bromophenyl)propanal **5.10** was followed by the palladium-catalyzed Heck arylation of allylic alcohols as reported.^[1c] The reaction of *para*-bromoiodobenzene with allyl alcohol catalyzed by Pd(PPh₃)₄ in the presence of sodium bicarbonate and *tetra-n*-butylammonium chloride provided aldehyde **5.10** in 84% yield. Acetalization of aldehyde **5.10** with ethylene glycol led to ethylene acetal **5.11** in 89% yield. Bromine/lithium exchange of acetal-protected bromoarene **5.11** with *n*-BuLi at $-78 ^\circ\text{C}$ and subsequent trapping of the aryllithium intermediate with dichlorotetramethyl disiloxane provided the diacetal disiloxane **5.12** in 90% yield. The hydrolysis of diacetal **5.12** was carried out with aqueous HCl at $60 ^\circ\text{C}$ in diethyl ether, and it provided dialdehyde **5.13** in 63% yield, which showed a slight cleavage of disiloxane bond at the hydrochloric acid treatment.^[5] The dialdehyde **5.13**

was converted into 1,3-bis[4-(4,4-dibromo-3-butenyl)phenyl]-1,1,3,3-tetramethyldisiloxane **5.14** by the standard Wittig dibromoolefination (Ramirez olefination).^[2] The palladium-catalyzed Negishi coupling of **5.14** with vinylzinc chloride proceeded with excellent regioselectivity to cleavable bis(2-bromo-1,3-diene) **5.1b** in 83% yield exclusively.^[3]

5-3-3. Palladium-Catalyzed Asymmetric Polymerization of Cleavable Bis(2-bromo-1,3-diene) with Cleavable Bifunctional Nucleophiles

Monomer **5.1b**, which was prepared as depicted in Scheme 5-1, and **4.3b** were subjected to the palladium-catalyzed asymmetric polymerization. The asymmetric polymerizations of **5.1b** with **4.3b** were catalyzed by 2 mol % of chiral palladium complexes generated from Pd(dba)₂ and chiral bisphosphine ligands at 40 °C for 5 days in THF in the presence of NaH (2.4 equiv to **4.3b**). The results of the palladium-catalyzed asymmetric polymerization are summarized in Table 5-1. At the outset, the polymerization catalyzed by a palladium complex generated from the Pd(dba)₂ and dpbp provided the corresponding polymer **5.8** in high yield (83%), which was purified by a precipitation from CHCl₃/hexane (1/2). The SEC measurement indicated a high $M_n = 22600$ with PDI = 1.50 in the polymer (entry 1). The palladium-catalyzed polymerization of bis(2-bromo-1,3-diene) **5.1b** in entry 1 took place with a high degree of polymerization ($DP = 20$), and the M_n value is two or three times higher than polymer **4.7** in Chapter IV. Moreover, the cyclic product ($n = 1$) was not be observed in a crude product, which is always formed in the palladium-catalyzed reactions between **3.1a** and **4.3a-c**. The palladium-catalyzed asymmetric polymerizations with chiral palladium complexes generated from Pd(dba)₂ and chiral biaryl bisphosphine ligands were examined, and polymers **5.8** were obtained in 70-85% yields and M_n value ranging from 15300 to 22400 with similar dispersities. In order to evaluate the enantioselectivity of axially chiral allenic polymers **4.8** in entries 2-5, treatment of **5.8**, which were prepared from **5.1b** and **4.3b** using a Pd/(*R*)-(biaryl-bisphosphine) catalyst, with excess aqueous hydrofluoric acid at 70 °C in MeOH cleaved the disiloxane junction cleanly to give the corresponding monomerized allene **5.9** quantitatively, of which enantiomeric excess could be determined by the standard chiral HPLC analysis. The results of the chiral

HPLC analysis of axially chiral allenic monomers **5.9** are also summarized in Table 5-1. The use of a palladium complex generated from Pd(dba)₂ and (*R*)-Segphos in palladium-catalyzed asymmetric polymerization provided the best enantioselectivity of 60% ee determined by a chiral HPLC analysis of the corresponding monomerized axially chiral allene **5.9** (entry 3). The use of a palladium complex generated from Pd(dba)₂ and (*R*)-DeBuPhos in the reaction showed the lowest enantioselectivity of 13% ee, although the same catalytic conditions provide the polymer **4.7b** in excellent enantioselectivity of 90% (entry 5; *cf.* chapter IV, Table 4-3, entry 6). The optical rotation values for optically active allenic polymer (–)-**5.8** prepared using the (*R*)-segphos was determined to be $[\alpha]^{32}_{\text{D}} = -5.7$ (*c* 4.46, CHCl₃) (entry 3).

Table 5-1. Palladium-Catalyzed Asymmetric Polymerization of **5.1b** with **4.3b**.^a

entry	ligand	yield of 5.8 (%) ^c	M_n ^d	PDI ^{d, e}	ee of 5.9 (%) ^f
1	dppb	83%	22600	1.50	-
2	(<i>R</i>)-binap	74%	17300	1.72	30
3	(<i>R</i>)-segphos	86%	15300	1.63	60
4	(<i>R</i>)-DTBMsegphos	85%	21900	1.42	56
5	(<i>R</i>)-DeBuPhos	70%	22400	1.43	13

^a The reaction was carried out with **5.1b** (0.20 mmol), **4.3b** (0.20 mmol) and NaH (0.48 mmol) at 40 °C for 5 days in THF (1.5 mL) in the presence of a palladium catalyst (2 mol %) generated from $\text{Pd}(\text{dba})_2$ and a given ligand. ^b Determined by ^1H NMR. ^c Precipitated from CHCl_3 /hexane = 1/2. ^d Estimated by SEC (CHCl_3 , polystyrene standard). ^e Polydispersity index, M_w/M_n . ^f Determined by chiral HPLC analysis.

Section 4.

Proposed Mechanism of Palladium-Catalyzed Polymerization of Bis(2-bromo-1,3-diene) with Bifunctional Nucleophile.

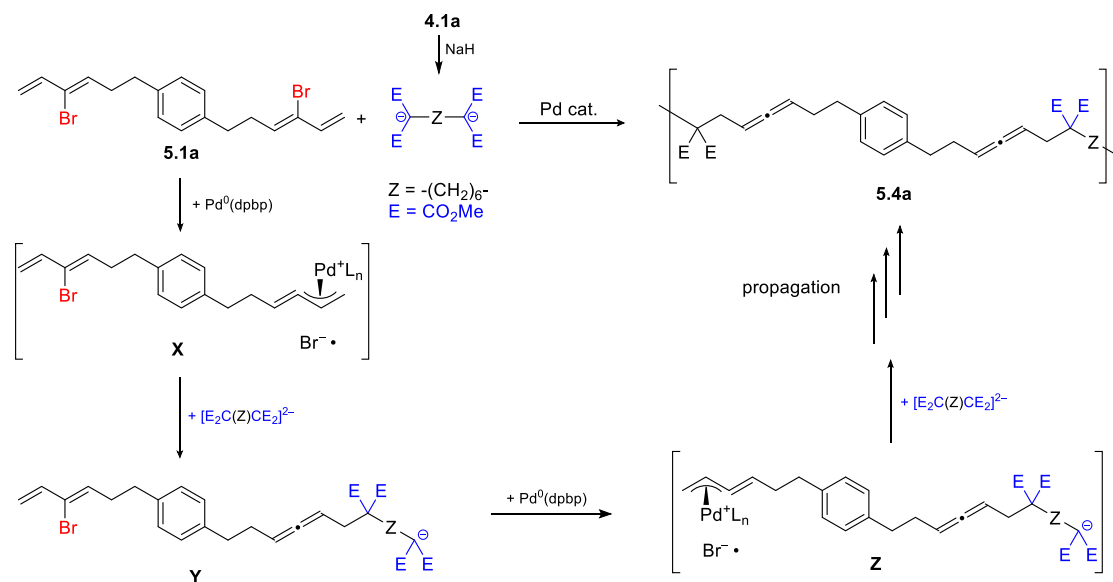


Figure 5-5. Proposed Mechanism of Palladium-Catalyzed Polymerization of **5.1a**

The proposed mechanism of the palladium-catalyzed polymerization of **5.1a** and bifunctional nucleophile **4.1a** is shown in Figure 5-5. Substrate **5.1a** possesses two same sites (marked in red) susceptible to activation with palladium catalysis. Treatment of **5.1a** with a nucleophile generated from **4.1a** and NaH in THF in the presence of the Pd/dppb catalyst afforded a monosubstituted intermediate **Y** proceeding via an (alkylidene- π -allyl)palladium intermediate **Y**, the oxidative addition of the vinylic C–Br to Pd(0) takes place in the palladium-catalyzed process. The oxidative addition of the remaining vinylic C–Br in monosubstituted intermediate **Y** to Pd(0) provided an intermediate **Z**, and a repetitive propagation process would afford the polymer **5.4a**.

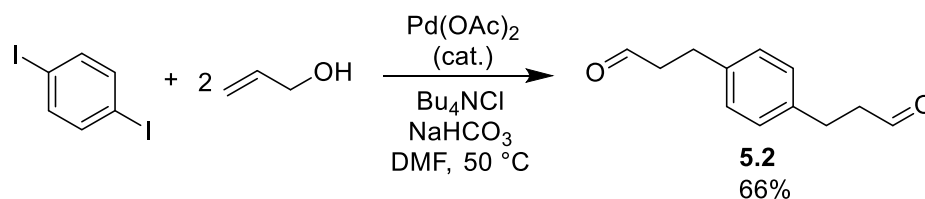
Conclusions for Chapter V

In this chapter, I have demonstrated that bis(2-bromo-1,3-diene)s **5.1a-b** are excellent precursors to prepare the allenic polymers. The reaction is effectively catalyzed by an appropriate palladium complex, and **5.1a** and bifunctional nucleophiles generated from **4.1a** undergo the repetitive nucleophilic substitution via a formal S_N2' process to give the allenic polymers in good to high yields with comparable M_n . Cleavable bis(2-bromo-1,3-diene) **5.1b** was an excellent monomer for the palladium-catalyzed polymerization. By the use of a chiral palladium catalyst, axially chiral allenic polymers **5.8** were obtained in high yields with high M_n reaching up to 22400. These chiral polymers were cleaved easily by the treatment with aqueous hydrofluoric acid to give the corresponding enantioenriched **5.9** quantitatively with up to 60% ee.

Experimental Section for Chapter V

General. All anaerobic and/or moisture sensitive manipulations were carried out with standard Schlenk techniques under predried nitrogen or with glovebox techniques under prepurified argon. ^1H NMR (400 MHz), ^{13}C NMR (101 MHz), and ^{19}F NMR (376 MHz) chemical shifts are reported in ppm downfield of internal tetramethylsilane. Tetrahydrofuran was distilled from benzophenone-ketyl under nitrogen prior to use. Dichloromethane and DMF were distilled from CaH_2 under nitrogen prior to use. The following compounds were prepared according to the reported methods: tetramethyl octane-1,1,8,8-tetracarboxylate (**4.1a**),^[6] and tetramethyl butane-1,1,4,4-tetracarboxylate (**4.1b**).^[7] All the other chemicals were obtained from commercial sources and used as received unless otherwise noted.

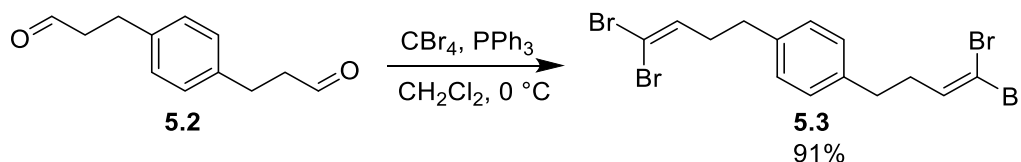
Synthesis of 3,3'-(1,4-Phenylene)dipropanal (**5.2**)^[1b]



The procedure of preparation of **5.2** was followed by the palladium-catalyzed Heck coupling reaction reported by Brückner.^[1b] A mixture of NaHCO_3 (6.36 g, 75.8 mmol), 1,4-diiodobenzene (5.00 g, 15.2 mmol), Bu_4NCl (8.43 g, 30.3 mmol) and $\text{Pd}(\text{OAc})_2$ (133 mg, 591 μmol ,) was dissolved in anhydrous and degassed DMF (50 mL), and Allyl alcohol (2.55 g, 44.0 mmol.) was added to the mixture. The reaction mixture was stirred at $50\text{ }^\circ\text{C}$ and monitored by TLC. After complete conversion of 1,4-diiodobenzene, the crude reaction was diluted with Et_2O (70 mL), washed with H_2O (3 x 100 mL), brine (100 mL), and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (benzene/ EtOAc = 9/1) to give the **5.2** (1.90 g, 66% yield)

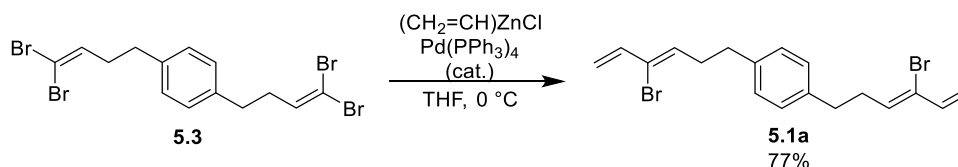
a colorless solid. ^1H NMR (CDCl_3): δ 2.74-2.79 (m, 4H), 2.91-2.95 (m, 4H), 7.12 (s, 4H), 9.82 (t, $J = 1.4$ Hz, 2H).

Synthesis of 1,4-Bis(4,4-dibromo-3-butenyl)benzene (**5.3**)



To a CH_2Cl_2 (80 mL) solution of CBr_4 (7.35 g, 22.2 mmol) was added PPh_3 (11.62 g, 44.3 mmol) portionwise at $0\text{ }^\circ\text{C}$, and the solution was allowed to stir at this temperature for 20 min. A solution of **5.2** (1.62 g, 8.52 mmol) in CH_2Cl_2 (20 mL) was added dropwise at $0\text{ }^\circ\text{C}$, and the mixture was stirred at the same temperature for 30 min. After the reaction mixture was quenched with a small amount of water (ca. 1 mL), the mixture was concentrated under reduced pressure. Addition of hexane (100 mL) to the concentrated solution precipitated triphenylphosphine oxide as pale yellow solid, which was removed by filtration. The filtrate was evaporated, and the residue was purified by chromatography on silica gel (with hexane) to give the **5.3** (3.90 g, 91% yield) as a white solid. ^1H NMR (CDCl_3): δ 2.37-2.43 (m, 4H), 2.69-2.73 (m, 4H), 6.41 (t, $J = 7.2$ Hz, 2H), 7.12 (s, 4H). ^{13}C NMR (CDCl_3): δ 33.6, 34.8, 89.6, 128.7, 137.8, 138.6.

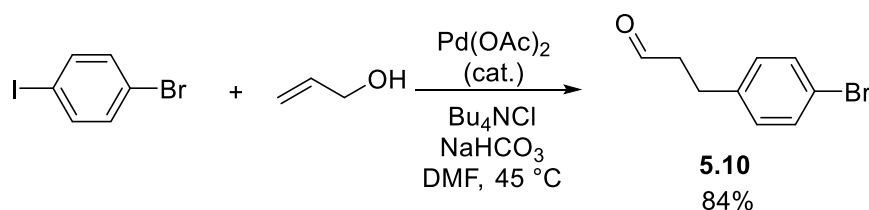
Synthesis of 1,4-Bis((*Z*)-4-bromohexa-3,5-dienyl)benzene **5.1a**



To a suspension of $(\text{CH}_2=\text{CH})\text{ZnCl}$ in THF (15 mL), prepared from dry ZnCl_2 (1.29 g, 9.46 mmol) and vinylmagnesium chloride (1.35 M THF solution; 7 mL; 9.45 mmol), was added a solution of **5.3** (2.00 g, 4.0 mmol) and $\text{Pd(PPh}_3)_4$ (185 mg, 0.20 mmol) in

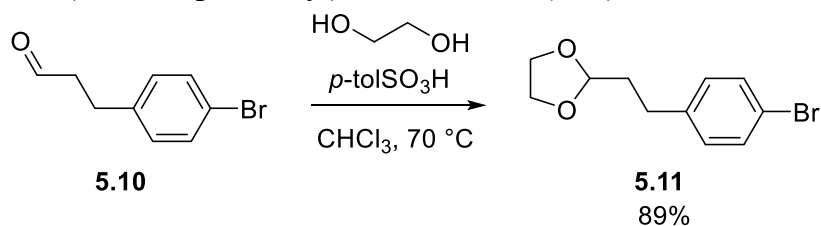
THF (10 mL) at 0 °C. The reaction mixture was stirred at 0 °C and monitored by ^1H NMR. After complete conversion of **5.3**, the crude reaction was diluted with hexane, filtered, and evaporated to dryness. The residue was purified by chromatography on silica gel (hexane/benzene) and further purified by recycle GPC to give the **5.1a** (0.88 g, 77% yield) as a white solid. ^1H NMR (CDCl_3): δ 2.60-2.66 (m, 4H), 2.71-2.77 (m, 4H), 5.17 (d, J = 10.4 Hz, 1H), 5.54 (d, J = 16.3 Hz, 1H), 6.01 (t, J = 6.9 Hz, 2H), 6.30 (dd, J = 16.3 and 10.4 Hz, 1H), 7.12 (s, 4H). ^{13}C NMR (CDCl_3): δ 33.4, 34.1, 117.7, 126.6, 128.6, 134.0, 135.9, 139.0. APCI-HRMS Calcd for $\text{C}_{18}\text{H}_{20}\text{Br}_2\text{H}$ ($\text{M} + \text{H}$) $^+$: 396.9991. Found: 396.9991.

Synthesis of 3-(4-Bromophenyl)propanal (**5.10**)^[1c]



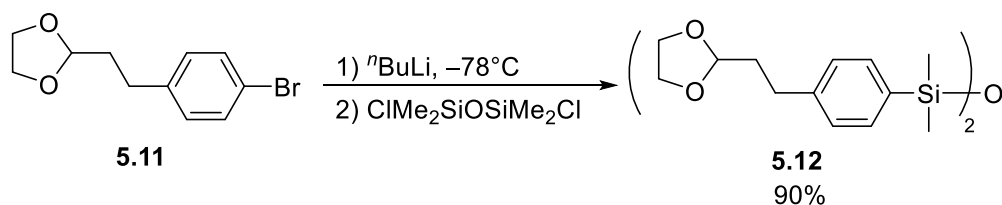
The procedure of preparation of **5.10** was followed by the palladium-catalyzed Heck coupling reaction reported by Liu.^[1c] A mixture of NaHCO_3 (14.85 g, 176.7 mmol), 1-bromo-4-iodobenzene (20.00 g, 70.7 mmol), Bu_4NCl (19.84 g, 71.4 mmol) and $\text{Pd}(\text{OAc})_2$ (317 mg, 1.42 mmol,) were dissolved in anhydrous and degassed DMF (100 mL), and Allyl alcohol (6.16 g, 106.0 mmol.) was added to the mixture. The reaction mixture was stirred at 50 °C and monitored by TLC. After complete conversion of 1,4-diiodobenzene, the crude reaction was diluted with Et_2O (400 mL), washed with H_2O (3 x 300 mL), brine (300 mL), and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (hexane/ EtOAc = 5/1) to give the **5.10** (12.60 g, 84% yield) a colorless solid. ^1H NMR (CDCl_3): δ 2.75-2.80 (m, 2H), 2.89-2.94 (m, 2H), 7.05-7.09 (m, 2H), 7.39-7.43 (m, 2H), 9.81 (t, J = 1.1 Hz, 2H).

Synthesis of 2-(4-Bromophenethyl)-1,3-dioxolane (5.11)



A solution CHCl₃ (450 mL) of aldehyde **5.10** (12.60 g, 59.1 mmol), ethylene glycol (5.50 g, 88.7 mmol), and *p*-tolSO₃H (2.25 g, 11.8 mmol) was heated at 70 °C with a Dean–Stark apparatus. The reaction was finished after that water had been removed completely. The organic layer was washed with 2 M NaOH (3 x 70 mL), brine (2 x 200 mL), dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (hexane/EtOAc = 5/1) and distillation to give the **5.11** (13.50 g, 89% yield) as a colorless solid. ¹H NMR (CDCl₃): δ 1.92-1.98 (m, 2H), 2.68-2.73 (m, 2H), 3.85-3.92 (m, 2H), 3.95-4.02 (m, 2H), 4.88 (t, *J* = 4.8 Hz, 1H), 7.07-7.10 (m, 2H), 7.38-7.41 (m, 2H). ¹³C NMR (CDCl₃): δ 29.7, 35.4, 65.1, 103.7, 119.8, 130.3, 131.6, 140.7. ESI-HRMS Calcd for C₁₁H₁₃BrO₂Na (M + Na): 278.9997. Found: 279.0001.

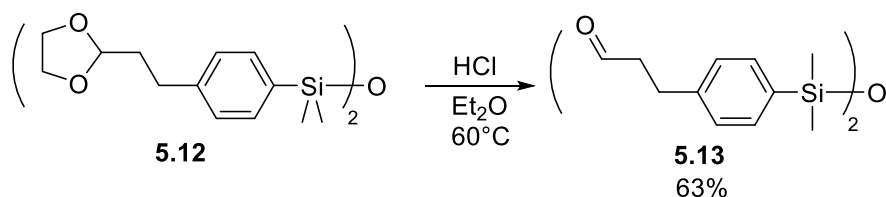
Synthesis of 1,3-Bis[4-{2-(1,3-dioxolan-2-yl)ethyl}phenyl]-1,1,3,3-tetramethyldisiloxane (5.12)



A solution THF (180 mL) of acetal **5.11** (13.29 g, 51.7 mmol) was cooled to -78 °C. Next, ⁿBuLi (1.6 M in hexanes, 32 mL, 51.2 mmol) was added dropwise and the solution was stirred for 2 h. Dichlorotetramethyl disiloxane (5.00 g, 24.6 mmol) was added and the mixture was stirred at -78 °C for 1 h and then at room temperature

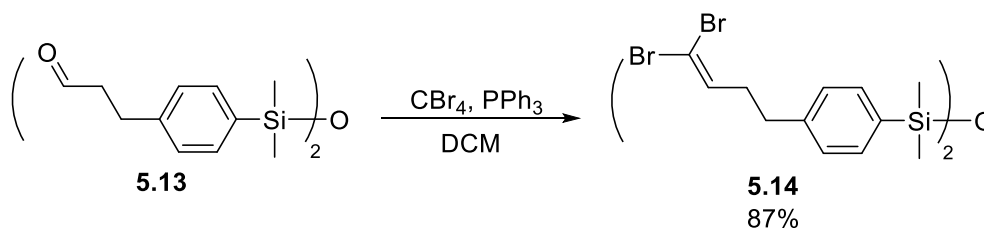
overnight. The mixture was poured into $\text{NH}_4\text{Cl}_{aq}$ (200 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layer was dried over MgSO_4 and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (hexane/EtOAc/ Et_3N = 90/10/1) to give the **5.12** (10.81 g, 90% yield) as a colorless solid. ^1H NMR (CDCl_3): δ 0.31 (s, 12H), 1.98-2.02 (m, 4H), 2.72-2.77 (m, 4H), 3.87-3.93 (m, 4H), 3.95-4.01 (m, 4H), 4.90 (t, J = 4.6 Hz, 2H), 7.19-7.22 (m, 4H), 7.45-7.47 (m, 4H). ^{13}C NMR (CDCl_3): δ 1.1, 30.3, 35.5, 65.1, 104.0, 128.0, 133.3, 137.2, 142.8. ESI-HRMS Calcd for $\text{C}_{26}\text{H}_{38}\text{O}_5\text{Si}_2\text{Na}$ ($M + \text{Na}$): 509.2155. Found: 509.2152.

Synthesis of 3,3'-[(1,1,3,3-Tetramethyldisiloxane-1,3-diyl)bis(4,1-phenylene)]dipropenal (5.13**)**



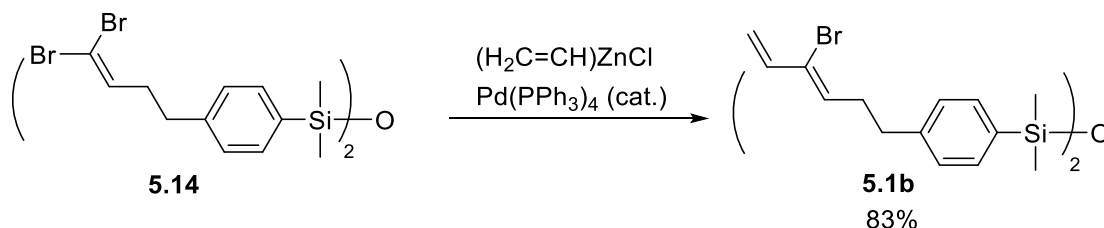
To a solution Et_2O (80 mL) containing diacetal **5.12** (10.80 g, 22.2 mmol) was added concd. HCl (35%, 7 mL, 67.2 mmol) at room temperature. The reaction was heated at 60 °C for 6 h, then diluted with H_2O (100 mL), extracted with Et_2O (3 x 100 mL). The organic layer was washed with saturated NaHCO_{3aq} (2 x 100 mL), brine (2 x 200 mL), dried over MgSO_4 , and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (hexane/EtOAc = 3/1) to give the **5.13** (5.51 g, 63% yield) as a colorless oil. ^1H NMR (CDCl_3): δ 0.31 (s, 12H), 2.77-2.82 (m, 4H), 2.94-2.98 (m, 4H), 7.18-7.20 (m, 4H), 7.45-7.48 (m, 4H), 9.83 (t, J = 1.3 Hz, 2H). ^{13}C NMR (CDCl_3): δ 1.1, 28.2, 45.3, 127.9, 133.5, 137.7, 141.6, 201.7. ESI-HRMS Calcd for $\text{C}_{22}\text{H}_{30}\text{O}_3\text{Si}_2\text{Na}$ ($M + \text{Na}$): 421.1631. Found: 421.1624.

Synthesis of 1,3-Bis[4-(4,4-dibromo-3-butenyl)phenyl]-1,1,3,3-tetramethyldisiloxane (5.14)



To a CH_2Cl_2 (120 mL) solution of CBr_4 (11.92 g, 35.9 mmol) was added PPh_3 (18.85 g, 71.9 mmol) portionwise at 0 °C, and the solution was allowed to stir at this temperature for 20 min. A solution of **5.13** (5.51 g, 13.8 mmol) in CH_2Cl_2 (30 mL) was added dropwise at 0 °C, and the mixture was stirred at the same temperature for 30 min. After the reaction mixture was quenched with a small amount of water (ca. 2 mL), the mixture was concentrated under reduced pressure. Addition of hexane (200 mL) to the concentrated solution precipitated triphenylphosphine oxide as pale-yellow solid, which was removed by filtration. The filtrate was evaporated, and the residue was purified by chromatography on silica gel (hexane/EtOAc = 20/1) to give the **5.14** (8.55 g, 87% yield) as a pale-yellow oil. ^1H NMR (CDCl_3): δ 0.31 (s, 12H), 2.37-2.45 (m, 4H), 2.70-2.75 (m, 4H), 6.42 (t, J = 7.2 Hz, 2H), 7.16-7.19 (m, 4H), 7.46-7.49 (m, 4H). ^{13}C NMR (CDCl_3): δ 1.1, 34.0, 34.7, 89.6, 127.9, 133.5, 137.6, 137.8, 141.8. ESI-HRMS Calcd for $\text{C}_{24}\text{H}_{30}\text{Br}_4\text{OSi}_2\text{Na}$ ($M + \text{Na}$): 732.8428. Found: 732.8425.

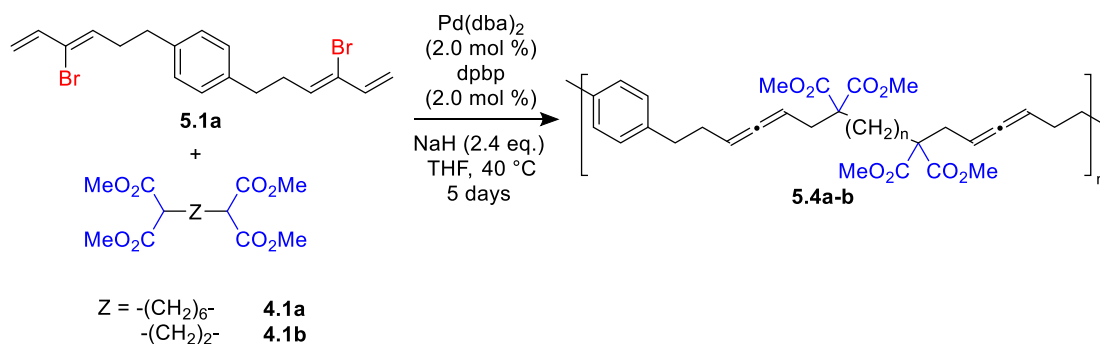
Synthesis of 1,3-Bis[4-((Z)-4-bromohexa-3,5-dienyl)phenyl]-1,1,3,3-tetramethyldisiloxane (5.1b)



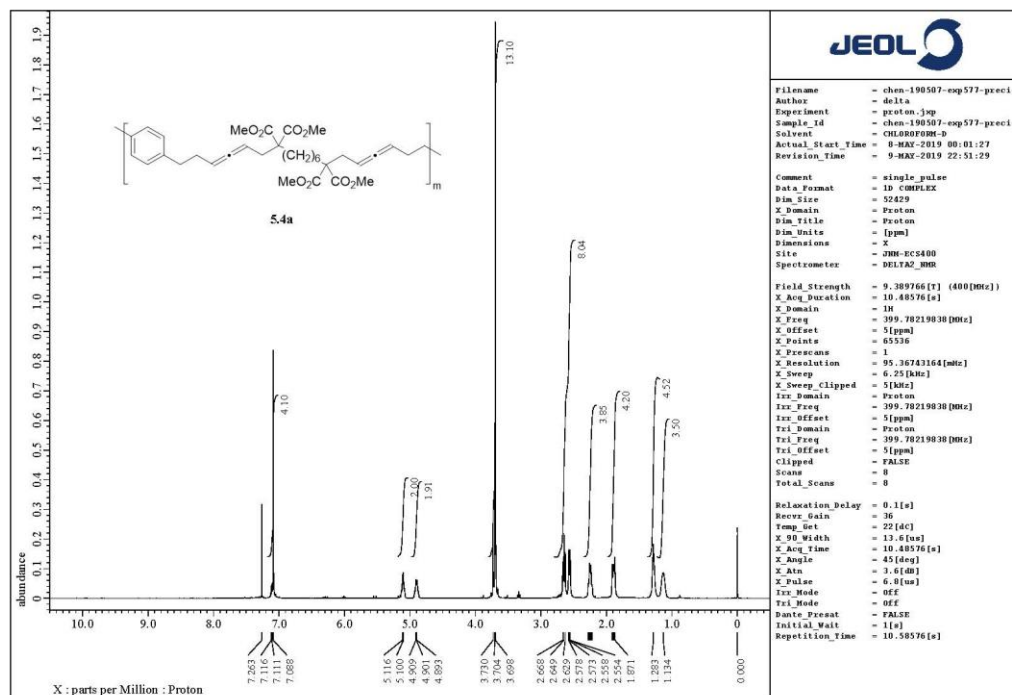
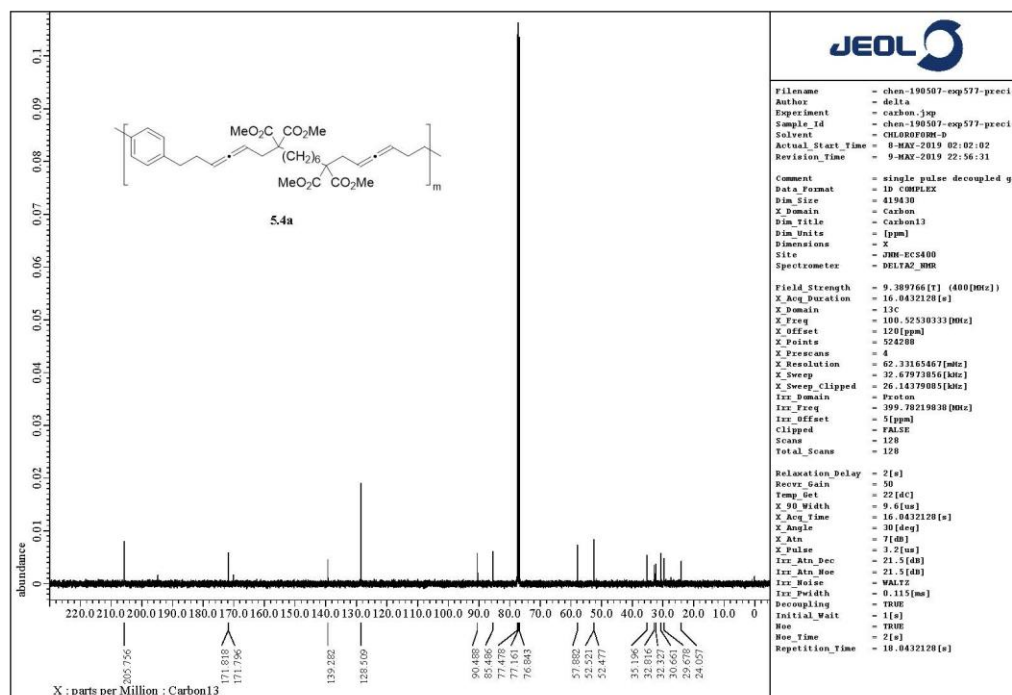
To a suspension of $(\text{CH}_2=\text{CH})\text{ZnCl}$ in THF (25 mL), prepared from dry ZnCl_2 (1.50

g, 11.0 mmol) and vinylmagnesium chloride (1.35 M THF solution; 7.2 mL; 9.7 mmol), was added a solution of **5.14** (3.00 g, 4.22 mmol) and Pd(PPh₃)₄ (98 mg, 84 μmol) in THF (25 mL) at 0 °C. The reaction mixture was stirred at 0 °C and monitored by ¹H NMR. After complete conversion of **5.14**, the crude reaction was diluted with hexane, filtered, and evaporated to dryness. The residue was purified by chromatography on silica gel (hexane/benzene) and further purified by recycle GPC to give the **5.1b** (2.11 g, 83% yield) as a pale-yellow oil. ¹H NMR (CDCl₃): δ 0.32 (s, 12H), 2.63-2.68 (m, 4H), 2.74-2.78 (m, 4H), 5.17 (d, *J* = 10.5 Hz, 1H), 5.54 (d, *J* = 16.3 Hz, 1H), 6.02 (t, *J* = 6.9 Hz, 2H), 6.30 (dd, *J* = 16.3 and 10.5 Hz, 1H), 7.19-7.22 (m, 4H), 7.46-7.49 (m, 4H). ¹³C NMR (CDCl₃): δ 1.1, 33.2, 34.5, 117.7, 126.6, 128.0, 133.4, 133.9, 137.4, 135.9, 142.4. ESI-HRMS Calcd for C₂₈H₃₆Br₂OSi₂Na (M + Na): 627.0588. Found: 627.0551.

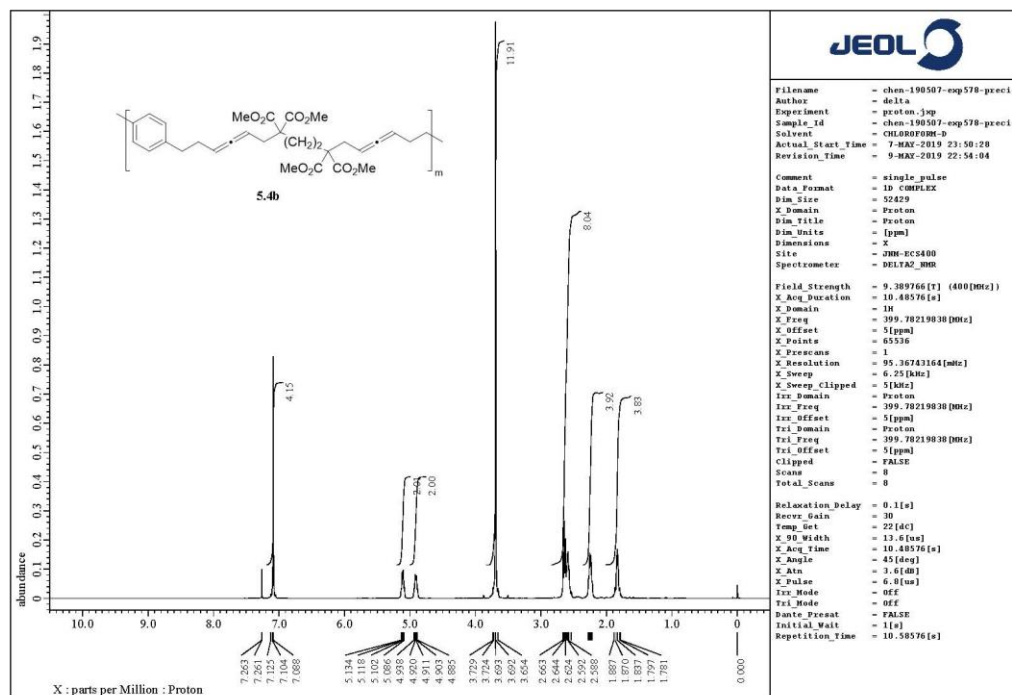
Palladium-Catalyzed Polymerization of **5.1a** with **4.1a-b**



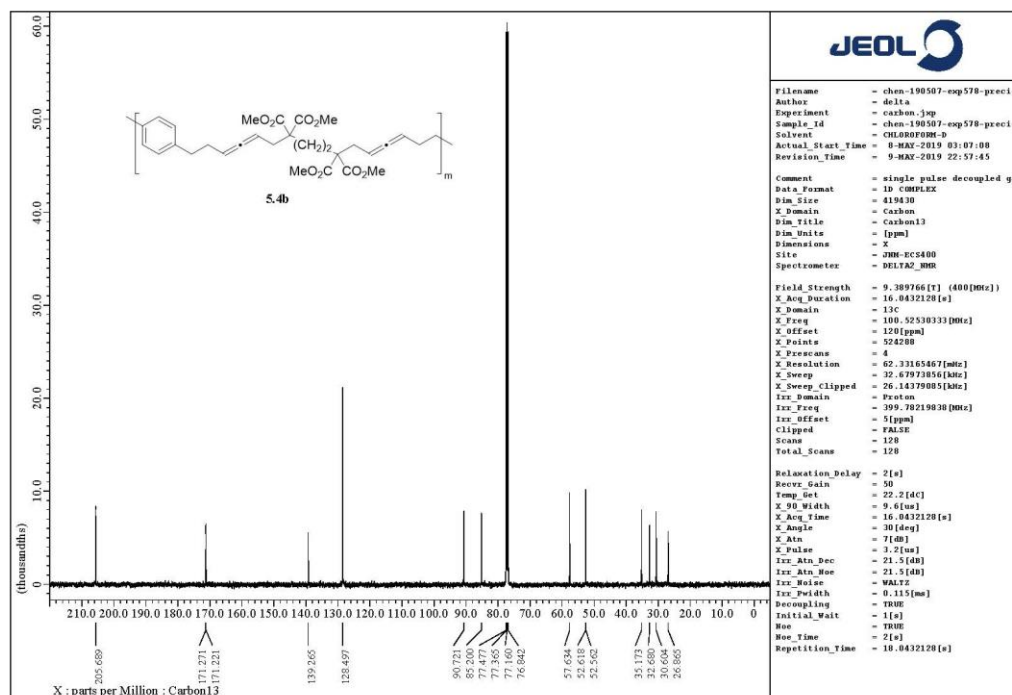
The reaction conditions and the results are summarized in Scheme 5-2. To a mixture of Pd(dba)₂ (2.9 mg, 5 μmol), ligand (5.5 μmol), **4.1** (0.25 mmol), and an appropriate base (0.60 mmol) in THF (1.5 mL) was added **5.1a** (100 mg, 0.25 mmol). After being stirred for 5 days at 40 °C, the mixture was added 3 mL of H₂O, and extracted with a small amount of CHCl₃ three times. The combined organic solution was dried over MgSO₄ and evaporated to dryness under reduced pressure. The residue was purified by precipitation from CHCl₃ and hexane to give corresponding polymer **5.4**. The ¹H NMR and ¹³C NMR charts of allenic polymer **5.4a-b** are listed below.

¹H NMR of polymer **5.4a** ^{13}C NMR of polymer **5.4a**

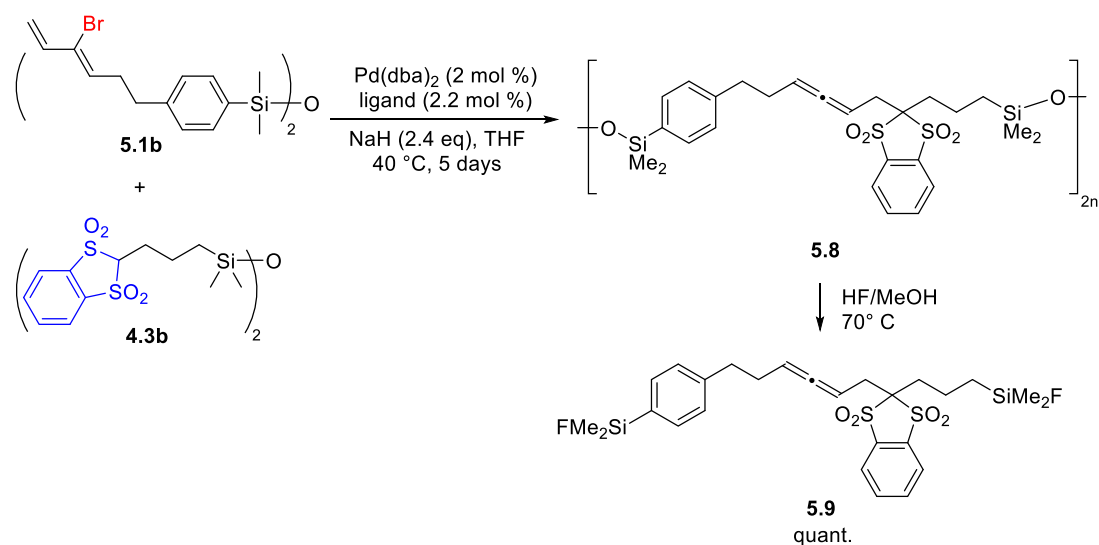
¹H NMR of polymer **5.4b**



¹³C NMR of polymer **5.4b**

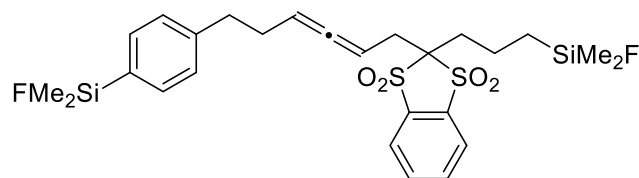


Palladium-Catalyzed Asymmetric Polymerization of **5.1b** with **4.3b** (Table 5-1)



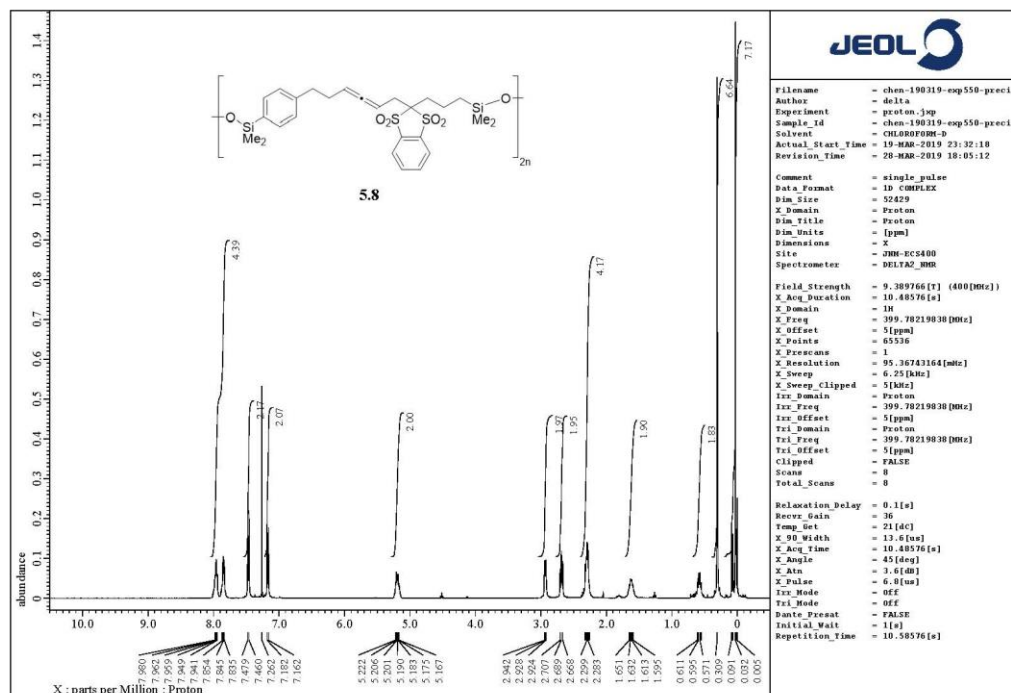
The reaction conditions and the results are summarized in Table 5-1. To a mixture of $\text{Pd}(\text{dba})_2$ (2.3 mg, 4 μmol), ligand (4.4 μmol), **4.3b** (0.20 mmol), and an appropriate base (0.48 mmol) in THF (1.5 mL) was added **5.1b** (121 mg, 0.20 mmol) by means of syringe under nitrogen. After being stirred for 5 days at 40 °C, the mixture was added 3 mL of H_2O , and extracted with a small amount of CHCl_3 three times. The combined organic solution was dried over MgSO_4 and evaporated to dryness under reduced pressure. The residue was purified by precipitation from CHCl_3 and hexane to give corresponding polymer **5.8**. The degradation of polymer **5.8** was carried out as the procedure below. To a 20 mL polypropylene flask containing polymer **5.8** (50 μmol) was added a mixture of MeOH (3 mL) and aqueous hydrofluoric acid (0.5 mL, 55%). After being stirred for 3 h at 70 °C, the mixture was neutralized by saturated $\text{NaHCO}_{3\text{aq}}$, and extracted with EtOAc three times. The combined organic solution was dried over MgSO_4 and evaporated to dryness under reduced pressure. The residue was purified by recycle GPC separation to give corresponding polymer **5.9** quantitatively. The ^1H NMR and ^{13}C NMR charts of allenic polymer **5.8**, and dimethylfluorosilane **5.9** are listed below.

2-[6-(4-(Fluorodimethylsilyl)phenyl)hexa-2,3-dienyl]-2-[3-(fluorodimethylsilyl)propyl]-benzodithiole 1,1,3,3-tetraoxide (5.9)

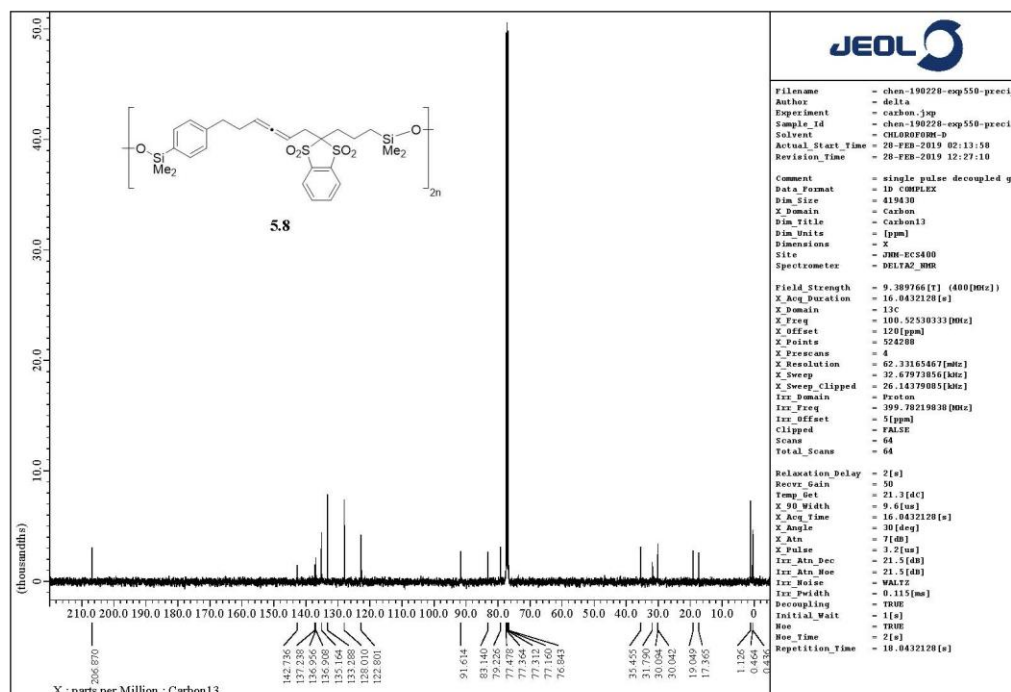


^1H NMR (CDCl_3): δ 0.21 (d, $J_{\text{H-F}} = 1.5$ Hz, 3H), 0.23 (d, $J_{\text{H-F}} = 1.5$ Hz, 3H), 0.47 (s, 3H), 0.49 (s, 3H), 0.74-0.77 (m, 2H), 1.69-1.71 (m, 2H), 2.30-2.33 (m, 4H), 2.70-2.74 (m, 2H), 2.85-2.90 (m, 2H), 5.19-5.23 (m, 2H), 7.23 (d, $J = 7.7$ Hz, 2H), 7.50-7.51 (m, 2H), 7.87-7.90 (m, 2H), 7.98-8.05 (m, 2H). ^{13}C NMR (CDCl_3): δ -1.4 (d, $J_{\text{CF}} = 3.3$ Hz), -1.2 (d, $J_{\text{CF}} = 3.3$ Hz), -1.1, -0.9, 16.6 (d, $J_{\text{CF}} = 1.2$ Hz), 17.3 (d, $J_{\text{CF}} = 14.2$ Hz), 29.9, 30.0, 31.4, 35.4, 79.1, 83.1, 91.5, 122.91, 122.92, 128.4 (2C), 133.3, 133.4, 135.2, 135.3, 136.7, 136.8, 143.907, 143.914, 207.0. ^{19}F NMR (CDCl_3): δ -160.8--160.9 (m), -161.5--161.6 (m), ESI-HRMS Calcd for $\text{C}_{22}\text{H}_{34}\text{F}_2\text{O}_4\text{S}_2\text{Si}_2\text{Na}$ ($\text{M} + \text{Na}$): 591.1303. Found: 591.1306. $[\alpha]^{32}_{\text{D}} = -12.0$ (c 1.99, CHCl_3 for the sample of (*R*)-60% ee). Chiral HPLC Analysis Conditions: Chiralpak IB; eluent: hexane/*i*PrOH = 100/1; flow rate: 1.2 mL/min; wave length: 254 nm. t_1 [(*R*)-enantiomer] = 38.4 min, t_2 [(*S*)-enantiomer] = 46.0 min.

¹H NMR of polymer **5.8**



¹³C NMR of polymer **5.8**



- [1] For palladium-catalyzed arylation of allylic alcohols, see: (a) Zhao, H.; Cai, M.-Z.; Hu, R.-H.; Song, C.-S. *Synth. Commun.* **2001**, *31*, 3665. (b) Engesser, T.; Brückner, R. *Eur. J. Org. Chem.* **2017**, 5789. (c) Liu, J.; He, S.; Jian, T.; Dobbelaar, P. H.; Sebhat, I. K.; Lin, L. S.; Goodman, A.; Guo, C.; Guzzo, P. R.; Hadden, M.; Henderson, A. J.; Pattamana, K.; Ruenz, M.; Sargent, B.; Swenson, B.; Yet, L.; Tamvakopoulos, C.; Peng, Q.; Pan, J.; Kan, Y.; Palyha, O.; Kelly, T. M.; Guan, X.-M.; Howard, A. D.; Marsh, D.; Metzger, J.; Reitman, M. L.; Wyvratt, M. J.; Nargund, R. P. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2074.
- [2] (a) Desai, N. B.; McKelvie, N.; Ramirez, F. *J. Am. Chem. Soc.* **1962**, *84*, 1745. (b) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769.
- [3] For palladium-catalyzed selective substitutions of one of the two halides in 1,1-dihalo-1-alkenes, see: (a) Minato, A.; Suzuki, K.; Tamao, K. *J. Am. Chem. Soc.* **1987**, *109*, 1257. (b) Roush, W. R.; Koyama, K.; Curtin, M. L.; Moriarty, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 7502. (c) Uenishi, J.; Kawahama, R.; Yonemitsu, O.; Tsuji, J. *J. Org. Chem.* **1996**, *61*, 5716. (d) Shen, W.; Wang, L. *J. Org. Chem.* **1999**, *64*, 8873. (e) Zeng, X.; Hu, Q.; Qian, M.; Negishi, E. *J. Am. Chem. Soc.* **2003**, *125*, 13636.
- [4] Monomer with two chiral units for HPLC determination, see : (a) Nozaki, K.; Nakano, K.; Hiyama, T. *J. Am. Chem. Soc.* **1999**, *121*, 11008. (b) Nozaki, K.; Nakano, K.; Hiyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 5501. (c) Nakano, K.; Kosaka, N.; Hiyama, T.; Nozaki, K. *Dalton Trans.* **2003**, 4039.
- [5] Cleavage of disiloxanes by hydrogen chloride, see: Scheim, U.; Porzel, A. *J. Organomet. Chem.* **1988**, *356*, 141.
- [6] Newkome, G. R.; Baker, G. R.; Arai, S.; Saunders, M. J.; Russo, P. S.; Theriot, K. J.; Moorefield, C. N.; Rogers, L. E.; Miller, J. E.; Lieux, T. R.; Murray, M. E.;

Phillips, B.; Pascal, L. *J. Am. Chem. Soc.* **1990**, *112*, 8458.

[7] Marvel, S. C.; Vest, R. D. *J. Am. Chem. Soc.* **1959**, *81*, 984.

List of Publications

Chapter II

Palladium-Catalyzed S_N2'-Cyclization of Ambivalent (Bromoalkadienyl)malonates: Preparation of Medium- to Large-Membered Endocyclic Allenes

- (1) “Palladium-Catalyzed S_N2'-Cyclization of Ambivalent (Bromoalkadienyl) malonates: Preparation of Medium-to Large-Membered Endocyclic Allenes”, Hiroaki ichio, Hidetoshi Murakami, Yen-Chou Chen, Tamotsu Takahashi, Masamichi Ogasawara, *J. Org. Chem.* **2017**, *82*, 7503-7511.

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Yen-Chou Chen

September 2019