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Palladium-catalyzed selective alkoxycarbonylation of *N*-vinylphthalimide

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The palladium-catalyzed selective alkoxycarbonylation of enamide was studied using *N*-vinylphthalimide as the model substrate. Both palladium (0) and palladium (II) compounds can be used as the catalyst precursors. It was found that the efficiency and the regioselectivity of the reaction depended remarkably on phosphine ligands and other reaction parameters such as solvent, substrate concentration, temperature and promoters. Good yields and high regioselectivities of either the branched or linear products were obtained under optimum reaction conditions. The primary optical yield (12.3%) of *N*-Phthaloyl-L-alanine methyl ester (2) was obtained using (*S*)-(+)-BNPPA as the chiral ligand. A possible reaction mechanism for the alkoxycarbonylation of *N*-vinylphthalimide was also proposed. Copyright © 2006 John Wiley & Sons, Ltd.

KEYWORDS: alkoxycarbonylation; homogeneous catalysis; asymmetric induction; palladium; enamide; *N*-vinylphthalimide

INTRODUCTION

Amino acids and their derivatives are unequivocally one of the most important classes of organic compounds and possess a variety of biological functions. *N*-acyl-α-amino acids constitute interesting building blocks for organic synthesis, and are of commercial importance as industrial fine chemicals. Enantiomerically pure amino acids and their derivatives are not only the important constitution of organism but also a kind of multifunction chiral intermediate in organic synthesis and biochemical applications.

The amidocarbonylation reaction utilizing cobalt[1] and palladium[2] catalysts is an interesting tool for the synthesis of *N*-acyl amino acid from carbon monoxide, amides and aldehydes, but the products obtained above are mostly racemic *N*-acyl-α-amino acids. Beller and Eckert[3] only obtained about 10% e.e. in the palladium-catalyzed amidocarbonylation of isovaleradehyde to *N*-acetylleucine using 1-diphenylphosphanyle–thylbenzene as the chiral phosphane ligand. This may be attributed to some possible obstacles in the catalytic asymmetric synthesis in amidocarbonylation. One obstacle could be related to the undesired racemization of the chiral product under reaction conditions.[4] According to the reaction mechanism reported by Enzmann *et al.*,[5] the production of asymmetric induction on the carbon atom of carbonyl group of aldehydes is very difficult, especially in the insertion steps of PdL_2* into the C–X bond and carbon monoxide into the aminoalkyl–palladium bond. This would be another major obstacle to attempting to obtain significant enantioselectivity in the amidocarbonylation reaction. The development of synthetic chemical routes to optically active amino acids is still one of the great challenges in amino acid chemistry.

Functionalized olefins such as enamides and *N*-acyl imines most likely occur as intermediates in the amidocarbonylation reaction.[6] *N*-acyl amino acid and *N*-acyl amino acid esters can be easily obtained by alkoxycarbonylation of enamide. However, limited information on the palladium- and cobalt-catalyzed alkoxycarbonylation of enamides has been published. Cesa *et al.*[7] have investigated the palladium-catalyzed hydrocarboxylation of enamides, but the yields of amino acids and amino esters were very low. Recently, Klaus *et al.*[8] have reported the cobalt-catalyzed selective hydroalkoxycarbonylation of enamides in the absence of chiral ligands. In the publication by Becker *et al.*,[9] it is disclosed that only negligible optical yield (ca. 1%) was obtained in the asymmetric hydrocarboalkoxylation of *N*-vinylphthalimide. Cavinato *et al.*[10] obtained a very low optical yield (<2%) of *N*-phthaloyl-α-alanine methyl ester under harsh reaction conditions.

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Considering the particular synthetic importance of alkoxycarbonylation of enamides for the preparation of *N*-acyl amino acid esters, we also chose *N*-vinylphthalimide as a model substrate to investigate the palladium-catalyzed alkoxycarbonylation of enamides in detail. In the meantime, the synthesis of optical purity *N*-acyl amino acid esters was explored by asymmetric alkoxycarbonylation of *N*-vinylphthalimide.

EXPERIMENTAL

Materials

N-vinylphthalimide was purchased from Acros Chemical Company and used without further purification. $PdCl_2(PhCN)_2$,[11] $PdCl_2(PPh_3)_2$[12] and $Pd(dba)_2$[13] were prepared according to the literature. 1,2-bis (diphenylphosphino) ethane (dppe), 1,4-bis (diphenylphosphino) butane (dppb) and 1,1′-bis (diphenylphosphino) ferrocene (dppf) were prepared by literature methods.[14,15] The chiral ligand (*S*)-(+)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate [(*S*)-(+)-BNPPA], as shown in Scheme 2, was synthesized according to the literature.[16] Unless otherwise noted, the reagents were purchased from Shanghai Chemical Reagent Company and used without further purification. Methanol was distilled and dried using known procedures before use. Other solvents were purified by distillation after dried with suitable drying reagents.

Analysis

^1H and ^{13}C NMR spectra were recorded on a Bruker Avance Digital 400 (400 MHz for ^1H NMR; 100MHz for ^{13}C NMR) spectrometers in $CDCl_3$ with TMS as the internal standard; chemical shifts are quoted in ppm and *J*-values are given in Hz. The conversion of *N*-vinylphthalimide and regioselectivity (*b*/*l*) were determined by GLC analysis with a Fuli GC-9790 (FID) equipped with an OV-101 capillary column (30 m × 0.33 mm × 0.32 μm). Pure esters were isolated by column (silica gel, 200–300 mesh) and thin-layer (silica gel, GF254) chromatography and characterized by ^1H NMR and ^{13}C NMR. Melting points are uncorrected. The enantiomeric excess of the chiral product was determined by HPLC (Agilent 1100 Series) with a chiral column (*S*,*S*-whelk-01). The absolute configuration of *N*-phthaloyl-α-alanine methyl ester was determined by the comparison of the retention time with that of a pure authentic sample.

General procedure

A 60 ml stainless steel autoclave with mechanical stirrer was used as a bath reactor that was enclosed in an electric furnace. A thermocouple and a PID temperature controller were equipped to monitor and control the reaction temperature. In a typical experiment, a solution of 2.5 mmol MeOH, 0.1 ml HCl and 2 mmol *N*-vinylphthalimide in 20 ml toluene was introduced into the autoclave containing the catalyst precursor (0.02 mmol $PdBr_2$, 0.04 mmol $CuCl_2$ and 0.08 mmol PPh_3). The gas phase in the reactor was purged three times with carbon monoxide and then pressurized to 6.0 MPa. Then the reactor was heated to 90 °C and maintained for 32 h. After the reaction, the reactor was cooled to room temperature and vented. The reaction mixture was removed and immediately analyzed by GLC.

Analytical data

N-Phthaloyl-α-alanine methyl ester, **2**

White crystal, m.p. 69–70 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.88–7.86 (m, 2H), 7.77–7.75 (m, 2H), 5.00–4.98 (m, $J = 7.336$ Hz, 1H), 3.75 (s, 3 H), 1.72–1.70 (d, $J = 7.348$ Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 167.2, 134.1, 131.8, 123.4, 52.7, 47.3, 15.2.

N-Phthaloyl-β-alanine methyl ester, **3**

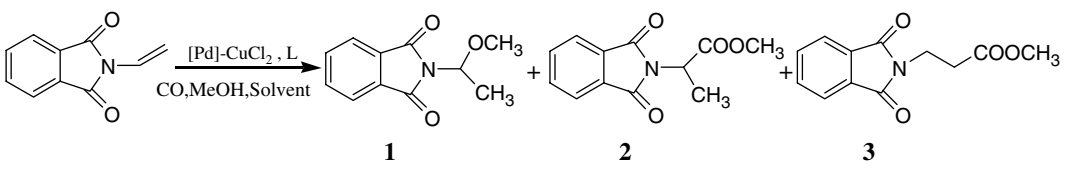
White crystal, m.p. 56–58 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.76–7.74 (m, 2 H), 7.64–7.62 (m, 2H), 3.92–3.88 (t, $J = 7.230$ Hz, 2H), 3.59 (s, 3 H), 2.66–2.63 (t, $J = 7.238$ Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 167.8, 134.0, 131.9, 123.2, 51.8, 33.6, 32.6.

RESULTS AND DISCUSSION

The alkoxycarbonylation reaction of *N*-vinylphthalimide is shown in Scheme 1. Esters (branched **2** and linear **3**) are the desired products while the ether (**1**) is considered to be a byproduct formed from the acid-catalyzed addition of methanol to *N*-vinylphthalimide. The polarization of the double bond in *N*-vinylphthalimide is greater than that in the case of styrene, therefore more ether product was formed under alkoxycarbonylation conditions. Reaction parameters were varied in an effort to seek optimum reaction conditions.

Influence of different catalysts on reaction performance

It can be seen from Table 1 that both palladium (0) (entries 6 and 7) and palladium (II) (entries 1–5) compounds can



Scheme 1. Alkoxycarbonylation of *N*-vinylphthalimide.

Table 1. Activity of palladium-catalysts in alkoxycarbonylation of *N*-vinylphthalimide[a]

Entry	Catalyst	Conversion (%)	Yield (%) **2** + **3**	Ratio of **2**:**3**
1	$PdBr_2$	71.2	63.7	73.7:26.3
2[b]	$PdBr_2$	43.6	40.3	44.4:55.6
3	$Pd(OAc)_2$	53.4	37.7	84.6:15.4
4[c]	$PdCl_2(PhCN)_2$	61.0	45.6	78.7:21.3
5[c]	$PdCl_2(PPh_3)_2$	37.2	35.4	76.2:23.8
6[d]	$Pd(dba)_2$	60.5	41.2	87.0:13.0
7	Pd/C	52.5	37.4	83.3:16.7

[a] *N*-vinylphthalimide, 2 mmol; catalyst, 0.02 mmol; $CuCl_2$, 0.04 mmol; PPh_3, 0.08 mmol; MeOH, 4 mmol; HCl, 0.1 ml; solvent, toluene 20 ml; P_{CO}, 6.0 MPa; 90 °C; 32 h.
[b] $CuBr_2$ was used instead of $CuCl_2$.
[c] PPh_3: 0.04 mmol.
[d] dba = 1,5-diphenyl-1,4-pentadien-3-one (Ph–CH=CHCOCH=CH–Ph).

be used as catalyst precursors; palladium (II) bromide, in particular, exhibited high activity (entry 1). The role of $CuCl_2$ in the reaction catalyzed by palladium (II) is well-known to reoxidize Pd (0) to Pd (II) [equation (1)].[17]

$$Pd^0 + 2CuCl_2 \longrightarrow PdCl_2 + 2CuCl \quad (1)$$

In this work, the most significant effect of $CuCl_2$ in Pd complex was to improve the selectivity of the branched isomer. While $CuBr_2$ was used instead of $CuCl_2$ (entry 2), the linear isomer was more easily formed than the branched one.

Effect of halide additives

Halide ion played a crucial role in the carbonylation reaction. The regioselectivity of alkoxycarbonylation has been shown to be strongly dependent on the anion of the catalyst as presented in Table 2. The coordination ability of halide ions is as follows: $F^- > Cl^- > Br^- > I^-$. One can see from Table 2 that the activity of the catalysts was obviously enhanced by replacing the strongly coordinating anion with a weakly coordinating one (entries 1 and 2 vs entries 4 and 5). The conversion of *N*-vinylphthalimide was 88.9% when Bu_4NI was used as halide additive (entry 5). Branched esters were favored with strongly coordinated Cl^- (entries 2 and 3), however while the weakly bound one such as Br^- and I^- was used, the formation of linear esters (entries 4 and 5) was easier.

Table 2. Influence of halide additives on reaction performance[a]

Entry	Additive	Conversion (%)	Yield (%) **2**+**3**	Ratio of **2**:**3**
1	Bu_4NF	23.9	23.0	41.2:58.8
2	LiCl	49.3	45.1	70.6:29.4
3[b]	Bu_4NCl	83.4	57.1	94.6:5.4
4	LiBr	86.7	73.3	23.1:76.9
5	Bu_4NI	88.9	86.4	9.1:90.9

[a] *N*-vinylphthalimide, 2 mmol; $PdBr_2$, 0.02 mmol; $CuCl_2$, 0.04 mmol; halide additives, 0.1 mmol; PPh_3, 0.08 mmol; halide additive, 0.1 mmol; MeOH, 4 mmol; HCl, 0.1 ml; solvent, toluene 20 ml; P_{CO}, 6.0 MPa; 90 °C; 32 h.
[b] $PdCl_2(PPh_3)_2$ (0.04 mmol) was used instead of $PdBr_2$, 75 °C.

Effect of different acidic promoters

The results in Table 3 show that the alkoxycarbonylation reaction rate was extremely slow in the absence of acid, giving only 2.9% conversion (entry 1). Among the acids tested, HCl provided the best result (entry 2) and formic acid was completely unreactive (entry 3). The conversion was obviously decreased by the addition of H_2SO_4 (entries 4–6) and *p*-TsOH (*p*-toluenesulfonic acid; entry 7). In entries 5–7, the catalysts did show some activity, possibly due to the formation of HX *in situ* via the reactions of $CuCl_2$, LiBr with H_2SO_4 or $CuCl_2$ with *p*-TsOH.

It can be seen from Table 3 that hydrochloric acid as a source of additional chloride ion was essential for an efficient catalyst system. HCl can provide chlorine, which serves as a ligand of an active Pd-complex [equations (2) and (3)].[18]

$$LnPd + HX \longrightarrow HLnPdX \quad (2)$$

$$HLnPdX + HX \longrightarrow LnPdX_2 + H_2 \quad (3)$$

Effect of reaction temperature

Table 4 shows the effect of the reaction temperature on the conversion and the selectivity of the alkoxycarbonylation of *N*-vinylphthalimide when chiral ligand (*S*)-(+)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate [(*S*)-(+)-BNPPA; Scheme 2) was used.

Table 3. Influence of acidic promoters on reaction performance[a]

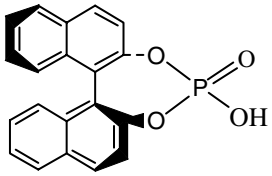
Entry	Acid	Conversion (%)	Yield (%) **2** + **3**	Ratio of **2**:**3**
1	None	2.9	2.4	41.2:58.8
2	HCl (0.1 ml)	71.2	63.7	73.7:26.3
3	HCOOH (0.6 mmol)	0.7	0	—
4[b]	H_2SO_4 (0.2 mmol)	0.3	0	—
5	H_2SO_4 (0.2 mmol)	21.0	15.6	56.5:43.5
6[c]	H_2SO_4 (0.2 mmol)	29.2	27.5	47.4:52.6
7	*p*-TsOH (0.2 mmol)	25.5	18.0	47.4:52.6

[a] *N*-vinylphthalimide, 2 mmol; $PdBr_2$, 0.02 mmol; $CuCl_2$, 0.04 mmol; PPh_3, 0.08 mmol; MeOH, 2.5 mmol; Solvent, toluene 20 ml; P_{CO}, 6.0 MPa; 90 °C; 32 h.
[b] No $CuCl_2$ was added.
[c] *N*-methylpyrrolidone (NMP) 20 ml was used as solvent, LiBr 0.1 mmol was used in place of $CuCl_2$, 100 °C.

Table 4. Influence of reaction temperature on the reactivity of alkoxycarbonylation[a]

Entry	Temperature (°C)	Conversion (%)	Yield (%) **2** + **3**	Ratio of **2**:**3**
1	105	19.3	15.6	54.5 : 45.5
2	90	37.6	32.5	81.1 : 18.9
3[b]	75	45.7	36.0	94.4 : 5.6
4	75	80.0	53.8	93.3 : 6.7
5	60	55.9	46.0	97.5 : 2.5
6	45	16.6	12.6	100 : 0

[a] *N*-vinylphthalimide, 2 mmol; $PdBr_2$, 0.02 mmol; $CuCl_2$, 0.04 mmol; PPh_3, 0.04 mmol; (*S*)-(+)-BNPPA, 0.04 mmol; MeOH, 4 mmol; HCl, 0.1 ml; solvent, toluene 20 ml; P_{CO}, 6.0 MPa; 32 h.
[b] THF(20 ml) was used as solvent.



Scheme 2. (*S*)-(+)-BNPPA.

From Table 4 one can see that the conversion of *N*-vinylphthalimide was enhanced from 16.6 to 80.0% as the temperature was increased from 45 to 75 °C (entries 4–6). The conversion and yield of the products (**2** + **3**) deteriorated when the temperature was further increased. The conversion was only 19.3% when the reaction temperature was up to 105 °C (entry 1). It has also shown that the decrease in temperature favors the formation of the branched ester. When the reaction temperature was decreased to 45 °C there was no linear ester formed at all (entry 6). This was a quite a valuable result.

Effect of solvents

The effect of solvents was studied and the results are given in Table 5. The solvent had a noticeable influence on both the yield and the regioselectivity of the reaction. Both the α-regioselectivity and the yield were high in nonpolar solvents (entries 1 and 7), which afforded branched ester in superior yields than in polar solvents. In THF (tetrahydrofuran) and CH_3CN, the reaction was also highly α-regioselective, but the yields of esters were only 10.7 and 27.6% (entries 3 and 4). The reaction rate was extremely slow in basic solvents like DMF (*N*, *N*-dimethylformamide), which gave only 0.7% yields of esters (entry 2). While solvents with moderate polarity give modest results (entry 5). However, in the case of methanol, ether (1) became the main product (entry 6). Since ether can be formed in the absence of palladium, it indicated that the catalyst had less efficiency in polar solvent than that in nonpolar solvent.

Table 5. The solvent effect on reaction performance[a]

Entry	Solvent	Conversion (%)	Yield (%) **2** + **3**	Ratio of **2**:**3**
1	Toluene	71.2	63.7	73.7 : 26.3
2	DMF	1.9	0.7	100 : 0
3	CH_3CN	12.0	10.8	100 : 0
4	THF	29.1	27.6	85.1 : 14.9
5[b]	MEK	44.2	32.7	54.5 : 45.5
6	Methanol	63.1	19.2	41.2 : 58.8
7	1,4-Dioxane	64.9	47.3	82.1 : 17.9
8	Cyclohexane	52.3	32.7	73.0 : 27.0
9[c]	DCE	62.1	44.8	41.7 : 58.3

[a] *N*-vinylphthalimide, 2 mmol; $PdBr_2$, 0.02 mmol; $CuCl_2$, 0.04 mmol; PPh_3, 0.08 mmol; MeOH, 4 mmol; HCl, 0.1 ml; volume of solvent, 20 ml; P_{CO}, 6.0 MPa; 90 °C; 32 h.
[b] Reactions were performed at 80 °C, MEK = 2-butanone.
[c] DCE = 1,2-dichloroethane.

Table 6. A comparison of different ligands on reactivity of $PdBr_2$ catalyst[a]

Entry	Ligand	Conversion (%)	Yield (%) **2** + **3**	Ratio of **2**:**3**
1	—	14.2	1.7	100 : 0
2	PPh_3	71.2	63.7	73.7 : 26.3
3	dppe	0	0	—
4	dppb	8.8	7.9	37.5 : 62.5
5	dppf	29.1	26.6	54.5 : 45.5
6[b]	(*S*)-(+)-BNPPA	37.6	32.5	81.1 : 18.9
7	P (o-tol)$_3$	22.4	3.6	100 : 0
8	P (p-tol)$_3$	54.1	37.1	81.8 : 18.2

[a] *N*-vinylphthalimide, 2 mmol; $PdBr_2$, 0.02 mmol; $CuCl_2$, 0.04 mmol; ligand, 0.08 mmol; MeOH, 4 mmol; HCl, 0.1 ml; Solvent, toluene 20 ml; P_{CO}, 6.0 MPa; 90 °C; 32 h.
[b] Ligand: PPh_3 (0.04 mmol), (*S*)-(+)-BNPPA (0.04 mmol); a 12.3% e.e. (S) asymmetric induction was obtained.

Effect of ligands

The ligands can not only stabilize palladium species of complex during alkoxycarbonylation, but also fundamentally influence their reactivity. The effect of the different phosphorous ligands on the alkoxycarbonylation of *N*-vinylphthalimide is summarized in Table 6. PPh_3 is the most widely employed ligand for homogeneous metal catalyst systems, especially for palladium. No catalytic activity was observed in the absence of phosphorous ligands, and the precipitation of metallic palladium black under experimental conditions was obvious (entry 1). Phosphines having substituents in the benzene ring (PPh_3), such as tri-*o*-tolylphosphine and tri-*p*-tolylphosphine, gave lower activity than PPh_3 (entries 7 and 8). The catalysts showed either no or poor activity when bidentate diphosphines such as dppe and dppb were employed as the ligands, which form a *cis*-chelate with palladium (entries 3 and 4). However, when

dppf was used as the ligand, which is also a *cis*-chelating diphosphine, the catalyst did show some catalytic activity (entry 5). Because the P–Pd–P bond angle in the *in-situ*-prepared Pd–dppf complex is fairly large compared with that in Pd-dppe or Pd-dppb complex, it can be inferred that a great deal of strain exists in Pd–dppf complex. Dissociation of one of the phosphine groups from palladium would relieve such strain and yield catalytically active species.[19] It also shows that monodentate phosphorous ligands give high values of regioselectivity to branched isomer (entries 2 and 6–8), while bidentate diphosphines favor linear one (entries 4 and 5). Finally a 12.3% e.e. (S) asymmetric induction was obtained using chiral ligand (*S*)-(+)-BNPPA combined with PPh_3 (Table 6, entry 6). This is an attractive result in the enantioselective alkoxycarbonylation of *N*-vinylphthalimide.

Effect of the amounts of solvent

The influence of toluene amount on the reaction performance of the present catalyst system is given in Table 7. It can be seen that the amount of solvent had a clear effect on the efficiency of the catalytic system. At lower *N*-vinylphthalimide concentration both the conversion and yield of the ester products were low (entry 1). The conversion of *N*-vinylphthalimide was enhanced with the decrease of the volume of toluene. In addition, the regioselectivity toward branched ester was better at higher concentration of substrate. The conversions were 70.1 and 89.2% in 20 and 15 ml of toluene, respectively (entries 2 and 3). The conversion and yield of the reaction increased with further decrease in the volume of toluene to 12.5 ml, but the regioselectivity of the branched ester reduced slightly and more ether product was formed (entry 4). For economy, it was the optimum solvent amount when toluene was 15 ml (entry 3) with the yield of ester nearly 80% and good regioselectivity towards the branched isomer (the ratio of *b* : *l* was 94.8 : 5.2).

Table 7. The effect of the amounts of toluene on the yield[a]

Entry	Toluene (ml)	Conversion (%)	Yield (%) **2** + **3**	Ratio of **2** : **3**
1	30	30.0	24.8	91.2 : 8.8
2	20	70.1	56.4	94.4 : 5.6
3	15	89.2	78.9	94.8 : 5.2
4	12.5	94.3	79.7	94.6 : 5.4

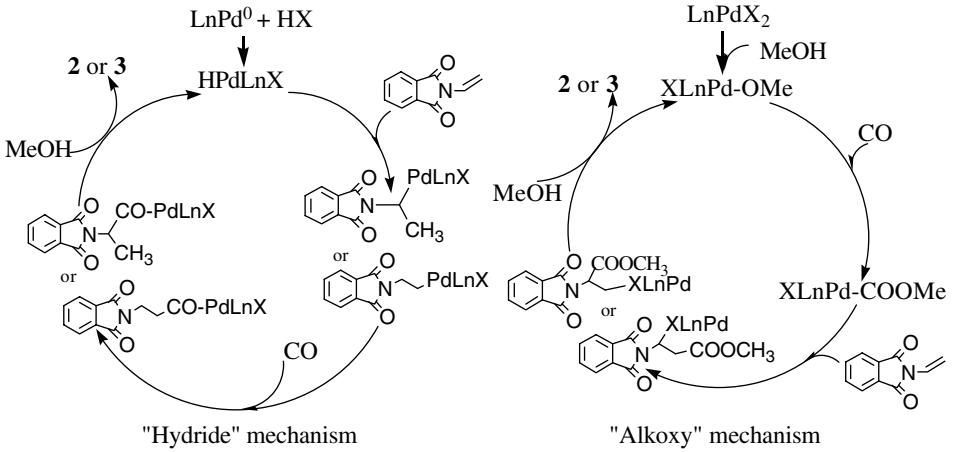
[a] *N*-vinylphthalimide, 2 mmol; $PdBr_2$, 0.02 mmol; $CuCl_2$, 0.04 mmol; PPh_3, 0.04 mmol; (*S*)-(+)-BNPPA; 0.08 mmol; MeOH, 4 mmol; HCl, 0.1 ml; P_{CO}, 6.0 MPa; 70 °C, 32 h.

POSSIBLE REACTION MECHANISM

The mechanisms of the palladium-catalyzed alkoxycarbonylation reaction have been extensively studied, and two kinds of mechanism have been proposed: hydride mechanism[20] and alkoxy mechanism[21] (Scheme 3). According to the hydride mechanism, a palladium hydride intermediate initiates the catalytic cycle by reacting with the alkene substrate. In the alkoxy mechanism, the catalytic cycle is initiated by the formation of a Pd-alkoxy complex that reacts with CO, yielding the palladium alkoxycarbonyl intermediate. In both mechanisms the termination step involves the alcohol.

A notable difference between these two mechanisms in relation to regioselectivity is that a bulky ligand would promote the selective formation of linear ester in the hydride mechanism, while branched ester formation would be preferred in the alkoxy mechanism.[22] *cis*-Chelating diphosphines would make the palladium coordination sphere more crowded than monodentate phophine ligands would. Hence, the fact that bidentate phophine ligands dppb and dppf promote selective formation of the linear ester might be taken as the evidence for the hydride mechanism.

Our experimental results revealed that both palladium (0) and palladium (II) complexes could be used as the catalyst



Scheme 3. Possible mechanism for alkoxycarbonylation of *N*-vinylphthalimide.

precursors, and in the alkoxy mechanism, palladium (II) complex combining with alcohol initiates catalytic cycle. This means that the alkoxy mechanism may also be possible, but the palladium (II) complex can also be converted into palladium hydride intermediate in the presence of MeOH [equation (4)].

$$LnPdX_2 + MeOH \longrightarrow HPdLnX + MeO^- + X^- \qquad (4)$$

The fact that HCl is absolutely necessary gives a strong support to the hydride mechanism. Although neither mechanism can be excluded based on the above experimental results, the hydride route seems to be more acceptable for alkoxycarbonylation of *N*-vinylphthalimide.

CONCLUSIONS

It has been demonstrated in this study that the palladium-catalyzed alkoxycarbonylation of *N*-vinylphthalimide afforded both branched and linear *N*-acyl amino acid esters in moderate to good yield. High regioselectivities towards either the branched or linear isomer were observed according to the optimum experimental parameters. The effect of HCl addition was essential in order to provide H^+ and Cl^-, which enhanced the regioselectivity towards branched ester. The most significant role of $CuCl_2$ is to promote selectivity towards the branched isomer. Asymmetric induction (12.3% e.e.) was observed using (*S*)-(+)-BNPPA as the chiral ligand, although reaction conditions were not optimized. The experimental results seem to support the hydride mechanism for alkoxycarbonylation reaction.

Further investigations on synthesis of optical purity *N*-acyl amino acid and *N*-acyl amino acid esters using enamides and *N*-acyl imines by hydrocarboxylation and alkoxycarbonylation are now in progress.

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