sterically hindered olefins were cyclized in comparable yields to those obtained by using complexes **3** and **4**.

Since all of the starting materials are air stable, we tried setting up the RCM reaction on the benchtop, thus eliminating the use of a drybox or vacuum line. The solid components (commercially available) were weighed in air into a reaction flask. The atmosphere was purged with argon followed by the addition of reagent grade hexanes, *tert*-butyl acetylene, and diethyl diallylmalonate. After 10 h at 80 °C, ring-closed product was obtained in 88 % yield. The reaction rate and yield were comparable to those when degassed solvents and drybox procedures were employed (96 %, Table 1, entry 1 g).

In conclusion, when coordinated to a bulky imidazolylidene ligand, ruthenium vinylidene complexes are effective catalysts for a variety of metathetical reactions. Although reaction rates were slower, their general reactivity profile towards a variety of substrates was similar to the analogous highly active ruthenium alkylidenes (**3** and **4**). In addition, the catalysts can be generated in situ from inexpensive, air stable, and commercially available starting materials, which circumvents the need for a drybox or special Schlenk equipment.

Experimental Section

Representative procedure: In a drybox, [{(*p*-cymene)$RuCl_2$}$_2$] (0.02 mmol), ligand **1**Cl (0.045 mmol), and NaO*t*Bu (0.045 mmol) were weighed directly into a screw cap vial. A stir bar was added followed by hexanes (2 mL). Substrate (0.85 mmol) and *tert*-butyl acetylene (0.045 mmol) were added and the vial was sealed with a PTFE lined cap. The vial was removed from the drybox and the contents stirred at 80 °C. The reaction was monitored by GC and after complete consumption of substrate, the products were purified by chromatography on silica gel. All products listed in Table 1 have been previously characterized.

Selected NMR data for **8**: ^{1}H NMR (300 MHz, C_6D_6): $\delta = 6.76$ (s, 2H; NCHCHN), 5.99 (s, 1H; C(*t*Bu)H), 2.78 – 2.67 (m, 3H, 3CH of PCy_3), 2.44 (s, 9H; $3CH_3$), 2.14 (s, 9H; $3CH_3$), 2.14 – 2.09 (m, 8H; CH_2 of PCy_3), 1.69 – 1.58 (m, 14H; CH_2 of PCy_3), 1.28 – 1.17 (m, 8H; CH_2 of PCy_3), 1.12 (s, 9H; $C(CH_3)_3$); ^{31}P NMR (121.4 MHz, C_6D_6): $\delta = 17.4$ (s).

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Highly Enantioselective Palladium-Catalyzed Ene-Type Cyclization of a 1,6-Enyne**

Manabu Hatano, Masahiro Terada, and Koichi Mikami*

Dedicated to Professor Barry M. Trost on the occasion of his 60th birthday

Transition metal catalyzed ene-type carbocyclizations of 1,6-enynes such as cycloisomerization[1] and the ene reaction[2] are powerful synthetic methods leading to five-membered rings.[3–5] However, examples for the corresponding enantioselective catalysis are limited,[6] hence it is a challenge to establish high levels of asymmetric induction as well as high yields. Herein we report a highly efficient catalysis by chiral palladium(II) complexes for enantioselective ene-type carbocyclizations of the 1,6-enyne **1** leading to highly enantioenriched five-membered rings [Eq. (1)].

The palladium(II)-catalyzed carbocyclization reactions of 1,6-enynes have generally been performed with $Pd(OAc)_2$ or by the combined use of Pd^0 species (e.g. $[Pd_2(dba)_3]\cdot CHCl_3$) (dba = *trans*,*trans*-dibenzylidene acetone) and a weak acid such as acetic acid or trifluoroacetic acid.[3] However, in the presence of a chiral bidentate phosphane ligand, such as BINAP (BINAP = 2,2′-bis(diphenylphosphanyl)-

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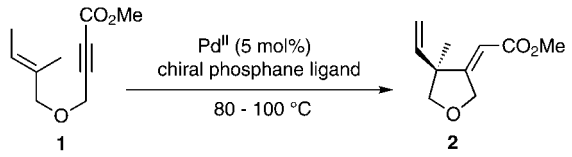
Supporting information for this article is available on the WWW under http://www.angewandte.com or from the author.



1 2 (1)

1,1′-binaphthyl),these typical palladium catalysts were ineffective with the 1,6-enyne **1** exhibiting insufficient catalytic activity and low levels of asymmetric induction (Table 1: entries 1–3). The Pd^{II}-catalyzed asymmetric cyclization of **1** to 1,4-diene (*S*)-**2** was successfully achieved in quantitative yield and with high enantioselectivity (93% *ee*) (entry 4) by using 5 mol% of $Pd(OCOCF_3)_2$ and 10 mol% of (*R*)-BINAP in thoroughly degassed C_6D_6 at 100°C. The absolute configuration of **2** was determined, by X-ray crystallographic analysis, as a chiral amine salt of the corresponding carboxylic acid with (*S*)-1-phenylethylamine.[7] Furthermore, decreasing the ratio of BINAP to Pd^{II} from 2:1 to 1.1:1 and lowering the temperature (entry 5) did not compromise enantioselectivity.[8]

Table 1. Enantioselective ene-type carbocyclization of the 1,6-enyne **1** catalyzed by BINAP–Pd complexes[a].

Entry	Pd species (mol%)	Solvent	Reaction time [h]	Yield [%]	*ee* [%][b] (Config.)
1	$Pd(OAc)_2$ (5)	C_6D_6	72	68	11 (*S*)
2[c]	$[Pd_2(dba)_3]\cdot CHCl_3$ (2.5)/AcOH (12)	C_6D_6	96	18	77 (*S*)
3[c]	$[Pd_2(dba)_3]\cdot CHCl_3$ (2.5)/TFA (12)	C_6D_6	96	25	84 (*S*)
4	$Pd(OCOCF_3)_2$ (5)	C_6D_6	24	>99	93 (*S*)
5[c,d]	$Pd(OCOCF_3)_2$ (5)	C_6D_6	80	>99	94 (*S*)
6[c]	$Pd(OCOCF_3)_2$ (5)	DMSO	16	>99	72 (*S*)
7[c]	$[(MeCN)_4Pd](BF_4)_2$ (5)	DMSO	6	>99	73 (*S*)

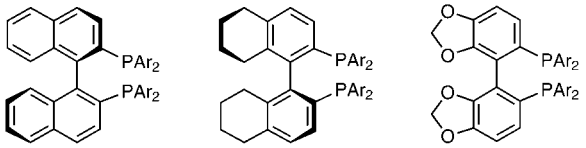
[a] Reactions were carried out in thoroughly degassed solvents at 100°C with 5 mol% of Pd catalyst and 10 mol% of (*R*)-BINAP as a chiral ligand unless otherwise noted. [b] The *ee* value was based on chiral GC analysis of **2**. [c] Reactions were carried out at 80°C. [d] 5.5 mol% of (*R*)-BINAP was used.

A remarkable solvent effect was also observed in this catalytic reaction. In a "polar solvent" such as DMSO, the reaction was completed within a shorter period of time at lower reaction temperature (entry 6), but the enantiomeric excess decreased to 72% *ee* as compared with that in the "less-polar solvent" (entry 4).[9] The dicationic Pd^{II} species, $[(MeCN)_4Pd](BF_4)_2$, was found to dramatically accelerate the reaction in DMSO (entry 7). Nevertheless these reactions suffered from lower enantioselectivity with (*R*)-BINAP (entries 6 and 7).

Further exploration of modified BINAP ligands[10] with either the $Pd(OCOCF_3)_2/C_6D_6$ or the $[(MeCN)_4Pd](BF_4)_2$/DMSO system led to a remarkable improvement in the enantioselectivity (Table 2). In the less-polar solvent ($Pd(OCOCF_3)_2/C_6D_6$ system), we eventually obtained the enantiopure product (**2**) by using (*R*)-SEGPHOS (SEGPHOS = seagull phosphane)[11] as a bidentate phosphane ligand. (*R*)-tol-BINAP and (*S*)-H_8-BINAP ligands were effective (entries 1 and 2), but did not afford enantioselectivities significantly higher than that with the parent BINAP ligand. The use of the sterically more demanding (*S*)-xylyl-H_8-BINAP ligand resulted in a significant lowering in enantioselectivity (entry 3). Presumably because of its bulkiness, (*S*)-xylyl-H_8-BINAP is forced to dissociate from the Pd^{II} complex during the catalysis generating an achiral Pd^{II} species. We finally achieved the virtually complete enantioselectivity with (*R*)-SEGPHOS to give the cyclized product **2** in quantitative yield and in an enantiopure form (>99% *ee*) (entry 4). The (*R*)-SEGPHOS ligand is also effective in the polar solvent. Thus, the $[(MeCN)_4Pd](BF_4)_2$/DMSO system (entry 5) exhibited a higher enantioselectivity than that with BINAP. Noteworthy is that a further improvement in the enantioselectivity was achieved by using the sterically demanding (*S*)-xylyl-H_8-BINAP ligand (entry 6) in sharp contrast to the low enantioselectivity observed in the less-polar solvent using $Pd(OCOCF_3)_2/C_6D_6$ system (entry 3). By the combination of a SEGPHOS skeleton and a bulky xylyl substituent in the (*S*)-xylyl-SEGPHOS ligand, highly enantioselective catalysis (96% *ee*) could be envisioned in the $[(MeCN)_4Pd](BF_4)_2$/DMSO system (entry 7).

We next turned our attention to the mechanism of this highly efficient enantioselective catalysis. The key to clarifying the catalytic cycle is to determine whether or not hydride–palladium (H–Pd) is the active species. Taking advantage of hydride exchange between D_2O and H–Pd to generate D–Pd species,[12] we examined the reactions under excess D_2O (600 mol%) conditions (Figure 1 and Table 3). Consequently, the deuterated product at the vinylic position was obtained without diminution of catalytic activity under either polar or less-polar conditions. These results indicate that the hydride(deuteride)–palladium is the active species. The possible catalytic cycle would be completed as shown in

Table 2. Ene-type carbocyclization of **1** catalyzed by $Pd(OCOCCF_3)_2/C_6D_6$ or $[(MeCN)_4Pd](BF_4)_2$/DMSO with modified BINAP ligands.



(*R*)-BINAP (Ar = Ph) (*S*)-H_8-BINAP (Ar = Ph) (*R*)-SEGPHOS (Ar = Ph)
(*R*)-tol-BINAP (Ar = *p*-MeC_6H_4) (*S*)-xylyl-H_8-BINAP (Ar = 3,5-$Me_2C_6H_3$) (*S*)-xylyl-SEGPHOS (Ar = 3,5-$Me_2C_6H_3$)

Entry	System[a]	Ligand	Reaction time [h]	Yield [%]	*ee* [%] (Config.)
1	$Pd(OCOCF_3)_2/C_6D_6$	(*R*)-tol-BINAP	43	>99	94 (*S*)
2	$Pd(OCOCF_3)_2/C_6D_6$	(*S*)-H_8-BINAP	48	>99	95 (*R*)
3	$Pd(OCOCF_3)_2/C_6D_6$	(*S*)-xylyl-H_8-BINAP	20	>99	12 (*R*)
4	$Pd(OCOCF_3)_2/C_6D_6$	(*R*)-SEGPHOS	37	>99	>99 (*S*)
5	$[(MeCN)_4Pd](BF_4)_2$/DMSO	(*R*)-SEGPHOS	6	>99	90 (*S*)
6	$[(MeCN)_4Pd](BF_4)_2$/DMSO	(*S*)-xylyl-H_8-BINAP	12	>99	94 (*R*)
7	$[(MeCN)_4Pd](BF_4)_2$/DMSO	(*S*)-xylyl-SEGPHOS	14	>99	96 (*R*)

[a] Reactions were carried out with 5 mol% of Pd catalyst and 10 mol% of chiral ligand in thoroughly degassed solvents at 100°C in the $Pd(OCOCF_3)_2/C_6D_6$ system or at 80°C in the $[(MeCN)_4Pd](BF_4)_2$/DMSO system.

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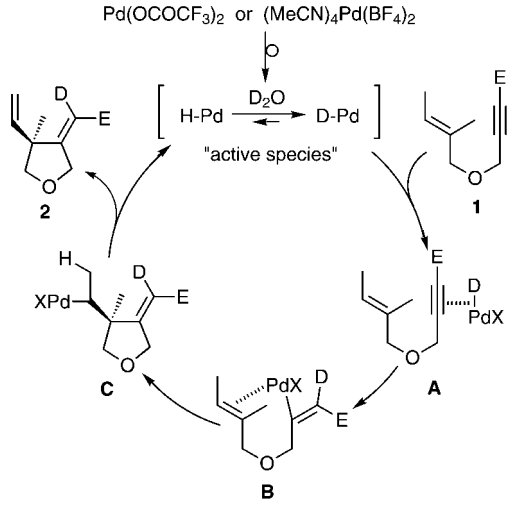

Figure 1. Catalytic cycle involving H(D)–Pd as the active species.

Table 3. Ene-type carbocyclization of **1** in the presence of D_2O[a].

Entry	Pd^{II} catalyst	Solvent	Reaction time [h]	Yield [%]	D-Content [%]	*ee* [%]
1	$Pd(OCOCF_3)_2$	C_6D_6	30	>99	56	93
2	$Pd(OCOCF_3)_2$	DMSO	24	>99	74	68
3	$[(MeCN)_4Pd](BF_4)_2$	DMSO	24	>99	77	65

[a] Reactions were carried out at 100 °C with 5 mol % of Pd^{II} catalyst and 10 mol % of (*R*)-BINAP in the presence of 600 mol % of D_2O.

Figure 1:[13] the initially formed H–Pd coordinates to acetylene (**A**), followed by insertion (**B**), cyclization (**C**), and β-H elimination to give the product **2** and regenerate the H–Pd species.

It should be pointed out that this Pd-catalyzed carbocyclization reveals a) the dependence of both the enantioselectivity and the catalytic activity on the solvent polarity (Table 1: entries 4 and 6 and Table 3: entries 1 and 2) and b) the independence of the enantioselectivity on the Pd^{II} source, $Pd(OCOCF_3)_2$ or $[(MeCN)_4Pd](BF_4)_2$, under the polar conditions (Table 3, entries 2 and 3). These observations are fully rationalized on the basis of coordination modes (**B-4C** and **B-5C**;[14] Figure 2) in the intermediates (**B**). In the

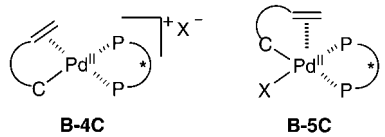

Figure 2. Four- and five-coordinate intermediates (**B-4C**, **B-5C**).

polar solvent, the $[(MeCN)_4Pd](BF_4)_2$/DMSO system facilitates the generation of a cationic four-coordinate intermediate (**B-4C**) as result of the solvent polarity and the weakly coordinating nature of the BF_4^- ion. The same levels of enantioselectivity are obtained under the polar conditions regardless of the Pd^{II} sources and imply that the reaction proceeds via the identical intermediate (**B-4C**) in the Pd-$(OCOCF_3)_2$/DMSO system. In the polar solvent, $Pd(OCOCF_3)_2$ associatively releases the counter anion, even a CF_3COO^- ion, to offer one coordination site on the square-planar cationic complex. The olefin moiety is able to occupy this site to give the four-coordinate intermediate (**B-4C**) identical to that obtained in the $[(MeCN)_4Pd](BF_4)_2$/DMSO system (Figure 2). The catalytic activity of the $[(MeCN)_4Pd](BF_4)_2$/DMSO system is higher than in the $Pd(OCOCF_3)_2$/DMSO system (Table 1: entries 7 vs. 6), consistent with the stabilization of the cationic intermediates by the counter ion, that is BF_4^- versus CF_3COO^-. In contrast, in the less-polar solvent ($Pd(OCOCF_3)_2/C_6D_6$ system), the counter anion remains coordinated to the Pd^{II} species. The olefin moiety is forced to coordinate to the fully occupied square-planar Pd^{II}, generating a relatively unfavorable *five*-coordinate intermediate (**B-5C**) as a neutral complex (Figure 2).[15] The higher catalytic activity under the polar conditions is rationalized by the preferred *four*-coordinate intermediate (**B-4C**). The high enantioselectivity obtained by sterically demanding xylyl-BINAP under the polar conditions (Table 2: entries 6 and 7) contrasts sharply to the low enantioselectivity under the less polar conditions (Table 2: entry 3). Under the less polar conditions the bulky xylyl-H_8-BINAP ligand is forced to dissociate from the sterically congested *five*-coordinate intermediate (**B-5C**) to generate an achiral Pd^{II} species. The dependence of the enantioselectivity on the solvent polarity reveals strong evidence that the reaction takes place via different coordination modes.

The high enantioselectivities are rationalized on the basis of these intermediates (Figure 3). Under the polar conditions, the reaction took place via the *four*-coordinate transition states (**4C-1** and **4C-2**) to afford the cyclized product (*S*)-**2** and (*R*)-**2**, respectively. The transition state (**4C-2**) is relatively less favorable because of steric repulsion between the terminal Me group of the substrate **1** and the equatorial Ph group of (*R*)-BINAP or its analogue. On the other hand, the transition state (**4C-1**) avoids this repulsion, eventually affording (*S*)-**2** through β-H elimination. Under the less-polar conditions, the olefin is forced to coordinate to the Pd^{II} center on one side of the Z-axis to reach the *five*-coordinate transition states (**5C-1** and **5C-2**). The repulsive interaction between the terminal Me group of the substrate **1** and the equatorial Ph group of the (*R*)-BINAP ligand or its analogue is significant in the transition state (**5C-2**), giving (*R*)-**2** in higher %*ee*. The reaction takes place entirely via the transition state (**5C-1**) to afford (*S*)-**2**.

In summary, we have developed a highly efficient palladium(II)-catalyzed ene-type carbocyclization of a 1,6-enyne leading to enantiopure five-membered rings. This highly enantioselective catalysis is applicable for the construction of an enantioenriched quaternary chiral center.[16] Possible mechanisms including neutral and cationic intermediates have been proposed.

Experimental Section

Thoroughly degassed C_6D_6 (2.0 mL) was injected under argon into a pyrex Schlenk tube containing $Pd(OCOCF_3)_2$ (8.3 mg, 0.025 mmol) and (*R*)-BINAP (31.1 mg, 0.050 mmol), and this suspension was stirred at room temperature for 5–10 min at which time the solution become clear. Then **1** (91.1 mg, 0.500 mmol) was added, the tube was sealed with a screw cap. The mixture was stirred at 100 °C for 24 h. The crude mixture was checked by

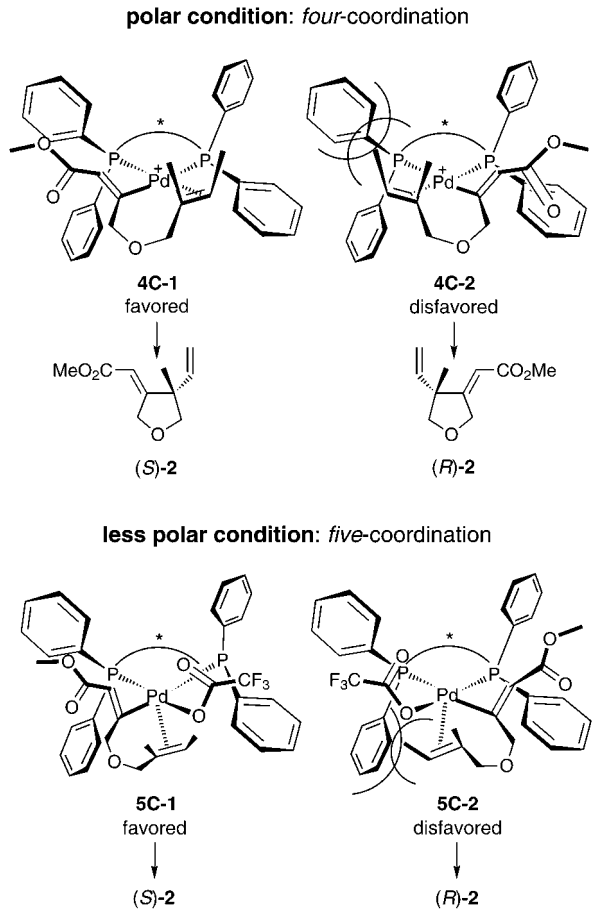

Figure 3. Transition states for enantioselective carbocyclization catalyzed by chiral Pd^{II} complexes under polar or less-polar conditions.

^{1}H NMR spectroscopy (C_6D_6), before purification by column chromatography (on a short, neutral silica-gel column, pentane/ether = 100/3) to afford (*S*)-**2**, 93 % *ee* ($[\alpha]_D^{29} = +37.6$ ($c = 0.586$ in $CHCl_3$): chiral GC column; CP-Cyclodextrin-β-2,3,6-M-19 (0.25 mm × 25 m, CHROMPACK, GL Sciences Inc.; $t_R = 31.8$ min (*R*) and 33.7 min (*S*)) in quantitative yield. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.26$ (s, 3H), 3.62 (d, $J = 8.7$ Hz, 1H), 3.69 (s, 3H), 3.72 (d, $J = 9.0$ Hz, 1H), 4.77 (dd, $J = 17.7$, 2.4 Hz, 1H), 4.91 (dd, $J = 17.7$, 2.4 Hz, 1H), 5.16 (d, $J = 11.1$ Hz, 1H), 5.17 (d, $J = 17.7$ Hz, 1H), 5.63 (t, $J = 2.4$ Hz, 1H), 5.79 (dd, $J = 17.7$, 10.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 22.2$, 50.7, 51.4, 72.2, 78.3, 111.0, 114.9, 140.7, 166.8, 169.4.

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[7] Compound **2** was converted into the corresponding carboxylic acid through hydrolysis, and then crystallized as a diastereomeric salt of (*S*)-1-phenylethylamine in an Et_2O/CH_2Cl_2 mixture at room temperature Figure 4. X-ray data for this salt: formula $(C_9H_{12}O_3)_2 \cdot C_8H_{11}N$, monoclinic, space group $P2_1$, $a = 12.0888(7)$, $b = 6.1803(4)$, $c = 16.859(1)$ Å, $\beta = 91.042(3)^\circ$, $V = 1259.3(2)$ Å^3, $Z = 2$, and $\rho = 1.207$ g cm^{-3}. X-Ray diffraction data were collected on a Rigaku RAXIS-RAPID Imaging Plate diffractometer with graphite-monochromated $Mo_{K\alpha}$ ($\lambda = 0.71069$ Å) at $-160\,^\circ$C and the structure was solved by direct methods (SIR97). The final cycle of full-matrix least-squares refinement was based on 2100 observed reflections ($I > 3\sigma(I)$) and 297 variable parameters and converged to $R = 0.067$ and $Rw = 0.094$. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-149520. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

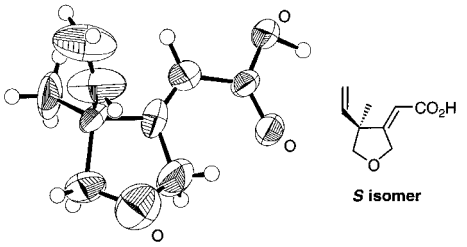

Figure 4. ORTEP representation and the structural formula of the chiral amine salt. The chiral amine was omitted for clarity.

[8] Two-molar amount (based on Pd) of chiral ligands was used to aid reproducibility thus assisting further exploration of the reaction and to shorten the reaction time at 100 °C.

[9] Other polar solvents such as *N*,*N*-dimethylacetamide and acetonitrile gave the same results.

[10] Chiral monophosphane ligands such as MAP (2-(diphenylphosphanyl)-2′-(*N*,*N*-dimethylamino)-1,1′-binaphthyl); a) Š. Vyskocil, M. Smrcina, V. Hanuš, M. Polášek, P. Kocovský, *J. Org. Chem.* **1998**, *63*, 7738–7748; b) K. Ding, Y. Wang, H. Yun, J. Liu, Y. Wu, M. Terada, Y. Okubo, K. Mikami, *Chem. Eur. J.* **1999**, *5*, 1734–1737 and MOP (2-(diphenylphosphanyl)-2′-methoxy-1,1′-binaphthyl); Y. Uozumi, A. Tanahashi, S. Y. Lee, T. Hayashi, *J. Org. Chem.* **1993**, *58*, 1945–1948 resulted in nearly racemic products. The diphosphane chelation to Pd was found to be necessary to achieve a high enantioselectivity.

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[13] We cannot completely rule out the Pd^{II}–Pd^{IV} (palladacycle) mechanism, because the identical deuterated products are formed by either mechanism. However, our further research suggests that the reaction

  1433-7851/01/4001-0252 $ 17.50+.50/0

proceeds by the hydride(deuteride)–palladium mechanism (Figure 1), not via the palladacycle intermediate.

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