Enantioselective Palladium Catalyzed Allylic Amination Using New Chiral Pyridine-Phosphine Ligands

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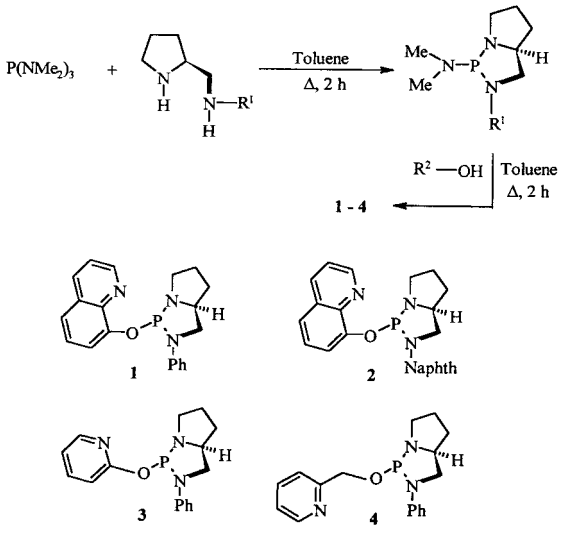
Received 8 October 1997

Abstract: Asymmetric palladium catalyzed allylic amination of **5** with various amines has been studied using a new class of chiral pyridine-phosphine ligands. High enantioselectivities of up to 94% *ee* have been observed using benzylamine, veratrylamine or morpholine as nucleophiles.

In recent years, various C_2-symmetric and non symmetric chiral ligands bearing phosphine(s), nitrogen(s) and/or sulfur(s) have been developed and used in numerous transition metal catalyzed reactions[1] such as hydrogenations[2] and allylic substitutions[3]. Thus, a wide class of non symmetric chiral PN-, SN- type ligands were efficiently used as ligands for catalytic asymmetric reactions, on the basis of their electronic as well as steric effects[4,5]. In almost these cases, the phosphorus atom is not stereogenic, the chirality being induced by a chiral oxazoline or imidazoline group which have been recognized as effective parts inducing high enantioselectivity[4b].

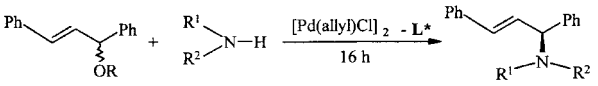
Recently, we described the use of a new non symmetric chiral ligand bearing the chirality at the phosphorus atom in a palladium catalyzed asymmetric alkylation with enantioselectivities up to 87%[6]. We report the preparation of various analogues of chiral ligand **1** and their application to the palladium catalyzed asymmetric allylic amination[7].

Diastereoselective synthesis of ligands **1-4** was accomplished by exchange reaction in refluxing toluene between tris(dimethylamino)phosphine and (*S*)-2-anilinomethylpyrrolidine or (*S*)-2-naphthylaminomethylpyrrolidine followed by addition of the corresponding hydroxyquinoline, hydroxymethylpyridine or hydroxypyridine[8,9].



Asymmetric allylic amination of 1,3-diphenyl-2-propenyl acetate **5a** or 1,3-diphenyl-2-propenyl carbonate **5b** with primary or secondary amines was carried out with palladium(II)-phosphines **1-4** complex catalysts (Table 1).

Table 1 . Enantioselective palladium catalyzed allylic amination of rac-(*E*)-**5a** or **5b** with various amines



5a : R = Ac
5b : R = COOMe

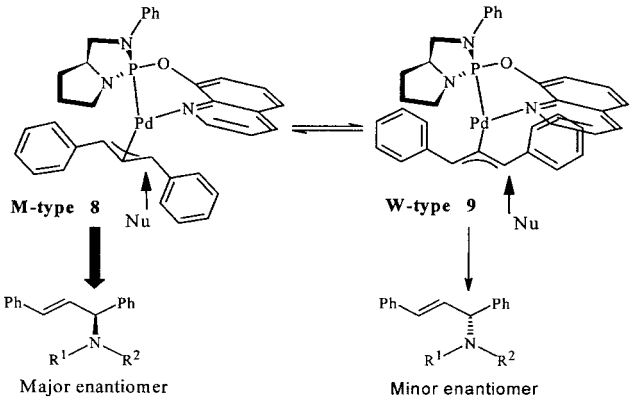
6 **7**

Entry[a]	Ligand	Temp (°C)	Substrate	Amine	Conv (%)[b]	*ee* (%)[c]
1	**1**	-10	**5a**	$PhCH_2NH_2$	70	77 (*S*)[d]
2	**1**	-10	**5a**	$PhCH_2NH_2$	100	79 (*S*)[d]
3	**1**	-20	**5a**	$PhCH_2NH_2$	100	84 (*S*)[d]
4	**1**	-20	**5b**	$PhCH_2NH_2$	100	80 (*S*)[d]
5	**1**	20	**5a**	$PhCH_2NH_2$	100	73 (*S*)[d]
6	**1**	**-10**	**5a**	**$PhCH_2NH_2$**	**95**	**93 (*S*)**[d]
7	**2**	-10	**5a**	$PhCH_2NH_2$	36	78 (*S*)[d]
8	**3**	-10	**5a**	$PhCH_2NH_2$	70	92 (*S*)[d]
9	**4**	**-10**	**5a**	**$PhCH_2NH_2$**	**95**	**93 (*S*)**[d]
10	**1**	**-10**	**5a**	**$PhCH_2NH_2$**	**75**	**92 (*S*)**[d]
11	**1**	**-10**	**5a**	**Veratrylamine**	**97**	**94 (*S*)**[e]
12	**1**	-10	**5b**	Veratrylamine	98	93 (*S*)[e]
13	**1**	-10	**5a**	Morpholine	88	88 (*S*)[f]

[a] All experiments were performed on a 0.5 mmole scale in toluene during 16 hours using 2 mol% of $[\{(\eta^3\text{-}C_3H_5)PdCl\}_2]$ (Pd/L* =1/4) except for entry 1 and 2, respectively performed in diethylether and dichloromethane. [b] Conversion determined by HPLC analysis. [c] Ee measured on a Daicel Chiralcel OD-H column at λ = 254 nm. [d] flow rate 0.5 mL/Min ; eluent : hexane/*i*-PrOH 200/1 , t_R = 21.0 min, t_S = 22.3 min. [e] flow rate 1.2 mL/Min ; eluent : hexane/*i*-PrOH/NEt_3 90/10/0.05 , t_R = 9.9 min, t_S = 18.9 min. [f] Ee measured by CPG analysis on a chiral Lipodex E column

Using benzylamine as test nucleophile, a dramatic solvent effect on the conversion is observed. Thus, under various experimental conditions no reaction occurred in THF. Diethylether (entry 1) and dichloromethane (entry 2) led respectively to 70% and 100% conversion of **5a** with a good enantiomeric excess (*ee*) (77 and 79% *ee* respectively). Nevertheless, the best results were obtained using toluene as solvent. A total conversion was observed and the desired product **7** obtained with an *ee* up to 93% (entry 6). Moreover, a significant effect of the temperature has been noticed and the best results were obtained at -10°C (entries 3-6). The effect of the ligand used has also been taken into account. Ligands **1** and **4** led to excellent results in terms of enantioselectivity at -10°C (93% *ee*) (entries 6 and 9). Nevertheless, under the best experimental conditions, ligands **2** and **3** led to the desired product with lower ee and an incomplete conversion (entries 7 and 8). Even with 1 mol% of the palladium catalyst, the reaction proceeded in high enantioselectivity (92% *ee*, entry 10) and the product was isolated in 80% chemical yield. Excellent results have been also obtained using veratrylamine (94% ee, entries 11 and 12) and morpholine (88% *ee*, entry 13) as nucleophiles.

It is generally well assumed that the enantioselective step in palladium catalyzed allylic amination is the substitution of π-allyl complexes with nucleophiles, the nucleophilic attack occurring predominantly at the alkyl terminus *trans* to the better π-acceptor (P>>N)[4,10,11]. Since the (*S*) product was obtained as the major enantiomer the reaction probably proceeds through an M-type.



This model proposes that trapping of the π-allyl species occurs opposite to the phosphine, as its superior π-accepting properties makes C-1 of the allylic acetate electron deficient. Therefore, based on this analysis, **8** rather than **9** would be the diastereomeric complex responsible for the product[12].

In summary, we have demonstrated that palladium complexes derived from new chiral pyridine-phosphine ligands are efficient catalysts for allylic aminations leading to enantioselectivities up to 94% *ee*. Further studies are under current investigation in order to use these new ligands in other asymmetric reactions.

References and Notes

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(7) Various groups have already reported high ee in asymmetric palladium catalyzed allylic amination, for example see : (a) Hayashi, T.; Yamamoto, A.; Ito, Y.; Nishioka, E.; Miura, H.; Yanagi, K. *J. Am. Chem. Soc*. **1989**, *111*, 6301. (b) Trost, B. M.; Van Vranken, D. L. *J. Am. Chem. Soc*. **1993**, *115*, 444. (c) Togni, A.; Burkhardt, U.; Gramlich, V.; Pregosin, P. S.; Salzmann, R. *J. Am. Chem. Soc*. **1996**, *118*, 1031. (d) Von Matt, P.; Loiseleur, O.; Koch, G.; Pfaltz, A.; Lebefer, C.; Feucht, T.; Helmchen, G. *Tetrahedron Asymmetry* **1994**, *5*, 573.

(8) The reaction was monitored by ^{31}P NMR spectroscopy and after 2 h, the solvent was removed under vacuum. The product was purified by column chromatography (eluent : AcOEt/petroleum ether) affording the corresponding ligands **1-4** in good chemical yields and in a total *anti* diastereoselectivity. *Syn* diastereomer could not be obtained due to the highly unstable intermediate compound which totally epimerizes at the phosphorus atom to produce the thermodynamic diastereomer *anti*. (a) Cros, P.; Buono, G.; Peiffer, G.; Denis, D.; Mortreux, A.; Petit, F. *New. J. Chem.* **1987**, *11*, 573. (b) Arzoumanian, H.; Buono, G.; Choukrad, M'B.; Petrignani, J. F. *Organometallics* **1988**, *7*, 59. (c) Brunel, J. M.; Chiodi, O.; Faure, B.; Fotiadu, F.; Buono, G. *J. Organomet. Chem.* **1997**, *529*, 285. The definitions of the *syn* and *anti* isomers are according to the position of the pyrrolidine ring and the aryl group. If they are at the same side of the five membered phosphorus-containing ring, we call it a *syn* isomer; otherwise, it is an *anti* isomer.

(9) **1** : White solid ; m.p. = 135°C ; $[\alpha]^{20}_D$ = -45.6 (*c* = 1, CH_2Cl_2) ; ^{1}H NMR δ (ppm, $CDCl_3$) 1.52-2.27 (m, 4H), 3.38-3.64 (m, 2H), 3.81-4.03 (m, 3H), 7.02-7.57 (m, 9H), 8.18-8.28 (dd, J = 16 Hz, 1H), 8.95-9.05 (dd, J = 16 Hz, 1H) ; ^{13}C δ (ppm, $CDCl_3$) 26.5, 26.6, 31.9, 47.6, 48.2 (d, J = 13 Hz), 53.7, 62.5, 115.3 (d, J = 13 Hz), 119.4, 121.0, 121.7, 127.2, 128.9, 130.1, 135.7, 148.7 ; ^{31}P δ (ppm, $CDCl_3$) 128.6. **2** : White solid ; m.p. = 152°C ; $[\alpha]^{20}_D$ = -39.3 (*c* = 1, CH_2Cl_2) ; ^{1}H NMR δ (ppm, $CDCl_3$) 1.51-2.12 (m, 4H), 3.29-3.42 (m, 2H), 3.74-4.03 (m, 3H), 7.01-7.86 (m, 12H), 8.15-8.25 (dd, J = 16 Hz, 1H), 8.97-9.02 (dd, J = 16 Hz, 1H) ; ^{13}C δ (ppm, $CDCl_3$) 26.5, 26.6, 31.9, 47.6, 48.2 0 (d, J = 12 Hz), 53.7, 62.5, 115.3 (d, J = 13 Hz), 119.2, 121.2, 121.5, 121.7, 123.2, 124.8, 127.2, 128.9, 130.1, 135.7, 148.7 ; ^{31}P δ (ppm, $CDCl_3$) 138.0. **3** : Pale yellow oil ; $[\alpha]^{20}_D$ = -39.2 (*c* = 1, CH_2Cl_2) ; ^{1}H NMR δ (ppm, $CDCl_3$) 1.77-1.99 (m, 5H), 3.12-3.46 (m, 3H), 3.80-4.30 (m, 1H), 6.76-7.34 (m, 9H) ; ^{13}C δ (ppm, $CDCl_3$) 26.4, 31.6, 46.4, 50.0 (d, J = 13 Hz), 53.8, 116.5, 116.7 (d, J = 14 Hz), 121.4, 121.8, 121.9, 124.9, 129.2, 129.5 ; ^{31}P δ (ppm, $CDCl_3$) 124.1. **4** : White solid ; $[\alpha]^{20}_D$ = -35.2 (*c* = 1, CH_2Cl_2) ; ^{1}H NMR δ (ppm, $CDCl_3$) 1.77-1.89 (m, 5H), 3.15-3.46 (m, 3H), 3.80-4.52 (m, 3H), 6.76-7.34 (m, 9H) ; ^{13}C δ (ppm, $CDCl_3$) 26.4 (d, J = 3Hz),, 30.6, 40.5, 46.4, 49.5 (d, J = 13 Hz), 53.10 (d, J = 5 Hz), 116.5 (d, J = 14 Hz), 116.7, 119.4, 120.8, 120.9, 123.9, 129.2, 130.5 ; ^{31}P δ (ppm, $CDCl_3$) 122.1.

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(12) In the structure of diastereomeric complexes **8** and **9**, the absolute configuration at the phosphorus atom has been well established by X-ray analysis structure of ligand **1**. Brunel, J. M.; Constantieux, T.; Buono, G. Unpublished results.