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Regioselective hydroesterification of styrene catalyzed by cationic palladium(II) complexes under mild conditions

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Abstract

The cationic palladium(II) complex $[Pd(MeCN)_2(PPh_3)_2](BF_4)_2$ was found to be an active catalyst for hydroesterification of styrene using CO and methanol under very mild conditions. The system, $Pd(OAc)_2$–PPh_3-*p*-toluenesulfonic acid, which should give rise to a cationic species in situ, was also effective to produce the branched ester regioselectively in an excellent yield at ambient temperature. Asymmetric hydroesterification of styrene by the use of chiral phosphines as ligands was also studied.

Keywords: Hydroesterification; Styrene; Carbon monoxide; Palladium

1. Introduction

Hydroesterification of olefins using CO and alcohols produces industrially valuable carboxylic acid esters, such as 2-arylpropionic acids, which are the most important class of nonsteroidal antiinflammatory agents like ibuprofen and naproxen [1]:

$$RCH{=}CH_2 + CO + R'OH \xrightarrow{cat.} RCH(CH_3)COOR' + RCH_2CH_2COOR'$$

The most investigated catalysts are cobalt [2] and palladium [3] compounds. The synthesis of esters with palladium catalysts requires relatively lower temperatures (50–125°C) as compared to cobalt catalysts (> 140°C). However, mixtures of regio isomers are often obtained and a rather high pressure of CO (100 atm or more) is required for the palladium-catalyzed reaction [4]. Hydroesterification of functionalized olefins like fluoroalkenes and vinylsilanes by palladium-based catalysts has been reported to proceed with high regioselectivity [5]. As for arylethenes, palladium-catalyzed hydroesterification of 6-methoxy-2-naphthylethene was found to proceed at 50°C to 100°C, affording 2-(6-

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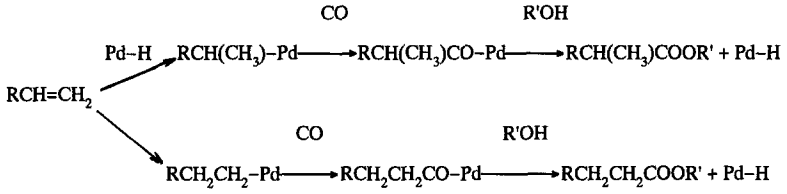
methoxy-2-naphthyl)propionate with high regioselectivity [6]. A catalyst system of $PdCl_2$–$CuCl_2$–PPh_3 was demonstrated recently to convert 4-methylstyrene to the branched acid ester at 100°C and 41 atm of CO [7]. Palladium immobilized on montmorillonite was revealed to be an effective catalyst for the hydroesterification of styrene in the presence of PPh_3 and an acid promoter under CO pressure of 41 atm at 125°C [8]. Two major mechanisms have been proposed for alkene hydroesterification. One involves a hydridopalladium species and another involves an alkoxycarbonylpalladium species as an intermediate [9,10]. Recently, however, the latter is evidenced not to be an intermediate in the catalytic cycle, but rather a byproduct [10] The hydride mechanism is shown below. It is suggested that the hydridopalladium species may exist in an ion pair like $[H–PdL_3]^+X^-$ [8].



In this study, we employed cationic palladium complexes as catalyst precursors for the hydroesterification of styrene in order that these complexes might generate smoothly such ionic hydridopalladium species in situ, and found that this type of complexes are highly active under very mild conditions to afford the branched ester regioselectively.

2. Results and discussion

The effects of various reaction conditions on the hydroesterification of styrene using CO and methanol, catalyzed by several cationic palladium complexes, are given in Table 1. The yield of the

Table 1
Hydroesterification of styrene [a]

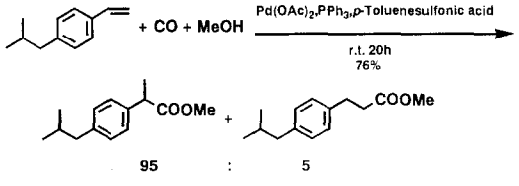
Entry	Catalyst	p_{CO} (atm)	Temp. (°C)	Product yield (%)	1:2
1	$PdCl_2(MeCN)_2$	5	80	0	—
2	$PdCl_2(PPh_3)_2$	5	80	21	26:74
3	$[Pd(MeCN)_2(PPh_3)_2](BF_4)_2$	2	80	88	27:73
4		5	80	94	29:71
5		20	80	91	40:60
6		20	50	55	83:17
7	$[Pd(PhCN)_2(PPh_3)_2](BF_4)_2$	5	80	92	30:70
8	$[Pd(PhCN)_2(DPPE)](BF_4)_2$	5	80	0	—
9	$[Pd(PhCN)_2(DPPP)](BF_4)_2$	5	80	7	15:85
10	$[Pd(PhCN)_2(DPPB)](BF_4)_2$	5	80	29	18:32
11 [b]	$Pd(OAc)_2$–PPh_3–CF_3SO_3H	20	50	97	75:25
12 [b]		20	30	37	90:10
13 [b]		20	RT	19	90:10
14 [b]	$Pd(OAc)_2$–PPh_3-*p*-toluenesulfonic acid	20	RT	37	96:4
15 [b,c]		20	RT	95	93:7

[a] Reaction conditions: 2 mmol styrene; 0.04 mmol Pd complex; 2.5 cm^3 methanol; 4 h.
[b] 0.04 mmol $Pd(0Ac)_2$; 0.08 mmol PPh_3; 0.10 mmol acid.
[c] 20 h.

products, that is, methyl 2-phenylpropionate **1** and methyl 3-phenylpropionate **2**, was calculated by GLC.

$$PhCH{=}CH_2 + CO + CH_3OH \xrightarrow{Pd^{2+}} \underset{\mathbf{1}}{PhCH(CH_3)COOCH_3} + \underset{\mathbf{2}}{PhCH_2CH_2COOCH_3}$$

The neutral complexes, $PdCl_2(MeCN)_2$ and $PdCl_2(PPh_3)_2$, showed little (entry 1) or only a small (entry 2) catalytic activity at a reaction temperature of 80°C and CO pressure of 5 atm. The cationic palladium complex, $[Pd(MeCN)_2(PPh_3)_2](BF_4)_2$, was an efficient catalyst affording the linear ester **2** as the main product under similar reaction conditions. The decrease in CO pressure from 5 to 2 atm or the increase from 5 to 20 atm did not give considerable effects on the yield; however, the selectivity to the branched ester **1** declined slightly as the pressure was decreased (entries 3–5). A decrease in reaction temperature from 80°C to 50°C brought about a marked decrease in the yield and a significant increase in the product selectivity to the branched ester **1** (entries 5, 6). The cationic complexes coordinated by diphosphines such as DPPE ($Ph_2P(CH_2)_2PPh_2$), DPPP ($Ph_2P(CH_2)_3PPh_2$), and DPPB ($Ph_2P(CH_2)_4PPh_2$) were generally less efficient catalysts, giving rise to the esters in only modest yields (entries 8–10). In order to investigate the effects of the counter anion of the cationic palladium complexes, we employed a catalyst system of $Pd(OAc)_2$–PPh_3–strong acid (molar ratio: 1:2:2.5). This method should provide a cationic palladium complex in situ [11]. When the reaction was carried out with the catalyst system of $Pd(OAc)_2$–PPh_3–CF_3SO_3H at 50°C and 20 atm of CO for 4 h, the yield reached 97% with the branched ester **1** as the major product (entry 11). The branched ester **1** was formed regioselectively as the reaction temperature was reduced from 50°C to 30°C or RT, although the rate declined markedly (entries 11–13). In entry 14, *p*-toluenesulfonic acid was employed as acid instead of trifluoromethanesulfonic acid. The reaction at RT for 4 h and 20 atm of CO pressure produced the esters in a moderate combined yield of 37% with 96% selectivity to the branched ester **1**. When the reaction was allowed to be conducted for 20 h at RT, the yield increased to 95% with 93% selectivity to **1** (entry 15). Thus, the selectivity to **1** increased with both increase in CO pressure and decrease in reaction temperature. With these results in mind, we employed 4-isobutylstyrene as the substrate for the hydroesterification reaction, of which the branched product is related to ibuprofen. The reaction of 2 mmol 4-isobutylstyrene with 20 atm CO in 2.5 cm^3 methanol at RT for 20 h in the presence of 2 mol% $Pd(OAc)_2$, 4 mol% PPh_3 and 5 mol% *p*-toluenesulfonic acid produced the corresponding esters in an isolated yield of 76% with 95% selectivity to the branched ester.



In order to investigate the scope, various olefins were employed as substrates in the hydroesterification reaction (Table 2). The reaction with the substrates listed in Table 2 by the cationic palladium complex $[Pd(MeCN)_2(PPh_3)_2](BF_4)_2$ was rather sluggish. A relatively high reaction temperature of 100°C was required to attain a reasonable yield. 1-octene afforded the corresponding esters in a combined GLC yield of 61% with 76% selectivity to the linear ester after 20 h and 5 atm CO in 2.5 cm^3 methanol in the presence of 2 mol% of the cationic complex (entry 16). 3-Methyl-1-pentene

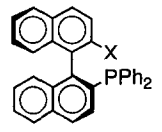
Table 2
Hydroesterification of various olefins [a]

Entry	Olefin	Product yield (%)	Branch:linear
16	1-octene	61	24:76
17	3-methyl-1-pentene	26	0:100
18	2-methyl-2-pentene	tr.	—
19	norbornene	74	
20	cyclopentene	36	
21	cyclohexene	69	
22	cyclooctene	28	

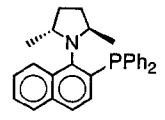
[a] Reaction conditions: 2 mmol olefin; 0.04 mmol $[Pd(MeCN)_2(PPh_3)_2](BF_4)_2$; 2.5 cm^3 methanol; 5 atm CO; 100°C; 20 h.

produced the linear ester regioselectively in a modest yield of 26% (entry 17). The reaction did not take place with a trisubstituted olefin, i.e., 2-methyl-2-pentene (entry 18), indicating that the steric factor plays an important role. Norbornene, cyclopentene, cyclohexene, and cyclooctene afforded the corresponding product in 74, 36, 69, and 28% yield, respectively. The relative reactivity of the cyclic olefins showed a somewhat different order as that established for hydroformylation; there the order was norbornene > cyclopentene > cyclooctene > cyclohexene [12].

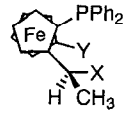
Next we attempted asymmetric hydroesterification of styrene employing several chiral phosphines as ligands (Fig. 1). In spite of the rapid development of asymmetric homogeneous catalysis by transition metal complexes, reports concerning asymmetric hydroesterification of styrene are rather scant. An asymmetric induction of 2.3% has been reported in hydroesterification of styrene in the presence of $PdCl_2$ and (−)-DIOP (*R*,*R*)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphos-



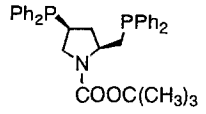
(*S*)-MOP : X=OCH_3
(*S*)-BINAP : X=PPh_2



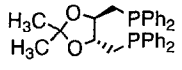
Aminonaphthylphosphine **3**



(*S*)-(*R*)-PPFA : X=$N(CH_3)_2$,Y=H
(*S*)-(*R*)-BPPFOAc : X=OAc,Y=PPh_2
(*S*)-(*R*)-BPPFOH : X=OH,Y=PPh_2
(*S*)-(*R*)-BPPFA : X=$N(CH_3)_2$,Y=PPh_2



(2*S*,4*S*)-BPPM



(-)-DIOP

Fig. 1. Chiral phosphines.

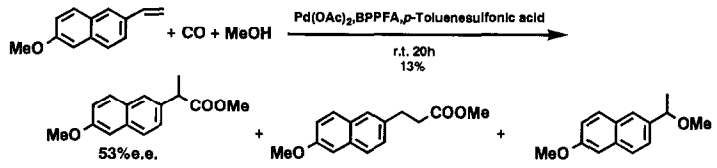
phino)butane. A moderate ee of the product (52% ee; branch:linear = 94:6) has been realized with a catalyst system of $Pd(dba)_2$-neomenthyldiphenylphosphine-trifluoroacetic acid at a stage of low turnover (dba = dibenzylideneacetone).

First, the effect of a chiral sulfonic acid was investigated. The catalyst system, $Pd(OAc)_2$–PPh_3-(+)-10-camphorsulfonic acid, was active at RT and a CO pressure of 10 atm to give the esters in 98% combined yield after 20 h with a selectivity to the branched ester of 90%. However, the asymmetric induction was not observed. Then the effects of several chiral monophosphines were studied with the catalyst system of $Pd(OAc)_2$-*p*-toluenesulfonic acid. A binaphthyl-based monophosphine ligand (*S*)-MOP ((*S*)-2-diphenylphosphino-2′-methoxy-1,1′-binaphthyl) effected a product yield of 96% with a selectivity to the branched ester of 94%. However, the asymmetric induction was disappointingly low: 2%. Monophosphines such as aminonaphthylphosphine **3** (1-[(2*R*,5*R*)-2,5-dimethylpyrrolidinyl]-2-diphenylphosphinonaphthalene) and (*S*)-(*R*)-PPFA ((*S*)-1-[(*R*)-2-(diphenylphosphino)ferrocenyl]ethyldimethylamine) were poor ligands and gave the products only scarcely. Moderate to modest product yields were obtained with bidentate chiral phosphines including (*S*)-BINAP ((*S*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl), (2*S*)-(4*S*)-BPPM ((2*S*,4*S*)-1-*tert*-butoxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine), (*S*)-(*R*)-BPPFOAc ((*S*)-1-[(*R*-1′,2-bis(diphenylphosphino)ferrocenyl]ethyl acetate), (*S*)-(*R*)-BPPFOH ((*S*)-1-[(*R*)-1′,2-bis(diphenylphosphino)ferrocenyl]ethanol), and (−)-DIOP, with the selectivity to the branched ester ranging from 31 to 48%. Modest asymmetric inductions of 10–29% were obtained in these systems. Ferrocene-containing aminophosphine, (*S*)-(*R*)-BPPFA ((*S*)-1-[(*R*)-1′,2-bis(diphenylphosphino)ferrocenyl]ethyldimethylamine), realized a high asymmetric induction of 86% at a low combined product yield of 17% with a selectivity to the branched ester of 44%. Finally, this asymmetric catalyst system using (*S*)-(*R*)-BPPFA was applied to the reaction of 6-methoxy-2-vinylnaphthalene, the branched product of which is related to naproxen. In this case three products were formed. The branced ester and the linear ester were expected carbonylation products. The third product was ether which arised from the starting olefin and methanol without addition of CO, the formation of which is catalyzed by an acid [7]. The combined isolated yield of the three products was only 13%. The ratio branched ester:linear ester:ether was 27:27:46. An optical yield of 53% to the branched (*S*)-ester was attained (Table 3).

Table 3
Asymmetric hydroesterification of styrene by the $Pd(OAc)_2$–chiral phosphine–*p*-toluenesulfonic acid system [a]

Phosphine	Product yield (%)	**1**:**2**	Optical yield of **1** (%)
(*S*)-MOP	96 [b]	94:6	2 (*R*)
Aminonaphthylphosphine **3**	tr.	—	—
(*S*)-(*R*)-PPFA	5 [c]	60:40	15 (*S*)
(*S*)-BINAP	5	48:52	12 (*S*)
(2*S*,4*S*)-BPPM	72	38:62	29 (*R*)
(*S*)-(*R*)-BPPFOAc	42	31:69	19 (*S*)
(*S*)-(*R*)-BPPFOH	17	33:67	10 (*S*)
(−)-DIOP	44	31:69	17 (*R*)
(*S*)-(*R*)-BPPFA	17	44:56	86 (*S*)

[a] Reaction conditions: 2 mmol styrene; 0.04 mmol $Pd(OAc)_2$; 0.08 mmol monophosphine; 0.04 mmol diphosphine; 0.10 mmol *p*-toluenesulfonic acid; 2.5 cm^3 methanol; 20 atm CO; RT; 20 h.
[b] 50°C; 10 h.
[c] 0.20 mmol *p*-toluenesulfonic acid.



In conclusion, the cationic palladium complex $[Pd(MeCN)_2(PPh_3)_2](BF_4)_2$ is an active catalyst for hydroesterification of styrene using CO and methanol under very mild conditions. The system, $Pd(OAc)_2$–PPh_3-*p*-toluenesulfonic acid, is also effective to give the branched ester regioselectively in an excellent yield at RT. Relatively high asymmetric induction has been realized in the hydroesterification of styrene by the use of a ferrocene-containing chiral aminophosphine, (*S*)-(*R*)-BPPFA, although the product yield and the selectivity to the branched ester are not satisfactory.

3. Experimental

3.1. Materials

Phosphines, i.e. DPPE, DPPP, DPPB, DIOP, PPFA, BPPM, BPPFOAc, BPPFOH, and BPPFA, were commercially obtained. MOP and the aminonaphthylphosphine **3** were kindly donated by Professor S. Miyano, Tohoku University. BINAP was donated by Takasago International. The cationic palladium complexes were prepared according to the reported procedure [13].

3.2. Analytical procedure

The structures of the products were determined by GC–MASS, IR, ^1H and ^{13}C NMR spectroscopy. The optical purity of the asymmetric hydroesterification product of *p*-isobutylstyrene was determined by GLC analysis using Chiraldex G-TA 20 m × 0.25 mm (Astec) at 80°C. The determination of enantiomeric purity of the hydroesterification product of 6-methoxy-2-vinylnaphthalene was performed by HPLC equipped with Chiralcel OD (5% 2-propanol/hexane; 0.5 cm^3/min). The absolute stereochemistry of the products was determined by comparison of the retention times with those of pure authentic samples.

3.3. Typical procedure for the hydroesterification

Into a stainless steel autoclave were added 0.04 mmol of $Pd(OAc)_2$, 0.08 mmol of PPh_3, 0.1 mmol of *p*-toluenesulfonic acid, 2.5 cm^3 of methanol, and 2 mmol of styrene under nitrogen atmosphere. The reaction vessel was then pressurized with 20 atm of CO. The reaction was allowed to proceed with stirring at RT. After 20 h, the reaction mixture was analyzed by GLC.

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