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Palladium-Catalyzed Preparation of Vinylallenes from 2-Bromo-1,3,5-trienes via an Alkylidene-π-allylpalladium-Mediated Formal S_N2'' Pathway

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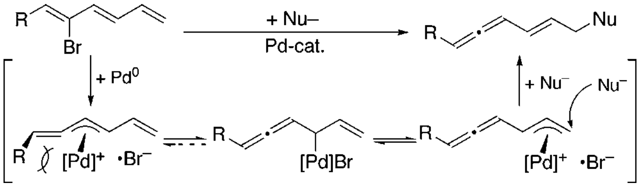
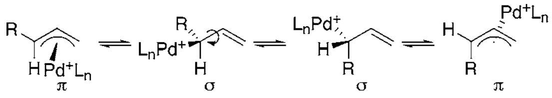
ABSTRACT



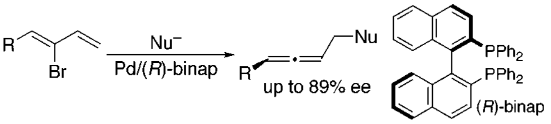
A novel Pd-catalyzed reaction to prepare conjugated vinylallenes from 2-bromo-1,3,5-triene and a soft nucleophile via a formal S_N2'' pathway was developed. The reaction proceeds via alkylidene-π-allylpalladium and allenyl-π-allylpalladium intermediates, and a dynamic process involving the two palladium intermediates played important roles in determining the selectivity of the Pd-catalyzed reaction. The reaction was extended to an asymmetric counterpart, and an axially chiral vinylallene was obtained with up to 81% ee.

In many palladium-catalyzed reactions, π-allylpalladium species have been recognized as key intermediates of the catalytic cycles, and their dynamic behavior via a $\pi-\sigma-\pi$ process plays an important role in determining the stereoselectivity of the reactions (eq 1).[1]



(1)

Recently, we developed a palladium-catalyzed reaction to prepare functionalized allenes from 2-bromo-1,3-dienes.[2] The Pd-catalyzed reaction was extended into an asymmetric counterpart using a Pd/(*R*)-binap catalyst, and enantiomerically enriched axially chiral allenes were obtained with up to 89% ee (eq 2).[2b,c,e] Negishi and co-workers revealed that



(2)

analogous 2-bromo-1,3-dienes were also used as unique substrates in Pd-catalyzed *E*/*Z*-selective preparation of conjugated dienes.[3]

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[1] (a) Negishi, E., Ed. *Handbook of Organopalladium Chemistry for Organic Synthesis*; John Wiley and Sons: New York, 2002; p 1663. (b) Tsuji, J. *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*; John Wiley and Sons: Chichester, 2004; p 431.

[2] (a) Ogasawara, M.; Ikeda, H.; Hayashi, T. *Angew. Chem., Int. Ed.* **2000**, *39*, 1042. (b) Ogasawara, M.; Ikeda, H.; Nagano, T.; Hayashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 2089. (c) Ogasawara, M.; Ueyama, K.; Nagano, T.; Mizuhata, Y.; Hayashi, T. *Org. Lett.* **2003**, *5*, 217. (d) Ogasawara, M.; Ge, Y.; Uetake, K.; Fan, L.; Takahashi, T. *J. Org. Chem.* **2005**, *70*, 3871. (e) Ogasawara, M.; Nagano, T.; Hayashi, T. *J. Org. Chem.* **2005**, *70*, 5764. (f) Ogasawara, M.; Ge, Y.; Uetake, K.; Takahashi, T. *Org. Lett.* **2005**, *7*, 5697.

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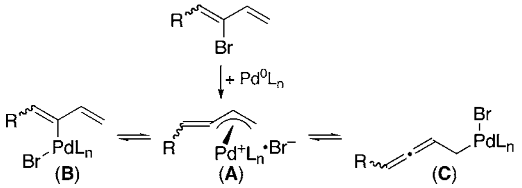
An alkylidene-π-allylpalladium species (**A**) is suggested as a possible intermediate[4] in protocols of preparing both allenes and conjugated dienes, and apparently, the dynamic behavior of such a Pd intermediate controls the stereoselectivity of the two Pd-catalyzed reactions.[2b,3a] Asymmetric dynamic kinetic resolution of racemic allenylmethyl esters reported by Imada et al.[4i,k] and by Trost et al.[4j] was also proposed to proceed via analogous alkylidene-π-allylpalladium intermediates. The two terminal carbons of an η^3-allyl moiety in **A** (Scheme 1) are electronically diverse: one is sp- and the other is sp^2-hybridized. Thus, η^1-σ-coordination at either carbon might produce σ-(1,3-dien-2-yl)palladium (**B**) or σ-(allenylmethyl)palladium (**C**), respectively. Green et al. demonstrated that palladium species analogous to **A** and **B** were prepared either from 2-chloro-1,3-butadienes or from 4-chloro-1,2-butadienes; however, Pd species such as **C** were not observed.[5,6]

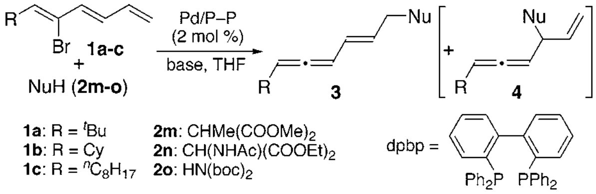
Scheme 1



Here we wish to report a novel Pd-catalyzed reaction that yields conjugated vinylallenes from 2-bromo-1,3,5-trienes via a formal S_N2'' pathway, in which a dynamic process involving both alkylidene-π-allylpalladium (**A**) and σ-(allenylmethyl)palladium (**C**) plays important roles in determining the selectivity of the reaction.

Although the σ-(allenylmethyl)palladium species **C** has been neither detected nor isolated, its existence as a transient intermediate was proposed in several reactions.[3a,4b,c,g,h,7] Accordingly, a palladium-catalyzed reaction of an 1-alkyl-2-bromo-1,3,5-hexatriene **1** with a soft nucleophile **2** was explored for a possible formal S_N2'' reaction (Scheme 2, Table 1).[8] As we expected, treatment of a 2-bromo-1,3,5-triene **1a**, which was with a ^{t}Bu group at the C(1) position of the trienyl skeleton, with a pronucleophile **2m** in the presence of NaH and a palladium catalyst (2 mol %), which was generated in situ from [PdCl(π-allyl)]$_2$ and dpbp[9] at 23 °C, gave a conjugated vinylallene **3am** in 96% yield as a sole allenic product (Table 1, entry 1). Analogous vinylallenes **3an** and **3ao** were also obtained cleanly in 80 and 96% yields, respectively, by the reactions of **1a** with either **2n** or **2o** (entries 2 and 3). Products from **1b** and **1c**, which were with sterically less bulky alkyl substituents at the C(1) position, were obtained as mixtures of vinylallenes **3** and nonconjugated allylallenes **4** (two diastereomers). The **3**/**4** selectivity decreased as the R substituents in **1** became smaller (entries 1, 4, and 9; entries 2 and 7). On the other hand, formation of the allylallenes **4** was suppressed by the use of the less-reactive (slow-reacting) pronucleophile **2n** in place of **2m** (entries 4 and 7).

Scheme 2



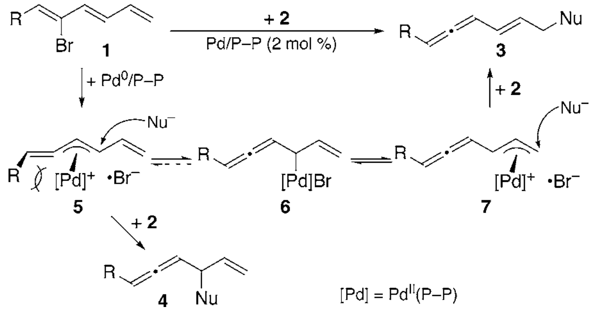
A plausible mechanism of the Pd-catalyzed reactions is shown in Scheme 3. An initially formed alkylidene-π-allylpalladium species **5** is in equilibrium with a σ-(allenylmethyl)palladium intermediate **6**, whose structure is similar to that of the type-**C** species (see Scheme 1), and coordination of the vinyl pendent in **6** to the Pd center forms an allenyl-π-allylpalladium species **7**. The nucleophile highly selectively attacks the unsubstituted π-allyl terminal in **7**[1,8,10] to afford **3**. The isomerization of **5** to **7** becomes slower when the R group is sterically more compact because the steric interaction between the R group and the Pd^{II}(P−P) moiety in **5** is less operative. Thus, a part of **5** reacts with the nucleophile prior to the isomerization to **7** giving **4**. On the other hand, formation of **4** is suppressed in a reaction with a less-reactive

Table 1. Palladium-Catalyzed Reactions of 2-Bromo-1,3,5-trienes **1** with Soft Nucleophiles **2**[a]

entry	bromotriene **1**	NuH **2**	base	Pd precursor	P−P	temp/°C	yield of **3** + **4**/%[b]	**3**/**4**[c]
1	**1a**	**2m**	NaH	[PdCl(π-allyl)]$_2$	dpbp	23	96 (**3am**)	>99:nd[d]
2	**1a**	**2n**	KH	[PdCl(π-allyl)]$_2$	dpbp	23	80 (**3an**)	>99:nd[d]
3	**1a**	**2o**	KH	[PdCl(π-allyl)]$_2$	dpbp	23	96 (**3ao**)	>99:nd[d]
4	**1b**	**2m**	NaH	[PdCl(π-allyl)]$_2$	dpbp	23	98 (**3bm** + **4bm**)	77:23
5	**1b**	**2**	NaH	Pd(dba)$_2$	dpbp	50	73 (**3bm** + **4bm**)	87:13
6	**1b**	**2m**	NaH	Pd(dba)$_2$	dppp	50	76 (**3bm** + **4bm**)	91:9
7	**1b**	**2n**	KH	[PdCl(π-allyl)]$_2$	dpbp	23	98 (**3bn** + **4bn**)	91:9
8	**1b**	**2n**	KH	Pd(dba)$_2$	dppp	50	77 (**3bn** + **4bn**)	96:4
9	**1c**	**2m**	NaH	[PdCl(π-allyl)]$_2$	dpbp	23	80 (**3cm** + **4 cm**)	69:31
10	**1c**	**2m**	NaH	Pd(dba)$_2$	dppp	50	98 (**3cm** + **4cm**)	84:16

[a] The reactions were carried out in THF in the presence of a Pd catalyst (2 mol %) generated from an appropriate palladium precursor and a bisphosphine ligand. [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] Allylallene products were not detected by ^{1}H NMR.

Scheme 3

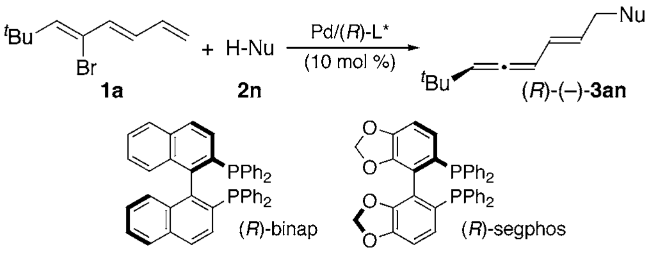


nucleophile because the lifetime of the palladium intermediates becomes longer and **5** has enough time to isomerize to **7**.

The analyses of the Pd-catalyzed reaction shown in Scheme 3 implied that the vinylallene **3** might be formed more preferentially with an appropriate Pd catalyst which reacts more slowly with the nucleophiles. A variety of Pd precursors and phosphine ligands were examined in the reaction of **1b** with **2m**, and the **3bm**/**4bm** ratio in the products was monitored by ^{1}H NMR. It was found that Pd catalysts generated from Pd(dba)$_2$ improved the **3bm**/**4bm** ratio, and the use of dppp as an ancillary ligand further improved the selectivity (Table 1, entries 4−6). Yields of the allenic products were lower (∼30%) for the reactions catalyzed by Pd(dba)$_2$/P−P at 23 °C because of lower catalytic activity of the palladium species. However, the allenes were obtained in reasonable yields at higher temperature (50 °C) without loss of selectivity. Under the optimized conditions, **3bm** was obtained in 91% selectivity (entry 6). The catalyst generated from Pd(dba)$_2$ and dppp was also applied to the reactions of **1b** with **2n** (entry 8) and of **1c** with **2m** (entry 10), and the vinylallenes **3bn** and **3cm** were obtained in much better selectivity.

Although the bromotriene substrates **1** are achiral, the vinylallene products **3** are axially chiral. Accordingly, the present reaction could be extended into an asymmetric counterpart by using a chirally modified palladium catalyst. It should be mentioned that examples of transition-metal-catalyzed asymmetric synthesis of axially chiral allenes are still very rare.[2b,c,e,4i−k,11−13] The asymmetric extension of the process was explored for a reaction of **1a** with **2n**, and the results are summarized in Table 2. A Pd catalyst generated from Pd(dba)$_2$ and (*R*)-binap afforded the vinylallene (−)-(*R*)-**3an**[14] with 67% ee in 60% yield in THF at 23 °C in the

Table 2. Palladium-Catalyzed Asymmetric Synthesis of Vinylallene **3an** from Bromotriene **1a** and Pronucleophile **2n**[a]



entry	L*	solvent	base	temp/°C	yield/%[b]	% ee[c]
1	binap	THF	CsO^{t}Bu	23	60	67
2	segphos	THF	CsO^{t}Bu	23	35	70
3	segphos	EtOH	CsO^{t}Bu	23	48	75
4	segphos	EtOH	CsO^{t}Bu	40	66	77
5	segphos	EtOH	CsO^{t}Bu	70	25	77
6	segphos	EtOH	NaO^{t}Bu	40	56	81[d]

[a] The reactions were carried out with a Pd catalyst generated from Pd(dba)$_2$ and a chiral ligand L*. [b] Isolated yield by silica gel chromatography. [c] Determined by HPLC analysis with a chiral stationary phase column (Daicel Chiralpak AS-H). [d] $[\alpha]^{27.5}_{D} = -26$ (c 0.99, CHCl$_3$).

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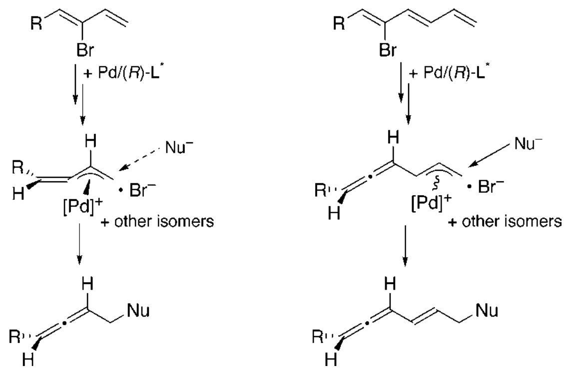
(14) The absolute configuration of **3an** was deduced by the Lowe−Brewster rule. See: (a) Lowe, G. *Chem. Commun.* **1965**, 411. (b) Brewster, J. H. *Top. Stereochem.* **1967**, *2*, 1.

presence of CsO^{t}Bu (entry 1). The Pd/(*R*)-segphos[15] catalyst showed a better enantioselectivity than the (*R*)-binap analogue (entries 2−5). It was found that the use of a more polar solvent (EtOH) and slightly higher temperature (at 40 °C) improved the enantioselectivity (entries 3 and 4). However, a reaction at 70 °C decreased the chemical yield of **3an** (entry 5). Under the optimized conditions with NaO^{t}Bu as base, (*R*)-**3an** was obtained in the highest enantioselectivity with 81% ee (entry 6).[16]

A comparison between the two asymmetric processes of producing axially chiral allenes, one with the bromodienes (eq 2)[2b,c,e] and the other with the bromotrienes **1** (Table 2), is illustrated in Scheme 4. In the reaction of a bromodiene substrate, the configuration of an axially chiral allene is determined at a nucleophilic attack of Nu$^-$ to an alkylidene-π-allylpalladium intermediate (Scheme 4, left). In the reaction of the bromotriene substrate **1**, however, the local allenic configuration is already determined prior to the nucleophilic attack of Nu$^-$ to an allenyl-π-allylpalladium intermediate.

In summary, we have developed a novel Pd-catalyzed reaction to prepare conjugated vinylallenes from 2-bromo-1,3,5-triene and a soft nucleophile. The reaction proceeds via a formal S$_N$2″ pathway, and a dynamic process of Pd intermediates determines the selectivity of the Pd-catalyzed reaction. The reaction was extended to an asymmetric counterpart, and an axially chiral vinylallene was obtained with up to 81% ee.

Scheme 4



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Supporting Information Available: Detailed experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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