Effects of Solvents and Additives in the Asymmetric Heck Reaction of Alkenyl Triflates: Catalytic Asymmetric Synthesis of Decalin Derivatives and Determination of the Absolute Stereochemistry of (+)-Vernolepin

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Abstract: Studies on the palladium-catalyzed asymmetric cyclization of alkenyl triflates **3** including the effects of solvents and additives such as alcohol and potassium acetate on the reaction are described. Reaction of **3** in polar solvents such as DMSO, acetonitrile, and NMP gave the cyclized products **2** in low chemical and optical yield while reaction in toluene gave **2** of high enantiomeric excess. Reaction in 1,2-dichloroethane also afforded **2** in excellent optical yield but in very low chemical yield. The chemical yield was greatly improved by the addition of pinacol or potassium acetate to the reaction mixture in 1,2-dichloroethane. Thus the decalin derivatives **2** were obtained in good chemical yield and with excellent asymmetric induction (up to 95% ee). Using derivative **2a** as a chiral building block, the first asymmetric synthesis of (+)-vernolepin (**9**) has been accomplished and its absolute stereochemistry has been determined. Furthermore, we have found through a series of ^{31}P-NMR experiments that the catalytically active LnPd(0) species are readily oxidized to $LnPdCl_2$ in 1,2-dichloroethane but that the addition of pinacol or potassium acetate prevents this process.

Introduction

The synthesis of optically active compounds is an extremely important undertaking because enantiomer recognition plays an important role in many biological systems. Many successful methods for catalytic asymmetric reductions and oxidations are known,[1] but it is only recently that several successful catalytic asymmetric C−C bond-forming reactions[2] have been reported. The development of new methodologies for catalytic asymmetric C−C bond formation is now also one of the major interests for many synthetic chemists.

In 1989, we reported the first example of an asymmetric Heck reaction.[3] Since then, we[4] and others[5] have demonstrated that this type of catalytic asymmetric C−C bond-forming reaction is a powerful method for the synthesis of various optically active compounds.

Alkenyl iodides **1** were the first substrates used in our studies of the asymmetric Heck reaction and have been found to cyclize to *cis*-decalin derivatives **2**. Silver salt is essential to the facile and clean formation of **2**, and the optical yield of these decalin derivatives **2** significantly depends on the counteranion of the silver salt.[3,4a,6] Solvent effects were also investigated, and 1-methyl-2-pyrrolidinone (NMP) has proven to be the best solvent for this system. Generally, polar solvents gave better optical yields, while nonpolar solvents such as toluene gave

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(6) Recently, Overman *et al.* have reported that Heck reaction in the absence of silver salt using 1,2,2,6,6-pentamethylpiperidine as a base also gives high asymmetric induction. Interestingly these conditions gave the enantiomer opposite to that obtained in reactions using silver salt in some cases. See refs 5c and 5j.

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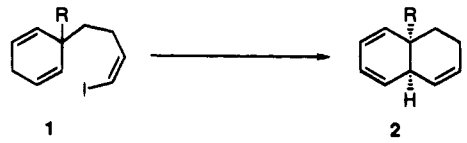
Scheme 1



R = COOMe, $CH_2OSi^tBuMe_2$, CH_2OAc

Scheme 2

3a	R = COOMe	**2a**
3b	R = CH_2OPv	**2b**
3c	R = $CH_2OSi^tBuMe_2$	**2c**
3d	R = CH_2OAc	**2d**

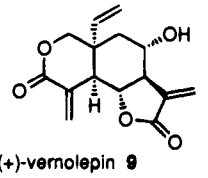
products of lower ee with these alkenyl iodides. For example, cyclization of **1** (R = $CH_2OSi^tBuMe_2$) in the presence of [(*R*)-binap]$PdCl_2$ (10 mol %), Ag_3PO_4 (2 molar equiv), and $CaCO_3$ (2.2 molar equiv) in NMP at 60 °C afforded **2** in up to 80% ee (Scheme 1).

We have also examined the asymmetric cyclization of alkenyl triflates **3**.[4c] In contrast to the cyclization of **1**, cyclization of alkenyl triflates **3** proceeded smoothly in the absence of silver salt to give **2** with up to 92% ee (Scheme 2). This fact seems to be consistent with our hypothesis that formation of the squareplaner 16-electron Pd^+ intermediate **5** is required for high asymmetric induction (Scheme 3). Preliminary results on the effect of solvent on the cyclization of alkenyl triflates **3** have indicated that nonpolar solvents such as toluene give far better ee than polar solvents such as NMP.[4c,d] Overman *et al.*[5a] and Hayashi *et al.*[5b,d–f,h,i] have reported similar results in their studies of aryl or alkenyl triflates in the asymmetric Heck reaction.

We have also reported our recent results on the asymmetric cyclization of **7** (Scheme 4).[4g,j] In this case reaction in benzene or toluene gave cyclized product **8** with low ee (28% ee) while reaction in 1,2-dichloroethane afforded far better asymmetric induction (76% ee). Interestingly, the low chemical yield (37%) obtained in the latter reaction improved significantly on addition of ^{t}BuOH to the reaction mixture, and under optimal conditions **8** was obtained in 76% chemical and 86% optical yield. The drastic effects of solvent and ^{t}BuOH prompted us to reinvestigate the asymmetric cyclization of **3**. In this paper we describe the full details of our studies on the asymmetric cyclization of triflates **3** including the effects of solvents and additives such as alcohol and acetate anion on the reaction.

(+)-Vernolepin (**9**) (Figure 1) is an elemanolide sesquiterpene dilactone with antitumor activity.[7] The structure of **9**, including the relative stereochemistry, was elucidated by Kupchan *et al.*, and while its absolute stereochemistry has been assigned in analogy with the related elemanolides, it has not been confirmed by physical or chemical methods. This compound has attracted the attention of many synthetic chemists because of its unique structure and its biological activity. In spite of several total syntheses of (±)-**9**,[8] no asymmetric synthesis of (+)-**9** has been achieved so far, although several approaches have been considered.[9]

To demonstrate the synthetic utility of the asymmetric Heck reaction, we planned to synthesize (+)-**9** starting from **2**. We are pleased to report the first asymmetric total synthesis of (+)-vernolepin (**9**) starting from (+)-(*S*,*S*)-**2a**, by which the absolute stereochemistry of (+)-**9** has been unequivocally determined.



(+)-vernolepin **9**

Figure 1.

Results and Discussions

Synthesis of Prochiral Triflates. The substrates for the asymmetric Heck reactions were readily prepared as shown in Scheme 5. Treatment of the lithium enolate generated from **10**[10] with 1-iodo-4,4-dimethoxybutane[11] in THF at 0 °C gave **11** in 76% yield. After deprotection of the acetal functionality, a solution of the resultant aldehyde in 1,2-dichloroethane was refluxed with triflic anhydride and 2,6-di-*tert*-butylpyridine affording alkenyl triflate **3a** in 63% yield together with the corresponding *E*-isomer (12%). The *Z*-alkenyl triflate **3a** was reduced with lithium aluminum hydride to give alcohol **3e** in 85% yield. This alcohol was further converted to pivaloyl ester **3b** (98%), silyl ether **3c** (95%), and acetate **3d** (96%) as indicated.

Effect of Solvents. The reaction of **3a** with $Pd(OAc)_2$ (5 mol %), (*R*)-BINAP[12] (5.5 mol %), and *N*,*N*-diisopropylethylamine (2 equiv) in various solvents was investigated first (Table 1, entries 1–4). Reaction in polar solvents such as DMSO, acetonitrile, and NMP gave the cyclized product **2a** in low chemical and optical yield while reaction in toluene at 60 °C gave **2a** of 82% ee.[13] Unfortunately, the chemical yield was only 31%, and starting material **3a** was recovered. Apparently, deactivation of the catalyst occurs gradually under the reaction conditions. However, the chemical and optical yield of **2a** could be improved to 54% and 91%, respectively, using K_2CO_3 (2 molar equiv) as a base and increasing the (*R*)-BINAP/Pd ratio from 1.1 to 2 (entry 6). Under the same conditions, triflates **3b**–**3d** afforded the decalin derivatives **2b**–**2d** with excellent enantiomeric excess (entries 7–9). Reaction in THF was also examined with some success (entry 10). The cyclization of **3a** and **3b** in 1,2-dichloroethane was very slow, resulting in a poor yield of **2a** and **2b** and the recovery of a significant amount of starting material. While cyclization of alcohol **7** in 1,2-dichloroethane gave **8** in 37% yield,[4g,j] this solvent was less effective for reactions of **3a** and **3b**. Very high optical yields were obtained (**2a**, 87% ee and **2b**, 92% ee), but the reactions proceeded exceedingly slowly (entries 11 and 12). As the

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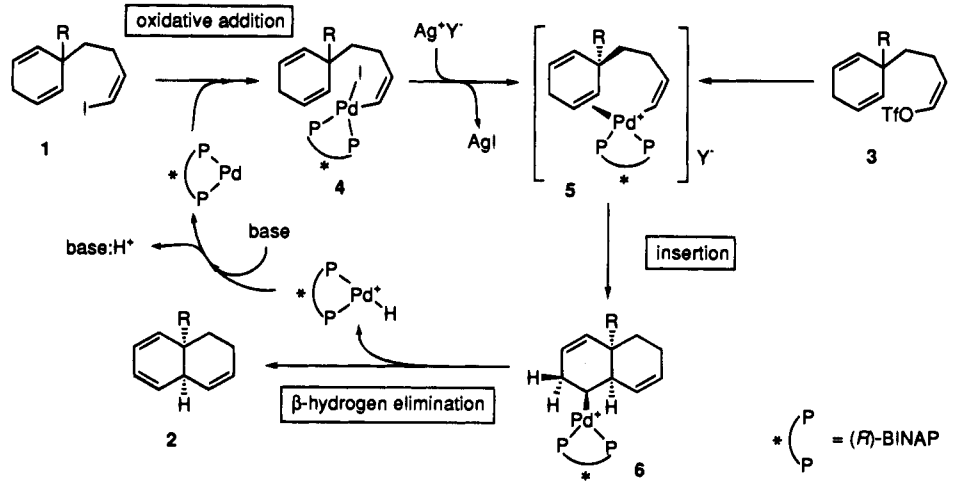
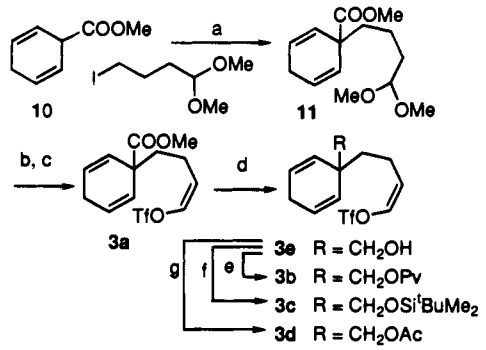
(13) The ee of **2a**–**d** was determined by conversion to **2e** and HPLC analysis (DAICEL CHIRALCEL OJ, 10% 2-propanol in hexane) of **2e**.[41]

Scheme 3



Scheme 4

Scheme 5



[a] (a) LDA, THF, 0 °C (76%); (b) TsOH, acetone, room temperature (100%); (c) Tf_2O, 2,6-di-*tert*-butylpyridine, 1,2-dichloroethane, reflux (63%); (d) $LiAlH_4$, Et_2O, −78 °C (85%); (e) PvCl, pyridine, DMAP, CH_2Cl_2 (98%); (f) TBDMSCl, imidazole, DMF (95%); (g) Ac_2O, pyridine, DMAP, CH_2Cl_2 (96%).

cyclization of **7** in 1,2-dichloroethane improved with the addition of ^{t}BuOH, in terms of reaction rate and chemical and optical yield of **8**, we next investigated the effect of alcohols on the asymmetric Heck reaction of **3** in 1,2-dichloroethane.

Effect of Alcohols. The effect of ^{t}BuOH on the reaction was examined first. On addition of 15 mol equiv of ^{t}BuOH to the reaction mixture (Table 2, compare entries 1 and 2), the chemical yield of **2b** increased from 6% to 23%, while the optical yield remained the same (92% and 93% ee). Encouraged by this result, we then examined the effect of a variety of alcohols (entries 3−8) and found that pinacol (2,3-dimethylbutane-2,3-diol) had the most dramatic effect, affording **2b** in 78% yield and 95% ee (entry 8). Both the chemical and optical yields are superior to those observed on reaction in toluene (see Table 1, entry 7), indicating that this pinacol−1,2-dichloroethane solvent system is also effective for the asymmetric Heck reaction of alkenyl triflates.[14]

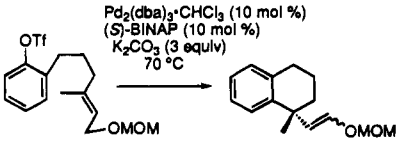
Studies have shown that addition of a tertiary alcohol generally improves the chemical yield without changing the optical purity of the product, whereas the addition of a primary or secondary alcohol lowers the enantiomeric excess of the product. It is noteworthy that 2,4-dimethylpentane-2,4-diol (entry 7) and 2,5-dimethylhexane-2,5-diol (entry 6) were markedly less effective than pinacol. The sensitivity of the reaction to the alcohol structure may suggest that a specific chelation effect is involved.

Large excesses of pinacol (15 equiv to the substrate) were required when the reaction was carried out in dilute solution (0.07 M, entries 8−10); however, 1 equiv of pinacol was fairly effective in concentrated reaction mixtures (1 M, entries 10, 11, and 14−17). The ratio of pinacol to 1,2-dichloroethane seems to be more important than the ratio of pinacol to substrate.

When the Pd(0) complex Pd[(*R*)-binap]$_2$ was used instead of $Pd(OAc)_2$ as the catalyst precursor, the effect of pinacol on the reaction disappeared (Table 3).[15] It is known that Pd(0) is formed from $Pd(OAc)_2$ in the presence of BINAP and base,[16] and to examine the effect of pinacol on this process, $Pd(OAc)_2$ (5 mol %), (*R*)-BINAP (10 mol %), and K_2CO_3 (2 molar equiv) in 1,2-dichloroethane were stirred at 60 °C for 2 h in the presence and absence of pinacol. Substrate **3a** (and pinacol in latter case) was then added to initiate the reaction (Scheme 6). The yield of cyclized product **2a** was 47% when pinacol was present at the start, while it was only 18% when pinacol was added at the same time as the substrate. Preheating in the absence of pinacol and substrate seems to result in the formation of a "less active Pd species", and the mechanism of this deactivation will be discussed in the separate section.

Effect of Acetate Anion. The major byproduct isolated from the reaction mixture in the cyclization of **3a** is the acetate **12** (entries 8 and 11 of Table 1), and one possible pathway for the formation of **12** is shown in Scheme 7. After cyclization and

(14) Improvement of chemical and optical yields by the addition of pinacol was also observed in the following system (Takemoto, T.; Sodeoka, M.; Shibasaki, M. Unpublished results).



(15) The chemical yield of **8** in the asymmetric cyclization of **7** to **8** improved on addition of ^{t}BuOH using either of catalyst precursor, $Pd(OAc)_2$ (4 mol %, 37% → 53%) or $Pd_2(dba)_3$ (9 mol %, 58% → 76%).[4g,j] See also ref 14.

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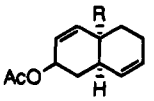
Table 1. Base and Solvent Effects in the Asymmetric Cyclization of **3**[a]

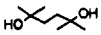
entry	substrate	base (2 equiv)	solvent	$Pd(OAc)_2$/(*R*)-BINAP (mol %)	time (h)	recovery of **3**	product	yield (%)	ee (%)
1	**3a**	$^iPr_2NEt$	DMSO	5/5.5	78	6	**2a**	29	5
2	**3a**	$^iPr_2NEt$	CH_3CN	5/5.5	68	39	**2a**	9	10
3	**3a**	$^iPr_2NEt$	NMP	5/5.5	49	36	**2a**	<15	43
4	**3a**	$^iPr_2NEt$	toluene	5/5.5	31	39	**2a**	31	82
5	**3a**	K_2CO_3	toluene	5/5.5	21	24	**2a**	50	83
6	**3a**	K_2CO_3	toluene	5/10	55	trace	**2a**	54	91
7	**3b**	K_2CO_3	toluene	5/10	27		**2b**	60	91
8	**3c**	K_2CO_3	toluene	5/10	74	13	**2c**[b]	35	92
9	**3d**	K_2CO_3	toluene	5/10	45		**2d**	44	89
10	**3a**	K_2CO_3	THF	5/10	41		**2a**	33	82
11	**3a**	K_2CO_3	$ClCH_2CH_2Cl$	5/10	162	50	**2a**[b]	13	87
12	**3b**	K_2CO_3	$ClCH_2CH_2Cl$	5/10	106	63	**2b**	6	91

[a] Reactions were carried out at 60 °C. The initial concentration of the substrate was 0.1 M (entries 1–9) or 0.07 M (entries 10–12). [b] Acetoxy derivatives **12c** (entry 8) and **12a** (entry 11) were formed in 9% and 5% yield respectively.



12a R = COOMe
12c R = $CH_2OSi^tBuMe_2$

Table 2. Effect of Alcohols in the Asymmetric Cyclization of **3**[a]

entry	substrate	additive (mol equiv)	time (h)	recovery of 3	product	yield (%)	ee (%)
1	3b	-	106	63	2b	6	92
2	3b	^{t}BuOH (15)	68	55	2b	23	93
3	3b	EtOH (15)	100	49	2b	18	86
4	3b	 (15)	100	49	2b	11	71
5	3b	 (15)	95	54	2b	6	63
6	3b	 (15)	100	48	2b	42	93
7	3b	 (15)	100	57	2b	20	93
8	3b	 (15)	47	-	2b	78	95
9	3b	 (5)	100	30	2b	28	94
10	3b	 (2)	100	45	2b	9	92
11	3b	 (1)	108	5	2b	47	90
12	3a	-	162	50	2a	13	87
13	3a	^{t}BuOH (15)	162	47	2a	17	87
14	3a	 (15)	162	33	2a	28	91
15	3a	-	75	56	2a	6	83
16	3a	 (1)	75	20	2a	21	91
17	3a	 (1)	84	-	2a	51	92

[a] Reactions were carried out using $Pd(OAc)_2$ (5 mol %), (*R*)-BINAP (10 mol %), and K_2CO_3 (2 equiv) in $ClCH_2CH_2Cl$ at 60 °C. Initial concentration of **3**: entries 1–10 and 12–14, 0.07 M; entries 15 and 16, 0.5 M; entries 11 and 17, 1 M.

β-hydrogen elimination, a hydrido–olefin complex **13** is formed that might be expected to undergo olefin insertion to form the cationic π-allylpalladium intermediate **14**. Nucleophilic attack of the acetate anion generated from $Pd(OAc)_2$ on this π-allylpalladium intermediate **14** would then afford **12**. Acetate **12** is expected to be a useful chiral building block if it could be obtained in good chemical and optical yield. If the proposed mechanism is correct, addition of a stoichiometric amount of acetate anion might be expected to improve the yield of **12**. In fact, the addition of potassium acetate (1 equiv) to **3a**, $Pd(OAc)_2$, (*R*)-BINAP, and K_2CO_3 in 1,2-dichloroethane resulted in only a slight improvement of the yield of **12a** (Scheme 8). However, a great enhancement of the reaction rate was observed, and the yield of **2a** improved from 13% to 70% (compare to 54% obtained on reaction in toluene, entry 6, Table 1). In addition, the enantiomeric excess of product **2a** (86% ee) is comparable to that of **2a** obtained from the reactions without potassium acetate in 1,2-dichloroethane (87% ee, entry 12, Table 2) or in toluene (91% ee, entry 6, Table 1).

In contrast to the effects of pinacol on the cyclization of **3a**, potassium acetate was effective even when added with the substrate after preheating of $Pd(OAc)_2$, (*R*)-BINAP, and K_2CO_3 at 60 °C for 6 h (Scheme 9). While the mechanism of this rate enhancement will be discussed further, the lack of improvement in the yield of **12** deserves comment. Hayashi *et al.* have reported that acetate anion prevents product isomerization in the intermolecular Heck reaction by enhancing dissociation of the cationic hydridopalladium from the olefin.[5h] Acetate anion is essential to produce **12**, but it may also enhance the dissociation of (binap)Pd^+H from **13** to prevent formation of **14**. The lack of improvement in the yield of **12** on addition of potassium acetate might be a result of such an effect of acetate anion on the formation of **12**. These results indicate that potassium acetate is another powerful additive for accerelation of the asymmetric Heck reaction in 1,2-dichloromethane.[17]

A Catalytic Asymmetric Synthesis of (+)-Vernolepin (9) Using Decalin Derivative 2a. Having achieved the asymmetric synthesis of decalin derivatives **2a–d** of high ee, we have gone on to demonstrate the usefulness of this class of compounds as chiral building blocks. We planned to determine the absolute stereochemistry of (+)-vernolepin (**9**) by its asymmetric synthesis from optically active **2**. Methyl ester (+)-(*S,S*)-**2a** (86% ee), whose absolute configuration has been unequivocally determined by the CD exciton chirality method,[3,4l] was converted to Danishefsky's intermediate (+)-**18**[4g,j,8a] as shown in Scheme 10. Diene (+)-**2a** was selectively transformed to enones **15** and **16** by a bromohydrin formation–debromination–oxidation sequence, and after separation of regioisomer **15**, (+)-**16** was converted to allylic alcohol (+)-**17** in three steps. Inversion of the alcohol and lactonization afforded (+)-**18** with spectral data identical to that reported by Danishefsky for (±)-**18**.[8a] This intermediate was further converted to (+)-vernolepin (**9**) according to Danishefsky's route. As both the synthetic sample and natural product[7] have positive optical rotations, the absolute configuration of (+)-vernolepin (**9**) has been determined to be the one shown in Scheme 10.

NMR Studies. In the previous sections we have described the remarkable effects of two additives, pinacol and potassium

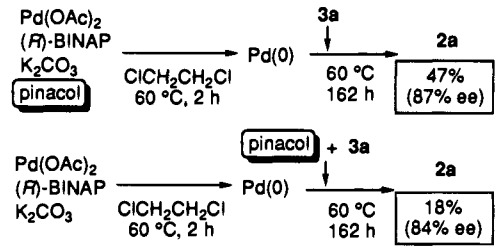
(17) Positive effect of acetate anion on the Heck reaction has been reported. See: (a) Bumagin, N. A.; More, P. G.; Beletsukaya, I. P. *J. Organomet. Chem.* **1989**, *371*, 397. (b) Larock, R. C.; Baker, B. E. *Tetrahedron Lett.* **1988**, *29*, 905.

Table 3. Effect of Pinacol in the Asymmetric Cyclization of **3b**[a]

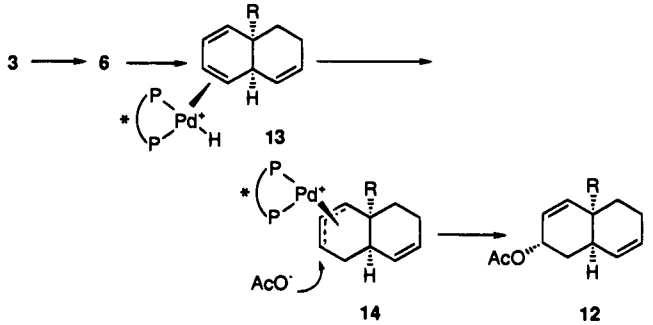
entry	catalyst	pinacol	time (h)	recovery of **3b** (%)	yield of **2b** (%)	ee (%)
1	$Pd(OAc)_2$ (5 mol %), (*R*)-BINAP (10 mol %)		106	63	6	92
2	$Pd(OAc)_2$ (5 mol %), (*R*)-BINAP (10 mol %)	15 equiv	47		78	95
3	Pd[(*R*)-binap]$_2$ (5 mol %)		144	80	9	87
4	Pd[(*R*)-binap]$_2$ (5 mol %)	15 equiv	144	74	8	79

[a] Reactions were carried out using K_2CO_3 (2 equiv) in $ClCH_2CH_2Cl$ at 60 °C. The initial concentration of **3b** was 0.07 M.

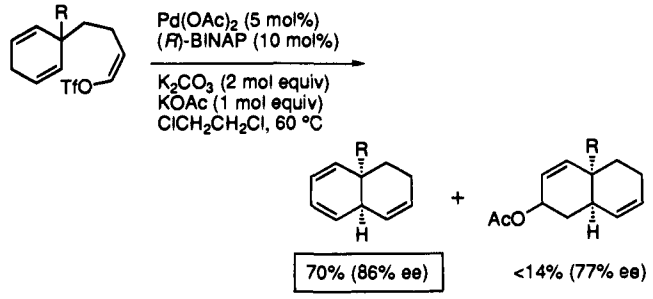
Scheme 6



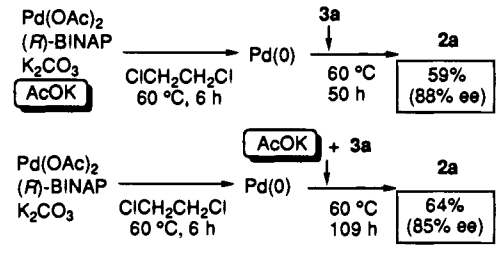
Scheme 7



Scheme 8



Scheme 9



acetate, on the asymmetric Heck reaction in 1,2-dichloroethane. These observations can be summarized as follows: (1) Reaction in 1,2-dichloroethane is very slow compared with that in toluene. (2) The enantiomeric excess of the reaction product in 1,2-dichloroethane is generally higher than that of the reaction in benzene.[4g,j,14] (3) Tertiary alcohols enhance the reaction rate in 1,2-dichloroethane without affecting the ee of the product,[4g,j,14] and pinacol has the most dramatic effect. (4) Pinacol is an effective accelerant only when $Pd(OAc)_2$ is used as the catalyst precursor in the cyclization of **3**. (5) Potassium acetate also enhances the reaction rate in 1,2-dichloroethane. (6) Preheating of a $Pd(OAc)_2$–(*R*)-BINAP–base mixture in 1,2-dichloroethane results in formation of a "less active Pd species". (7) Pinacol cannot reactivate this "less active Pd species", but potassium acetate can.

Scheme 11 depicts a hypothetical sequence that might be used to explain the results summarized. Reduction of $Pd(OAc)_2$ to a catalytically active Pd(0) species such as **22** (S = solvent) is expected to proceed first and known reducing agents for this process include phosphine ligands, olefinic substrates,[18] amines,[19] and alcohols.[20] In our cases, BINAP and the substrate might participate in this manner. In the presence of excess BINAP, the reduced species **22** might be converted to Pd[(*R*)-binap]$_2$ (**23**), and with its stable 18-electron configuration, **23** may be a candidate for the less active species that is formed. In aromatic solvents (e.g., benzene, toluene) with π-electrons capable of coordinating to a transition metal, **22** might be expected to be present in greater amounts than **23**, the latter of which might predominate in 1,2-dichloroethane. Pinacol and acetate might prevent the otherwise preferred formation of **23** in 1,2-dichloroethane by acting as the solvent in **22** and coordinating weakly to the Pd to form **24** and **25**. With the intention of verifying these hypotheses and gaining further insight to the mechanism of the asymmetric Heck reaction, we undertook a series of $^{31}P\{^1H\}$-NMR experiments.

To understand the nature of the Pd(0) species formed in each solvent, we measured the $^{31}P\{^1H\}$-NMR spectra of Pd[(*R*)-binap]$_2$ (**23**)[5h] in benzene and 1,2-dichloroethane. Figure 2A shows the spectra of **23** in benzene. The small signals at 28.3, 23.3, and −11.3 ppm were observed in addition to the major signal for **23** (29.6 ppm). The signals at 28.3 and −11.3 ppm have been assigned to (*R*)-BINAP monoxide (**26**)[16a] after comparison with an authentic sample, and this compound is believed to be formed from trace amounts of dissolved oxygen.[21] The peak at 23.3 ppm may be assigned as the active species **22**. It should be also noted that the spectrum of Pd[(*R*)-binap]$_2$ did not change after 2 h, and the color of the mixture remained the same deep red that was initially observed.

In contrast, the $^{31}P\{^1H\}$-NMR spectra of Pd[(*R*)-binap]$_2$ in 1,2-dichloroethane taken over 8 h showed considerable change (Figure 2B). The signal for **23** at 32.7 ppm that predominated after 10 min completely disappeared after 8 h, and the color of the mixture changed from deep red to yellow, consistent with the formation of Pd(II) species. A new signal appeared at 34.8 ppm over the course of this change and has been assigned to [(*R*)-binap]$PdCl_2$ (**27**) by comparison with an authentic sample.[5h] The appearance of **27** indicates that Pd(0) can be oxidized quite efficiently by 1,2-dichloroethane.[22] It is known that oxygen-bound Pd(II) species such as $Pd(OAc)_2$ are readily reduced by phosphine ligands, whereas $PdCl_2$ is not.[16b] Given these facts, we suggest that the slow reactions observed in 1,2-dichloroethane are a result of the rapid conversion of the catalytically

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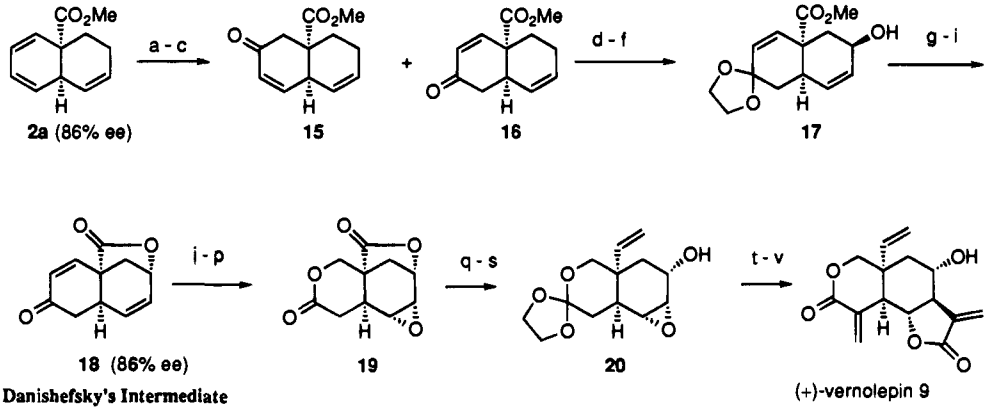
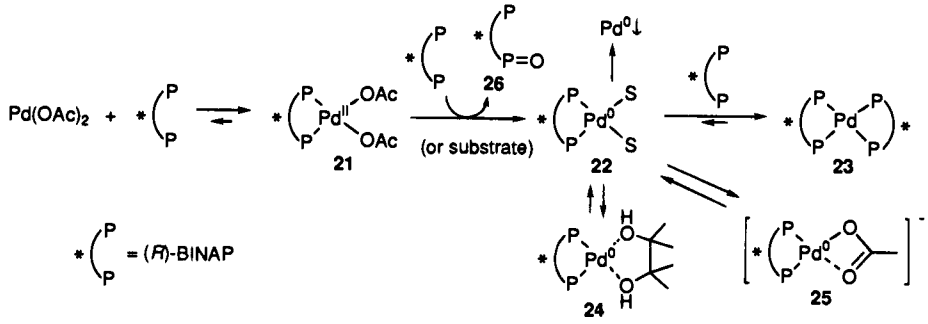
(19) McCrindle, R.; Ferguson, G.; Arsenault, G.; McAlees, A. J. *J. Chem. Soc., Chem. Commun.* **1983**, 571.
(20) Tamaru, Y.; Yamada, Y.; Inoue, K.; Yamamoto, Y.; Yoshida, Z. *J. Org. Chem.* **1983**, *48*, 1286.
(21) (a) Takahashi, S.; Sonogashira, K.; Hagihara, N. *J. Chem. Soc. Jpn.* **1966**, *87*, 610. (b) Nyman, C. J.; Wymore, C. E.; Wilkinson, G. *J. Chem. Soc. A* **1968**, 561. (c) Kashiwagi, T.; Yasuoka, N.; Kasai, N.; Kakudo, M. *Chem. Commun.* **1969**, 743.

Scheme 10



[a] (a) NBS, H_2O–DMF–DMSO; (b) Bu_3SnH, AIBN; (c) PCC; **15** (30%, three steps); **16** (30%, three steps); (d) $HOCH_2CH_2OH$, cat. *p*-TsOH (81%); (e) CrO_3, DMP (54%); (f) $NaBH_4$, $CeCl_3$ (92%); (g) AcOH, PPh_3, DEAD; H^+; (h) LiOH; (i) Ac_2O, AcONa (36%, three steps); (j) NaOH; (k) *m*-CPBA; (l) Ac_2O, AcONa; (m) OsO_4, $Ba(ClO_3)_2$; (n) $Pb(OAc)_4$, MeOH; (o) $LiAlH(O^tBu)_3$; (p) Amberlite IRC-50; (q) $HOCH_2CH_2OH$, cat. *p*-TsOH, Dowex 50W-X8; (r) DIBAL; (s) $Ph_3P{=}CH_2$; (t) (i) $LiCH_2COOLi$, (ii) H_3O^+, (iii) CH_2N_2; (u) cat. *p*-TsOH; (v) (i) LDA, (ii) $CH_2{=}N^+Me_2I^-$, (iii) MeI, (iv) $NaHCO_3$.

Scheme 11



active Pd(0) species to inactive [(*R*)-binap]$PdCl_2$. Beside the signals of [(*R*)-binap]$PdCl_2$ (**27**) and free (*R*)-BINAP (−9.0 ppm), those of BINAP monoxide (**26**, −8.9 and 32.9 ppm) were also observed, and the signal at 33.7 ppm was identical with that of BINAP bisoxide.[23]

We have reported that the cyclization of allylic alcohol **7** in 1,2-dichloroethane ($Pd(OAc)_2$, BINAP, K_2CO_3) afforded **8** in 37% yield with no recovery of **7** (compare to the cyclization of **3b**, Table 1, entry 12). The increased yield and loss of starting material might be explained by regeneration of zerovalent palladium from [(*R*)-binap]$PdCl_2$ by the bis(allylic) alcohol moiety in **7**. In fact, trienone **30** was isolated from the reaction mixture as a byproduct and is probably formed from cyclization of dienone **29** generated as shown in Scheme 12. It is important to note that the ee of **8** obtained from the reaction in 1,2-dichloroethane was higher (76% ee) than that obtained from the reaction in benzene (28% ee). It is likely that strongly coordinating solvents can stabilize Pd(0) species without BINAP to give **32**, and this highly unsaturated species may catalyze the formation of racemic product. While **22** is expected to be the major catalytically active species in aromatic solvents and to afford product of high ee, the low asymmetric induction observed in some cases may result from participation of **32**. In 1,2-dichloroethane, however, this highly coordinatively unsaturated species **32** is expected to be quite unstable and may not participate, resulting in high asymmetric induction.

To know the role of additives in the deactivation of the active Pd(0) species, we also measured the $^{31}P\{^1H\}$-NMR spectra of a mixture of Pd[(*R*)-binap]$_2$ (**23**) and pinacol or potassium acetate in 1,2-dichloroethane. As shown in Figure 3A, the addition of pinacol only slightly retarded the formation of [(*R*)-binap]$PdCl_2$ (**27**, 34.8 ppm), and the signal for **23** completely disappeared after 8 h. In contrast, the addition of potassium acetate to the same mixture suppressed formation of **27**; a signal for **23** (32.7 ppm) was observed even after 22 h (Figure 3B), and the reaction mixture remained red.

Some additional information may be gained on the role of acetate ion in these reactions from several reports on the positive effects of halide ion on the Heck reaction.[24] Among these is the report by Amatore *et al.*[25] that chloride ion can stabilize the low-ligated zelovalent Pd species generated from **33** by electroreduction. As shown in Scheme 13, the Pd(0) is present in the form of three anionic species, **34**, **35**, and **36**, in the presence of excess chloride anion. They have also suggested that acetate anion may stabilize Pd(0)[16b] in a manner similar to chloride anion, and the unassigned peaks at 32.3 and 32.8 ppm may be acetate anion-associated anionic Pd(0) species **25** and

(22) The mechanism of the formation of **27** is unknown. Tsubomura *et al.* have reported that $Pd_2(dpm)_3$, [dpm = bis(diphenylphosphino)methane] and CH_2Cl_2 react with or without irradiation to give (dpm)$PdCl_2$ via $Pd_2(dpm)_2(\mu\text{-}CH_2)Cl_2$. They have also reported that reaction of $Pd_2(dpm)_3$ with 1,2-dichloroethane under irradiation affords Pd(I) dimer complex, $Pd_2(dpm)_2Cl_2$ and ethylene. See: Itsuki, A.; Sakai, K.; Tsubomura, T. *Abstract for 39th Symposium on Organometallic Chemistry, Japan (Tokyo)* **1992**, 247. See also: Balch, A. L.; Hunt, C. T.; Lee, C.-L.; Olmstead, M. M.; Farr, J. P. *J. Am. Chem. Soc.* **1981**, *103*, 3764.

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(24) (a) Jeffery, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1287. (b) Larock, R. C.; Yum, E. K.; Yang, H. *Tetrahedron* **1994**, *50*, 305. (c) Burns, B.; Grigg, R.; Santhakumar, V.; Sridharan, V.; Stevenson, P.; Worakun, T. *Tetrahedron* **1992**, *48*, 7297. (d) Acadi, A.; Bernocchi, E.; Cacchi, S.; Marinelli, F. *Tetrahedron* **1991**, *47*, 1525. (e) Merlic, C. A.; Semmelhack, M. F. *J. Organomet. Chem.* **1990**, *391*, C23. (f) Jeffery, T.; Galland, J. *Tetrahedron Lett.* **1994**, *35*, 4103 and references cited therein. See also references cited in ref 25.

(25) Amatore, C.; Azzabi, M.; Jutand, A. *J. Am. Chem. Soc.* **1991**, *113*, 8375.

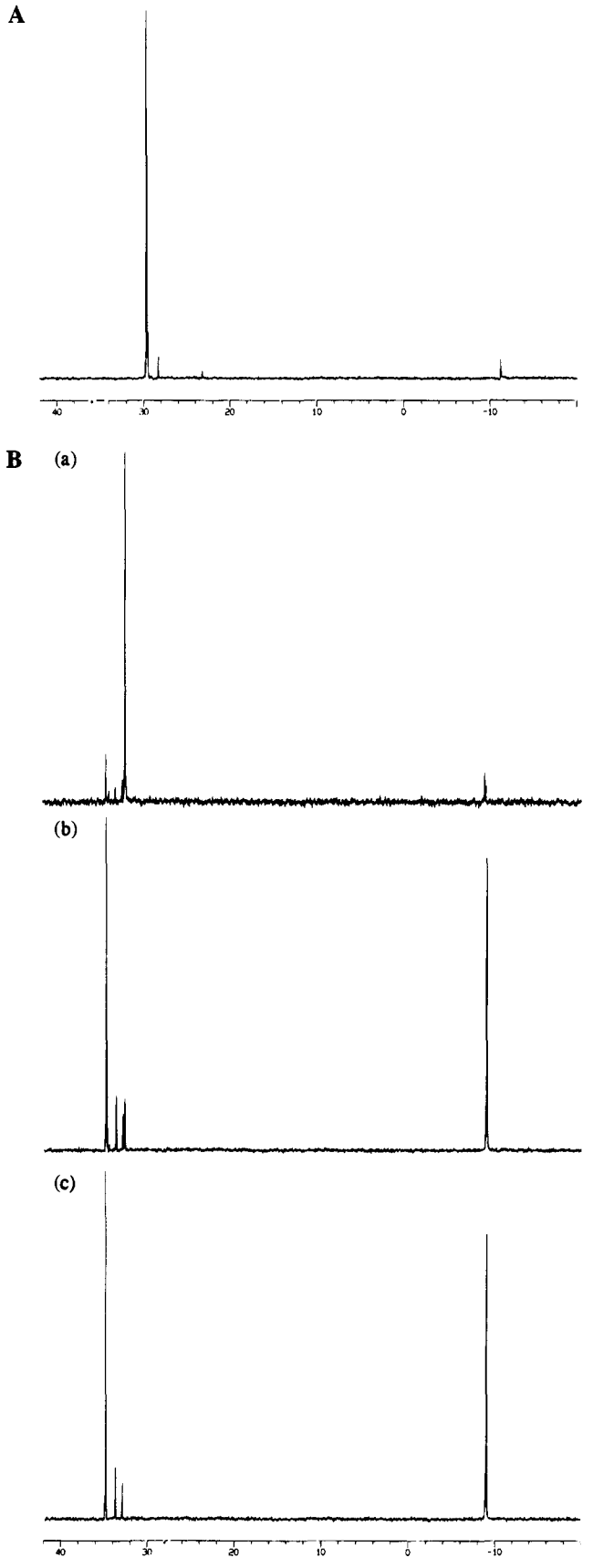


Figure 2. (A) $^{31}P\{^1H\}$-NMR spectrum of Pd[(*R*)-binap]$_2$ in C_6D_6 at 40 °C after 1.5 h with an accumulation time of 2 h. (B) $^{31}P\{^1H\}$-NMR spectra of Pd[(*R*)-binap]$_2$ in $ClCH_2CH_2Cl$ at 40 °C after (a) 10 min, (b) 40 min, (c) 480 min; accumulation times: (a) 5 min and (b and c) 2 h.

38 (Scheme 14). Following a kinetic study of the reactivity of **35**, Amatore *et al.*[26] concluded that oxidative addition of an aryl iodide to the anionic Pd(0) species **35** is faster than that to the neutral Pd(0) species **37**. It is possibile that the anionic Pd(0) species **25** is more reactive than **22** in the oxidative addition step. In Figure 3B (22 h) a signal for [(*R*)-binap]Pd-(OAc)$_2$ (**21**) (32.0 ppm) was observed, suggesting that in the presence of a large amount of potassium acetate, the [(*R*)-binap]-$PdCl_2$ (**27**) formed might be easily reactivated to give a Pd(0) species via **21** by BINAP. Thus acetate anion may enhance the reaction rate in multiple ways by (1) slowing formation of **27**, (2) accelerating the oxidative addition of the substrate, and (3) reactivating **27**.

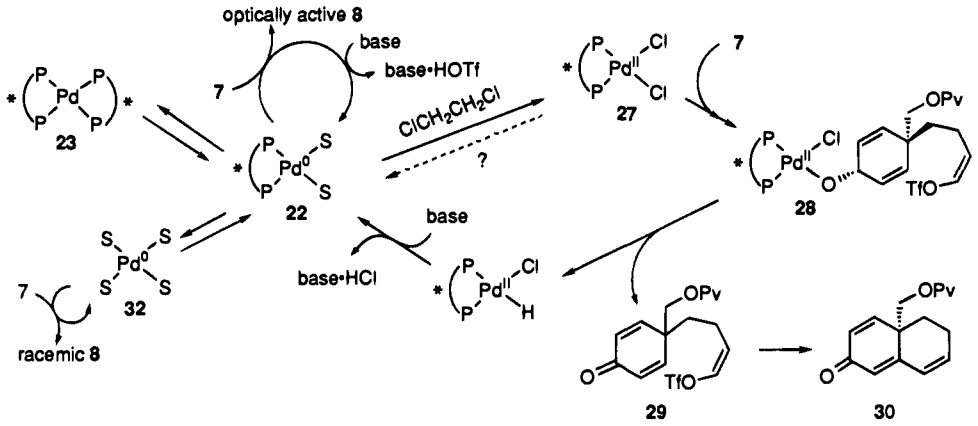
Pinacol alone has little effect on the formation of **27** from **23**. This fact is in accord with the observation that pinacol has no positive effect on the reaction when **23** is used as the catalyst precursor. After 8 h, $^{31}P\{^1H\}$-NMR shows two major signals at 34.9 (**27**) and −9.0 ppm (free BINAP) and three minor signals at −8.9, 33.4 (**26**), and 34.1 ppm (BINAP bisoxide). It is noteworthy that the chemical shift of phosphine oxides is lower in the presence of pinacol, suggesting an interaction of the P=O moiety with pinacol (Figure 3A).

We have also followed the time course by $^{31}P\{^1H\}$-NMR of a mixture of Pd(OAc)$_2$, (*R*)-BINAP (2 equiv to Pd), and base (50 equiv of NEt_3 to Pd was used instead of K_2CO_3 because of solubility problems) in 1,2-dichloroethane in the presence and absence of pinacol (20 equiv to Pd). After formation of [(*R*)-binap)]Pd(OAc)$_2$ (**21**, 32.0 ppm) from Pd(OAc)$_2$ and (*R*)-BINAP, **23** (32.7 ppm), **27** (34.8 ppm), **26** (−8.9 and 32.9 (no pinacol) or 33.4 (with pinacol) ppm), and BINAP bisoxide (33.7 (no pinacol) or 34.2 (with pinacol) ppm) were formed by the addition of NEt_3 with consumption of **21** and free (*R*)-BINAP (−9.0 ppm). The formation of **27** was slower in the presence of pinacol than in its absence, and even after 9 days, some of **23** remained with pinacol present. The only signals observed after 9 days in the absence of pinacol were for **27**, BINAP bisoxide (33.7 ppm), **26**, and free BINAP. These experiments indicate that pinacol effectively prevents the decomposition of the Pd(0) species **23** in the presence of acetate anion. In the spectrum of Figure 4A (1 and 4 h), two wide signals at 32.3 and 32.8 ppm were observed that are identical with those observed in the spectrum of **23** with potassium acetate (Figures 4A and 3B). These signals may be from the anionic acetate-ligated Pd(0) species **25** and **38** (Scheme 14). In the presence of pinacol (Figure 4B), a signal at 32.8 ppm was also observed and that at 32.3 ppm seemed to shift to 32.6 ppm. This low-field shift might indicate some interaction of **25** or **38** with pinacol; this interaction may help to stabilize them.

Possible pathways in the reaction mixture are summarized in Scheme 14. The coordinatively unsaturated Pd(0) species **22** is very unstable in 1,2-dichloroethane and is readily oxidized to inactive **27**. This process may be prevented by coordination of either pinacol (→**24**) or acetate anion (→**25** or **38**) to the complex. Pinacol alone seems to have a weak effect on preventing the formation of **27**; however, in the presence of acetate anion (even only 2 equiv to Pd), pinacol works cooperatively to retard the formation of **27** (Figure 4). In the actual reaction mixture, the anionic Pd(0) species **25** may work both as a reservoir for the Pd(0) species, preventing formation of **27**, and as an active catalytic species accelerating the formation of **2**. It is also possible that acetate anion and pinacol increase the reaction rate via other steps in the catalytic cycle such as the formation of the cationic intermediate **5**, insertion of the olefin to the alkenyl−Pd bond, or regeneration of Pd(0) species.

(26) Amatore, C.; Jutand, A.; Suarez, A. *J. Am. Chem. Soc.* **1993**, *115*, 9531.

Scheme 12



Conclusions

We have succeeded in developing a new method for the catalytic asymmetric synthesis of decalin derivatives **2** with excellent asymmetric induction (up to 95% ee). Using derivative **2a** as a chiral building block, the first asymmetric synthesis of (+)-vernolepin (**9**) has been accomplished and its absolute stereochemistry has been determined. Furthermore we have found through a series of ^{31}P-NMR experiments that the catalytically active LnPd(0) species are readily oxidized to $LnPdCl_2$ in 1,2-dichloroethane but that the addition of pinacol or potassium acetate prevents this process. These novel conditions ($Pd(OAc)_2$, chiral phosphine ligand, and pinacol or potassium acetate in 1,2-dichloroethane) for the asymmetric Heck reaction afford products in high chemical and optical yield and should be useful for further applications of the asymmetric Heck reaction to the synthesis of a variety of complex molecules.

Experimental Section

Infrared (IR) spectra were recorded on a JASCO A-300 diffraction grating infrared spectrophotometer. NMR spectra were measured on JEOL JNM-FX-100 or JEOL JNM-FX-270 spectrometers, operating at 100 or 270 MHz for ^{1}H and 68 MHz for ^{13}C NMR. Chemical shifts, in $CDCl_3$ solution, are reported downfield from TMS (0 ppm) for ^{1}H and relative to the central $CDCl_3$ resonance (77.00 ppm) for ^{13}C spectra. ^{31}P{^{1}H}-NMR spectra were obtained on a JEOL JNM-GSX-500 spectrometer, operating at 202 MHz with H_3PO_4 (85% H_3PO_4 0.75 mL and D_2O 0.15 mL; for locking) as an external standard. All ^{31}P{^{1}H}-NMR spectra were carried out in well-dried 5-mm diameter NMR tubes equipped with rubber septa. Mass spectra (MS) were measured on a JEOL JMS-DX303, JMS-D300, or JMS-HX100 instruments. Optical rotation was measured on a JASCO DIP-140 polarimeter. In general, reactions were carried out in dry solvents under an argon atmosphere, unless otherwise mentioned. IR, NMR, and MS data were obtained on all intermediates described herein using chromatographically homogeneous samples.

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium benzophenone ketyl. 1,2-Dichloroethane, dichloromethane, *N*,*N*-dimethylformamide (DMF), 1-methyl-2-pyrrolidinone (NMP), acetonitrile (CH_3CN), and dimethyl sulfoxide (DMSO) were distilled from calcium hydride. Benzene and toluene were distilled from sodium.

Palladium acetate (Wako Pure Chemical Industries, Ltd.) was treated with boiling benzene and the mixture filtered while hot. The hot filtrate was then concentrated to dryness to give purified $Pd(OAc)_2$.

Methyl 1-(4,4-Dimethoxybutyl)-2,5-cyclohexadiene-1-carboxylate (11). To a solution of LDA (20.5 mmol) in THF (30 mL) was gradually added a solution of **10** (2.37 g, 17.2 mmol) in THF (29 mL) at 0 °C, and the mixture was stirred for 1 h at the same temperature. To this enolate solution was then added a solution of 1-iodo-4,4-dimethoxybutane (4.58 g, 18.8 mmol) in THF (29 mL) at 0 °C, and the whole mixture was stirred at 0 °C for 1 h. It was then diluted with saturated aqueous NH_4Cl and extracted with ether. The organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel (17% ether in hexane) to give **11** (3.30 g, 76%) as a colorless oil: IR (neat) 1732, 1130 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.42−1.80 (m, 6H), 2.56−2.70 (m, 2H), 3.29 (s, 6H), 3.68 (s, 3H), 4.33 (t, J = 5.8 Hz, 1H), 5.57−6.00 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 19.4, 26.1, 32.6, 39.3, 47.8, 52.1, 52.6, 104.3, 125.8, 127.1, 175.3; MS *m/z* 254 (M^+), 223, 191, 163, 131 (base peak), 105; HR-MS calcd for $C_{14}H_{22}O_4$ 254.1518, found 254.1492.

Methyl 1-(4-Oxobutyl)-2,5-cyclohexadiene-1-carboxylate. To a stirred solution of **11** (2.62 g, 10.3 mmol) in acetone (35.0 mL) was added *p*-TsOH•H_2O (98.0 mg, 0.520 mmol) at 23 °C. The reaction mixture was stirred at 23 °C for 9 h and neutralized with saturated aqueous $NaHCO_3$. After evaporation of acetone, the aqueous layer was extracted with EtOAc, and the organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel (25% ether in hexane) to give the aldehyde (2.15 g, 100%) as a colorless oil: IR (neat) 1728 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.40−1.70 (m, 4 H), 2.40 (br t, J = 6.5 Hz, 2H), 2.60−2.71 (m, 2H), 3.69 (s, 3H), 5.60−6.02 (m, 4 H), 9.74 (t, J = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 17.0, 26.1, 38.6, 43.9, 47.8, 52.3, 126.3, 126.7, 175.1, 202.2; MS *m/z* 176 (M^+ − MeOH), 149 (M^+ − CO_2-Me), 137, 131 (base peak).

Methyl 1-[4-[[(Trifluoromethyl)sulfonyl]oxy]-3(*Z*)-butenyl]-2,5-cyclohexadiene-1-carboxylate (3a). To a stirred solution of the aldehyde (2.15 g, 10.3 mmol) in 1,2-dichloroethane (35.0 mL) were added 2,6-di-*tert*-butylpyridine (4.5 mL, 18.7 mmol) and Tf_2O (2.1 mL 12.5 mmol) at 23 °C. The reaction mixture was refluxed with stirring for 20 min, cooled, and concentrated. The semisolid residue was diluted with hexane and filtered. Remaining filtrate was washed with 2% aqueous HCl and brine, dried (K_2CO_3), and concentrated. The residue was purified by column chromatography on silica gel (10% ether in hexane) to give **3a** (2.22 g, 63%) and the *E*-isomer (0.41 g, 12%) as colorless oils: IR (neat) 1732, 1424, 1144 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.72−1.82 (m, 2H), 2.06−2.18 (m, 2H), 2.64−2.71 (m, 2H), 3.70 (s, 3H), 5.24 (br t, J = 5.5, 7.7 Hz, 1H), 5.70 (ddd, J = 10.3, 2.0, 2.0 Hz, 2H), 5.95 (ddd, J = 10.3, 3.3, 3.3 Hz, 2H), 6.52 (br d, J = 5.5 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 19.4, 26.1, 37.6, 47.7, 52.3, 118.6 (q, J = 325 HZ) 120.3, 126.2, 126.7, 135.4, 174.8; MS *m/z* 340 (M^+), 281 (M^+ − CO_2Me), 147, 131 (base peak), 91; HR-MS calcd for $C_{13}H_{15}F_3O_5S$ 340.0592, found 340.0604.

4-[1-(Hydroxymethyl)-2,5-cyclohexadien-1-yl]-1(*Z*)-butenyl Trifluoromethanesulfonate (3e). To a stirred solution of $LiAlH_4$ (52.0 mg, 1.37 mmol) in Et_2O (8.0 mL) was added a solution of **3a** (447 mg, 1.31 mmol) in Et_2O (10.0 mL) at −78 °C. The reaction mixture was stirred at the same temperature for 20 min and quenched by the addition of EtOAc. Solid Na_2SO_4•$10H_2O$ was then added, and the mixture was stirred at 23 °C for 12 h and filtered through Celite. The filtrate was concentrated, and the residue was purified by column chromatography on silica gel (50% ether in hexane) to give the alcohol (357 mg, 87%) as a colorless oil: IR (neat) 3389, 1424, 1211, 1144 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.20−1.50 (m, 3H), 2.00−2.20 (m, 2H), 2.60−2.70 (m, 2H), 3.35 (br d, J = 6.1 Hz, 2H), 5.10−5.40 (m, 3H), 6.04 (ddd, J = 10.5, 3.4, 3.4 Hz, 2H), 6.47 (br d, J = 5.6 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 19.9, 26.6, 35.7, 43.4, 70.4, 118.6 (q, J = 325

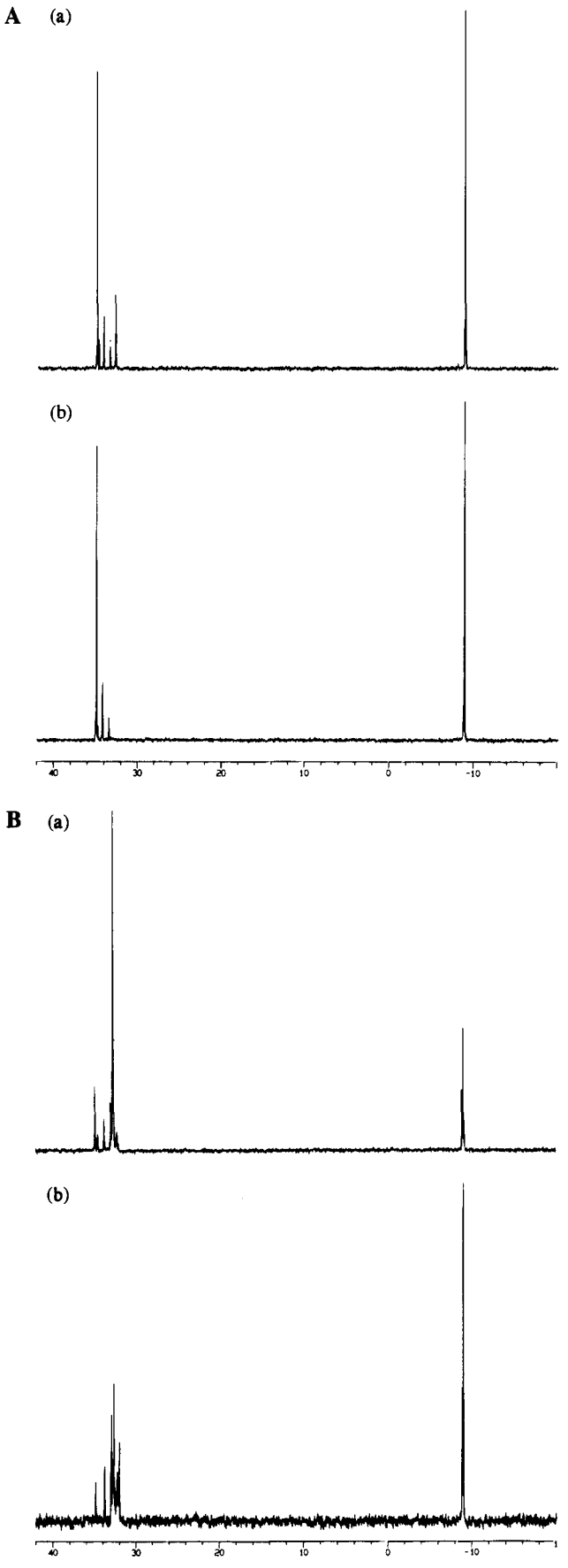


Figure 3. (A) $^{31}P\{^1H\}$-NMR spectra of Pd[(*R*)-binap]$_2$ with pinacol in $ClCH_2CH_2Cl$ at 40 °C after (a) 50 min, (b) 480 min; accumulation times: (a and b) 2 h. (B) $^{31}P\{^1H\}$-NMR spectra of Pd[(*R*)-binap]$_2$ with AcOK in $ClCH_2CH_2Cl$ at 40 °C after (a) 1 h, (b) 22 h; accumulation times: (a) 2 h, (b) 0.5 h.

Hz), 121.0, 128.5, 128.8, 135.1; MS *m/z* 295 ($M^+ - OH$), 280, 145, 131, 91 (base peak); HR-MS calcd for $C_{12}H_{14}F_3O_3S$ 295.0615, found 295.0606.

4-[1-[[(*tert*-Butylcarbonyl)oxy]methyl]-2,5-cyclohexadien-1-yl]-1(*Z*)-butenyl Trifluoromethanesulfonate (3b). To a stirred solution of **3e** (157 mg, 0.500 mmol) in CH_2Cl_2 (2.0 mL) were added pyridine (0.20 mL, 2.50 mmol), pivaloyl chloride (0.12 mL, 1.00 mmol), and (*N,N*-dimethylamino)pyridine (DMAP) (6.0 mg, 0.0500 mmol) at 0 °C. The reaction mixture was stirred at 23 °C for 23 h, diluted with H_2O, extracted with Et_2O, washed successively with 5% aqueous HCl, saturated aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography on silica gel (10% ether in hexane) to give **3b** (195 mg, 98%) as a colorless oil: IR (neat) 1730, 1426, 1211, 1146 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 1.18 (s, 9H), 1.30–1.60 (m, 2H), 1.90–2.30 (m, 2H), 2.50–2.70 (m, 2H), 3.86 (s, 2H), 5.10–5.50 (m, 3H), 5.91 (ddd, J = 10.5, 3.4, 3.4 Hz, 2H), 6.48 (br d, J = 5.9 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 19.8, 26.5, 27.2, 35.9, 38.9, 40.9, 70.6, 118.6 (q, J = 325 Hz), 121.0, 127.1, 128.3, 135.1, 178.3; MS *m/z* 295 ($M^+ - OPv$), 280, 145, 131, 91 (base peak); HR-MS calcd for $C_{12}H_{14}F_3O_3S$ 295.0616, found 295.0606.

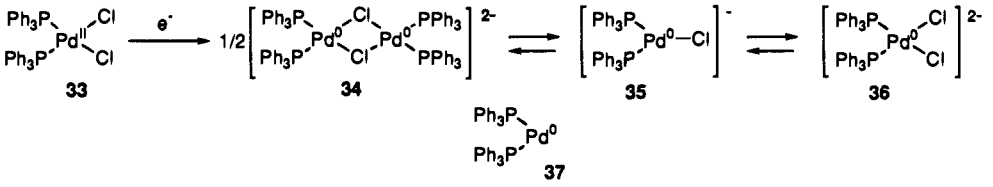
4-[1-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-2,5-cyclohexadien-1-yl]-1(*Z*)-butenyl Trifluoromethanesulfonate (3c). To a stirred solution of **3e** (98 mg, 0.31 mmol) in DMF (1.0 mL) were added imidazole (43 mg, 0.62 mmol) and *tert*-butyldimethylsilyl chloride (72.0 mg, 0.480 mmol) at 0 °C. The reaction mixture was stirred at 23 °C for 1.5 h, quenched by the addition of saturated aqueous NH_4Cl at 0 °C, extracted with EtOAc, washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel (hexane) to give **3c** (126 mg, 95%) as a colorless oil: IR (neat) 1426, 1211, 1146, 1111 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 0.01 (s, 6H), 0.88 (s, 9H), 1.10–1.50 (m, 2H), 1.90–2.30 (m, 2H), 2.50–2.70 (m, 2H), 3.36 (s, 2H), 5.10–5.50 (m, 3H), 5.85 (ddd, J = 10.5, 3.4, 3.4 Hz, 2H), 6.45 (br d, J = 5.0 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ −5.5, 18.3, 20.1, 25.9, 26.9, 35.7, 42.2, 71.1, 118.6 (q, J = 321 Hz), 121.7, 126.0, 129.6, 134.8; MS *m/z* 411 ($M^+ - Me$), 369 ($M^+ - t$-Bu), 295, 207, 145, 131, 89 (base peak); HR-MS calcd for $C_{14}H_{20}F_3O_4SSi$ 369.0803, found 369.0810.

4-[1-(Acetoxymethyl)-2,5-cyclohexadien-1-yl]-1(*Z*)-butenyl Trifluoromethanesulfonate (3d). To a stirred solution of **3e** (147 mg, 0.470 mmol) in CH_2Cl_2 (2.0 mL) were added pyridine (0.19 mL, 2.40 mmol), Ac_2O (0.09 mL, 0.950 mmol), and DMAP (6.0 mg, 0.0500 mmol) at 0 °C. The reaction mixture was stirred at 23 °C for 23 h, diluted with H_2O, extracted with Et_2O, washed successively with 5% aqueous HCl, saturated aqueous $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated. The residue was purified by column chromatography on silica gel (10% ether in hexane) to give **3d** (159 mg, 96%) as a colorless oil: IR (neat) 1744, 1424, 1215, 1144 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 1.30–1.60 (m, 2H), 1.96–2.25 (m, 2H), 2.05 (s, 3H), 2.50–2.70 (m, 2H), 3.89 (s, 2H), 5.10–5.55 (m, 3H), 5.93 (ddd, J = 10.5, 3.4, 3.4 Hz, 2H), 6.48 (br d, J = 5.9 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 19.8, 20.8, 26.5, 35.8, 40.6, 71.0, 118.6 (q, J = 321 Hz), 121.0, 127.2, 128.2, 135.1, 171.0; MS *m/z* 295 ($M^+ - OAc$), 281, 145, 131, 91 (base peak); HR-MS calcd for $C_{12}H_{14}F_3O_3S$ 295.0616, found 295.0601.

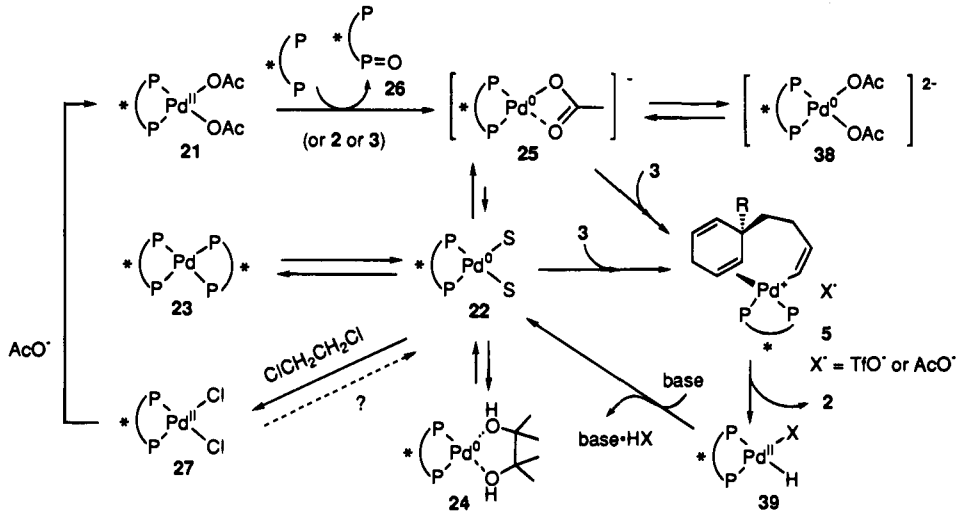
Methyl (4a*S*,8a*S*)-3,8a-Dihydro-4a(4*H*)-naphthalenecarboxylate (2a). To a mixture of $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), (*R*)-BINAP (12.4 mg, 0.02 mmol), K_2CO_3 (55.3 mg, 0.4 mmol), and potassium acetate (19.6 mg, 0.2 mmol) was added a solution of **3a** (68.1 mg, 0.2 mmol) in 1,2-dichloroethane (2.8 mL). The mixture was degassed and stirred at 60 °C under an argon atmosphere until the reaction was complete (41 h). It was then diluted with Et_2O, washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel (10% ether in hexane) to give **2a** (26.6 mg, 70%, 86% ee) as a colorless oil: $[\alpha]^{20}_D$ +459.2° (*c* 0.84, $CHCl_3$) (86% ee); IR (neat) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.85–1.90 (m, 2H), 1.93–2.10 (m, 2H), 3.61 (m, 1H), 3.72 (s, 3H), 5.56 (br d, J = 9.5Hz, 1H), 5.60–5.75 (m, 3H), 5.79 (dddd, J = 9.5, 5.1, 2.2, 0.7 Hz, 1H), 5.94 (ddd, J = 9.5, 5.1, 0.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.7, 27.4, 36.1, 46.0, 52.3, 120.6, 124.0, 125.7, 126.7, 128.9, 129.7, 176.1; MS *m/z* 190 (M^+), 131 (base peak), 115, 105, 91; HR-MS calcd for $C_{12}H_{14}O_2$ 190.0994, found 190.0994.

(4a*S*,8a*S*)-(3,8a-Dihydro-4a(4*H*)-naphthalenyl)methyl 2,2-Dimethylpropionate (2b). To a mixture of $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), (*R*)-BINAP (6.2 mg, 0.01 mmol), K_2CO_3 (27.6 mg, 0.2 mmol), and pinacol (2,3-dimethylbutane-2,3-diol) (177 mg, 1.5 mmol) was

Scheme 13



Scheme 14



added a solution of **3a** (39.6 mg, 0.1 mmol) in 1,2-dichloroethane (1.4 mL). The mixture was degassed and stirred at 60 °C under an argon atmosphere until the reaction was complete (47 h). It was then diluted with Et_2O, washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel (10% ether in hexane) to give **2b** (19.2 mg, 78%, 95% ee) as a colorless oil: $[\alpha]^{26}_D$ +398.2° (*c* 0.70, $CHCl_3$) (95% ee); IR (neat) 1731 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (s, 9H), 1.50−1.80 (m, 2H), 1.85−2.20 (m, 2H), 2.80 (br s, 1H), 3.95 (s, 2H), 5.26 (d, *J* = 10.0 Hz, 1H), 5.40−6.01 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 21.9, 27.1, 27.2, 36.2, 37.2, 39.0, 68.2, 121.4, 124.7, 126.2, 126.6, 128.3, 131.7, 178.5; MS *m/z* 246 (M^+), 230, 160, 144, 129, 115, 91, 85, 57 (base peak); HR-MS calcd for $C_{16}H_{22}O_2$ 246.1620, found 246.1645.

(4a*S*,8a*S*)-*tert*-Butyl[(3,8a-dihydro-4a(4*H*)-naphthalenyl)methoxy]-dimethylsilane (2c): $[\alpha]^{20}_D$ +278.3°(*c* 0.88, $CHCl_3$) (92% ee); IR (neat) 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.01 (s, 6H), 0.87 (s, 9H), 1.59 (dt, *J* = 12.8, 5.1 Hz, 1H), 1.77 (ddd, *J* = 13.2, 9.2, 5.5 Hz, 1H), 1.96 (m, 1H), 2.09 (m, 1H), 2.88 (m, 1H), 3.34 (d, *J* = 9.5 Hz, 1H), 3.50 (d, *J* = 9.5 Hz, 1H), 5.37 (d, *J* = 9.5 Hz, 1H), 5.45 (ddd, *J* = 9.9, 4.8, 2.2 Hz, 1H), 5.59 (dd, *J* = 9.2, 5.1 Hz, 1H), 5.69−5.78 (m, 2H), 5.88 (dd, *J* = 9.9, 5.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −5.4, 18.3, 22.2, 25.9, 27.0, 35.5, 38.9, 67.0, 121.3, 124.0, 126.1, 127.4, 128.5, 133.7; MS *m/z* 276 (M^+), 219 (M^+ − *t*-Bu), 144, 131, 115, 89; HR-MS calcd for $C_{17}H_{28}OSi$ 276.1910, found 276.1901.

(4a*S*,8a*S*)-3,8a-Dihydro-4a(4*H*)-naphthalenyl acetate (2d): $[\alpha]^{20}_D$ +396.1° (*c* 1.16, $CHCl_3$) (89% ee); IR (neat) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.62 (ddd, *J* = 13.2, 8.8, 5.9 Hz, 1H), 1.72 (dt, *J* = 13.2, 5.3 Hz, 1H), 1.90−2.20 (m, 2H), 2.07 (s, 3H), 2.80−2.90 (m, 2H), 3.98 (s, 2H), 5.35 (d, *J* = 9.5 Hz, 1H), 5.47 (ddd, *J* = 9.9, 5.5, 2.0 Hz, 1H), 5.63 (dd, *J* = 9.5, 5.1 Hz, 1H), 5.72−5.83 (m, 2H), 5.94 (ddd, *J* = 9.5, 5.1, 0.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.0, 21.9, 27.1, 36.1, 37.0, 68.4, 121.4, 124.9, 126.1, 126.5, 128.3, 131.7, 171.3; MS *m/z* 204 (M^+), 144, 131 (base peak), 116, 91; HR-MS calcd for $C_{13}H_{16}O_2$ 204.1150, found 204.1167.

(4a*S*,8a*S*)-3,8a-Dihydro-4a(4*H*)-naphthalenemethanol (2e). To a solution of the ester **2b** (12.0 mg, 0.0489 mmol) in THF (1.0 mL) was added $LiAlH_4$ (19.0 mg, 0.502 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 20 min, quenched by the addition of $Na_2SO_4{\cdot}10H_2O$, and stirred at 23 °C for 4 h. It was then filtered through Celite and concentrated. The residue was purified by column chromatography on silica gel (33% ether in hexane) to give **2e** (5.0 mg, 63%) as a pale yellow oil. The absolute configuration of **2e** was unequivocally determined by HPLC analysis (DAICEL CHIRALCEL OJ, 10% 2-propanol in hexane).[3] Compounds **2a**, **2c**, and **2d** were converted to **2e** according to the same procedure as reported in ref 4l: $[\alpha]^{26}_D$ +517.2° (*c* 1.17, $CHCl_3$) (86% ee); IR (neat) 3330 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.51−1.65 (m, 2H), 1.70 (dt, *J* = 12.8, 5.1 Hz, 1H), 1.90−2.20 (m, 2 H), 2.87−2.93(m, 1 H), 3.47 (d, *J* = 10.6 Hz, 1H), 3.53 (d, *J* = 10.6 Hz, 2H), 5.35 (d, *J* = 9.5 Hz, 1H), 5.47 (ddd, *J* = 9.5, 5.1, 2.9 Hz, 1H), 5.65 (dd, *J* = 9.5, 5.1 Hz, 1H), 5.72−5.82 (m, 2H), 5.99 (ddd, *J* = 9.5, 5.1, 1.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.9, 27.2, 36.2, 38.8, 68.9, 121.2, 125.2, 126.1, 127.0, 128.9, 132.3; MS *m/z* 162 (M^+), 144 ($M^+ - H_2O$), 131 (base peak), 116, 91; HR-MS calcd for $C_{11}H_{14}O$ 162.1045, found 162.1060.

Methyl (4a*S*,8a*R*)-1,5,6,8a-Tetrahydro-2-oxo-4a(2*H*)-naphthalenecarboxylate (16). To a stirred solution of **2a** (86% ee) (19 mg, 0.1 mmol) in DMF (0.5 mL), DMSO (0.5 mL), and H_2O (20 μL) was added *N*-bromosuccinimide (18.7 mg, 0.105 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h, diluted with brine, and extracted with EtOAc. The organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel with 17% EtOAc in hexane to give the bromohydrin as a colorless oil (22.0 mg): IR (neat) 3422, 1728 cm^{-1}; MS *m/z* 288 (M^+), 286 (M^+), 256 (M^+ − MeOH), 254 (M^+ − MeOH), 147, 129, 91, 77; HR-MS calcd for $C_{12}H_{15}{}^{79}BrO_3$ 286.0204, found 286.0171; calcd for $C_{12}H_{15}{}^{81}BrO_3$ 288.0184, found 288.0174.

To a stirred solution of the above oil (22.0 mg) in benzene (1.0 mL) were added tri-*n*-butyltin hydride (19 μL, 0.069 mmol) and AIBN (1.5 mg, 0.009 mmol) at 23 °C. The reaction mixture was refluxed with stirring for 1 h, cooled, and concentrated. The residue was diluted with dichloromethane (4.0 mL) and H_2O (2.0 mL). To the resulting suspension was added potassium hydrogen fluoride (10.0 mg) at 23 °C, and the mixture was stirred at this temperature for 1 h. It was then filtered, and the filtrate was washed with H_2O, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel with 25% EtOAc in hexane to give the allyl alcohol as a colorless oil (8.2 mg): IR (neat) 3396, 1732 cm^{-1}; MS *m/z* 208 (M^+), 176, 149, 148, 91; HR-MS calcd for $C_{12}H_{16}O_3$ 208.1099, found 208.1106.

To a suspension of the oil (8.2 mg) consisting of sodium acetate (1.3 mg, 0.016 mmol) and molecular sieves, 4A, in dichloromethane (1.0 mL) was added pyridinium chlorochromate (12.7 mg, 0.059 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, diluted with

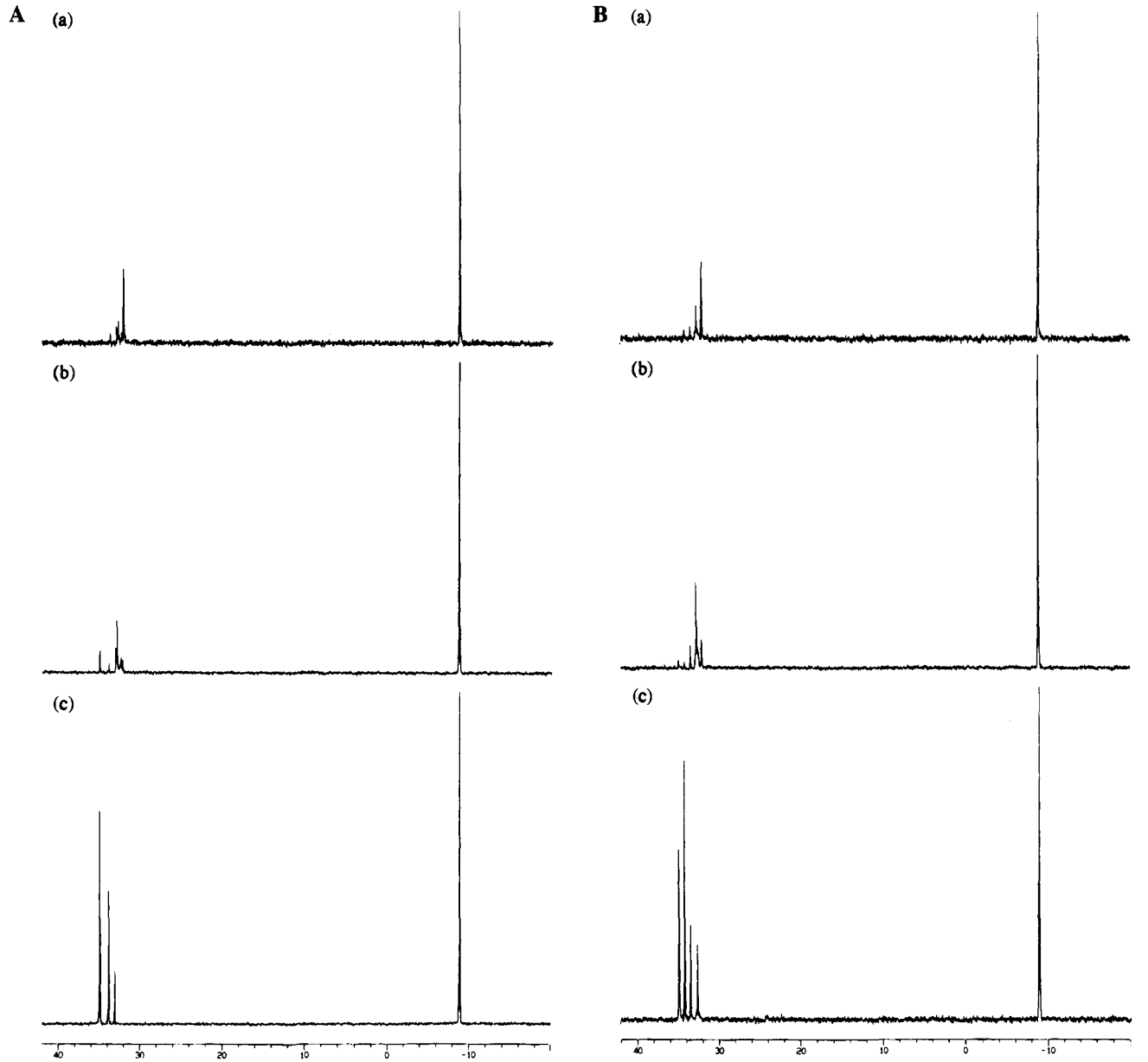


Figure 4. (A) $^{31}P\{^1H\}$-NMR spectra of the reaction of $Pd(OAc)_2$ with BINAP and Et_3N in $ClCH_2CH_2Cl$ at 40 °C after (a) 1 h, (b) 4 h, (c) 9 days; accumulation times: (a) 15 min and (b and c) 50 min. (B) $^{31}P\{^1H\}$-NMR spectra of the reaction of $Pd(OAc)_2$ with BINAP, Et_3N, and pinacol in $ClCH_2CH_2Cl$ at 40 °C after (a) 1 h, (b) 4 h, (c) 9 days; accumulation times: (a) 15 min and (b and c) 50 min.

Et_2O, and filtered through Florisil. The filtrate was concentrated, and the residue was purified by column chromatography on silica gel with 17% EtOAc in hexane to give **16** (5.3 mg, 30%, three steps) and **15** (5.1 mg, 30%) as colorless oils. The spectral data of **16** were as follows: $[\alpha]^{26}_D$ +56.3° (*c* 0.63, $CHCl_3$) (86% ee); IR (neat) 1730, 1686 cm^{-1}; ^1H NMR δ 1.91−2.20 (m, 4H), 2.31 (dd, J = 16.5, 5.8 Hz, 1H), 2.75 (dd, J = 16.5, 5.5 Hz, 1H), 3.28−3.38 (m, 1H), 3.76 (s, 3H), 5.45−5.55 (m, 1H), 5.67−5.76 (m, 1H), 6.01 (d, J = 10.2 Hz, 1H), 6.71 (dd, J = 10.2 Hz, 1.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 22.0, 30.2, 36.3, 41.3, 47.3, 52.7, 126.7, 128.4, 130.1, 148.4, 173.8, 198.0; MS *m/z* 206 (M^+), 147 (base peak), 146, 117, 91, 28; HR-MS calcd for $C_{12}H_{14}O_3$ 206.0943, found 206.0949.

Methyl (3′*R*,4′a*S*,8′a*R*)-8′,8′a-Dihydro-3′-hydroxyspiro[1,3-dioxolane-2,7′(3′*H*)-naphthalene]-4′a(4*H*)-carboxylate (17). A mixture of benzene (1.0 mL) and ethylene glycol (6 μL, 0.11 mmol) was refluxed with stirring and the moisture removed using a water collector. To this mixture were added *p*-toluenesulfonic acid (0.5 mg, 0.003 mmol) and a solution of **16** (2.3 mg, 0.011 mmol) in benzene (1.0 mL). The mixture was refluxed with stirring for 2 h, neutralized with saturated aqueous $NaHCO_3$ solution at 0 °C, and extracted with EtOAc. The organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel (20% EtOAc in hexane) to give the ketal (2.3 mg, 82%) as a colorless oil: $[\alpha]^{24}_D$ −4.4 ° (*c* 0.98, $CHCl_3$) (86% ee); IR (neat) 1732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.53−1.65 (m, 2H), 1.86−2.13 (m, 4H), 3.03−3.18 (m, 1H), 3.68 (s, 3H), 3.83−4.13 (m, 4H), 5.53−5.70 (m, 3H), 5.82 (d, J = 9.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 22.9, 27.9, 33.6, 37.1, 47.1, 52.3, 64.5, 64.8, 104.8, 125.6, 128.5, 129.8, 134.4, 174.8; MS *m/z* 250 (M^+), 191 (base peak), 147, 112; HR-MS (M^+) calcd for $C_{14}H_{18}O_4$ 250.1205, found 250.1197.

To a suspension of CrO_3 (1.39 g, 13.9 mmol) in CH_2Cl_2 (9.0 mL) was added 3,5-dimethylpyrazole (1.33 g, 13.9 mmol) in one portion at −20 °C. After stirring at −20 °C for 30 min, a solution of the ketal (244 mg, 0.924 mmol) in CH_2Cl_2 (9.0 mL) was added, and the reaction mixture was stirred at 0 °C for 9 h. After the suspension was diluted with ether, Celite was added. The mixture was stirred at 23 °C for 1 h and filtered through Florisil. Remaining filtrate was concentrated, and the residue was puified by column chromatography on silica gel (50% ether in benzene) to give the enone (131 mg, 54%) as a pale yellow oil and unreacted starting material (52.0 mg, 21%): $[\alpha]^{24}_D$ +29.5° (*c* 1.65, $CHCl_3$) (86% ee); IR (neat) 1733, 1684 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.85 (dd, J = 13.5, 11.6 Hz, 1H), 2.08 (dd, J = 13.5, 3.6 Hz, 1H), 2.49 (d, J = 16.5 Hz, 1H), 2.88 (d, J = 16.5 Hz, 1H), 3.41−3.50 (m, 1H), 3.69 (s, 3H), 3.86−4.10 (m, 4H), 5.74 (s, 2H), 6.01 (br d, J = 10.2 Hz, 1H), 6.84 (dd, J = 10.2, 4.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 36.1, 36.8, 43.4, 49.9, 54.1, 65.9, 66.2, 105.4, 129.7, 130.4, 132.8,

151.7, 174.7, 196.7; MS *m/z* 264 (M^+), 205, 183, 112 (base peak); HR-MS (M^+) calcd for $C_{14}H_{16}O_5$ 264.0998, found 264.1006.

To a solution of the enone (32.0 mg, 0.121 mmol) in MeOH (2.0 mL) were added $CeCl_3 \cdot 7H_2O$ (180 mg, 0.484 mmol) and $NaBH_4$ (18.3 mg, 0.484 mmol) at −78 °C, and the reaction mixture was stirred at −78 °C for 1 h. It was then quenched by the addition of acetone, diluted with H_2O, and extracted with ether. The organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel (33% ether in hexane) to give **17** (29.3 mg, 92%) as a pale yellow oil: $[\alpha]^{24}_D$ +24.0° (*c* 1.35, $CHCl_3$) (86% ee); IR (neat) 3416, 1734 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.53−1.83 (m, 3H), 1.95 (dd, J = 12.9, 3.6 Hz, 1H), 2.36 (dd, J = 12.9, 5.6 Hz, 1H), 3.10−3.20 (m, 1H), 3.68 (s, 3H), 3.83−4.06 (m, 4H), 4.20−4.30 (m, 1H), 5.67 (d, J = 10.2 Hz, 1H), 5.67−5.83 (m, 2H), 5.84 (d, J = 10.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 33.5, 36.3, 36.6, 47.7, 52.6, 64.6, 64.9, 65.3, 104.9, 128.7, 129.6, 131.6, 133.9, 174.2; MS *m/z* 266 (M^+), 248, 207, 112 (base peak); HR-MS (M^+) calcd for $C_{14}H_{18}O_5$ 266.1154, found 266.1160.

(3*S*,5a*R*,9a*S*)-5a,6-Dihydro-1*H*-3,9a-methano-2-benzoxepine-1,7-(3*H*)-dione (18). To a solution of **17** (22.5 mg, 0.0845 mmol) in THF (0.4 mL) was added HMPA (50 μL), PPh_3 (44.3 mg, 0.169 mmol) and acetic acid (10 μL, 0.169 mmol). Diethyl azodicarboxylate (DEAD) (27 μL, 0.169 mmol) was added dropwise with stirring to this mixture at 0 °C. The whole reaction mixture was then stirred at 0 °C for 30 min, diluted with 10% aqueous HCl, and extracted with ether. The organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel with 20% ether in hexane to give a mixture of the acetate and trace amounts of impurities. This mixture was used for the next step without further purification. It was thus dissolved in 0.4 mL of 15% H_2O in MeOH, and $LiOH \cdot H_2O$ (20.0 mg, 0.477 mmol) was added. The reaction mixture was stirred at 23 °C for 30 min, acidified with aqueous HCl, and extracted with EtOAc. The organic extracts were dried (Na_2SO_4) and concentrated. The residual oil was dissolved in 0.2 mL of Ac_2O, and NaOAc (6.0 mg, 0.0731 mmol) was added. The reaction mixture was gradually warmed to 30 °C with stirring and maintained at 30 °C for 1 h. The solution was cooled to 23 °C, NaOAc was filtered off, and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (33% ether in hexane) to give **18** (5.8 mg, 36%) as a colorless crystal. This compound showed spectral properties identical with those reported by Danishefsky *et al.*,[8a] $[\alpha]^{24}_D$ −34.6° (*c* 0.66, $CHCl_3$) (86% ee).

The synthesis of (+)-vernolepin (**9**), from Danishefsky's intermediate (**18**), was completed utilizing the synthetic routes described by Danishefsky *et al.*[8a] Spectral data of all the corresponding synthetic intermediates were comparable to those which they reported.

(4a*S*,6*S*,8a*R*)-1,5,6,8a-Tetrahydro-6-hydroxy-2-oxo-4a(2*H*)-naphthalenecarboxylic acid: $[\alpha]^{26}_D$ +68.6° (*c* 0.94, acetone) (86% ee).

(1a*R*,2*S*,4a*S*,8a*S*,8b*R*)-1a,8,8a,8b-Tetrahydro-4*H*-2,4a-methanooxireno[*d*][2]benzoxepine-4,7(2*H*)-dione: $[\alpha]^{26}_D$ −11.4° (*c* 0.16, acetone) (86% ee).

(1a*R*,2*S*,4a*R*,8a*S*,8b*R*)-1a,8,8a,8b-Tetrahydro-4*H*-5(*S),6(*S**)-dihydroxy-2,4a-methanooxireno[*d*][2]benzoxepine-4,7(2*H*)-dione:** $[\alpha]^{26}_D$ −24.0° (*c* 0.11, acetone) (86% ee).

(1a*R*,2*S*,4a*R*,8a*S*,8b*R*)-Tetrahydro-5*H*-2,4a-methano-4*H*-oxireno-[*c*]pyrano[4,3-*e*]oxepine-4,7(2*H*)-dione (19): $[\alpha]^{24}_D$ −47.5° (*c* 0.54, acetone) (86% ee).

(1′a*R*,2′*S*,3′a*R*,7′a*S*,7′b*R*)-Hexahydro-2′-hydroxyspiro[1,3-dioxolane-2,6′-(6*H*)oxireno[*f*][2]benzopyran]-3′a(4′*H*)-carboxaldehyde: $[\alpha]^{24}_D$ −11.1° (*c* 0.54, acetone) (86% ee).

(1′a*R*,2′*S*,3′a*R*,7′a*S*,7′b*R*)-3′a-Ethenyloctahydrospiro[1,3-dioxolane-2,6′-(6*H*)oxireno[*f*][2]benzopyran]-2′-ol (20): $[\alpha]^{24}_D$ −13.4° (*c* 0.70, $CHCl_3$) (86% ee).

(4a*S*,5*R*,6*R*,7*S*,8a*R*)-8a-Ethenyloctahydro-5,7-dihydroxy-3-oxo-1*H*-2-benzopyran-6-acetic acid methyl ester: $[\alpha]^{24}_D$ +24.5° (*c* 0.67, $CHCl_3$) (86% ee).

Bisnorvernolepin: $[\alpha]^{24}_D$ +110.6° (*c* 0.42, acetone) (86% ee).

Vernolepin: $[\alpha]^{23}_D$ +56.2° (*c* 0.65, acetone) (86% ee) [lit.[7a] $[\alpha]^{28}_D$ +72° (*c* 1.04, acetone)].

NMR Experiments. To a NMR tube containing Pd[(*R*)-binap]$_2$ (10.7 mg, 0.0075 mmol) and potassium acetate (14.7 mg, 0.15 mmol) dried under vacuum were added 1,2-dichloroethane (distilled from CaH_2 before use) (0.5 mL) and 1,2-dichloroethane-d_4 (0.15 mL) (for locking) at 23 °C under argon. The tube was then warmed to 40 °C in NMR probe, and the $^{31}P\{^1H\}$-NMR spectra were measured at same temperature.

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