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A Catalytic Asymmetric Synthesis of Cyclopentanoids *via* π-Allylpalladium Complexes

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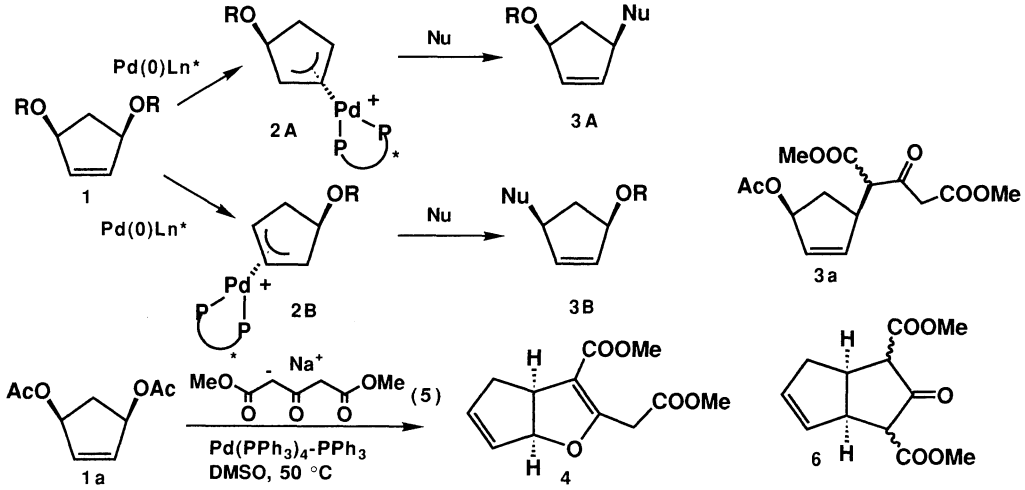
A catalytic asymmetric alkylation of cyclopentene diol derivatives was achieved by use of $Pd(OAc)_2$-(*S*)-BINAPO to give corresponding cyclopentanoids in up to 57% ee.

Homogeneous catalytic allylation with palladium complex is a facile transformation of wide applicability and in particular an asymmetric alkylation *via* π-allyl palladium complex is a fascinating process. Now we want to report a catalytic asymmetric synthesis[1] of cyclopentanoids from cyclopentene diol derivatives **1** by use of palladium(0)-chiral phosphine ligands. The catalytic process consists of two reaction steps.[1] The first step is oxidative addition of **1** to a palladium(0)-phosphine complex to produce π-allylpalladium complexes **2A** and **2B**. Then **2A** and **2B** should be attacked regioselectively by a nucleophile to produce **3A** and **3B** because of the steric demand of the nucleophile. The both steps proceed with inversion of configuration. Thus the overall process is net retention.



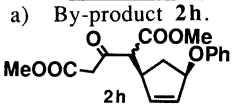
When allyl acetate **1a** was treated with dimethyl sodio-3-ketoglutarate (**5**) in the presence of $Pd(PPh_3)_4$ (6 mol%) and PPh_3 (20 mol%) in DMSO at 50 °C for 3 h, cyclized product **4** was obtained in 54% yield instead of **3a** or **6**, whose structure was confirmed by spectral data. Since **4** appeared to be a useful substrate for the synthesis of natural products, the reaction was further investigated by use of chiral

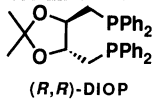
ligands such as (*R*,*R*)-DIOP, (*R*)-BINAP, (*S*,*R*)-BPPFA, (*S*,*S*)-BPPM, and (*S*)-BINAPO[2] and the results are shown in Table 1. The enantiomeric purity of the product was determined by HPLC with a chiral stationary phase column (CHIRAL CEL OJ, hexane/*i*-PrOH=9/1). From the data shown in Table 1, it is indicated that the bidentate ligands accelerate the reaction to give **4** in better yields. The enantioselectivity of the reaction using (*S*)-BINAPO as a chiral diphosphine was optimal in all the chiral ligands examined (Runs 1-5) and was roughly unaffected by highly coordinating solvents (Runs 5-8). Although allylic acetates are the most commonly used allylic substrates in Pd-catalyzed substitutions, the reaction of other allylic substrates with **5** was investigated as well. Though the enantioselectivity was

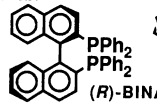
Table 1. An asymmetric synthesis of cyclopentene derivative **4**

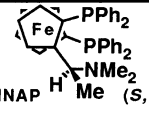
Run	Substrate	R	Ligand	Solvent	Temp/°C	Time/h	Yield/%	ee/%
1	1a	Ac	(*R*,*R*)-DIOP	DMSO	50	1.0	97	6
2	"	"	(*R*)-BINAP	DMSO	50	3.2	97	13
3	"	"	(*S*,*R*)-BPPFA	DMSO	rt	3.0	78	6
4	"	"	(*S*,*S*)-BPPM	DMSO	rt	3.7	84	0
5	"	"	(*S*)-BINAPO	DMSO	rt	0.5	94	21
6	"	"	"	DMF	rt	2.0	79	24
7	"	"	"	CH_3CN	50	0.8	85	27
8	"	"	"	THF	50	2.0	80	17
9	1b	COPh	"	CH_3CN	50	1.3	82	29
10	"	"	"	"	rt	1.3	80	35
11	"	"	"	"	0	72.3	73	40
12	1c	COC_6H_4-4-OMe	"	"	0	36.3	80	40
13	1d	COC_6H_4-4-F	"	"	0	107.5	74	42
14	1e	COC_6H_4-4-CF_3	"	"	0	70.5	65	48
15	1f	COOPh	"	"	0	70.3	53(7[a])	36
16	"	"	"	"	-20	63.8	57(8[a])	44
17	"	"	"	"	-40	148.0	72(13[a])	55[3]
18	1g	$P(O)(OEt)_2$	"	"	-40	62.5	64	35
19	"	"	"	CH_3CH_2CN	-70	81.0	46	46

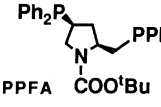
a) By-product **2h**.

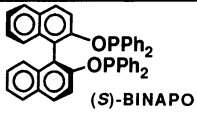












not improved by the reaction of allyl benzoate with **5** at 50 °C (Runs 7 and 9), it was found that the reaction of **1b** proceeded even at 0 °C to give **4** with higher ee. Allyl benzoate having electron withdrawing group on the aromatic ring improved the enantioselectivity (Runs 11-14). Encouraged by these results, next, phenyl carbonate **1f** and phosphate **1g** were prepared, because **1f** and **1g** were expected to react under milder reaction conditions due to the high reactivity of the leaving groups. As expected, enantioselectivity was improved (Runs 17 and 19) and **1f** gave the best result (72% yield, 55% ee).[3] The large influence of the nature of the leaving group[4] and the temperature dependency suggest that the oxidative addition step plays a key role in determining asymmetric induction. It was expected that the kinetic resolution would occur because the two diastereomeric π-allylpalladium complexes were formed two times at the each site. That is, if the reaction is quenched when monosubstituted compounds **3A** and **3B** remain in the reaction system, the enantiomeric excess of **4** would be lower and that of **3** would be higher. In fact, when the reaction of **1b** with **5** was carried out in the presence of $Pd(OAc)_2$-(*S*)-BINAPO at 0 °C and was quenched at 35 h, the enantiomeric excess of **4** was 30% (14% chemical yield) along with **3b**[5] (35% yield, 41% ee, Table 2). When the reaction was quenched after 72 h, the enantiomeric excess of **4** was 34% (54% chemical yield) along with **3b** (18% yield; 52% ee). The assignment of the absolute configuration of **3b** was achieved by an application of the CD exciton chirality method to allyl benzoate.[6] The absolute configuration of **4**, which was obtained directly from **1b** by treatment with **5** in the presence of $Pd(OAc)_2$ and (*S*)-BINAPO, was determined as comparison of the results of HPLC with chiral stationary phase

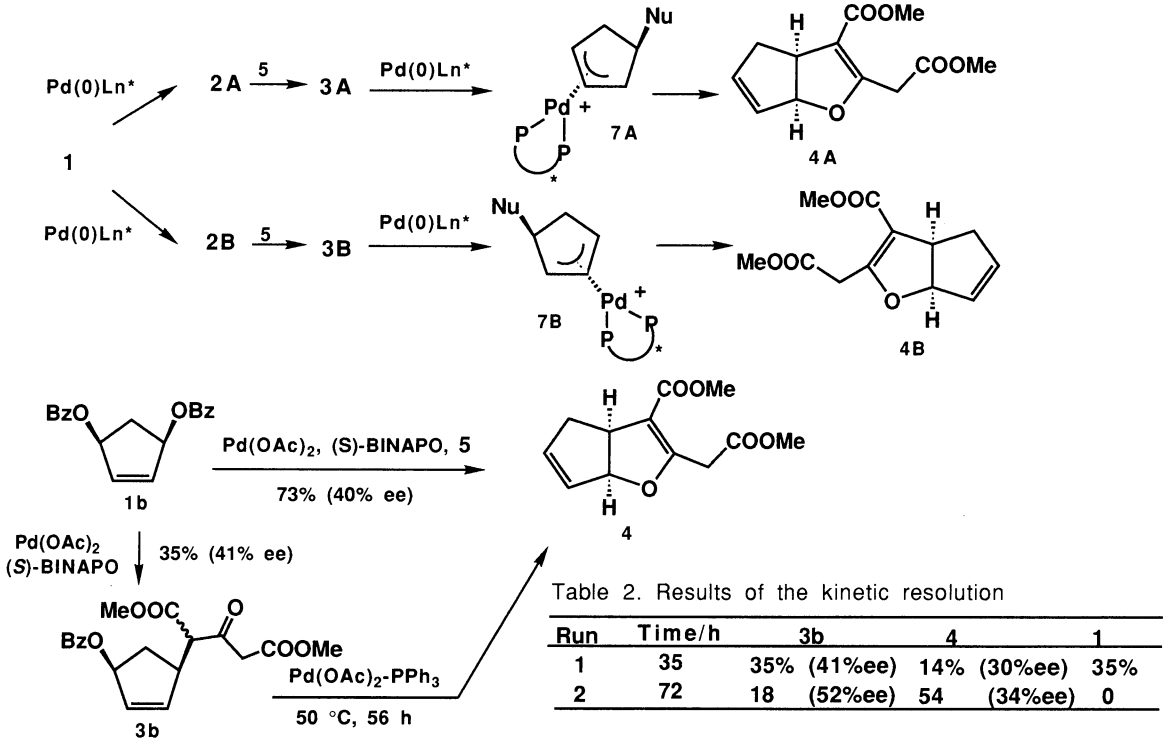
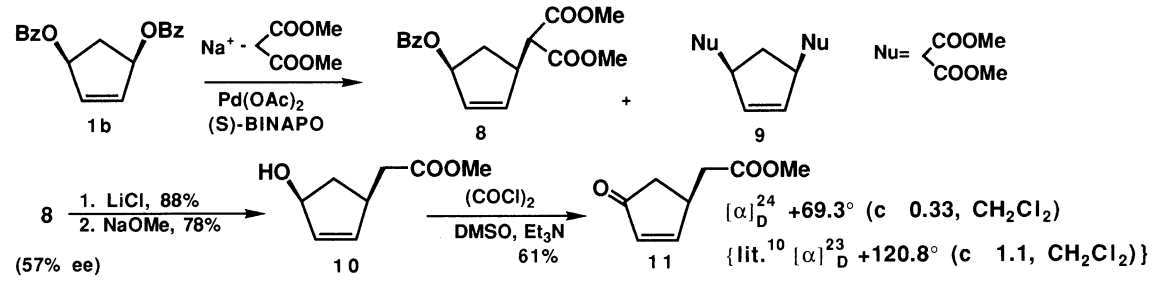


Table 2. Results of the kinetic resolution

Run	Time/h	3b	4	1
1	35	35% (41%ee)	14% (30%ee)	35%
2	72	18 (52%ee)	54 (34%ee)	0

column with that of **4**, which was prepared from **3b** by treatment with $Pd(OAc)_2$-PPh_3 in the presence of NaH in CH_3CN. Conversion of compound **4** to **6** by use of palladium catalyst is now under investigation.[7] Finally, an CH_3CN solution of **1b**, sodium dimethyl malonate as a nucleophile, $Pd(OAc)_2$ (3 mol%), and (*S*)-BINAPO (6 mol%) was stirred at 0 °C for 41 h to give monoalkylated compound **8** in 38% yield (57% ee)[8] along with disubstituted compound **9** (32% yield) and the starting material (14% yield). Compound **8** was easily converted to the intermediates **10** and **11** for the syntheses of methyl jasmonate[9] and brefeldin A.[10]



Although the enantioselectivity is modest, the results described in this paper pave the way for further improvements. Further studies are in progress.

References

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2) R. H. Grubbs and R. A. DeVries, *Tetrahedron Lett.*, **1977**, 1879; B. M. Trost and D. J. Murphy, *Organometallics*, **4**, 1143 (1985); B. M. Trost and D. L. Van Vranken, *J. Am. Chem. Soc.*, **112**, 1261(1990).

3) An CH_3CN solution of compound **2h**, $Pd(OAc)_2$, PPh_3, and NaH was refluxed for 2.4 h to give **4** in 93% yield, but the HPLC with a chiral column showed that the main product was antipode of **4** (64% ee). Presumably, the internal enolate can not attack π-allylpalladium complex **7B** with (*S*)-BINAPO because of its steric demand, and it was attacked by phenoxide ion to give **2h**.

4) J-C. Fiaud and J-Y Legros, *J. Org. Chem.*, **55**, 4840 (1990).

5) The enantiomeric purity of compound **3** was determined by conversion of **3** to **4** by treatment with $Pd(OAc)_2$-PPh_3 in the presence of NaH in CH_3CN.

6) The CD spectrum of allyl benzoate **3** at 230 nm showed negative cotton effect.

7) B. M. Trost, T. A. Runge, and L. N. Jungheim, *J. Am. Chem. Soc.*, **102**, 2840 (1980).

8) The enantiomeric purity of compound **8** was determined by the HPLC (CHIRAL CEL OJ, hexane/*i*-PrOH=9/1) and the absolute configuration of **8** was determined by the application of the CD exciton chirality method to allyl benzoate **8**.

9) F-P. Montforts, I. Gesing-Zibulak, and W. Grammenos, *Helv. Chim. Acta*, **72**, 1852 (1989).

10) E. J. Corey and P. Carpino, *Tetrahedron Lett.*, **31**, 7555 (1990).

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