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

Yen-Chou Chen[†,‡] *and Masamichi Ogasawara*[*,†]

[†]Department of Natural Science, Graduate School of Science and Technology and Research Cluster on "Innovative Chemical Sensing", Tokushima University, Tokushima 770-8506, Japan

[‡]Graduate School of Life Science, Hokkaido University, Kita-ku, Sapporo 001-0021, Japan

ogasawar@tokushima-u.ac.jp

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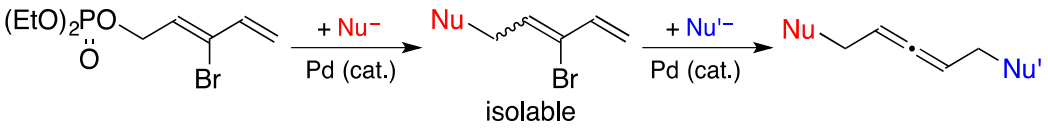


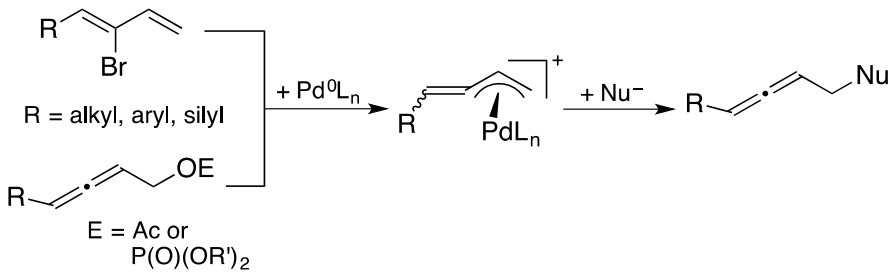
Abstract. Readily available 3-bromopenta-2,4-dienyl esters (**1x**, acetate; **1y**, benzoate; **1z**, diethyl phosphate) were applied to the palladium-catalyzed reaction with various soft nucleophiles. The reaction proceeded through the twofold nucleophilic substitution via formal S_N2'- and S_N2-processes giving the various doubly functionalized allenes **2** in good yields. In the reactions of carboxylates **1x** and **1y**, the first substitution took place at the C-Br bond to form (allenyl)methyl ester intermediates **3**. Because the

second substitution on **3** proceeded faster than the first substitution on **1x** or **1y**, **3** were not isolable and C_2-symmetric allenes **2** were obtained even in the presence of remaining **1x** and **1y**. On the other hand, the phosphate moiety was more reactive than the C-Br moiety in **1z**. The initial products from **1z** were 5-Nu-3-bromopenta-1,3-dienes **4** which were less reactive than **1z**. Monosubstitution products **4** were isolable, and the stepwise introduction of two different Nu groups in C_1-symmetric allenes **2** was realized starting with **1z** under the controlled reaction conditions. By the use of a chiral palladium catalyst, axially chiral doubly functionalized allenes were obtained in up to 95% ee.

Introduction

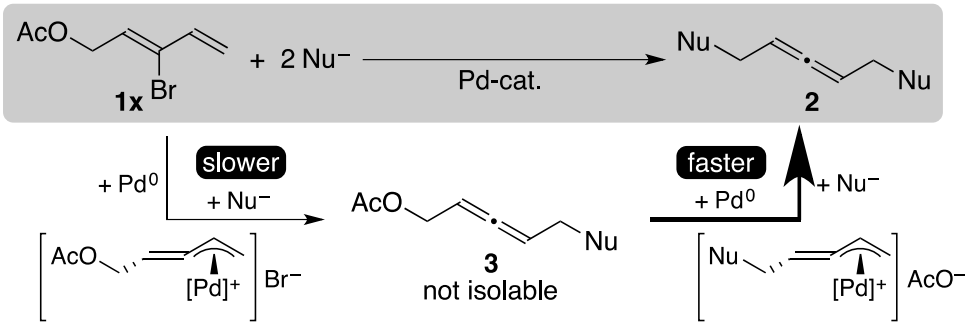
Development of novel and efficient methods of preparing allenic compounds has been an important subject due to synthetic usefulness of allenes in organic chemistry.[1] In 2000, we reported a palladium-catalyzed reaction for preparing various functionalized allenes starting with an easily accessible 1-hydrocarbyl- or 1-silyl-2-bromo-1,3-diene and a soft nucleophile (Scheme 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 1, bottom).[7] As shown in Scheme 1, the two Pd-catalyzed processes are closely related to each other.

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



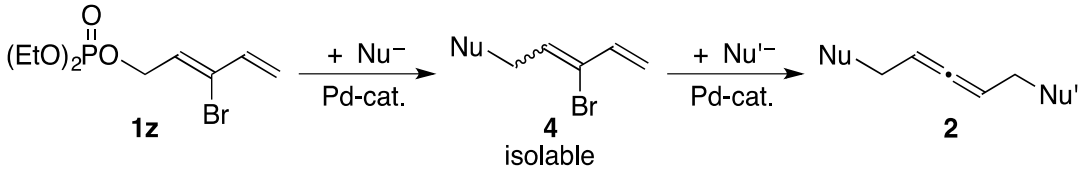
In 2012, we introduced 3-bromopenta-2,4-dienyl acetate (**1x**) as a unique bifunctional electrophile in the palladium-catalyzed reaction.[8] Compound **1x** possesses properties and substructures of both 2-bromo-1,3-dienes and allylic acetates, and it undergoes the "twofold Pd-catalyzed nucleophilic substitution" to give doubly functionalized C_2-symmetric allenes **2** in high yields with excellent regioselectivity. The vinylic C-Br bond in **1x** is more reactive than the allylic acetate moiety in the addition to Pd(0), and thus the primal intermediary product is allenylmethyl acetate **3**. Whereas monosubstituted intermediate **3** is more reactive than **1x** in the palladium-catalyzed reaction, generated **3** is consumed faster than **1x**. Accordingly, **3** is *not* isolable nor detectable, and C_2-symmetric doubly substituted allene **2** is obtained preferentially even in the presence of remaining **1x** (Scheme 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 **1x**.

Scheme 2. Palladium-Catalyzed Double Nucleophilic Substitution on 3-Bromo-2,4-pentadienyl Acetate **1x**.



In this article, we examine 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 (**1z**) is different from that of the corresponding carboxylates. The allylic phosphate moiety is the better leaving group than the vinylic bromide in **1z**, and the monosubstituted intermediates, bromodienes **4**, can be isolated starting with **1z**. That is, stepwise introduction of two different Nu groups is realized starting with **1z** leading to various doubly substituted unsymmetric (C_1-symmetric) allenic products **2** (Scheme 3).

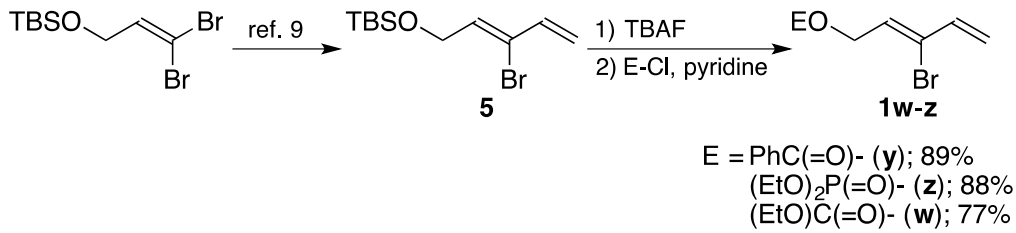
Scheme 3. Palladium-Catalyzed "Sequential" Double Nucleophilic Substitution on 3-Bromo-2,4-pentadienyl Diethyl Phosphate **1z**.



Results and Discussion

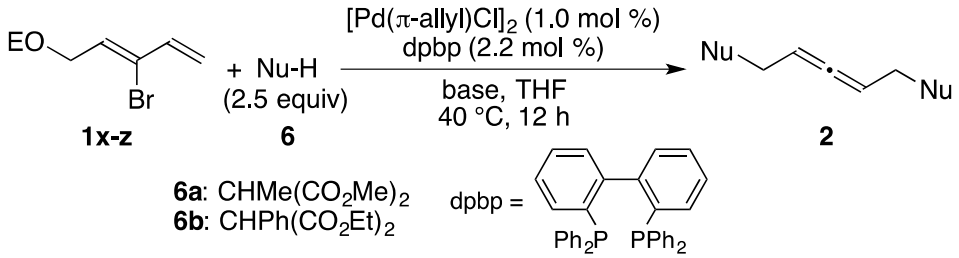
Preparation of 3-Bromopenta-2,4-dienyl Esters 1. The substrates for this study, 3-bromopenta-2,4-dienyl benzoate (**1y**), phosphate (**1z**), and carbonate (**1w**), were prepared as depicted in Scheme 4 starting with *O*-TBS-protected (*Z*)-3-bromopenta-2,4-dienol (**5**).[9] The fluoride-induced desilylation of **5** followed by reactions with benzoyl chloride, diethyl chlorophosphate, or ethyl chlorocarbonate afforded (*Z*)-**1w-z** 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 **1w** was found to be unstable and polymerize easily under the ambient conditions. Accordingly, **1w** was eliminated from further studies, and **1y** and **1z** were examined in the palladium-catalyzed reactions (vide infra).

Scheme 4. Preparation of 3-Bromopenta-2,4-dienyl Esters (**1w-z**).



Preparation of *C*$_2$-Symmetric Allenes by Palladium-Catalyzed Nucleophilic Double Substitution of 1. At the outset, substrates **1x-z** were applied in the Pd-catalyzed reaction in the presence of excess (2.5 equiv with respect to **1**) prototypical malonate pronucleophiles **6a** or **6b** (Table 1). All the three substrates reacted with **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 C_2-symmetric allene **2aa** was isolated in 83-89% yields (entries 1-3). Under the similar conditions, the reactions with phenylmalonate **6b** provided the corresponding C_2-symmetric allene **2bb** in good yields ranging 81% to 86% irrespective of the choice of the substrates (entries 4-6).

Table 1. Palladium-Catalyzed Reactions of **1x-z** with Excess Pronucleophile **6a** or **6b**.[a]



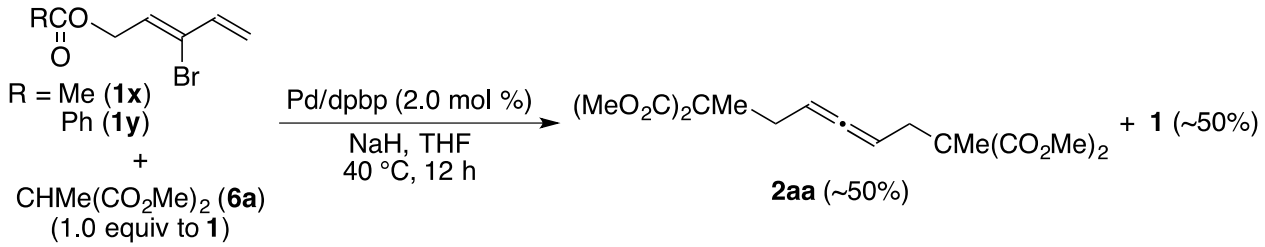
entry	substrate **1**	Nu-H **6**	base	yield of **2** (%)[b]
1[c]	**1x**	**6a**	NaH	83 (**2aa**)
2	**1y**	**6a**	NaH	89 (**2aa**)
3	**1z**	**6a**	NaH	87 (**2aa**)
4[c]	**1x**	**6b**	^{t}BuOK	84 (**2bb**)
5	**1y**	**6b**	^{t}BuOK	81 (**2bb**)
6	**1z**	**6b**	^{t}BuOK	86 (**2bb**)

[a] The reaction was carried out with **1** (0.50 mmol) and **6** (1.25 mmol) in THF in the presence of an appropriate base and a Pd-catalyst (2 mol %) generated from $[PdCl(\pi\text{-allyl})]_2$ and dpbp. [b] Isolated yield by silica gel chromatography. [c] Taken from ref. 8.

Palladium-Catalyzed Nucleophilic Single Substitution of 1z. While all three substrates **1x-z** showed the similar results in the palladium-catalyzed reaction with an excess (2.5 equiv. to **1**) soft nucleophile (Table 1), the carboxylates and the phosphate exhibited different reactivities in the reaction with a stoichiometric soft nucleophile.

Treatment of the carboxylate, **1x** or **1y**, with an equimolar mixture of **6a** and NaH (1 equiv with respect to **1**) in THF in the presence of the Pd/dpbp catalyst (2 mol %) afforded C_2-symmetric allene **2aa** in ca. 50% yield together with ca. 50% unreacted **1** (Scheme 5).[8] This result indicated that presumed intermediate **3** was more reactive than **1x** and **1y** in the palladium-catalyzed nucleophilic substitution (see Scheme 2).

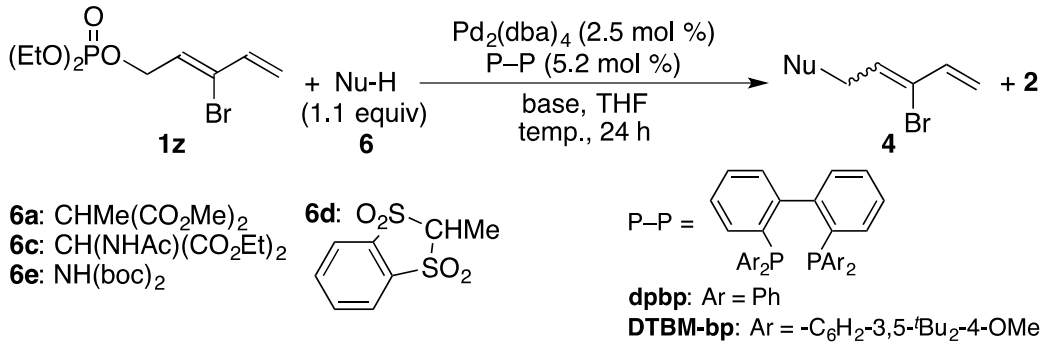
Scheme 5. Palladium-Catalyzed Reactions of Carboxylates **1x** and **1y** with Stoichiometric **6a**.



On the other hand, the palladium-catalyzed reactions of phosphate **1z** with stoichiometric soft nucleophiles provided the corresponding "single substitution" products, 5-(nucleophile-substituted)-3-bromopenta-1,3-dienes **4**, predominantly. The results of the nucleophilic single substitution of **1z** are listed in Table 2 with the detailed reaction conditions. The reactions of **1z** with methylmalonate (**6a**) or acetoamidomalonate (**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 **4a** and **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 **2**, was minor. On the other hand, the reaction with bissulfone pronucleophile **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 **4d** was obtained in modest yields, the concomitant formation of C_2-symmetric allene **2dd** was detected together with unreacted **1z**. 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 **4d** was obtained in up to 88% selectivity under the optimized conditions (entries 5 and 6). The relatively low isolated yield (50%) of **4d** was ascribed to the instability of the compound that polymerized/oligomerized slowly during chromatographic purification on silica gel. The reaction with *N*-pronucleophile **6e** also took place in excellent selectivity with the Pd/dpbp precatalyst, and the corresponding $(boc)_2N$-substituted bromodiene **4e** was isolated in 91% yield (entry 7). All 5-Nu-3-bromopenta-1,3-dienes **4** were obtained as mixtures of the two geometric isomers with the *E*-isomers predominant in 82-88%.

Table 2. Palladium-Catalyzed Reactions of **1z** with Stoichiometric Pronucleophiles **6**.[a]



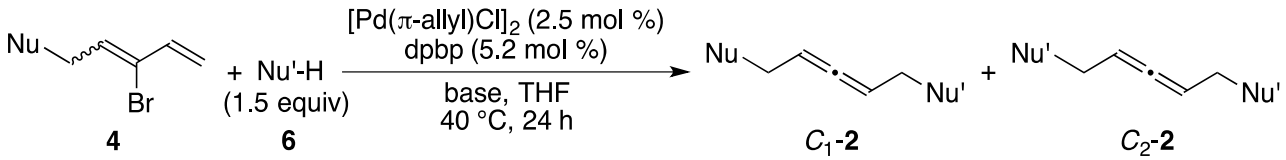
entry	Nu-H	base	temp.	P–P	**1z**/**4**/**2**[b]	yield of **4**[c]	*E*/*Z* in **4**[b]
1	**6a**	NaH	0 °C	dpbp	7/90/3	88% (**4a**)	84/16
2	**6c**	KO^{t}Bu	23 °C	dpbp	4/84/12	83% (**4c**)	82/18
3	**6d**	NaH	23 °C	dpbp	70/19/11	——	——
4	**6d**	$LiCH_2SiMe_3$	40 °C	dpbp	18/48/34	——	——

5	**6d**	$LiCH_2SiMe_3$	40 °C	DTBM-bp	48/49/3	——	——
6	**6d**	$LiCH_2SiMe_3$	60 °C	DTBM-bp	12/88/0	50% (**4d**)	88/12
7	**6e**	KO^{t}Bu	40 °C	dpbp	6/94/0	91% (**4e**)	88/12

[a] The reaction was carried out with **1z** (0.20 mmol) and **6** (0.22 mmol) in THF in the presence of an appropriate base (0.22 mmol) and a Pd-catalyst (5 mol %) generated from $Pd_2(dba)_4$ and a bisphosphine. [b] Determined by the ^{1}H-NMR measurements. [c] Isolated yield by silica gel chromatography.

Palladium-Catalyzed Synthesis of *C*$_1$-Symmetric Allenes 2. Single substitution products **4**, obtained from **1z** and a soft nucleophile Nu^- as in Table 2, were excellent substrates in the palladium-catalyzed "second" nucleophilic substitution to give doubly functionalized allenes **2**. When a nucleophile Nu'^- in the second palladium-catalyzed reaction was different from a Nu group in **4**, doubly substituted unsymmetric (C_1-symmetric) allenes **2** were obtained selectively (except for the reactions of **4e**; vide infra). These C_1-symmetric allenes **2** could not be prepared starting with acetate **1x** or benzoate **1y** (see Schemes 2 and 5). The results of preparing the C_1-symmetric allenes are listed in Table 3. Both methylmalonate- or acetoamidomalonate-tethered bromodienes **4a** and **4c** were equally reactive and the treatments with an appropriate **6** gave the corresponding C_1-symmetric allenes in high yields ranging 72–94% (entries 1-6). Allenes **2ad** and **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 **4d** with a malonate pronucleophile **6a** or **6c** provided **2ad** or **2cd** in 84% and 77% yields, respectively (entries 7 and 8). While the palladium-catalyzed reactions of **4a**, **4c**, and **4d** proceeded with excellent chemoselectivity to give the corresponding C_1-symmetric allenes exclusively, the products from **4e** comprised of the two allenic species. For example, the reaction between **4e** and **6a** afforded C_1-symmetric allene **2ae** in 21% yield together with C_2-symmetric allene **2aa** in 46% yield (entry 9). The reactions of **4e** with the other pronucleophile showed a similar trend (entries 10 and 11).

Table 3. Palladium-Catalyzed Synthesis of C_1-Symmetric Doubly Functionalized Allenes **2** from **4**.[a]

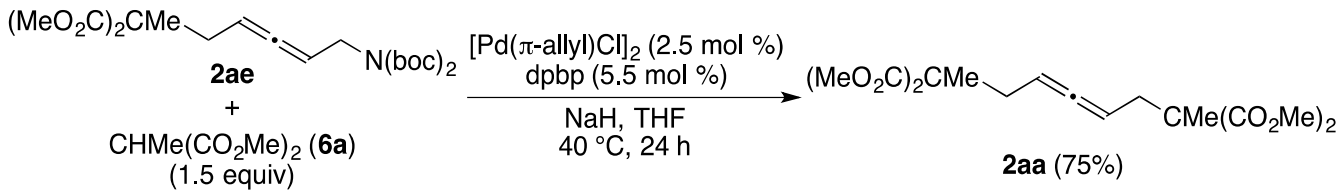


entry	bromodiene **4**	Nu'-H **6**	base	yield of C_1-**2** (%)[b]	yield of C_2-**2** (%)[b]
1	**4a**	**6c**	^{t}BuOK	87 (**2ac**)	——
2		**6d**	NaH	91 (**2ad**)	——
3		**6e**	^{t}BuOK	78 (**2ae**)	——
4	**4c**	**6a**	NaH	94 (**2ac**)	——
5		**6d**	NaH	72 (**2cd**)	——
6		**6e**	^{t}BuOK	93 (**2ce**)	——
7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

[a] The reaction was carried out with **4** (0.10 mmol) and **6** (0.15 mmol) in THF in the presence of an appropriate base and a Pd-catalyst (5 mol %) generated from [PdCl(π-allyl)]$_2$ and dpbp. [b] Isolated yield by silica gel chromatography.

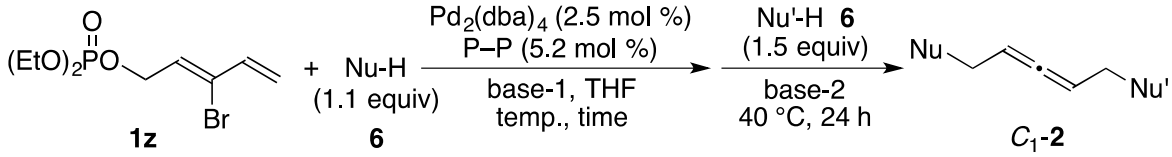
The C_2-symmetric allenes obtained from (boc)$_2$N-tethered **4e** do not possess the (boc)$_2$N group. These observations implied that the (boc)$_2$N moieties in **2ae**, **2ce**, and **2de** functioned as leaving groups under the palladium catalysis. Indeed, this possibility was confirmed by the reaction of **2ae** with excess **6a** in the presence of the Pd/dpbp species, which provided **2aa** in 75% yield (Scheme 6). The results in Table 3 and Scheme 6 clearly indicated that the (boc)$_2$N group needed to be introduced at the second step in the preparation of mono-N(boc)$_2$ C_1-symmetric allenes such as **2ae** and **2ce**.

Scheme 6. Palladium-Catalyzed Substitution at N(boc)$_2$ Moiety in **2ae**.



The C_1-symmetric doubly functionalized allenes could be prepared by the "one-pot" procedure directly from **1z** as outlined in Table 4. After the treatment of **1z** with slight excess pronucleophile **6** and an appropriate base (1.1 equiv. to **1z**) in the presence of the Pd/dpbp precatalyst until the total consumption of **1z** (checked by TLC), a second nucleophile, which was generated from **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 C_1-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 **4**, the operational simplicity of the procedure provided easier access to doubly substituted unsymmetric allenes **2**.

Table 4. Preparation of C_1-Symmetric Allenes **2** from **1z** by "One-Pot" Procedure.[a]

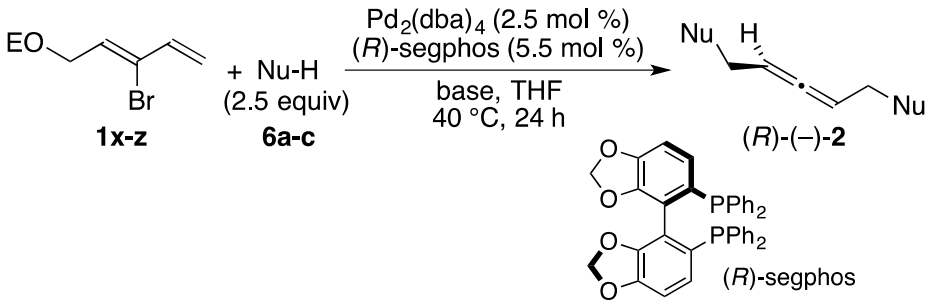


entry	Nu-H **6**	base-1	temp	time	Nu'-H **6**	base-2	yield of **2** (%)[b]
1	**6a**	NaH	0 °C	48 h	**6c**	^{t}BuOK	60 (**2ac**)
2					**6d**	NaH	76 (**2ad**)
3					**6e**	^{t}BuOK	81 (**2ae**)
4	**6c**	^{t}BuOK	23 °C	24 h	**6a**	NaH	62 (**2ac**)
5					**6d**	NaH	64 (**2cd**)
6					**6e**	^{t}BuOK	60 (**2ce**)

[a] The reaction was carried out starting with **1z** (0.20 mmol) in THF in the presence of a Pd-catalyst (5 mol %) generated from $Pd_2(dba)_4$ and dpbp. [b] Isolated yield by silica gel chromatography.

Palladium-Catalyzed Asymmetric Synthesis of Axially Chiral Allenes 2. Allenes **2** obtained in this study are axially chiral, and application of an appropriate chiral palladium species to the reaction may furnish **2** in enantiomerically enriched forms. Three malonate pronucleophiles **6a-c** were chosen, and their asymmetric reactions with bromopentadienyl esters **1x-z** were examined using a palladium precatalyst (5 mol %) generated from $Pd_2(dba)_4$ and (*R*)-segphos according to our previous studies (Table 5).[3] The enantioselective reactions with **6a** provided axially chiral allene **2aa** in excellent yields ranging 87% to 92% irrespective of the choice of substrates **1x-z**, and the highest enantioselectivity of 88% ee was observed in the reaction of phosphate **1z** (entries 1-3). The best result in the asymmetric synthesis of **2bb** was obtained in the reaction of **1y** in 99% yield and 85% ee (entry 5). Among the three pronucleophiles examined, **6c** showed the highest enantioselectivity (entries 7-9). The highest enantioselectivity of 95% ee was recorded in the reaction between **1y** and **6c** using ^{t}BuOCs as a base (entry 8). All the axially chiral allenes obtained in Table 5 were levorotatory and their absolute configurations were deduced to be (*R*) by the Lowe-Brewster rule.[10]

Table 5. Palladium-Catalyzed Asymmetric Synthesis of Axially Chiral Allenes **2**.[a]



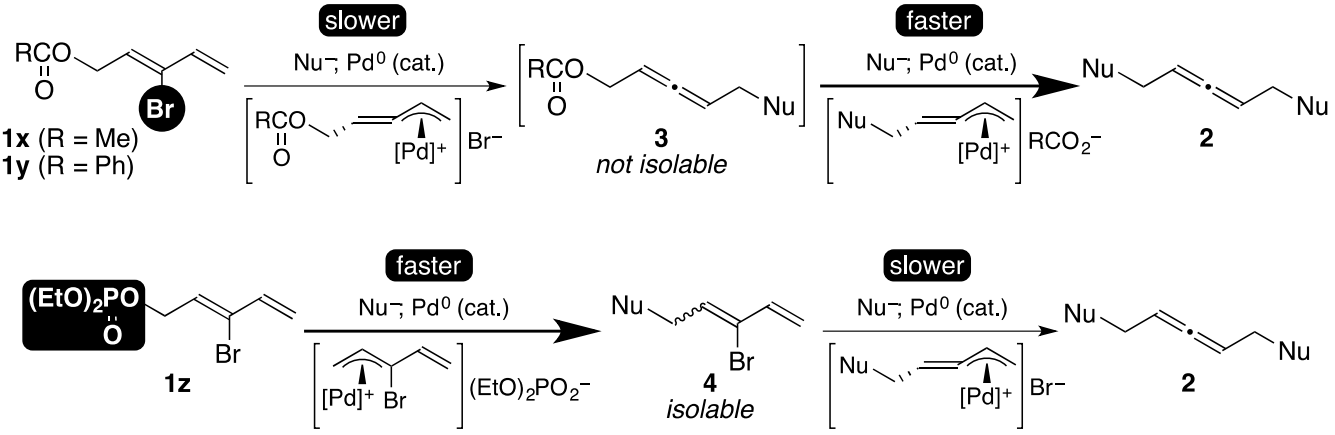
entry	substrate **1**	Nu-H **6**	base	yield of **2** (%)[b]	ee of **2** (%)[c]
1	**1x**	**6a**	NaH	87 (**2aa**)	79
2	**1y**			92 (**2aa**)	61
3	**1z**			91 (**2aa**)	88
4	**1x**	**6b**	^{t}BuOCs	79 (**2bb**)	80

5	**1y**			99 (**2bb**)	85
6	**1z**			77 (**2bb**)	81
7	**1x**	**6c**	^{t}BuOCs	72 (**2cc**)	86
8	**1y**			74 (**2cc**)	95
9	**1z**			77 (**2cc**)	86

[a] The reaction was carried out with **1** (0.20 mmol) and **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 $Pd_2(dba)_4$ and (*R*)-segphos. [b] Isolated yield by alumina chromatography [c] Determined by chiral HPLC analysis.

Consideration to Relative Reactivity between Carboxylate, Phosphate, and Bromide in 1. Substrates **1x-z** possesses 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 **1x** and **1y**, the initially formed monosubstitution intermediates should be **3**. The carboxylate moieties in **3** are more reactive than the bromide substituents in **1x** and **1y**, and intermediates **3** are consumed faster than **1** (Scheme 7, top). Accordingly, **3** are not isolable and C_2-symmetric allenes **2** are preferentially obtained even in the presence of remaining **1x** and **1y**.[8] On the other hand, the phosphate substituent is more reactive than the C-Br moiety in **1z**. Accordingly, the initial products from **1z** are bromodienes **4** which are less reactive than **1z**. Therefore monosubstitution products **4** are isolable, and the introduction of two different Nu groups in allenes **2** is realized starting from **1z** under the controlled reaction conditions (Scheme 7, bottom).

Scheme 7. Proposed Reaction Pathways from **1** to **2**.



Conclusions

In summary, we have demonstrated that readily available 3-bromopenta-2,4-dienyl esters **1x-z** are excellent precursors to a variety of doubly functionalized allenes **2**. The reaction of **1** and soft nucleophile **6** is catalyzed by the Pd/dpbp complex, and **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 **1z** leading to the C_1-symmetric allenes, which are not accessible from carboxylates **1x** and **1y**. By the use of a chiral palladium catalyst, axially chiral doubly functionalized allenes were obtained in up to 95% ee.

Experimental Section

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. ^{1}H NMR (at 400 MHz) and ^{13}C{^{1}H} NMR (at 101 MHz) chemical shifts are reported in ppm downfield of internal tetramethylsilane. ^{31}P{^{1}H} 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 (**5**),[9] 1,3-benzodithiole-1,1,3,3-tetraoxide,[11] dpbp,[12] and (*R*)-segphos[13] were prepared as reported. DTBM-bp was reported previously,[14] however, no characterization data were

given. Synthetic procedure and characterization data of DTBM-bp are described in Supporting Information. All other chemicals were obtained from commercial sources and used without additional purification.

(*Z*)-3-Bromopenta-2,4-dienyl Benzoate (1y). To a stirred solution of **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 NH_4Cl_{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 $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ethyl acetate = 20/1) followed by vacuum transfer to give **1y** as a pale-yellow oil. Yield: 2.59 g (89%). ^{1}H NMR ($CDCl_3$): 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). ^{13}C{^{1}H} NMR ($CDCl_3$): 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 $C_{12}H_{11}BrO_2Na$ (M + Na): 288.9840. Found: 288.9849.

(*Z*)-3-Bromopenta-2,4-dienyl Diethyl Phosphate (1z). This compound was prepared essentially in the same way of the synthesis of **1y** 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/Et_3N = 75/25/1) followed by vacuum transfer to give **1z** as a pale-yellow oil. Yield: 2.86 g (88%). ^{1}H NMR ($CDCl_3$): 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). ^{13}C{^{1}H} NMR ($CDCl_3$): 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. $^{31}P\{^{1}H\}$ NMR ($CDCl_3$): δ –0.28. EI-HRMS Calcd for $C_9H_{16}BrO_4PNa$ (M + Na): 320.9867. Found: 320.9875.

(*Z*)-3-Bromopenta-2,4-dienyl Ethyl Carbonate (1w). This compound was prepared essentially in the same way of the synthesis of **1y** using ethyl chloroformate (2.35 g, 21.6 mmol) instead of benzoyl chloride. The crude product was purified by silica gel chromatography (hexane/$CHCl_3$ = 3/1) followed by vacuum transfer to give **1w** as a pale-yellow oil. Yield: 1.95 g (77%). ^{1}H NMR ($CDCl_3$): 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). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 14.4, 64.5, 66.9, 120.5, 127.7, 128.2, 135.0, 155.1. EI-HRMS Calcd for $C_8H_{11}BrO_3Na$ (M + Na): 256.9789. Found: 256.9783.

2-Methyl-1,3-benzodithiole 1,1,3,3-Tetraoxide (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 ($CHCl_3$/hexane/benzene/Et_2O = 9/2/2/1) to give the title compound as a white solid. Yield: 2.95 g (92%). ^{1}H 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). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 6.9, 70.3, 122.9, 135.4, 137.7. ESI-HRMS Calcd for $C_8H_8O_4S_2Na$ (M + Na): 254.9762. Found: 254.9752.

Preparation of *C*$_2$-Symmetric Allenes 2 by Palladium-Catalyzed Double Substitution of 1. The reactions were conducted according to a reported procedure.[8] The reaction conditions and the results are summarized in Table 1. A mixture of $[PdCl(\pi\text{-allyl})]_2$ (1.8 mg, 10 μmol/Pd), dpbp (5.7 mg, 11 μmol), and **1** (0.50 mmol) was dissolved in THF (5 mL) and the solution was added to a mixture of **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 **2** in pure form. The ^{1}H- and ^{13}C-NMR spectra of **2aa** and **2bb** were consistent with those reported previously.[8]

Palladium-Catalyzed Nucleophilic Single Substitution of 1z. The reaction conditions and the results are summarized in Table 2. A mixture of $Pd_2(dba)_4$ (5.8 mg, 5.0 μmol), a bisphosphine ligand (10.5 μmol), and **1z** (60 mg, 0.20 mmol) was dissolved in THF (2 mL), and the solution was added to a mixture of **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 **4** in pure form. The characterization data of bromodiene products **6** are listed below.

Dimethyl 2-(3-Bromopenta-2,4-dienyl)-2-methylmalonate (4a). Colorless oil. Yield: 52 mg (88%) starting with **1c** (60 mg; 0.20 mmol). *E*/*Z* = 84/16. (*E*)-**4a**: ^{1}H 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{^{1}H} NMR ($CDCl_3$): δ 20.4, 37.9, 52.9, 53.7, 118.8, 128.9, 129.0, 135.8, 172.2. (*Z*)-**4a**: ^{1}H ($CDCl_3$): 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 $C_{11}H_{15}BrO_4Na$ (M + Na): 313.0051. Found: 313.0062.

Diethyl 2-Acetamido-2-(3-bromopenta-2,4-dienyl)malonate (4c). Pale-yellow oil. Yield: 60 mg (83%) starting with **1c** (60 mg; 0.20 mmol). *E*/*Z* = 82/18. (*E*)-**4c**: ^{1}H 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{^{1}H} 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*)-**4c**: ^{1}H 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). $^{13}C\{^1H\}$ 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 $C_{14}H_{20}BrNO_5Na$ (M + Na): 384.0423. Found: 384.0431.

2-(3-Bromopenta-2,4-dienyl)-2-methylbenzodithiole 1,1,3,3-Tetraoxide (4d). White solid. Yield: 38 mg (50%) starting with **1c** (60 mg; 0.20 mmol). *E*/*Z* = 88/12. (*E*)-**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). $^{13}C\{^1H\}$ 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*)-**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 $C_{13}H_{13}BrO_4S_2Na$ (M + Na): 398.9336. Found: 398.9350.

***N*,*N*-Di(*tert*-butoxycarbonyl)-*N*-(3-bromopenta-2,4-dienyl)amine (4e).** Pale-yellow oil. Yield: 66 mg (91%) starting with **1c** (60 mg; 0.20 mmol). *E*/*Z* = 88/12. (*E*)-**4e**: ^1H NMR ($CDCl_3$): 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). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 28.2, 47.8, 82.9, 118.9, 125.7, 131.3, 135.2, 152.3. (*Z*)-**4e**: ^1H NMR ($CDCl_3$): 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 $C_{15}H_{24}BrNO_4Na$ (M + Na): 384.0786. Found: 384.0775.

Preparation of *C*$_1$-Symmetric Allenes 2 by Palladium-Catalyzed Substitution of 4. The reaction conditions and the results are summarized in Table 3. A mixture of $[PdCl(\pi\text{-allyl})]_2$ (1.0 mg, 2.5 μmol), dpbp (2.9 mg, 5.5 μmol), and **4** (0.10 mmol) was dissolved in THF (1 mL), and the solution was added to a mixture of **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 **2** in pure form. The characterization data of C_1-symmetric allenes **2** are listed below.

Dimethyl 2-[6-Acetamido-6,6-di(ethoxycarbonyl)hexa-2,3-dienyl]-2-methylmalonate (2ac). ^{1}H NMR ($CDCl_3$): 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). ^{13}C{^{1}H} NMR ($CDCl_3$): 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 $C_{20}H_{29}NO_9Na$ (M + Na): 450.1740. Found: 450.1745.

2-[6,6-Di(methoxycarbonyl)hepta-2,3-dienyl]-2-methylbenzodithiole 1,1,3,3-Tetraoxide (2ad). ^{1}H NMR ($CDCl_3$): 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). ^{13}C{^{1}H} NMR ($CDCl_3$): 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 $C_{19}H_{22}O_8S_2Na$ (M + Na): 465.0654. Found: 465.0654.

Dimethyl 2-[5-{*N*,*N*-Di(*tert*-butoxycarbonyl)amino}penta-2,3-dienyl]-2-methylmalonate (2ae). ^{1}H NMR ($CDCl_3$): 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). ^{13}C{^{1}H} NMR ($CDCl_3$): 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 $C_{21}H_{33}NO_8Na$ (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 (2cd). ^{1}H NMR ($CDCl_3$): 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). ^{13}C{^{1}H} NMR ($CDCl_3$): 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 $C_{22}H_{27}NO_9S_2Na$ (M + Na): 536.1025. Found: 536.1037.

Diethyl 2-Acetamido-2-[5-{*N*,*N*-di(*tert*-butoxycarbonyl)amino}penta-2,3-dienyl]malonate (2ce). ^{1}H NMR ($CDCl_3$): 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). ^{13}C{^{1}H} NMR ($CDCl_3$): 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 $C_{24}H_{38}N_2O_9Na$ (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 (2de). ^{1}H NMR ($CDCl_3$): 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). ^{13}C{^{1}H} NMR ($CDCl_3$): 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 $C_{23}H_{31}NO_8S_2Na$ (M + Na): 536.1389. Found: 536.1389.

Palladium-Catalyzed Substitution of N(boc)$_2$ Moiety in 2ae with Malonate. A mixture of [PdCl(π-allyl)]$_2$ (0.73 mg, 2.0 μmol), dpbp (2.3 mg, 4.4 μmol), and **2ae** (34.0 mg, 79.5 μmol) was dissolved in THF (1 mL), and the solution was added to a mixture of **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 **2aa** (21 mg; 75% yield).

Palladium-Catalyzed "One-Pot" Synthesis of *C*$_1$-Symmetric Allenes 2. The reaction conditions and the results are summarized in Table 4. A mixture of $Pd_2(dba)_4$ (5.8 mg, 5.0 μmol), dpbp (5.8 mg, 11 μmol), and **1c** (60 mg, 0.20 mmol) was dissolved in THF (2 mL), and the solution was added to a mixture of first pronucleophile **4** (0.22 mmol) and an appropriate base (0.22 mmol) via a cannula under nitrogen. The reaction progress was monitored by TLC. When **1z** was consumed completely, a solution

of second pronucleophile **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 **2** in pure form. The ^{1}H- and ^{13}C-NMR analyses clarified that the allenic products obtained here were identical with those prepared from **4** (see Table 3).

Pd-Catalyzed Asymmetric Synthesis of (*R*)-(–)-2. To a mixture of $Pd_2(dba)_4$ (5.8 mg, 5.0 μmol), (*R*)-segphos (6.7 mg, 11 μmol), **6** (0.60 mmol), and an appropriate base (0.50 mmol) in THF (3 mL) was added **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 Al_2O_3 to remove precipitated inorganic salts. The Al_2O_3 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 Al_2O_3 to give (*R*)-(–)-**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 **2aa**, **2bb**, and **2cc** were reported previously as racemates.[8] The conditions for the chiral HPLC analyses are listed below. (*R*)-(–)-**2aa**: $[\alpha]^{29}_{D}$ = –21.5 (*c* 3.03, $CHCl_3$ 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] = 20.1 min, t_2 [(*R*)-enantiomer] = 21.8 min. (*R*)-(–)-**2bb**: $[\alpha]^{31}_{D}$ = –22.5 (*c* 4.77, $CHCl_3$ 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] = 33.5 min, t_2 [(*S*)-enantiomer] = 42.1 min. (*R*)-(–)-**2cc**: $[\alpha]^{21}_{D}$ = –51.8 (*c* 0.49, $CHCl_3$ for the sample of 95% ee). Chiral HPLC Analysis Conditions: Chiralpak AD-H; eluent, hexane/^{i}PrOH = 10/1; flow rate, 0.8 mL/min; t_1 [(*S*)-enantiomer] = 29.7 min, t_2 [(*R*)-enantiomer] = 31.9 min.

Supporting Information Available. Preparation of DTBM-bp, ^{1}H-, ^{13}C{^{1}H}-, and ^{31}P{^{1}H}-NMR spectra for all the new compounds, and chiral HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

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