July 1997 Notes Chem. Pharm. Bull. 45(7) 1209—1211 (1997) 1209

Chiral Palladium Complex-Catalyzed Synthesis of Optically Active Vinylchroman[1)]

Eisaku MIZUGUCHI and Kazuo ACHIWA*

School of Pharmaceutical Sciences, University of Shizuoka, Yada 52–1, Shizuoka 422, Japan.

Received February 17, 1997: accepted March 21, 1997

Optically active vinylchroman (1) was synthesized from a corresponding allyl carbonate (2) by catalytic and asymmetric allylic substitution with palladium complexes of chiral bisphosphine ligands. The reactivity and selectivity of the various chiral bisphosphine–palladium complexes were investigated.

Key words vitamin E analog drug; vinylchroman; palladium-catalyzed allylic substitution; P/M-chirality control

Recently, chroman derivatives have been attracting attention because of their anti-oxidant action and other biologically activities.[2)] We reported the synthesis of optically active chroman derivatives by using mainly enzymatic methods.[3)] Now we wish to describe a synthesis of optically active vinylchroman, which is a useful chiral intermediate to tocopherol (vitamin E) analog drugs, by catalytic and asymmetric allylic substitution of the prochiral allyl carbonate (**2**) with palladium complexes of chiral bisphosphine ligands.[4)] The allyl carbonate (**2**) was prepared as follows as a substrate for catalytic asymmetric allylation (Chart 1).

Trimethylhydroquinone (**3**) was converted to the hemiacetal (**5**) by Saucy's method.[5)] Compound **5** was then acetylated to afford the methyl ketone (**6**). Horner Emmons reaction of **6** with trimethyl phosphonoacetate gave the (*E*)-α,β-unsaturated ester (**7**) selectively, and reduction with diisobutylaluminum hydride (DIBAL-H) then afforded the (*E*)-allyl alcohol. Finally, esterification to the desired carbonate (**2**) was carried out by treatment with chloroformate.

The asymmetric allylic substitution reaction of allyl carbonate (**2**) with palladium complexes of various chiral bisphosphine ligands was carried out at 40 °C in tetrahydrofuran (THF). Representative results are shown in Table 1. In the reaction, a solution of $Pd(OAc)_2$ (0.85 mg, 3 mol%) in THF was added to the chiral bisphosphine ligands (6 mol%). The mixture was stirred at room temperature for one hour and then added to a solution of allyl carbonate (**2**) (50 mg, 0.13 mmol) in THF under an argon atmosphere. The mixture was stirred at 40 °C for 3—40 h and then the solvent was removed *in vacuo*. The residue was purified by silica gel chromatography to give the chiral vinylchroman (**1**).

The absolute configuration of the product (**1**) was determined after conversion to the aldehyde (**9**) by comparison with the reported sign of specific rotation[5)] (Chart 2), and the enantiomeric excess (%ee) was measured by HPLC analysis with a chiral column (Daicel Chiralcel OJ, hexane : isopropanol = 10 : 1).

From the data shown in the Table 1, the difference of reactivity with the ligands could be understood as an electronic effect of the groups on the phosphorus atoms.[6)] In the case of electron-donating groups, the oxidative addition of allyl carbonate (**2**) was accelerated, whereas electron-deficient groups accelerated the intramolecular nucleophilic addition to the π-allyl intermediate. These reaction steps are illustrated in Chart 3.

In the case of (*R*)-BIFUP possessing strongly electron-withdrawing groups (entry 1), the product yield was poor. Difficulty of oxidative addition of BIFUP–Pd complex to the substrate is the reason why this complex had low catalytic reactivity. The reaction with (*S*)-BINAP (entry 2) was optimal in all the ligands examined, because its reaction rates of the oxidative addition of substrate and subsequent nucleophilic addition of the π-allyl intermediate were balanced by the electronic effect of the non-substituted tri-aryl groups on the phosphorus atoms.

We have already proposed the P/M-chirality concept in asymmetric hydrogenation with bisphosphine rhodium catalysts.[7)] The results of Table 1 imply that the absolute configuration of the vinylchroman (**1**) depended on the P/M-chirality of ligands. The ligands of P-chirality gave the (*R*)-product and those of M-chirality gave the (*S*)-product, except for (*R*)(*S*)-BPPFA (entry 3), which has a neighboring group. This phenomenon could be ex-

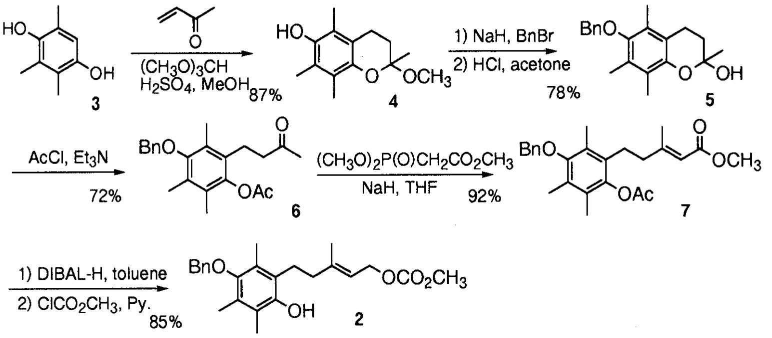
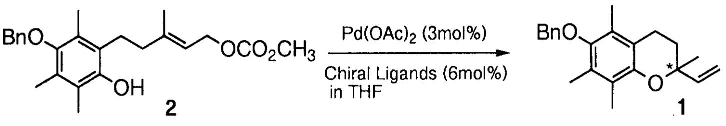


Chart 1

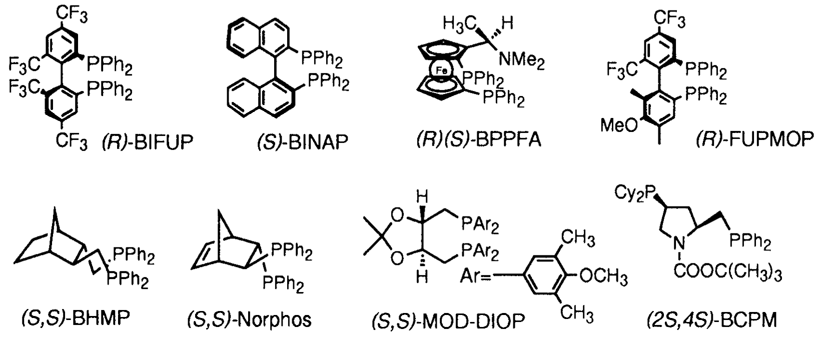
---

* To whom correspondence should be addressed.

Table 1. Chiral Palladium-Catalyzed Allylic Substitution Reaction



Entry	Ligand	P/M-Chirality	Temp. (°C)	Time (h)	Yield (%)	%ee (Confign.)
1	(*R*)-BIFUP	P	40	20	30	26.8 (*R*)
2	(*S*)-BINAP	M	40	3	89	40.8 (*S*)
3	(*R*,*S*)-BPPFA	P	40	20	55	54.4 (*S*)
4	(*R*)-FUPMOP	P	40	20	40	7.1 (*R*)
5	(*S*,*S*)-BHMP	P	40	20	57	19.0 (*R*)
6	(*S*,*S*)-Norphos	M	40	40	30	16.7 (*S*)
7	(*S*,*S*)-MOD-DIOP	P	40	40	27	5.9 (*R*)
8	(*S*,*S*)-BCPM	M (P)9)	40	40	15	9.5 (*R*)



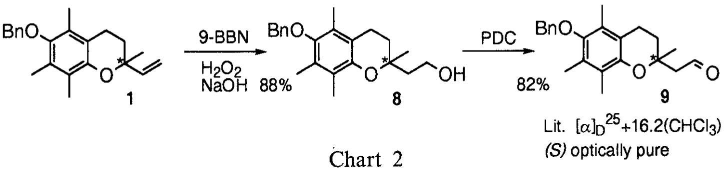


Chart 2

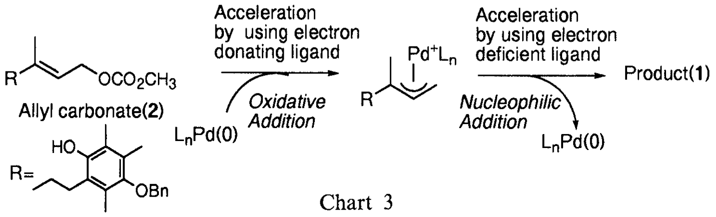


Chart 3

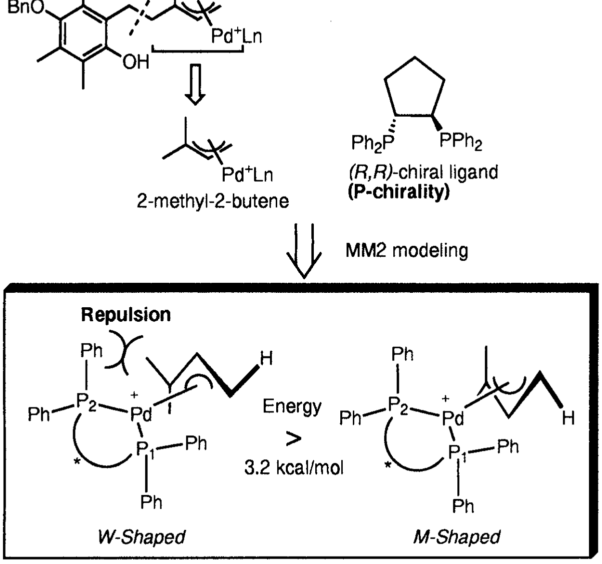


Fig. 1

plained by presuming that the (*R*)(*S*)-BPPFA formed an unsymmetrically crowded complex with transition metals owing to neighboring participation of its aminoethyl group. It is known that the reaction proceeds *via* π-allyl palladium complexes (W-shape or M-shape, which are in rapid equilibrium). We considered that the absolute configuration of the product was determined by the P/M-chirality of ligands, based on MM2 calculation (by the CAChe system) of the stability of both π-allyl intermediates using simplified analog models (Fig. 1). These calculation results showed that the W-shaped intermediate was more unstable relatively about 3.2 kcal/mol than the M-shaped intermediate owing to steric repulsion between the methyl group of the substrate and pseudo-axial phenyl group of the ligand. Therefore, the W-shaped intermediate was much more reactive and gave the (*R*)-product rapidly (Fig. 2). It was also proposed by Reiser and by Pfaltz8) that the unstable intermrdiate was more reactive than

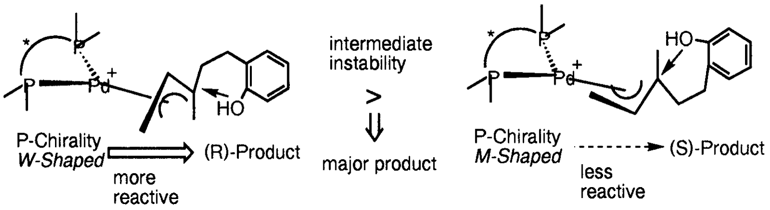


Fig. 2

the stable one in palladium-catalyzed allylic substitution reaction.

Experimental

All melting points are uncorrected. Specific rotations were measured with a JASCO DIP-140 digital polarimeter. IR spectra were recorded on a JASCO A-202 infrared spectrophotometer. ^{1}H-NMR spectra were taken on a JEOL JNM-GX 270 (270 MHz) spectrometer. The chemical shifts (δ) are given in ppm relative to Me_4Si ($\delta=0$) in $CDCl_3$ as an internal standard. The abbreviations of signal patterns are as follows: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Mass spectra (MS) were recorded on a JEOL JMS-SX102 spectrometer. Column chromatography was carried out on Silica gel 60 (70—230 mesh, Merck). Thin-layer chromatography (TLC) on Silica gel 60-F254 (Merck) was used to monitor the reaction and ascertain the purity of the reaction products.

4-(2-Acetoxy-5-benzyloxy-3,4,6-trimethylphenyl)-2-butanone (6) A solution of acetyl chloride (650 mg, 8.3 mmol) in THF (2 ml) was added to a solution of **5** (856 mg, 2.7 mmol) and triethylamine (1.3 g, 12.9 mmol) in THF (15 ml) at 0 °C. The mixture was stirred for 2 h at room temperature, then diluted with H_2O (20 ml) and extracted with AcOEt. The organic layer was dried and concentrated under reduced pressure. The residue was chromatographed on silica gel with hexane–AcOEt (3 : 1) to give **6** (698 mg, 72%), as pale yellow crystals, mp 95—96 °C. IR (KBr): 1740 (C=O), 1700 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.59 (3H, s, CH_3), 2.02 (3H, s, ArC$\underline{H}_3$), 2.15 (3H, s, ArC$\underline{H}_3$), 2.24 (3H, s, Ac), 2.34 (3H, s, ArC$\underline{H}_3$), 2.48—2.92 (4H, m, 2 × CH_2), 4.73 (2H, s, PhC$\underline{H}_2$), 7.34—7.52 (5H, m, Ar). MS *m/z*: 354 (M^+). *Anal.* Calcd for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.17; H, 7.53.

Methyl 5-(2-Acetoxy-5-benzyloxy-3,4,6-trimethylphenyl)-3-methyl-2-pentenoate (7) A solution of trimethyl phosphonoacetate (605 mg, 3.3 mmol) in THF (30 ml) was treated with 60% NaH in oil (127 mg, 3.2 mmol) at 0 °C. The mixture was stirred for 1 h at room temperature, and then a solution of **6** (562 mg, 1.59 mmol) in THF (10 ml) was added under an argon atmosphere. The reaction mixture was stirred for 20 h at room temperature, then quenched with H_2O and extracted with AcOEt. The organic layer was dried and concentrated under reduced pressure. The residue was chromatographed on silica gel with hexane–AcOEt (3 : 1) to give **7** (597 mg, 92%) as a white powder. mp 116—118 °C. IR (KBr): 1743 (C=O), 1720 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.03 (3H, s, CH_3), 2.23 (3H, s, ArC$\underline{H}_3$), 2.24 (3H, s, Ac), 2.25 (3H, s, ArC$\underline{H}_3$), 2.36 (3H, s, ArC$\underline{H}_3$), 2.50—2.85 (4H, m, 2 × CH_2), 3.71 (3H, s, OCH_3), 4.73 (2H, s, PhC$\underline{H}_2$), 5.72 (1H, s, =CH–), 7.31—7.57 (5H, m, Ar). MS *m/z*: 410 (M^+). *Anal.* Calcd for $C_{25}H_{30}O_5$: C, 73.15; H, 7.37. Found: C, 72.92; H, 7.71.

5-(2-Hydroxy-5-benzyloxy-3,4,6-trimethylphenyl)-3-methyl-2-pentenyl Methyl Carbonate (2) A solution of **7** (500 mg, 1.2 mmol) in toluene (10 ml) was treated with 1.5 M DIBAH in toluene (3.3 ml, 5.0 mmol) at 0 °C. The mixture was stirred for 5 h at room temperature, then carefully treated with dilute HCl and the grainy precipitate was removed by filtration. The filtrate was washed with H_2O, dried, then concentrated under reduced pressure. The residue (378 mg) was dissolved in CH_2Cl_2 (7 ml) and pyridine (300 mg, 3.8 mmol), and the solution was cooled to 0 °C. Methyl chlorocarbonate (131 mg, 1.4 mmol) was added to it and the mixture was stirred for 2 h at room temperature, diluted with H_2O (10 ml) and extracted with AcOEt. The organic layer was dried and concentrated under reduced pressure. The residue was chromatographed on silica gel with hexane–AcOEt (3 : 1) to give **2** (412 mg, 85%) as pale yellow crystals, mp 87—89 °C. IR (KBr): 3490 (OH), 1730 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.81 (3H, s, CH_3), 2.16 (3H, s, $ArCH_3$), 2.23 (3H, s, $ArCH_3$), 2.24 (3H, s, $ArCH_3$), 2.09—2.30 (2H, m, CH_2), 2.75 (2H, t, J = 8 Hz, CH_2), 3.78 (3H, s, OCH_3), 4.64—4.69 (4H, m, PhC$\underline{H}_2$, OCH_2), 5.44 (1H, t, J = 8 Hz, vinyl), 7.31—7.50 (5H, m, Ar). *Anal.* Calcd for $C_{24}H_{30}O_5$: C, 72.34; H, 7.59. Found: C, 71.99; H, 7.91.

6-Benzyloxy-2,5,7,8-tetramethyl-2-vinyl Chroman (Vinylchroman, 1) [54.4%ee(*S*), obtained by reaction with (*R*)(*S*)-BPPFA] Pale brown oil, $[\alpha]_D^{26}$ −26.7° (c = 0.44 $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, s, CH_3), 1.75—2.10 (2H, m, CH_2), 2.15 (3H, s, $ArCH_3$), 2.16 (3H, s, $ArCH_3$), 2.23 (3H, s, $ArCH_3$), 2.40—2.65 (2H, m, CH_2), 4.69 (2H, PhC$\underline{H}_2$), 5.03 (1H, d, J = 11 Hz), 5.14 (1H, d, J = 17 Hz), 5.87 (1H, dd, J = 17, 11 Hz), 7.28—7.67 (5H, m, Ar). MS *m/z*: 322 (M^+).

6-Benzyloxy-2,5,7,8-tetramethylchroman-2-ethanal (9) A solution of **1** (obtained by reaction with (*R*)(*S*)-BPPFA, 190 mg, 0.59 mmol) in THF (5 ml) was added to a solution of 0.5 M 9BBN in THF (3.6 ml, 1.8 mmol) under an argon atmosphere at 0 °C. The mixture was stirred for 20 h at room temperature, then cooled to 0 °C. Then 6 M NaOH (2 ml), 30% H_2O_2 (3 ml) was added, and the whole was stirred for 30 min. It was diluted with H_2O (20 ml) and extracted with AcOEt. The organic layer was dried and concentrated under reduced pressure. The residue (177 mg) was dissolved in CH_2Cl_2 (10 ml) and the solution was oxidized with pyridinum dichromate (PDC) (354 mg, 0.94 mmol) for 40 h at room temperature. The reaction mixture was filtered and the filtrate was washed with H_2O, then the organic layer was dried and concentrated under reduced pressure. The residue was chromatographed on silica gel with hexane–AcOEt (3 : 1) to give **9** (143 mg, 72%, two steps) as a colorless oil, $[\alpha]_D^{26}$ +8.31 (c = 0.86, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.42 (3H, s, CH_3), 1.85—1.97 (2H, m, CH_2), 2.10 (3H, s, $ArCH_3$), 2.18 (3H, s, $ArCH_3$), 2.23 (3H, s, $ArCH_3$), 2.53—2.77 (4H, m, 2 × CH_2), 4.70 (2H, s, PhC$\underline{H}_2$), 7.33—7.53 (5H, m, Ar), 9.94 (1H, t, J = 3 Hz, CHO). MS *m/z*: 338 (M^+).

Acknowledgment This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture of Japan.

References and Notes

1) Asymmetric Reactions Catalyzed by Chiral Metal Complexes. LXXV.
2) Schultz M., Leist M., Petrzika M., Gassmann B., Brigelius R. F., *Am. J. Clin. Nutr.*, **62**, 1527S—1534S (1995); Wechter W. J., Kantoci D., Murray E. D., Jr., D'Amico D. C., Jung M. E., Wang W.-H., *Proc. Natl. Acad. Sci. U.S.A.*, **93**, 6002—6007 (1996).
3) Mizuguchi E., Takemoto M., Achiwa K., *Tetrahedron: Asymmetry*, **4**, 1961—1964 (1993); Mizuguchi E., Achiwa K., *Tetrahedron: Asymmetry*, **4**, 2303—2306 (1993); Mizuguchi E., Suzuki T., Achiwa K., *Synlett*, **11**, 929—930 (1994); Mizuguchi E., Suzuki T., Achiwa K., *Synlett*, **8**, 743—744 (1996).
4) For general reviews, Consiglio G., Waymouth R., *Chem. Rev.*, **89**, 257—276 (1989); Frost C. G., Howarth J., Williams J. M. J., *Tetrahedron: Asymmetry*, **3**, 1089—1092 (1992); Hayashi T., "Catalytic Asymmetric Synthesis," ed. by Ojima I., VCH, Weinheim, 1993.
5) Scott J. W., Bizzarro F. T., Parrish D. R., Saucy G., *Helv. Chim. Acta*, **59**, 290—306 (1976).
6) Recently, electronic effects on nickel-catalyzed asymmetric hydrocyanation have been reported. RajanBabu T. V., Casalnuovo A. L., *J. Am. Chem. Soc.*, **118**, 6325—6326 (1996).
7) Sakuraba S., Morimoto T., Achiwa K., *Tetrahedron: Asymmetry*, **2**, 597—600 (1991).
8) Reiser O., *Angew. Chem. Int. Ed. Engl.*, **32**, 547—549 (1993); Pfaltz A., *Acc. Chem. Res.*, **26**, 339—345 (1993).
9) The configuration of (*S*,*S*)-BCPM with two cyclohexyl rings could be considered as nearly fixed in P-chirality based on the X-ray structure analysis of (*S*,*S*)-BPPM.