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Palladium-Catalyzed Asymmetric Synthesis of Axially Chiral Allenylsilanes and Their Application to S_E2' Chirality Transfer Reactions

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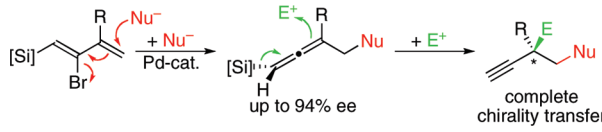
ABSTRACT



Stepwise application of the Pd-catalyzed S_N2' reaction and the desilylative S_E2' reaction to the ambivalent 2-bromo-1-silyl-1,3-dienes provides a novel route to the highly enantioselective construction of tertiary and quaternary propargylic stereogenic centers via axially chiral allenylsilanes.

Allenylsilanes are versatile intermediates for organic synthesis,[1,2] and their axially chiral counterparts are capable of transferring the allenic axial chirality into newly formed propargylic stereogenic centers by a regio- and stereospecific S_E2' reaction with an appropriate electrophile.[1,3] Although various protocols of preparing allenylsilanes have been reported,[2] methods to prepare enantiomerically enriched axially chiral allenylsilanes have not been well developed.[3] To the best of our knowledge, only three methods have been reported on the *catalytic asymmetric synthesis* of axially chiral allenylsilanes.[4] This can be attributed to the lack of general routes to scalemic axially chiral allenes by asymmetric catalysis.[4−7] Recently, we developed the Pd-catalyzed reaction of preparing various multisubstituted allenes,[8a−h] and the use of a

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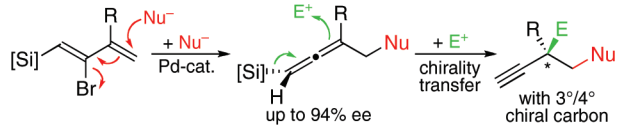
proper chiral Pd catalyst furnished axially chiral allenes with high enantioselectivity.[8i−m] In this communication, we report the application of the Pd-catalyzed reaction to the asymmetric synthesis of axially chiral allenylsilanes. The newly developed substrates for the present study, 2-bromo-1-silyl-1,3-dienes, possess both electrophilic and nucleophilic sites within single molecules. Stepwise application of the Pd-catalyzed S_N2' reaction and the desilylative S_E2' reaction to the ambivalent compounds provides a novel route to the asymmetric construction of chiral propargyl compounds in up to 94% ee (Scheme 1). Whereas the Pd-catalyzed reaction

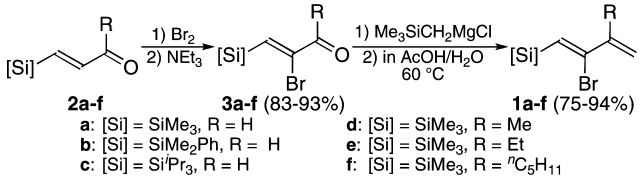
Scheme 1



is tolerant of various functional groups, a variety of substituents could be introduced in the allenylsilanes. The 3,3-dialkylallenylsilanes thus obtained can be converted to the corresponding propargylic compounds with an "all-carbon" quaternary stereogenic center by the S_E2' chirality transfer process.

To realize the Pd-catalyzed synthesis of allenylsilanes, first, the preparation of yet unknown 2-bromo-1-silyl-1,3-dienes was examined. A series of bromosilyldienes **1a**−**f** were obtained in good overall yields by the reaction sequence depicted in Scheme 2. Readily accessible β-silylenals/enones

Scheme 2



2 were converted into the corresponding α-bromo-β-silylenals/enones **3** by a successive Br_2 and NEt_3 treatment.[9] Conversion of **3** into **1** was achieved by Peterson's protocol: i.e., reaction of **3** with Me_3SiCH_2MgCl followed by an acidic treatment of the generated alcohols at 60 °C afforded **1** predominantly in (*Z*)-forms (>96%). The choice of the methylenation method in the final step is important for the high yields of **1**. While Peterson's protocol was highly effective for the transformation giving **1** in up to 94% yield, the Wittig reaction of **3a** with $Ph_3P{=}CH_2$ gave a complex mixture with less than 20% of **1a**. The bromosilyldienes **1** are fairly stable and purified by silica gel chromatography and/or vacuum distillation.

The bromosilyldienes **1** are excellent substrates for the Pd-catalyzed reaction with various carbon soft nucleophiles **4**, and various allenylsilanes **5**, including 1,3-disubstituted (Table 1, entries 1−9) and 1,3,3-trisubstituted (entries 10−12) allenylsilanes, were obtained in good to excellent yields in the presence of 2 mol % of a palladium catalyst generated in situ from $[PdCl(\pi\text{-allyl})]_2$ and dpbp.[8a,10] The substrates **1** were consumed completely within 18 h, and the NMR and GC analyses of the crude reaction mixtures revealed concomitant formation of the dehydrobrominated enynes $[Si]{-}C{\equiv}C{-}CR{=}CH_2$ **6**[11] as byproducts. Similar dehydrobromination was not apparent in the analogous palladium-catalyzed reaction of 1-hydrocarbyl-2-bromo-1,3-dienes.[8] Apart from the formation of **6**, the reaction was generally very clean and the allenylsilanes **1** were isolated in up to 93% yield by silica gel chromatography.

Whereas the synthetic usefulness of **1** in the Pd-catalyzed reaction was proven as above, enantioselective synthesis of the axially chiral allenylsilanes was examined. Under the reaction conditions similar to those in our previous report,[8i] i.e., with a palladium catalyst (10 mol %) generated from $Pd_2(dba)_4$ and (*R*)-binap, (*R*)-**5am** of 54% ee was obtained in 61% yield by a reaction of **1a** with **4m** at 23 °C (entry 13). The enantioselectivity was improved by the use of (*R*)-segphos[8j,k,12] in place of (*R*)-binap, and (*R*)-**5am** was obtained in 86% ee (entry 14). Despite the higher enantioselectivity, the Pd/(*R*)-segphos species was prone to give **5** in lower yields. To gain reasonable yields of **5** with the Pd/(*R*)-segphos, higher temperatures (up to 80 °C) were required, but the loss of the enantioselectivity was minimal to negligible. A variety of axially chiral allenylsilanes of excellent enantiopurity (up to 94% ee in 87% yield in **5an**; entry 15) were obtained under the optimized

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(10) dpbp = 2,2′-bis(diphenylphosphino)-1,1′-biphenyl. See: Ogasawara, M.; Yoshida, K.; Hayashi, T. *Organometallics* **2000**, *19*, 1567, and references cited therein.

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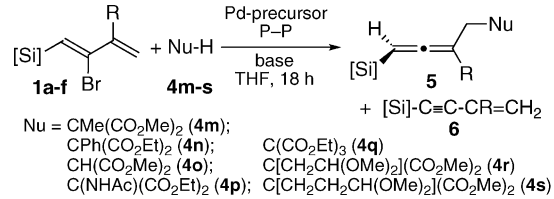
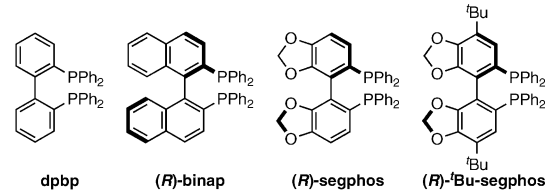
Table 1. Palladium-Catalyzed Synthesis of Axially Chiral Allenylsilanes **5**[a]





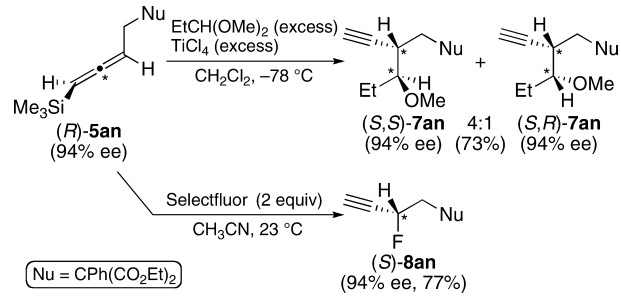
entry	substrate **1**	Nu−H **4**	base	Pd-precursor (mol %)	P−P	temp (°C)	yield of **5** (%)[b]	% ee[c] of **5** (config)[d]
1	**1a**	**4m**	NaH	$[PdCl(\pi\text{-allyl})]_2$ (1.0)	dpbp	23	88 (**5am**)	—
2	**1a**	**4n**	NaH	$[PdCl(\pi\text{-allyl})]_2$ (1.0)	dpbp	40	73 (**5an**)	—
3[e]	**1a**	**4o**	NaH	$[PdCl(\pi\text{-allyl})]_2$ (1.0)	dpbp	40	87 (**5ao**)	—
4	**1a**	**4p**	KH	$[PdCl(\pi\text{-allyl})]_2$ (1.0)	dpbp	50	72 (**5ap**)	—
5	**1a**	**4q**	NaH	$[PdCl(\pi\text{-allyl})]_2$ (1.0)	dpbp	40	81 (**5aq**)	—
6	**1a**	**4r**	NaH	$[PdCl(\pi\text{-allyl})]_2$ (1.0)	dpbp	40	72 (**5ar**)	—
7	**1a**	**4s**	NaH	$[PdCl(\pi\text{-allyl})]_2$ (1.0)	dpbp	40	92 (**5as**)	—
8	**1b**	**4m**	NaH	$[PdCl(\pi\text{-allyl})]_2$ (1.0)	dpbp	50	93 (**5bm**)	—
9	**1c**	**4r**	NaH	$[PdCl(\pi\text{-allyl})]_2$ (1.0)	dpbp	40	76 (**5cr**)	—
10	**1d**	**4m**	NaH	$[PdCl(\pi\text{-allyl})]_2$ (1.0)	dpbp	40	81 (**5dm**)	—
11	**1e**	**4m**	NaH	$[PdCl(\pi\text{-allyl})]_2$ (1.0)	dpbp	40	88 (**5em**)	—
12	**1f**	**4r**	CsO^{t}Bu	$[PdCl(\pi\text{-allyl})]_2$ (1.0)	dpbp	40	75 (**5fr**)	—
13	**1a**	**4m**	NaH	$Pd_2(dba)_4$ (5.0)	(*R*)-binap	23	61 (**5am**)	54 (*R*)
14	**1a**	**4m**	NaH	$Pd_2(dba)_4$ (5.0)	(*R*)-segphos	40	62 (**5am**)	86 (*R*)
15	**1a**	**4n**	CsO^{t}Bu	$Pd_2(dba)_4$ (5.0)	(*R*)-segphos	40	87 (**5an**)	94 (*R*)
16[e]	**1a**	**4o**	CsO^{t}Bu	$Pd_2(dba)_4$ (5.0)	(*R*)-segphos	40	82 (**5ao**)	80 (*R*)
17	**1a**	**4p**	CsO^{t}Bu	$Pd_2(dba)_4$ (5.0)	(*R*)-segphos	80	64 (**5ap**)	85 (*R*)
18	**1a**	**4q**	CsO^{t}Bu	$Pd_2(dba)_4$ (5.0)	(*R*)-segphos	40	67 (**5aq**)	91 (*R*)
19	**1a**	**4r**	CsO^{t}Bu	$Pd_2(dba)_4$ (5.0)	(*R*)-segphos	80	63 (**5ar**)	88 (*R*)
20	**1a**	**4s**	CsO^{t}Bu	$Pd_2(dba)_4$ (5.0)	(*R*)-segphos	80	63 (**5as**)	83 (*R*)
21	**1b**	**4m**	NaH	$Pd_2(dba)_4$ (5.0)	(*R*)-segphos	80	76 (**5bm**)	86 (*R*)
22	**1b**	**4n**	CsO^{t}Bu	$Pd_2(dba)_4$ (5.0)	(*R*)-segphos	40	86 (**5bn**)	91 (*R*)
23	**1c**	**4r**	CsO^{t}Bu	$Pd_2(dba)_4$ (5.0)	(*R*)-segphos	60	38 (**5cr**)	87 (*R*)
24	**1d**	**4m**	NaH	$Pd_2(dba)_4$ (5.0)	(*R*)-segphos	80	71 (**5dm**)	76 (*R*)
25	**1d**	**4r**	CsO^{t}Bu	$Pd_2(dba)_4$ (5.0)	(*R*)-segphos	40	24 (**5dr**)	79 (*R*)
26	**1d**	**4r**	CsO^{t}Bu	$Pd_2(dba)_4$ (5.0)	(*R*)-segphos	80	73 (**5dr**)	76 (*R*)
27	**1e**	**4m**	NaH	$Pd_2(dba)_4$ (5.0)	(*R*)-segphos	80	58 (**5em**)	60 (*R*)
28	**1f**	**4r**	CsO^{t}Bu	$Pd_2(dba)_4$ (5.0)	(*R*)-^{t}Bu-segphos	60	73 (**5fr**)	60 (*R*)

[a] The reaction was carried out in THF or dioxane (5 mL) for 18 h with **1** (0.50 mmol), **4** (0.65 mmol), and base (0.60 mmol) in the presence of Pd-precursor (5.0 μmol or 25 μmol) and bisphosphine (1.1 equiv to Pd). [b] Isolated yield by column chromatography. [c] Determined by chiral HPLC analysis (see Supporting Information for details). [d] The absolute configurations were deduced by the Lowe−Brewster rule (ref 12). [e] With 2.50 mmol of **4o** (ref 8k).

conditions. The bulkiness of the silyl substituents in **1** showed virtually no influence on the enantioselectivity (entries 14−15, 19 vs 21−23). The Me_3Si-substrate **1a** generally gave the allenylsilanes in higher yields than **1b** and **1c**. The present Pd-catalyzed reaction is tolerant of additional functional groups, and a proelectrophile moiety (dimethyl acetal) could be installed in the allenylsilanes by the use of **4r** and **4s** (entries 19, 20, 23, 25, 26, and 28). The Pd-catalyzed reactions of the 3-alkyl-2-bromo-1-trimethylsilyldienes **1d**−**f** were less enantioselective than those of **1a**, and the corresponding 3,3-dialkylallenylsilanes were obtained in up to 79% ee (entries 24−28). Note that catalytic asymmetric synthesis of 3,3-disubstituted allenylsilanes is realized for the first time in this study. All the allenylsilanes obtained here are levorotatory, and their absolute configurations are deduced to be (*R*) by the Lowe−Brewster rule.[13,14]

The obtained (*R*)-**5an** of 94% ee was allowed to react with propanal dimethyl acetal at −78 °C in the presence of $TiCl_4$ to give 73% of homopropargyl methyl ethers **7an**, which consists of (*S*,*S*)- and (*S*,*R*)-diastereomers in a ratio of 4:1 (Scheme 3,

Scheme 3



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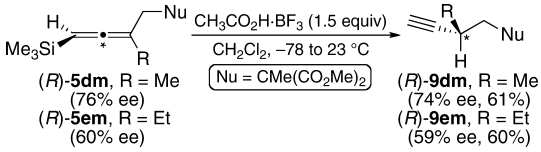
top).[15−17] The absolute configurations of the propargyl carbons in **7an** were deduced to be (*S*) based on the known *anti* stereochemistry in the S_E2' reactions of allenylsilanes.[15,16] Their enantiopurities, determined by chiral HPLC analysis, were found to be 94% ee for both diastereomers, demonstrating that the axial chirality of the allenylsilane was completely transferred to the propargylic stereogenic centers in **7an** in the S_E2' reaction with the acetal. In the same way, a treatment of (*R*)-**5an** (94% ee) with Selectfluor, an electrophilic fluorinating reagent, in acetonitrile at 23 °C afforded the levorotatory chiral propargylic fluoride **8an** in 94% ee in 77% yield with retention of the original enantiomeric purity in **5an** (Scheme 3, bottom). The absolute configuration of (−)-**8an** was deduced to be (*S*) based on the stereospecific *anti* S_E2' mechanism of the desilylative fluorination.[17]

Protodesilylation of the 3,3-dialkylallenylsilanes took place via the *anti* S_E2' pathway and resulted in the formation of a propargylic tertiary stereogenic center in the products with axial-to-central chirality transfer (Scheme 4).[18] The reactions

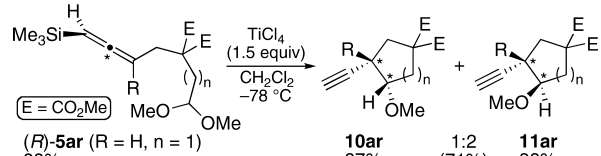
Scheme 4



of the optically active allenylsilanes (*R*)-**5dm** (76% ee) or (*R*)-**5em** (60% ee) with BF_3·CH_3CO_2H in dichloromethane gave the corresponding propargyl compounds (*R*)-**9dm** (74% ee, 61% yield) or (*R*)-**9em** (59% ee, 60% yield), respectively. Although a slight decrease in enantiopurity was detected in the protodesilylation, the axial-to-central transfer of chirality was still greater than 97%. The chirality transfer in protodesilylation has been unique and could be realized by the use of the 3,3-disubstituted allenylsilanes.

Treatment of the acetal-tethered allenylsilane (*R*)-**5ar** of 88% ee with $TiCl_4$ promoted cyclization via the S_E2' pathway. The five-membered carbocycles were obtained in 71% yield as a mixture of two diastereomers **10ar** and **11ar** in a 1:2 molar ratio. Both diastereomers retained the enantiopurity of (*R*)-**5ar** within experimental error (Scheme 5). The highly enantioenriched six-membered carbocycles

Scheme 5



(*R*)-**5ar** (R = H, n = 1) 88% ee	**10ar** 87% ee	1:2 (71%)	**11ar** 88% ee
(*R*)-**5as** (R = H, n = 2) 83% ee	**10as** 82% ee	1:6 (86%)	**11as** 83% ee
(*R*)-**5dr** (R = Me, n = 1) 76% ee	**10dr** 76% ee	1:1 (66%)	**11dr** 76% ee
(*R*)-**5fr** (R = $^nC_5H_{11}$, n = 1) 60% ee	**10fr** 60% ee	1:1 (71%)	**11fr** 60% ee

10as (82% ee) and **11as** (83% ee) were prepared in 86% yield in a 1:6 molar ratio from (*R*)-**5as** (83% ee) in the same way with the nearly complete transfer of chirality. The absolute configurations of the propargyl carbons in **10** and **11** were assigned to be (*S*) as in the case of **7an**.[13] The relative configurations of the adjacent stereogenic centers were determined by ^{1}H NMR NOE experiments, and thus the major enantiomers in the cyclized products were (*S*,*S*)-**10** and (*S*,*R*)-**11** as depicted in Scheme 5.

The reaction sequence could be applied to the asymmetric construction of quaternary chiral centers bonded to four carbon substituents.[19] The axial chirality of the trisubstituted allenylsilanes (*R*)-**5dr** (76% ee) and (*R*)-**5fr** (60% ee), which were prepared by the Pd-catalyzed asymmetric reaction of **1d** and **1f**, was transferred to the quaternary carbons in **10dr**, **11dr**, **10fr**, and **11fr** by the $TiCl_4$-promoted intramolecular S_E2' reaction with complete retention of the enantiomeric purity in (*R*)-**5dr** and (*R*)-**5fr** (Scheme 5). These results demonstrated that, with a proper R substituent in **1**, the asymmetric reaction shown in Table 1 could be an alternative to catalytic asymmetric synthesis of all-carbon quaternary centers.

In summary, we have developed a novel route to axially chiral allenylsilanes by asymmetric catalysis. The axial chirality in the allenylsilanes, which were prepared with high enantioselectivity (up to 94% ee), was transferred to tertiary and quaternary stereogenic centers without loss of their enantiomeric purity.

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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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(14) Previously, the validity of this deduction was confirmed by the asymmetric total synthesis of a naturally occurring allene of known configuration utilizing the Pd-catalyzed reaction as a key step (ref 8k).

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