Palladium-Catalyzed Asymmetric Synthesis of Axially Chiral Allenes: A Synergistic Effect of Dibenzalacetone on High Enantioselectivity

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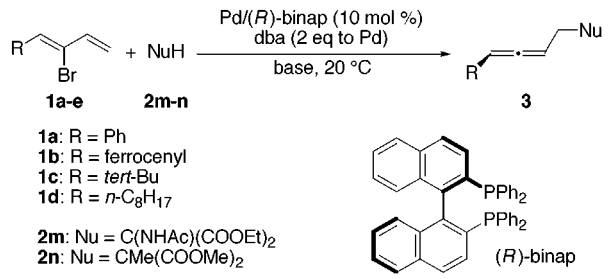
Received December 26, 2000

Allenes are an important class of compounds as useful synthons in synthetic organic chemistry,[1] and with proper substitution, they possess axial chirality. Despite these facts, application of optically active chiral allenes as chiral synthons has been limited so far,[2] which may be attributed to lack of efficient methods for supplying enantiomerically enriched allenes.[3] Most of the reported procedures require a stoichiometric amount of enantiomerically enriched chiral compounds either as substrates[3] or reagents.[4] Representative examples include chirality transfer from optically active chiral propargyl compounds[5] and resolution of racemic allenes.[3,6] To the best of our knowledge, only three examples are reported on asymmetric synthesis of axially chiral allenes using a substoichiometric amount of chiral transition metal catalysts, and none of them showed satisfactory enantioselectivity.[7]

We have recently reported a novel synthetic method for preparing a variety of functionalized allenes.[8] The reaction is catalyzed by a palladium−bisphosphine complex and the substrates are *achiral* conjugate dienes. An asymmetric modification of the catalyst could be easily achieved by using an appropriate chiral phosphine ligand, and thus the reaction would be an excellent prototype to catalytic asymmetric synthesis of chiral allenes. We report herein results of our studies to this goal. The enantioselectivity of the system is sufficiently high, up to 89% ee, which is one of the highest ee values reported to date for asymmetric synthesis of allenes with a chiral transition metal catalyst.[9] In the course of the investigations, we found an interesting role of dibenzalacetone (DBA), which was released from the catalyst precursor $Pd(dba)_2$, on the high enantioselectivity.

Scheme 1



In our original report of the allene synthesis,[8] a Pd-dpbp[10] complex was employed as a catalyst precursor. The dpbp ligand possesses a backbone similar to that of binap, thus binap was a logical choice as a chiral ligand for asymmetric extension of the reaction.[11] However, some initial trials of the asymmetric synthesis were disappointing. Treatment of 2-bromo-1-phenyl-1,3-butadiene (**1a**) with $HCMe(COOMe)_2$ (**2n**) and NaH (1 equiv to **2n**) in THF in the presence of $Pd[(R)\text{-binap}]_2$[12] (10 mol %) at 20 °C gave the chiral allene (**3an**) in 91% yield with very low enantioselectivity (11% ee). It was found that an analogous reaction with a catalyst generated in situ from $Pd(dba)_2$ and (*R*)-binap gave **3an** in 87% yield with 68% enantiomeric excess. The difference of the two reactions is the employed Pd-precursors, and the difference in enantioselectivity between the two is attributed to the absence or presence of DBA ,which is released from $Pd(dba)_2$ at the complexation with (*R*)-binap in the latter reaction. This hypothesis was confirmed by the following experiment. Addition of DBA (2 equiv to Pd) to the reaction of **1a** with the sodium salt of **2n** catalyzed by $Pd[(R)\text{-binap}]_2$ led to **3an** with 67% ee. Some other electron-deficient olefins showed a similar effect on enantioselectivity.[13] A probable mechanism of the present asymmetric reaction giving the optically active allene is shown in Scheme 2. A key intermediate, (*exo*-alkylidene-π-allyl)palladium species (**4**), exists as an equilibrium mixture of the two diastereoisomers and each diastereomeric palladium intermediate gives either (*S*)- or (*R*)-allene **3** by the reaction with nucleophile **2**. In this reaction scheme, the enantioselectivity of the allene formation is controlled by two factors: one is relative reactivity (toward **2**) between (2*S*)-**4** and (2*R*)-**4**, and the other is equilibrium (including the exchange rate) between the two diastereoisomers.[14]

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(6) A few transition metal-catalyzed kinetic resolutions of racemic chiral allenes have been reported and showed good enantioselectivity. 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.

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(9) Communicated in part: Ogasawara, M.; Ikeda, H.; Hayashi, T. *Abstracts*; 47th Symposium on Organometallic Chemistry, Japan, Nagoya, Octorber 2−3, 2000; Kinki Chemical Society: Japan, 2000; B103. Catalytic asymmtric symthesis of allenes from racemic allenylmethyl esters has been presented at the symposium; see: Imada, Y.; Ueno, K.; Kutsuwa, K.; Yamada, Y.; Murahashi, S.-I. *Abstracts*; 47th Symposium on Organometallic Chemistry, Japan, Nagoya, Octorber 2−3, 2000; Kinki Chemical Society: Japan, 2000; PB235.

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

(11) Indeed, the Pd-binap was the only species showing both good catalytic activity and high stereoselectivity. Other chiral phosphines examined are (*S*,*S*)-chiraphos, (*R*,*R*)-diop, (*R*)-(*S*)-bppfa, and (*R*)-mop.

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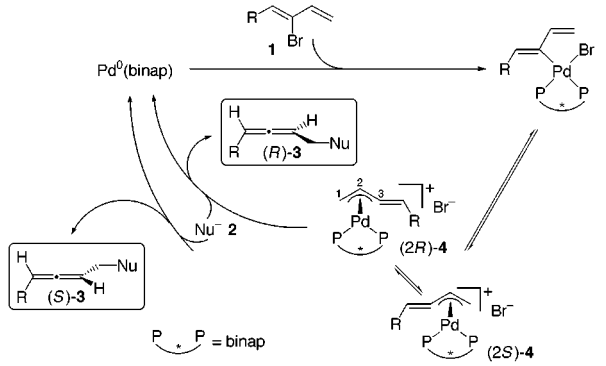
(13) The ee values obtained for the synthesis of **3an** under the analogous reaction conditions in the presence of the additives (2 equiv to Pd) are 68% (with *trans*-PhCH=CHCOPh), 64% (with *trans*-PhCH=CHCOMe), and 45% (with *N*-phenylmaleimide).

(14) If the exchange rate between (2*S*)-**4** and (2*R*)-**4** was *very* slow, the ee value of **3** was controlled by the relative abundance of the initially formed two diastereomers, even though there was a sufficient difference in the relative reactivity between (2*S*)-**4** and (2*R*)-**4** toward **2**.

10.1021/ja005921o CCC: $20.00
Published on Web 02/10/2001

Scheme 2. Catalytic Cycle of the Enantioselective Synthesis Reaction of Allenes



The intermediary benzylidene-π-allylpalladium species was isolated as a $BAr^F{}_4^-$ ($Ar^F = C_6H_3$-3,5-$(CF_3)_2$) salt (**5**) and it existed as an equilibrium mixture of the two diastereoisomers in a 34:66 molar ratio in $CDCl_3$ between 0 and 60 °C. The isolated complex **5** was applied to a stoichiometric reaction with the sodium salt of **2n** in THF at 20 °C and gave **3an** in good yield (76%). The enantioselectivity in the stoichiometric reactions was similar to that in the catalytic reactions: 13% ee without DBA and 64% ee with DBA (2 equiv to **5**). All these observations suggest the alkylidene-π-allylpalladium species as a key intermediate of the catalytic asymmetric synthesis of the allene. The solution behavior of **5** was monitored by ^{1}H NMR spectroscopy in $CDCl_3$ with or without DBA. The added DBA showed no influence on the relative abundance between the two diastereoisomers of **5**. On the other hand, slight broadening of the ^{1}H NMR signals was observed in the presence of DBA. It was found that coexisting DBA accelerates the equilibrium between the two diastereoisomers of **5**. The exchange rate constants of the equilibrium were determined by a spin-saturation transfer technique using the Forsén-Hoffman method[15] and the results are summarized in Table 1. Although the mechanism of the acceleration is not clear, the results clearly display the coexistent DBA accelerates the epimerization in **5** ca. 12−25 times faster, which is probably a main factor of the unique positive effect of DBA on the enantioselectivity of the present asymmetric reaction.

The results of the asymmetric synthesis of allenes are summarized in Table 2. The choice of the nucleophiles, including the countercations, is important for high enantioselectivity of the reaction. When **1a** was treated with acetamidomalonate **2m** and CsO^tBu in CH_2Cl_2 at 20 °C, the highest enantioselectivity (89% ee) was achieved in **3am** (entry 3). Analogous reactions with NaH or KO^tBu as base showed the lower enantioselectivity (entries 1 and 2). The solvent effect on the enantioselectivity is more remarkable. For the reactions with **2m**, dichloromethane was found to be the best solvent (entries 3−5). A variety of 1-substituted-2-bromo-1,3-butadienes **1** were converted into optically active allenes with good to moderate enantioselectivity (entries 3, 7−9). Although there were no general trends between the substituents and the enantioselectivity, the substrate with a sterically slender *n*-octyl group (**1d**) showed significantly lower selectivity (entry 9).

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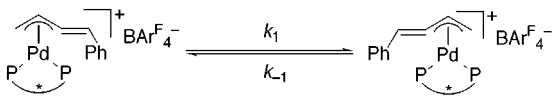
Table 1. Isomerization Rates between the Two Diastereoisomers of [(Benzylidene-π-allyl)Pd(binap)]$BAr^F{}_4$ (**5**) in $CDCl_3$[a]



temp/°C	[DBA]	k_1[b]/s^{-1}	k_{-1}[c]/s^{-1}	k_1/k_{-1}	[major]/[minor][d]
20	0	0.19	0.086[e]	2.2	1.9
	2 equiv	2.4	1.3	1.9	1.9
40	0	0.49	0.25	2.0	1.9
	2 equiv	>12[f]	5.4	>2.2	1.9

[a] The absolute configurations of the major and the minor isomers have not been determined. [b] The rate constants from the minor isomer to the major. [c] The rate constants from the major isomer to the minor. [d] The relative concentration of both isomers determined by ^{1}H NMR. [e] Due to the slowness of the exchange, the value contains some degree of uncertainty. [f] Due to the quickness of the exchange, the value contains some degree of uncertainty.

Table 2. Palladium-Catalyzed Asymmetric Synthesis of Allenes **3** from Bromodiene **1** and Nucleophile **2**[a]

entry	diene	NuH	base	solvent	yield[b]/%	% ee[c] (config)	$[\alpha]^{20}_D$ (*c* in $CHCl_3$)
1	**1a**	**2m**	NaH	CH_2Cl_2	59 (**3am**)	52 (*R*)	
2	**1a**	**2m**	KO^tBu	CH_2Cl_2	98 (**3am**)	75 (*R*)	
3	**1a**	**2m**	CsO^tBu	CH_2Cl_2	75 (**3am**)	89 (*R*)	−141 (0.66)
4	**1a**	**2m**	CsO^tBu	THF	77 (**3am**)	58 (*R*)	
5	**1a**	**2m**	CsO^tBu	toluene	61 (**3am**)	41 (*R*)	
6	**1a**	**2n**	NaH	THF	88 (**3an**)	68 (*R*)	−87 (0.50)
7	**1b**	**2m**	CsO^tBu	CH_2Cl_2	34 (**3bm**)	80 (*R*)	−314 (0.64)
8	**1c**	**2m**	CsO^tBu	CH_2Cl_2	74 (**3cm**)	75 (*R*)	−29 (0.50)
9	**1d**	**2m**	CsO^tBu	CH_2Cl_2	73 (**3dm**)	54 (*R*)	−33 (1.00)

[a] The reaction was carried out with bromodiene **1** (0.50 mmol), Nu-H **2** (0.55 mmol), and base (0.60 mmol) in a given solvent (5.0 mL) at 20 °C for 24 h in the presence of 10 mol % of the catalyst generated from $Pd(dba)_2$ and (*R*)-binap or Pd[(*R*)-binap]$_2$ and dba. [b] Isolated yield by silica gel or alumina chromatography. [c] Determined by HPLC analysis with chiral stationary phase columns: Daicel Chiralcel OJ (**3am**), AD (**3an**, **3cm**, **3dm**), and OD-H (**3bm**).

All the optically active allenes obtained by the Pd/(*R*)-binap catalyst are levorotatory, from which the absolute configurations of the major enantiomers of the allenes are deduced to be (*R*) by the Lowe−Brewster rule.[16]

In conclusion, we have developed the novel route to the enantiomerically enriched axially chiral allenes using the palladium-binap species as a chiral catalyst. Our method has enabled direct access to these important compounds starting from the achiral substrates.

Acknowledgment. This work was supported by the "Research for the Future" Program (Japan Society for the Promotion of Science) and a Grant-in-Aid for Scientific Research (Ministry of Education, Japan).

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

JA005921O

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