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Steric and chelate ring size effects on the enantioselectivity in palladium-catalyzed allylic alkylation with new chiral P,N-ligands

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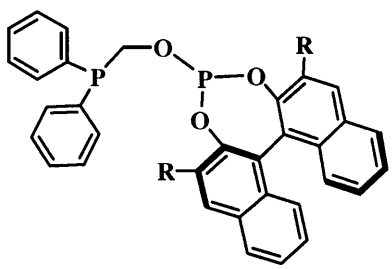
Abstract

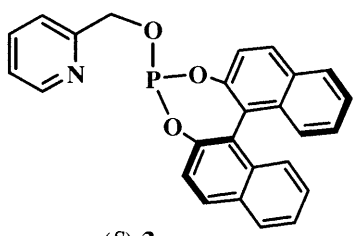
New chiral P,N-ligands derived from substituted pyridine and (*S*)-2,2′-binaphthol phosphorochloridite have been prepared and tested in asymmetric palladium-catalyzed allylic alkylations. The enantioselectivity was poorly dependent on the pyridine substituent, instead, a chelate ring size effect was apparent.

1. Introduction

During the last decade several chiral bidentate ligands have been found to achieve high levels of stereocontrol in enantioselective palladium-catalyzed allylic substitution reactions.[1] In this field, we recently described the synthesis of a new series of chiral phosphine-phosphite and pyridine-phosphite ligands[2] (Fig. 1) and their use in the asymmetric allylic alkylation of 1,3-diphenylprop-2-enyl acetate with the nucleophile derived from dimethyl malonate.



R = H (*S*)-**1**
R = $SiMe_3$ (*S*)-**2**



(*S*)-**3**

Figure 1.

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We found that the P,P-ligands (*S*)-**1** and (*S*)-**2** gave the substitution product with up to 71% e.e., while no asymmetric induction has been achieved with P,N-ligand **3**. This lack of enantiomeric excess was attributed to the poor structural control with ligand **3** due to the lower steric hindrance of the pyridine moiety with respect to the diphenylphosphino group in the allylic intermediates [Pd(η^3-PhCHCHCHPh(L–L′)]$^+$ (L–L′ = (*S*)-**1**–(*S*)-**3**). Indeed, as established by NMR spectroscopy, the low steric demand of the pyridine moiety leads to fast exchange of all the four possible configurational isomers of the Pd–allyl complexes present in solution. On the other hand, only the *exo–syn–syn* and *endo–syn–anti* isomers were found in solution with phosphine-phosphite ligands (*S*)-**1** and (*S*)-**2** which afforded the best e.e.s. Therefore, we verified that the number and the relative concentrations of the Pd–allyl conformers present in solution as intermediates in the allylic alkylation are a factor determining the enantioselectivity of the process.

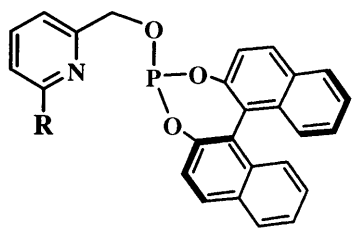
In light of these earlier results we have increased the steric hindrance of the pyridine–phosphite ligands by introducing different substituents on the 6-position in the pyridine moiety. Furthermore, with the aim of obtaining a greater conformational rigidity, starting from 2-aminopyridine, we have also synthesized chiral P,N-ligands which form a five-membered chelate ring with the metal center.

Here we report the preparation of these new P,N chiral ligands and their application in the asymmetric palladium-catalyzed allylic alkylation.

2. Results and discussion

2.1. Ligands synthesis

Ligands (*S*)-**4**–(*S*)-**6** (Fig. 2) were synthesized in good yields (78–80%) by reaction of the corresponding (6-substituited-pyridin-2-yl)methanol with 1 equivalent of (*S*)-2,2′-binaphthol phosphorochloridite in the presence of NEt_3 at 0°C in toluene. All the ligands were obtained as white moisture sensitive solids. The $^{31}P\{^1H\}$NMR spectra of (*S*)-**4**–(*S*)-**6**, in C_6D_6, show a single peak in the range 138.8–139.4 ppm as expected for phosphite compounds.[2]



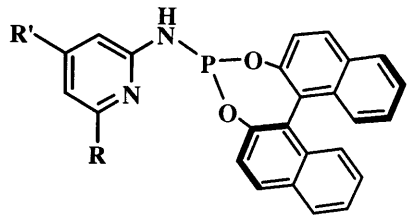
4 (R = Me)
5 (R = Br)
6 (R = Ph)

(*S*)

Figure 2.

Ligands (*S*)-**7** and (*S*)-**8** (Fig. 3) were readily accessible in moderate to good yields (58–77%) by reaction of the corresponding commercial 2-aminopyridine with the (*S*)-2,2′-binaphthol phosphorochloridite in a 2.5:1 ratio at −10°C in toluene. In a particular case, the 2-aminopy-

ridine was also used as a base to remove the HCl formed in the reaction course. The $^{31}P\{^{1}H\}$NMR spectra of (*S*)-**7** and (*S*)-**8**, in C_6D_6, show a single peak in the range 146.5–147 ppm as expected for phosphoroamidite compounds.[3]



7 (R = R' = H)
8 (R = R' = Me)

(*S*)

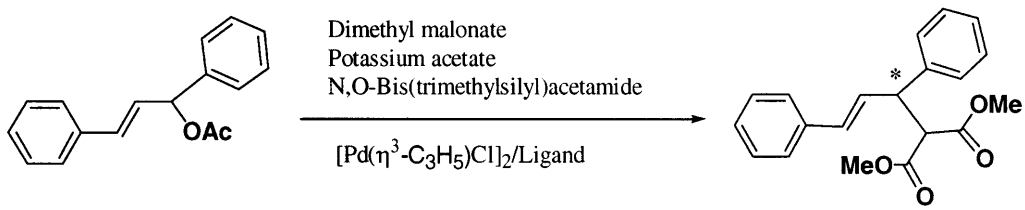
Figure 3.

2.2. Asymmetric allylic alkylation

These new chiral P,N-ligands were tested in the enantioselective palladium-catalyzed allylic substitution of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate according to Trost's procedure.[4] The results are summarized in Table 1.

All the catalytic systems Pd/L [(*S*)-**4**–(*S*)-**8**] afforded the dimethyl-1,3-diphenylprop-2-enyl-malonate in high yields although the enantioselectivity was rather low (7–37%). However, it is possible to draw some conclusions. The presence of a substituent in 6-position on the pyridine ring seems to have little influence on the enantioselectivity of the allylic alkylation (entries 2–4). Unexpectedly, the phenyl group greatly accelerates the reaction but the e.e. remains low (entry 4).

Table 1
Allylic alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate[a]



Entry	Ligand	Time, h	Yield[b]	% E.e.[c]
1	**3**	16	95	0
2	**4**	16	91	11 (*S*)
3	**5**	16	94	7 (*S*)
4	**6**	4	95	7 (*S*)
5	**7**	16	93	37 (*S*)
6	**8**	16	90	33 (*S*)

[a] $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (0.5 mol%), ligand (1.25 mol%), $H_2C(COOMe)_2$ (3 equiv.) BSA (3 equiv.), KOAc (1 mol%), CH_2Cl_2.[5]

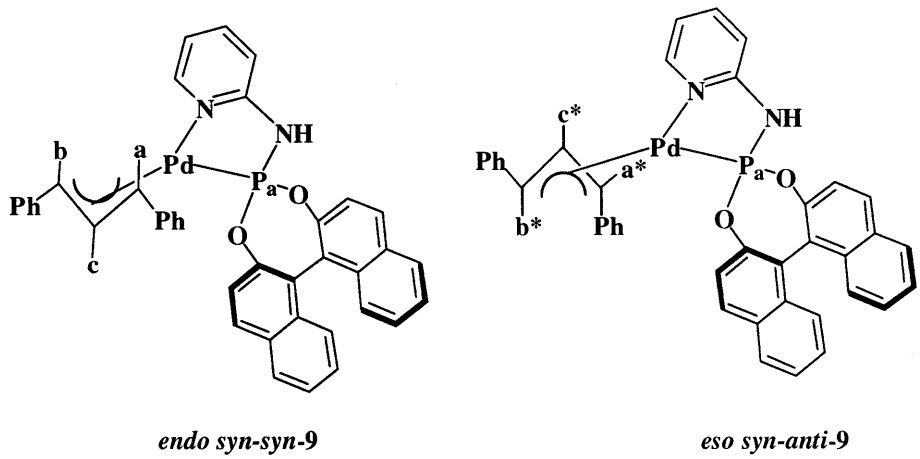
[b] Yield of analytically pure product after column chromatography.

[c] Determined by ^{1}H NMR spectroscopy ($CDCl_3$/0.25 equiv. $[Eu(hfc)_3]$).[5]

Data obtained with ligands (*S*)-**4**–(*S*)-**6** clearly show that Me, Br, and Ph groups in 6-position on the pyridine ring are, in such cases, not sufficient to exert a steric control on the palladium-catalyzed allylic alkylation of 1,3-diphenylprop-2-enyl acetate. In fact, as in the case of [Pd(PhCHCHCHPh)(*S*)-**3**]$^+$, NMR spectra of the allylic intermediates [Pd(PhCHCHCHPh)-((*S*)-**4**–(*S*)-**6**)]$^+$ proved that all four possible isomeric forms are present in the same concentration ratio and undergo fast exchange processes. Most probably, this is the reason for the modest enantioselectivity observed. However, it cannot be excluded that the introduction on the pyridine ring of a more bulky substituent than a *tert*-butyl group might improve the asymmetric induction. Unfortunately, up to now we have not been able to prepare the 6-*tert*-butylpyridine-phosphite ligand in good yields and high purity.

Ligands (*S*)-**7** and (*S*)-**8**, forming five-membered chelate rings, are more effective for the asymmetric induction than ligand (*S*)-**3**–(*S*)-**6** forming a six-membered chelate (entries 1 and 5). Besides, the chelate ring size shows a remarkable effect on the e.e. more than the introduction of a substituent on the 6-position of the pyridine ring (entries 1, 2 and 5). Probably, with these P,N-ligands, an increase in the rigidity of the intermediate Pd–allyl complex improves the enantioselectivity of the reaction. With the aim of clarifying this aspect we studied by NMR spectroscopy the behavior in solution of the π-phenylallyl-(*S*)-**7**–palladium complex.

$^{31}P\{^1H\}$ NMR spectrum of [Pd(PhCHCHCHPh)(*S*)-**7**]$^+$, **9**, in chloroform-*d* solution showed a broad signal at δ 146.42 ppm indicating that exchange processes are present in solution. By running ^1H 2D NOESY and ^{13}C, ^1H correlation spectra[6] it was possible to recognize in solution four different isomers, but we were able to determine only the structures of the two major conformers. The isomer present in greater amount (56%) was identified as *endo–syn–syn*–[Pd(PhCHCHCHPh)(*S*)-**7**]$^+$ (Fig. 4). In fact, the proton H_a at δ 6.54 ppm (broad doublet) showed an NOE with H_b (δ 6.25 ppm, broad multiplet); the absence of any cross peaks between H_a or H_b with H_c (δ 6.45 ppm, broad triplet) was a further confirmation[7] of the assigned structure. The ^{13}C NMR spectrum revealed allylic carbon resonances lying in a very narrow range: C_a, δ 127.37 ppm; C_b, δ 126.86 ppm; C_c, δ 114.37 ppm. The almost negligible chemical shift difference between the two allylic terminal carbons C_a and C_b is typical for nuclei residing in a similar chemical environment.[8]



***endo syn-syn*-9** ***eso syn-anti*-9**

Figure 4.

The second isomer (37%) presented a broad peak doublet at δ 5.07 ppm assigned as H_a^*, a broad multiplet at δ 6.15 ppm, H_b^*, and a broad triplet at δ 5.93 ppm, H_c^*. The presence of an NOE cross peak between H_a^* and H_c^* led us to confirm an *exo–syn–anti* conformation for this isomer. The $^{13}C,^1H$ correlation allowed us to assign allylic carbon atoms for this isomer: The allylic ^{13}C resonances had substantially different chemical shifts: C_a^*, δ 74.10 ppm; C_b^*, δ 116.92 ppm; C_c^*, δ 97.42 ppm. These results let us conclude that between the two terminal allylic carbons the more deshielded nucleus C_b^* is the preferred site for the nucleophilic attack in allylic alkylation.[8]

As NMR studies demonstrated, the five-membered chelate ring increases the ratio of the two Pd–allyl configurational isomers among the four possible[9] formed in solution, but this is not sufficient to obtain a high asymmetric induction.

3. Experimental

Solvents were dried by standard procedures. All experiments were performed under purified argon. For column chromatography, silica gel 60 (220–440 mesh) purchased from Fluka was used. 1D- and 2D-NMR experiments were carried out using a Bruker AMX R300 spectrometer. ^1H NMR spectra were referenced to internal tetramethylsilane and $^{31}P\{^1H\}$ spectra to external 85% H_3PO_4. Standard pulse sequences were employed for ^1H-2D-NOESY, $^{13}C,^1H$-, $^{31}P,^1H$-correlation studies.[10] The phase-sensitive NOESY experiments used mixing times of 0.8 s. Elemental analyses were performed by Redox s.n.c., Monza, Milan.

3.1. (S)-2-(3,5-Dioxa-4-phosphacyclohepta[2,1-a;3,4-a′]dinaphthalen-4-yloxymethyl)-6-methyl-pyridine **4**

A solution of (6-methyl-pyridin-2-yl)methanol (0.215 g, 1.75 mmol) and Et_3N (0.708 g, 7.00 mmol) in toluene (5 ml) was added dropwise to a solution of (*S*)-2,2′-binaphthol phosphorochloridite[10] (0.612 g, 1.75 mmol) in the same solvent (10 ml) at 0°C. The reaction mixture was stirred overnight at room temperature and then the precipitate of $Et_3N{\cdot}HCl$ formed was removed by filtration. The toluene was evaporated from the filtrate. The residue was washed with hexane (5 ml) and dried. A white solid was obtained in 78% yield (0.597 g, 1.36 mmol). ^1H NMR (C_6D_6) δ 2.41 (s, 3H), 5.20 (m, 2H), 6.65 (d, 1H, $J=6.0$ Hz), 7.01–7.71 (m, 14H). $^{31}P\{^1H\}$ NMR (C_6D_6) 139.4 (s). Anal. calc. for $C_{27}H_{20}NO_3P$: C, 74.14; H, 4.61; N, 3.20. Found: C, 74.35; H, 4.69; N, 3.14.

3.2. 2-Bromo-(S)-6-(3,5-dioxa-4-phosphacyclohepta[2,1-a;3,4-a′]dinaphthalen-4-yloxymethyl)pyridine **5**

This compound was obtained by an analogous procedure to **4**, as a white solid, by reaction of (6-bromopyridin-2-yl)methanol (synthesized by reduction of the corresponding aldehyde[11]) (0.282 g, 1.50 mmol) and (*S*)-2,2′-binaphthol phosphorochloridite (0.525 g, 1.50 mmol). Yield: 90% (0.678 g, 1.35 mmol). ^1H NMR (C_6D_6) δ 5.03 (m, 2H), 7.13–7.68 (m, 11H), 7.97–8.08 (m,

4H). $^{31}P\{^1H\}$ NMR (C_6D_6) 138.1 (s). Anal. calc. for $C_{26}H_{17}BrNO_3P$: C, 62.17; H, 3.41; N, 2.79. Found: C, 62.37; H, 3.34; N, 2.85.

3.3. (S)-2-(3,5-Dioxa-4-phosphacyclohepta[2,1-a;3,4-a′]dinaphthalen-4-yloxymethyl)-6-phenyl-pyridine **6**

This compound was obtained by an analogous procedure to **4**, as a white solid, by reaction of (6-phenylpyridin-2-yl)methanol[12] (0.185 g, 1.00 mmol) and (*S*)-2,2′-binaphthol phosphorochloridite (0.350 g, 1.00 mmol). Yield: 85% (0.361 g, 0.85 mmol). ^1H NMR (C_6D_6) δ 5.24 (m, 2H), 7.01–7.80 (m, 14H), 8.08–8.16 (m, 2H). $^{31}P\{^1H\}$ NMR (C_6D_6) 138.8 (s). Anal. calc. for $C_{32}H_{22}NO_3P$: C, 76.95; H, 4.44; N, 2.80. Found: C, 76.77; H, 4.36; N, 2.74.

3.4. (S)-(3,5-Dioxa-4-phosphacyclohepta[2,1-a;3,4-a′]dinaphthalen-4-yl)-pyridin-2-yl-amine **7**

A solution of (*S*)-2,2′-binaphthol phosphorochloridite (0.410 g, 1.17 mmol) in toluene (7 ml) was added dropwise to a solution of 2-aminopyridine (0.275 g, 2.92 mmol) in the same solvent (10 ml) at −10°C. The resulting solution was stirred overnight at room temperature and then the solvent was vacuum evaporated. The pure ligand **7** was extracted by toluene/hexane (3:1) from the resulting white powder. Yield 77% (0.368 g, 0.901 mmol). ^1H NMR (C_6D_6) δ 4.96 (s, 1H), 6.59–6.85 (m, 3H), 7.31–7.62 (m, 11H), 7.92–8.08 (m, 9H), 8.12 (d, $J=6.0$ Hz, 1H). $^{31}P\{^1H\}$ NMR (C_6D_6) 146.5 (s). Anal. calc. for $C_{25}H_{17}N_2O_2P$: C, 73.52; H, 4.20; N, 6.86. Found: C, 73.23; H, 4.29; N, 7.02.

3.5. (4,6-Dimethyl-pyridin-2-yl)-(S)-(3,5-dioxa-4-phosphacyclohepta[2,1-a;3,4-a′]dinaphthalen-4-yl)-amine **8**

This compound was obtained by an analogous procedure to **7**, as a white solid, by reaction of 4,6-dimethyl-pyridin-2-ylamine (0.275 g, 2.25 mmol) and (*S*)-2,2′-binaphthol phosphorochloridite (0.315 g, 0.90 mmol). Yield: 58% (0.228 g, 0.522 mmol). ^1H NMR (C_6D_6) δ 2.44 (s, 3H), 2.54 (s, 3H), 4.79 (s, 1H), 5.79 (s, 1H), 5.99 (s, 1H), 6.99–7.27 (m, 7H), 7.4–7.80 (m, 11H). $^{31}P\{^1H\}$ NMR (C_6D_6) 147.0 (s). Anal. calc. for $C_{27}H_{21}N_2O_2P$: C, 74.30; H, 4.85; N, 6.42. Found: C, 74.45; H, 4.93; N, 6.37.

3.6. [Pd(η^3-PhCHCHCHPh)((S)-**7**)]CF_3SO_3 **9**

A solution of **7** (0.255 g, 0.625 mmol) in CH_2Cl_2 (3 ml) was added to a stirred solution of [Pd(η^3-PhCHCHCHPh)(μ-Cl)]$_2$[13] (0.164 g, 0.250 mmol) in the same solvent (10 ml). After ca. 30 min, $AgCF_3SO_3$ (0.130 g, 0.500 mmol) was added, and the precipitated AgCl filtered on Celite. The filtrate was vacuum reduced to ca. 3 ml and addition of hexane (20 ml) gave a yellow solid. Yield: 86% (0.364 g, 0.425 mmol). ^1H ($CDCl_3$): δ 6.45 (br t, H_c), 6.05 (br d, H_a), 6.25 (br m, H_b) 5.93 (br t, H_c^*), 5.07 (br d, H_a^*), 6.15 (br m, H_b^*). ^{31}P $\{^1H\}$ ($CDCl_3$): δ 146.42 (br s). Anal. calc. for $C_{41}H_{30}F_3N_2O_5PPdS$: C, 57.45; H, 3.53, N, 3.27. Found: C, 57.56; H, 3.47 N, 3.20.

Acknowledgements

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