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Preparation and application of polymer-supported π-allylpalladium complex as a chiral catalyst in the asymmetric allylic alkylation

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Abstract

Chiral ferrocenylphosphine-imines **A**–**D** were synthesized and grafted to polystyrene to afford polymeric ligands **PA**–**PD**. Ligands **A**–**D** and **PA**–**PD** were used as ligands in the palladium-catalyzed asymmetric allylic alkylation. In the homogeneous reactions, the best result was obtained when the ligand **A** was used (99% yield and 82% ee). In the heterogeneous reactions, the highest ee value (73%) in the first run was obtained when **PA** was used as a ligand. Considering the enantioselectivity and reusability, the best result was obtained in the case of **PC**. The recycling of the polymer-supported π-allylpalladium catalyst gave unsatisfactory results: it can be reused three times with moderate enantioselectivities (60–70% ee). © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Allylic alkylation; Enantioselective; Palladium catalyst; Polymer-supported

1. Introduction

The use of polymers as supports has found many applications in catalysis [1–11]. The strategy of attaching a chiral ligand onto a polymer support offers several advantages in catalytic asymmetric synthesis over the use of homogeneous ligands. The advantages include easy separation, potential recycling of expensive chiral catalysts, and the possibility of carrying out the desired transformation in a continuous-flow system. Although chiral ligands attached to polymers are useful and practical, there are still some shortcomings such as lower catalytic activity and enantioselectivity compared with those recorded for their homogeneous counterparts. Thus, continuous research efforts in this area aim to narrow the gap between the homogeneous and heterogeneous catalysis approaches. Recently, the first asymmetric reaction with polymer-supported chiral π-allylpalladium catalysts have been reported by Yamamoto et al. [12]. Their catalyst was very stable and could be reused four times without losing catalytic activity. However, the enantioselectivities were rather low (up to 47% ee).

The palladium-catalyzed allylic alkylation is a synthetically important process in which new carbon–carbon bonds are formed. With chiral catalysts, high enantioselectivities have been often observed. Ferrocenyl ligands represent one of the most important classes for auxiliaries. They find application in a variety of transition-metal catalyzed reactions. We set-up a study aimed at incorporating ferrocenyl ligands into polymeric structures. This field has been pioneered by Hayashi et al., who first prepared planar chiral ferrocenyl phosphines [13]. The bidentate

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ligands of the type **A** are characterized by the presence of two ligand atoms (P, N) imbedded in different and easily modifiable steric and electronic environments. We report herein the preparation of polymer-supported ferrocenyl P, N-chelate ligands and their application in the palladium-catalyzed allylic alkylation. Moberg et al. also reported enantioselective allylic alkylation using polymer-supported palladium catalysts [14]. Their catalytic system shows high enantioselectivities (up to 80% ee). However, they did not discuss the reusability of the catalytic system.

2. Experimental

2.1. General

The ^{1}H NMR spectra were recorded in $CDCl_3$ at 300 MHz (Bruker DPX-300) unless otherwise stated. Combustion analysis (CE Instrument EA 1110) and ICP-AES (Shimadzu ICPS-1000IV) were done at the National Center for Inter-University Research Facilities in Seoul National University. Enantiomeric excess were determined by ^{1}H NMR using Eu(hfc)$_3$ as the chiral shift reagent. Merck Kieselgel 60H was used for flash chromatography. Polystyrene resin cross-linked with 1% divinylbenzene was used as a polymeric support. Compounds **1** and amines were prepared according to the literature procedures [15–18]. Aminated poly(styrene-*co*-divinylbenzene) (1% cross-linked, 200–400 mesh) was purchased from Aldrich Chem. Co. Polymers, (aminomethyl)polystyrene (AMPS) and 4-methylbenzhydrylamine (MBHA), were prepared by the previously reported methods [19]. The ee values were determined by ^{1}H NMR using a chiral shift reagent Eu(hfc)$_3$.

2.2. Synthesis of *2*

A procedure identical to that for **1** was applied. The IR ν(CO) 1683 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 10.15 (d, 2.13 Hz, 1H), 7.70–7.61 (m, 4H), 7.53–7.51 (d, 8.43 Hz, 2H), 7.31–7.22 (m, 2H), 5.13 (t, 1.34 Hz, 1H), 4.74 (t, 2.67 Hz, 1H), 4.26 (s, 5H), 4.00 (t, 1.42 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$): δ 193.1, 136.0, 135.9, 135.7, 133.3, 133.0, 132.8, 132.5, 126.3, 124.5, 76.4, 74.7, 73.7, 70.3, 70.0 ppm; HRMS for $C_{25}H_{17}F_6FeOP$ calcd. 534.0271, found 534.0268; $[\alpha]_D^{15}$ 130 (c 0.1, CH_2Cl_2).

2.3. Ligand *A*

Molecular sieve (4 Å) in a 50 ml of two-neck flask was flame-dried. To the flask were added **1** (0.20 g, 0.5 mmol), 20 ml of CH_2Cl_2, and benzylamine (0.06 ml, 0.55 mmol). The resulting solution was heated at reflux for 6 h. The color of the solution was changed from red to bright orange. After the solution was cooled to room temperature, the solution was filtered over a celite pad. The filtrate was evaporated to dryness. Recrystallization of the residue in Et_2O/pentane yielded orange solids (0.16 g, 0.37 mmol, 74%). Melting point (mp) 132–135°C; IR ν(CN) 1645 cm^{-1}; ^{1}H NMR: δ 8.55 (s, 1H), 7.59–7.13 (m, 15H), 5.11 (s, 1H), 4.68–4.52 (d, 13.3 Hz, 2H), 4.50 (m, 1H), 4.11 (s, 5H), 3.86 (m, 1H) ppm. Anal. found: C, 73.93; H, 5.38; N, 2.87. $C_{30}H_{26}FeNP$ calcd.: C, 74.13; H, 5.46; N, 2.85; $[\alpha]_D^{25}$ 340 (c 0.1, CH_2Cl_2).

2.4. Ligand *B*

The same procedure as the synthesis of **A** was employed except $NH_2CH(C_6H_5)(C_6H_4CH_3$-*p*) instead of benzylamine. Yield 69%; mp 146–148°C; IR ν(CN) 1628 cm^{-1}; ^{1}H NMR: δ 8.51 (s, 1H), 7.56–7.02 (m, 19H), 5.37 (s, 1H), 5.11 (s, 1H), 4.46 (m, 1H), 4.00 (s, 5H), 3.80 (s, 1H), 2.30 (s, 3H) ppm. Anal. found: 76.96; H, 5.59; N, 2.43. $C_{37}H_{32}FeNP$ calcd.: C, 76.92; H, 5.63; N, 2.42; $[\alpha]_D^{27}$ 109 (c 0.1, CH_2Cl_2).

2.5. Ligand *C*

The same procedure as the synthesis of **A** was employed except **2** instead of **1**. Yield 72%; mp 134–135°C; IR ν(CN) 1640 cm^{-1}; ^{1}H NMR: δ 8.42 (s, 1H), 7.65–7.07 (m, 13H), 5.04 (s, 1H), 4.68 (s, 1H), 4.51 (s, 2H), 4.15 (s, 5H), 3.75 (s, 1H) ppm. Anal. found: 61.66; H, 3.88; N, 2.25. $C_{32}H_{24}FeNP$ calcd.: C, 61.87; H, 3.88; N, 2.26; $[\alpha]_D^{25}$ 15 (c 0.1, CH_2Cl_2).

2.6. Ligand *D*

The same procedure as the synthesis of **A** was employed except **2** instead of **1**. Yield 80%; mp 139–141°C; IR ν(CN) 1642 cm^{-1}; ^{1}H NMR: δ 8.47 (s, 1H), 7.72–6.79 (m, 17H), 5.33 (s, 1H), 4.92 (s, 1H), 4.45 (s, 1H), 4.08 (s, 5H), 3.70 (s, 1H), 2.30 (s, 3H) ppm. Anal. found: 66.01; H, 4.50; N, 1.96.

$C_{39}H_{30}F_6FeNP$ calcd.: C, 65.65; H, 4.24; N, 1.96; $[\alpha]_D^{25}$ 199 (c 0.1, CH_2Cl_2).

2.7. Polymer-supported ligand *PA*

Schlenk flask was flame-dried. To the flask AMPS (1.0 g, 1 mmol/g) and 25 ml of benzene were added. The polymer was allowed to be swollen for several hours. A solution of **A** (80 mg, 0.2 mmol) in 5 ml of benzene was transferred via cannula to the polymer in benzene solution. The flask was fitted with a soxhlet and the solution was heated at reflux for 12 h. After the solution was cooled to room temperature, the resin was filtered, washed successively with benzene (10 ml), CH_2Cl_2 (10 ml), and methanol (20 ml), and dried in vacuo to give bright orange solid **PA**.

The active catalysts were then prepared by reaction of **PA** with $[(C_3H_5)PdCl]_2$ dissolved in THF. After the solution was stirred for 1 h and washed with a large excess of solvent, solid catalysts were isolated. Then the content of Pd (0.18 mmol/g) coordinated to the solid support **PA** was determined by the substraction of the amount of Pd (determined by ICP-AES) in the filtrate from the original amount of Pd. We presumed that the contents of Pd coordinated to the solid support **PA** was equal to the amount of the P, N-chelate ligand in **PA**.

2.8. Preparation of polymer-supported ligands *PB*, *PC*, and *PD*

The same procedure as the preparation of **PA** was applied. For the synthesis of **PC**, polymer AMPS was used and for the synthesis of **PB** and **PD** polymer MBHA was used. In the same way as the above, the contents of P, N-chelate ligand in **PB**–**PD** were determined: **PB** (0.13 mmol/g), **PC** (0.08 mmol/g), and **PD** (0.06 mmol/g).

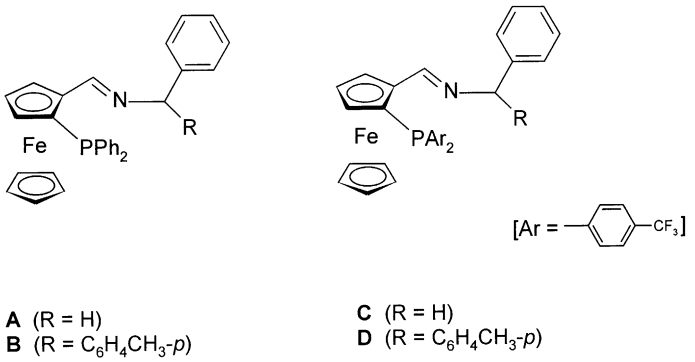
2.9. Catalytic reaction

A representative procedure for the allylation reaction of *rac*-1,3-diphenyl prop-2-en-1-yl acetate is as follows: to a mixture of polymer-supported chiral π-allylpalladium catalyst (2 mg, 0.005 mmol Pd) and substrate (0.145 mg, 0.58 mmol), sodium malonate (generated in situ by the reaction of NaH (30 mg) with dimethyl malonate (0.085 ml, 0.74 mmol) in 10 ml of THF at 25°C was added. The mixture was stirred for 24 h, and then filtered. The progress of the reaction was monitored by TLC. The catalyst was washed with THF, and the filtrates were combined. The solvent was removed under reduced pressure, and the crude product was purified by silica gel column chromatography (hexane:diethyl ether = 10:1), giving methyl-2-carbomethoxy-3,5-diphenylpent-4-enolate in 86% yield. The ee values were determined by ^1H NMR using a chiral shift reagent $Eu(hfc)_3$.

3. Results and discussion

3.1. Preparation of planar chiral ferrocenyl P, N-chelate ligand

Recently, we reported the use of planar chiral imino-phosphine chromium ligands in palladium-



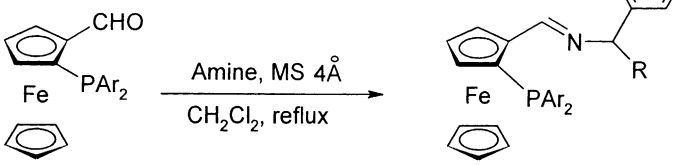
A (R = H)
B (R = $C_6H_4CH_3$-*p*)

C (R = H)
D (R = $C_6H_4CH_3$-*p*)

Scheme 1.

catalyzed asymmetric allylic alkylation [20]. In the reaction, high yields up to >98% ee were obtained. Thus, first we attempted to use the planar chiral imino-phosphine chromium ligands in the preparation of polymer-supported catalysts (For the first run, the yield and enantioselectivity were 35 and 12%, respectively). However, due to the facile decomposition of the chromium tricarbonyl moiety during the catalytic reaction, planar chiral imino-phosphine chromium ligands were not used in the preparation of the polymer-supported catalyst system. Instead, ferrocenyl ligands **A–D** were used as ligands (Scheme 1).

The planar chiral P, N-ligands **A–B** were synthesized from **1** (*S*)-α-(diphenylphosphino) ferrocenecarboxaldehyde (Eq. (1)).



1 (Ar = Ph)
2 (Ar = $C_6H_4CF_3$-*p*)

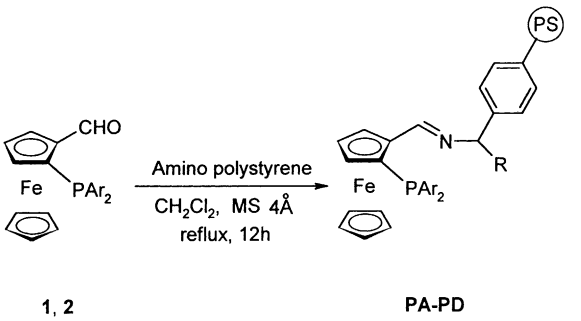
A-D

(1)

Compound **1** was previously prepared by Kagan et al. [15]. Treatment of **1** with primary amine in the presence of molecular sieves (4 Å) gave **A** and **B** in 74 and 69% yields, respectively. Due to the hydrolysis of the imino group, chromatographic purification of **A** and **B** on a silica gel column led to the conversion of **A** and **B** to **1**. Thus, **A** and **B** were purified by recrystallization. In the same way, **C** and **D** were obtained in 72 and 80% yields, respectively, from **2**.

3.2. Preparation of polymeric ligands

To retain the same chiral environment as in the homogeneous catalysis, the polymer was introduced through the phenyl group on the imnino moiety. The polymer-supported ligands **PA–PD** were prepared by reaction of amino-functionalized polystyrenes with an excess of ferrocenecarboxaldehyde in toluene at reflux for 12 h (Eq. (2)).



1, 2

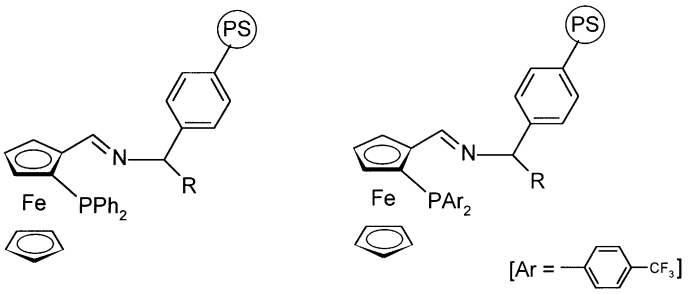
PA-PD

(2)

The syntheses of 4-methylbenzhydrylamine polystyrene (MBHA) and aminomethyl polystyrene (AMPS) were previously described by Hudson et al. [19]. These polymers have been reported to possess excellent swelling characteristics. After careful isolation of the light orange solid-supported ligands, they were characterized by infrared spectroscopy and elemental analysis. The active catalysts were then prepared by reaction of the polymer-supported ligand with $[(allyl)PdCl]_2$ dissolved in THF. Scheme 2 shows the polymeric ligands synthesized in this study. The ICP-AES analysis indicated that the contents of Pd were highly dependent upon the polymer-supported ligand: 0.18 mmol/g for **PA**, 0.13 mmol/g for **PB**, 0.08 mmol/g for **PC**, and 0.06 mmol/g for **PD**.

3.3. Catalytic reaction

Before investigating the polymer-supported catalysts, the reaction of the corresponding homogeneous catalysts was studied. The palladium-catalyzed asymmetric allylic alkylation of *rac*-1,3-diphenyl



PA (R = H)
PB (R = $C_6H_4CH_3$-*p*)

PC (R = H)
PD (R = $C_6H_4CH_3$-*p*)

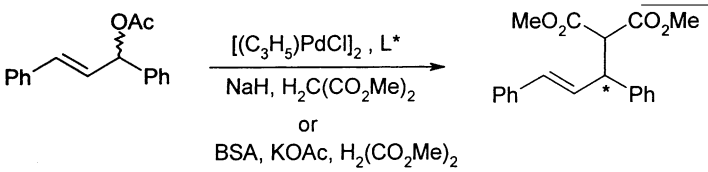
Scheme 2.

Table 1
Use of ligands **A–D** in Pd-catalyzed allylic alkylation

Entry	Base	L*	Solvent	Time (h)	Yield (%)[a]	ee (%)[b]
1	BSA	**A**	CH_2Cl_2	4	99	82
2	NaH	**A**	DMF	5	32	80
3	BSA	**B**	CH_2Cl_2	7.5	86	74
4	NaH	**B**	DMF	5.5	96	61
5	BSA	**C**	CH_2Cl_2	4	97	76
6	NaH	**C**	DMF	7	40	68
7	BSA	**D**	CH_2Cl_2	6	73	80
8	NaH	**D**	DMF	7	35	40

[a] Isolated yield.
[b] The ee values were determined by ^{1}H NMR using chiral shift reagent, Eu(hfc)$_3$.

prop-2-en-1-yl acetate with dimethyl malonate was carried out (Eq. (3) and Table 1).



(3)

The nucleophile was generated from dimethyl malonate in the presence of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and a catalytic amount of KOAc or sodium hydride. Our preliminary results showed that CH_2Cl_2 was the preferred choice for the reaction medium for BSA and DMF for NaH. The absolute configuration of the product was assigned as *R* from specific rotation determination and comparison with literature data. When BSA was used, the ee values (74–82%) were rather insensitive to the ligand, and the conversion yields (73–99%) were slightly dependent upon the ligand. However, when NaH was used, the ee values (40–80%) and conversion yields (32–96%) were highly dependent upon the ligand. The best result was obtained when the ligand **A** and BSA were used. Thus, neither the increase of the steric bulkiness of imine nor the introduction of the electron-withdrawing group helps increase the ee value and conversion rate.

Table 2
Use of ligands **PA–PD** in Pd-catalyzed allylic alkylation[a]

Entry	Run	Base	L*	Solvent	Time (day)	Yield (%)[a]	ee (%)[b]
1	1	BSA	**PA**	CH_2Cl_2	2	95	67
2	2	BSA	**PA**	CH_2Cl_2	2	64	59
3	3	BSA	**PA**	CH_2Cl_2	2	24	59
4	1	NaH	**PA**	DMF	2	72	73
5	2	NaH	**PA**	DMF	2	31	66
6	1	BSA	**PB**	CH_2Cl_2	3	82	27
7	2	BSA	**PB**	CH_2Cl_2	3	82	25
8	1	NaH	**PB**	DMF	3	86	67
9	2	NaH	**PB**	DMF	3	86	64
10	1	BSA	**PC**	CH_2Cl_2	2	57	70
11	2	BSA	**PC**	CH_2Cl_2	3	55	66
12	3	BSA	**PC**	CH_2Cl_2	5	44	60
13	1	NaH	**PC**	DMF	2	24	69
14	2	NaH	**PC**	DMF	3	14	21
15	1	BSA	**PD**	CH_2Cl_2	3	51	61
16	2	BSA	**PD**	CH_2Cl_2	5	50	61
17	3	BSA	**PD**	CH_2Cl_2	7	15	18
18	1	NaH	**PD**	DMF	3	52	57

[a] Isolated yield.
[b] The ee values were determined by ^{1}H NMR using chiral shift reagent, Eu(hfc)$_3$.

The polymer-supported palladium catalyst-catalyzed reaction of *rac*-1,3-diphenyl prop-2-en-1-yl acetate with dimethyl malonate was carried out (Table 2).

The absolute configuration of product, (*R*), is the same as would be anticipated from the results of the homogeneous reaction. When BSA was used as a base, in the first run the yields (51–95%) and ee values (27–70%) were highly dependent upon the P, N-chelate ligand. Comparing the yields and ee values, the best result was obtained when **PA** was used as a ligand. However, when the catalyst was reclaimed by filtration from the reaction mixture and was then reused with a new batch under identical conditions in the second run, the yield was decreased to 64% with a 59% ee value. In the third run, the yield was further decreased to 24% but the ee value was the same as for the second run. As the run continued, the solution after filtration became brown and eventually dark brown. When we considered only the enantioselectivity, the best result was obtained in the case of **PC**: 70% in the first run, 66% in the second run, and 60% in the third run. When NaH was used as a base, the yields (24–86%) were highly dependent upon the ligand but the ee values (57–73%) were relatively insensitive. The highest ee value (73%) in the first run was obtained when **PA** was used as a ligand. This is less than the value of 82% obtained in the homogeneous system. For the second run, the best result was obtained when **PB** was used as a ligand. When we compare the results of the first run for each polymer-supported ferrocenyl P, N-chelates, the best yield was obtained for polymer **PA** in CH_2Cl_2 and the best optical yield for polymer **PA** in DMF. Thus, as in the case of a homogeneous system neither the increase of the steric bulkiness of imine nor the introduction of electron-withdrawing group help increase the ee value and conversion rate.

4. Conclusion

In conclusion, we have prepared the polymer-supported π-allylpalladium catalyst for the asymmetric allylic alkylation. High ee's and conversions were obtained in the first run but decreased in the next runs. The catalyst can be reused three times with moderate enantioselectivities (60–70% ee).

Acknowledgements

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