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Palladium-Catalyzed Enantioselective Synthesis of Cyclohexene Derivatives *via* Kinetic Resolution

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Abstract: Reaction of (±)-methyl 2-arylcyclohexenyl carbonate with tosyl amide in the presence of a catalytic amount of $Pd_2dba{\cdot}CHCl_3$ and (*S*)-BINAPO produced 2-arylcyclohexenyl tosyl amide with a high ee along with the starting material with a high ee. The reaction involved two processes, and (+)- and (–)-methyl 2-arylcyclohexenyl carbonate gave the same (π-allyl)palladium complex with a chiral ligand, which gave 2-arylcyclohexenyl tosyl amide with a high ee by enantioselective substitution. The intermediary (π-allyl)palladium complex was synthesized, and the results of X-ray crystallography are shown.

Key Words: *Asymmetric Synthesis, (π-Allyl)palladium Complex, Kinetic Resolution, $Pd_2dba{\cdot}CHCl_3$, (S)-BINAPO*

Asymmetric synthesis *via* (π-allyl)palladium complex is a useful synthetic tool, and its mechanism has been ingeniously studied by Trost and others.[1] Many natural products have been synthesized *via* (π-allyl)palladium complex with a chiral ligand. During the course of our model study[2] on the total synthesis of (+)-crinamine, (–)-haemanthidine, and (+)-pretazettine, when (±)-**1a** was reacted with **3a** in the presence of $Pd_2dba{\cdot}CHCl_3$ and (*S*)-BINAPO, the desired product (*S*)-**2a** with 83% ee was obtained in 73% yield. We were very surprised to find that the recovered starting material (*R*)-**1a**[3] showed 60% ee in 12% yield. This means that kinetic resolution would occur upon the formation of (π-allyl)palladium complex. The fact that kinetic resolution occurred on palladium-catalyzed enantioselective allylic alkylation was found by Prof. Hayashi, and recently a few group reported in regard to this phenomenon.[4]

Scheme 1

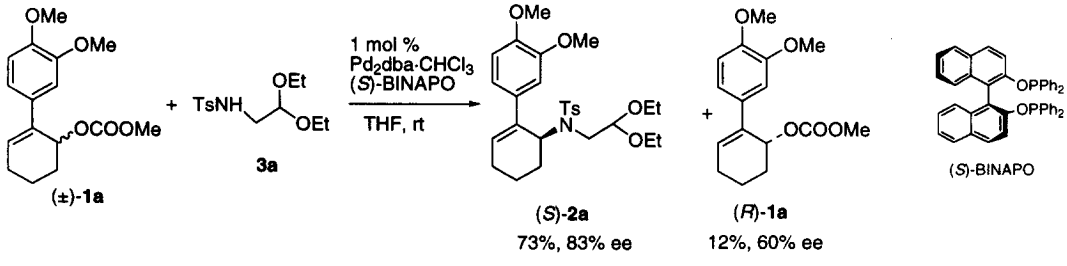

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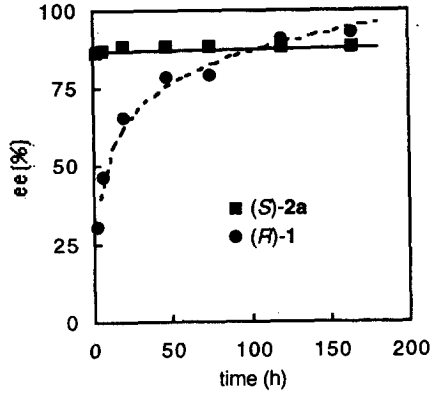
Table 1 Kinetic resolution of **1a**

run	time (h)	(*S*)-**2a** (% ee)	(*R*)-**1a** (% ee)
1	3	86	30
2	6	87	46
3	19	88	65
4	47	88	78
5	75	88	79
6	120	88	91
7	165	88	93

The reaction was carried out using 5 mol % of $Pd_2dba{\cdot}CHCl_3$ and 5 mol % of (*S*)-BINAPO in THF at 0 °C.

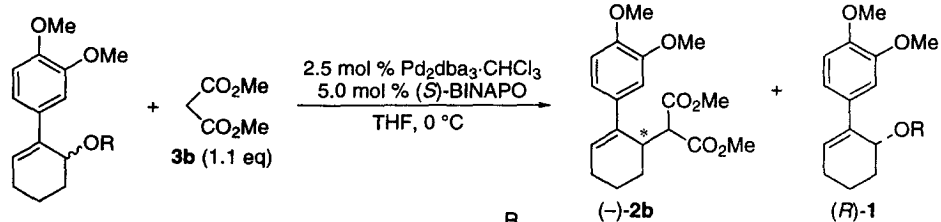
Figure 1 The ees of **2a** and **1a** on each time.



To confirm this, the same reaction was carried out at 0 °C and and the time courses of the ees of the product **2a** and the starting material **1a** were monitored by HPLC.[5] The results are shown in Table 1. Apparently, kinetic resolution was also shown in this reaction; that is, after 3 h, the ee of the product (*S*)-**2a** was 86%, while the ee of the recovered starting material (*R*)-**1a** was 30 % ee. Although the same ee of (*S*)-**2a** was obtained in each time, the ee of the recovered starting material (*R*)-**1a** gradually increased, and after 165 h, (*R*)-**1a** with 93% ee was obtained in 14% yield along with (*S*)-**2** with 88% ee in 60% yield. These results are shown in Figure 1.

On the other hand, when the reaction of (±)-**1a** with dimethyl malonate **3b** was carried out in the presence of a palladium catalyst and (*S*)-BINAPO, (–)-**2b** was obtained in 41% yield but the ee was only 30%. However, the recovered starting material showed 71% ee. When the same reaction was carried out using (±)-**1b** as the substrate in the presence of NaH, the ee of the recovered starting material was 96%, but the ee of **2b** was only 11%.

Scheme 2



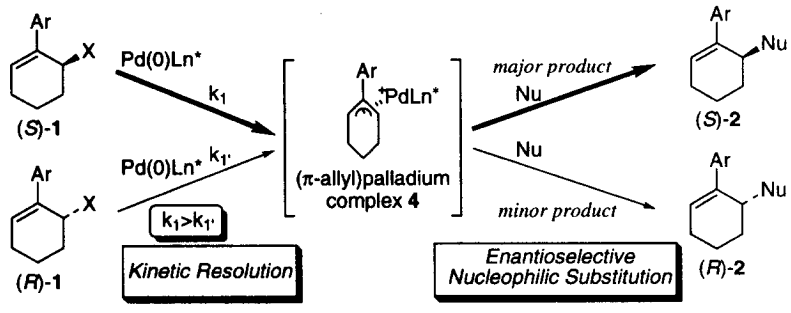
(±)-**1a** R = CO_2Me
(±)-**1b** R = Ac
(In the case of **1b**, NaH was used as a base.)

R	(–)-**2b**	(*R*)-**1**
CO_2Me	41%, 30% ee	28%, 71% ee
Ac	81%, 11% ee	14%, 96% ee

These results indicate that there are two independent pathways in the asymmetric synthesis of (*S*)-**2a**: that is, kinetic resolution and asymmetric substitution. If the reaction rate of (*S*)-**1** with Pd(0) having (*S*)-BINAPO is faster than that of (*R*)-**1** with Pd(0) having (*S*)-BINAPO, kinetic resolution would occur and (*R*)-

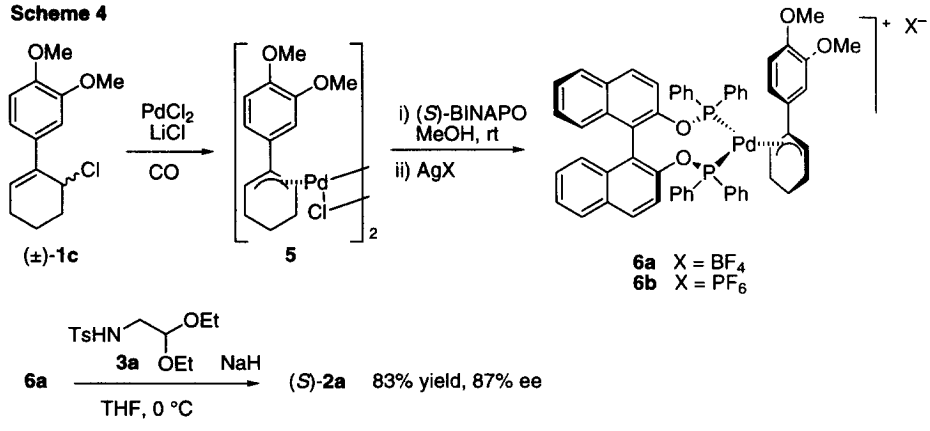
1 would remain unchanged. In this process, (*R*)-**1** also can react with Pd(0) having (*S*)-BINAPO to produce the same π-allylpalladium complex. The intermediary (π-allyl)palladium complex **4** reacts with nucleophile enantioselectively to give (*S*)-**2**. Thus, both (*S*)- and (*R*)-**1** can be converted into (*S*)-**2**. If the starting material is recovered, (*R*)-**1** with a high ee can be obtained.

Scheme 3



The structure of the intermediary chiral (π-allyl)palladium complex **4** was examined. Reaction of (±)-**1c** with $PdCl_2$ gave η^2-palladium complex **5**, which was reacted with (*S*)-BINAPO followed by treatment with silver salt to give (π-allyl)palladium complex **6** as colorless needles. Reaction of a stoichiometric amount of **6a** with **3a** in the presence of NaH in THF at 0 °C gave (*S*)-**2a** with 87% ee in 83% yield, the same as that obtained by a catalytic reaction. This indicates that **6** is an intermediate for this asymmetric reaction.

Scheme 4



The results of X-ray crystallography of **6b** are shown in Figure 1.[6] Interestingly, the cyclohexenyl ring coordinated by the palladium metal appears a chair-like form, and the bond lengths of C45-Pd, C46-Pd and C50-Pd are 2.22 Å, 2.24 Å, and 2.23 Å, respectively. Although the mechanism for the origin of the enantioselectivity is not clear from the ORTEP drawing of this X-ray crystallography, the result is quite interesting.

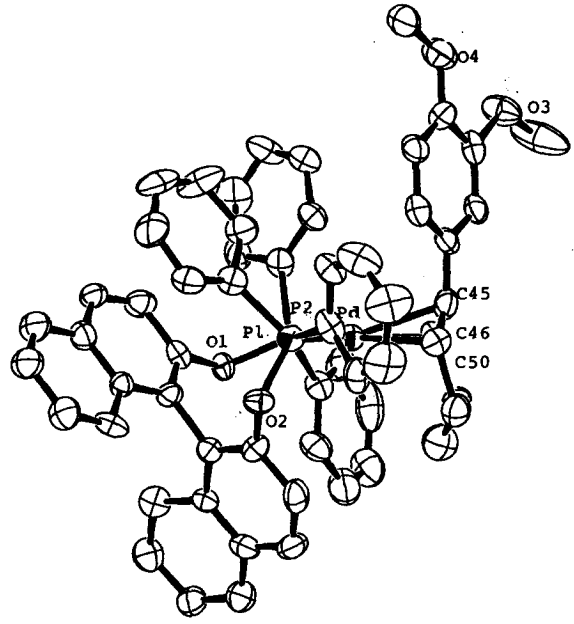
Table 2. Selected bond distances and bond angles.

Bond distances

bond	distance (Å)
Pd(1)–P(1)	2.309(3)
Pd(1)–P(2)	2.311(3)
Pd(1)–C(45)	2.22(1)
Pd(1)–C(46)	2.24(1)
Pd(1)–C(50)	2.23(1)
P(1)–O(1)	1.627(7)
P(2)–O(2)	1.609(7)
C(45)–C(46)	1.49(2)
C(45)–C(50)	1.45(2)
C(45)–C(51)	1.41(1)
C(46)–H(33)	0.97
C(50)–H(40)	0.99

Bond angles

bond	angle (deg)
P(1)–Pd(1)–P(2)	107.1(1)
Pd(1)–P(1)–O(1)	122.2(3)
Pd(1)–P(2)–O(2)	114.8(3)
P(1)–Pd(1)–C(46)	92.6(3)
P(1)–Pd(1)–C(50)	158.8(3)
C(46)–Pd(1)–C(50)	66.4(4)
C(46)–C(45)–C(50)	112(1)



In conclusion, there are two independent pathways in an asymmetric nucleophilic substitution into racemic methyl 2-arylcyclohexenyl carbonate in the presence of $Pd_2dba{\cdot}CHCl_3$ and (*S*)-BINAPO. The first step is the formation of chiral π-allyl palladium complex, which was obtained from both (*S*)- and (*R*)-methyl 2-arylcyclohexenyl carbonate. In this process, kinetic resolution was observed. The next step proceeded by nucleophilic substitution into the chiral (π-allyl)palladium complex to produce (+)- or (-)-2-arylcyclohexenyl derivatives along with the starting material with a high ee. Further studies are in progress.

References and Notes

1. Recent reviews: (a) Hayashi, T. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: Weinheim, 1993 and references cited therein. (b) Trost, B. M.; van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395 and references sited therein.
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3. The absolute configuration of (*R*)-**1** was determined as follows. Hydrolysis of (*R*)-**1** with K_2CO_3 in methanol gave allyl alcohol, which was treated with DEAD, PPh_3 and **3b** in THF to give (*S*)-**2a**.
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5. Reaction Procedure: A solution of (±)-**1a** (45.6 mg, 0.150 mmol), **3a** (47.4 mg, 0.165 mmol), $Pd_2dba{\cdot}CHCl_3$ (3.9 mg, 3.75 μmol), and (*S*)-BINAPO (4.9 mg, 7.5 μmol) in THF (1.5 mL) was stirred at 0°C. In each time, 10 μL of the solution was sucked up. The solution was developed on TLC (toluene/ethyl acetate, 9/1), and **2a** and the starting material were purified. The ees were determined by HPLC (DAICEL CHILALPAC AD, hexane/2-propanol, 9/1). The relative ratio k_S/k_R of **1a** (46%ee, 46% conversion) is calculated to be 5.2 using an established equation for kinetic resolution. $K_S/K_R=\ln[(1-C/100)(1-ee/100)]/\ln[(1-C/100)(1+ee/100)]$ (C=conversion); (*R*)-**1a**: $[\alpha]_D^{27}$ +123 (*c* 0.30, $CHCl_3$, 83% ee); (*S*)-**2a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08 (6 H, brt, *J* = 7.0 Hz), 1.53-2.21 (6 H, m), 2.41 (3 H, s), 3.03 (2 H, m), 3.23 (1 H, ddd, *J* = 7.0, 8.9, 14.3 Hz), 3.35 (1 H, ddd, *J* = 7.0, 9.2, 14.2 Hz), 3.51 (1 H, ddd, *J* = 6.8, 9.2, 14.2 Hz), 3.60 (1 H, ddd, *J* = 7.0, 9.0, 14.3 Hz), 3.85 (3 H, s), 3.87 (3 H, s), 4.57 (1 H, dd, *J* = 4.0, 6.0 Hz), 5.08 (1 H, brs), 6.09 (1 H, brs), 6.62 (1 H, d, *J* = 8.3 Hz), 6.68 (1 H, dd, *J* = 1.6, 8.3 Hz), 6.88 (1 H, d, *J* = 1.6 Hz), 7.19 (2 H, d, *J* = 8.0 Hz), 7.60 (2 H, d, *J* = 8.0 Hz); IR (neat) ν 2924, 1516, 1600 cm^{-1}; EI-MS *m/z* 503 (M^+), 457, 217; $[\alpha]_D^{25}$ -55.8 (*c* 0.63, $CHCl_3$, 92% ee). Anal. calcd for $C_{27}H_{37}NO_6S$: C, 64.39; H, 7.40; N, 2.78; S, 6.37. Found: C, 64.35; H, 7.41; N, 2.61; S, 6.25.
6. Crystal data for **6b**•$CHCl_3$•C_6H_6: empirical formula $C_{65}H_{56}Cl_3F_6O_4Pd$; orthorhombic; space group $P2_12_12_1$; *a* = 19.542(7) Å, *b* = 26.97(1) Å, *c* = 11.695(3) Å; No. of observations (I>2.50s(I)) 4446; *R* 0.068; *Rw* 0.074.