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Enantioselective Palladium Catalyzed Allylic Substitution with New Chiral Pyridine-Phosphine Ligands

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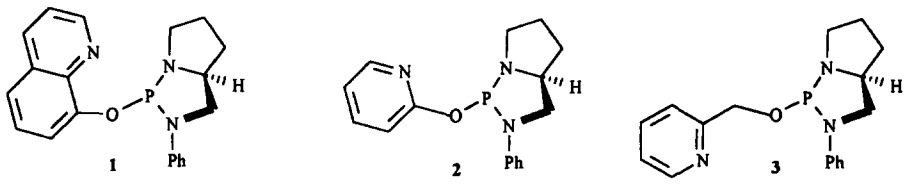
Abstract : The synthesis of new chiral pyridine-phosphine ligands **1-3** was achieved and assessed in the enantioselective palladium catalyzed allylic substitution of 1,3-diphenyl-2-propenyl acetate **4** with dimethylmalonate **5**. Enantioselectivities up to 87% were obtained. © 1997 Elsevier Science Ltd.

In the last few years, there was a great interest in asymmetric variants of palladium catalyzed allylic reaction[2]. In this context, we have witnessed to the design of chiral ligands capable of effective highly enantioselective reactions. Among them, C_2 symmetric diphosphines[3] and P,N-oxazolines[4] have been the most studied. Akermark *et al.*[5] were the first to report that the reactivity of the palladium allyl complex was dependent upon the nature of the ligands coordinated to the metal. Thus, strongly π-accepting ligands such as phosphines and phosphites generate highly reactive palladium complexes, whereas nitrogen ligands afford less reactive species. It seems that the allyl terminus *trans* to the π-accepting phosphorus atom was more electrophilic than the position *trans* to the nitrogen atom (which is not a π-acceptor)[6]. Although the use of chiral pyridine-phosphine ligands in palladium catalysis has also been described, only few attempts led to enantiomeric excesses (ee) up to 9%[7].

Based on these principles, the synthesis of new chiral pyridine-phosphine ligands and their ability to control enantioselective Pd-catalyzed allylic substitution have been investigated. Thus, contrarily to the usual methodology encountered in literature, we decided to prepare chiral ligands at the phosphorus atom and not on the pyridine moiety.

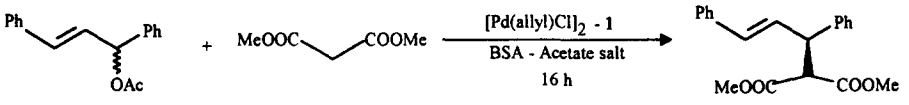
Synthesis of ligand **1-3** was readily achieved by exchange reaction in refluxing toluene between tris(dimethylamino)phosphine and (*S*)-(+)-2-anilinomethylpyrrolidine followed by of the corresponding pyridine. The reaction was monitored by ^{31}P NMR spectroscopy and after 1 hour the solvent was removed under vacuum. The product was purified by column chromatography affording the corresponding ligands **1-3** in good chemical yields and in total *anti* diastereoselectivity[8].



Scheme 1

We investigated the catalytic properties of the palladium complexes formed *in situ* from these ligands and $[Pd(allyl)Cl]_2$ in an allylic alkylation of 1,3-diphenyl-2-propenyl acetate **4** by the nucleophile generated from dimethylmalonate with bis-trimethylsilyl acetamide (BSA) and a small amount of an acetate salt (Table 1).

Table 1 : Enantioselective allylic alkylation of **4** with dimethylmalonate



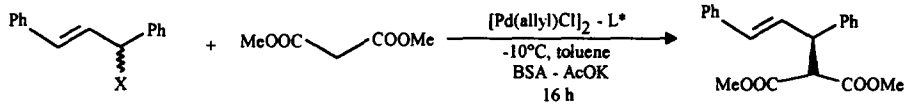
Entry[a]	Solvent	Temperature (°C)	Ratio **1**/Pd	Acetate salt	Conversion (%)[b]	ee (%)[c]
1	THF	20	1	AcONa	74	50 (*R*)
2	THF	20	2	AcONa	65	51 (*R*)
3	THF	20	3	AcONa	85	50 (*R*)
4	THF	20	4	AcONa	75	60 (*R*)
5	THF	20	5	AcONa	80	63 (*R*)
6	THF	-10	4	AcONa	100	70 (*R*)
7	THF	-10	4	AcOK	100	74 (*R*)
8	THF	-10	4	AcOCs	100	70 (*R*)
9	Et_2O	-10	4	AcOK	100	76 (*R*)
10	Toluene	20	4	AcOK	100	75 (*R*)
11	**Toluene**	**-10**	**4**	**AcOK**	**100**	**85 (*R*)**
12	DMF	-10	4	AcOK	100	73 (*R*)
13	CH_2Cl_2	-10	4	AcOK	100	80 (*R*)

[a] Experiments performed on a 0.5 mmole scale during 16 hours using 2 mol% of $[\{(\eta^3\text{-}C_3H_5)PdCl\}_2]$. [b] Conversion determined by HPLC analysis. [c] Ee measured on a Daicel Chiralcel OD-H column at λ = 254 nm ; flow rate 0.5 mL/Min ; eluent : hexane/*i*-PrOH 200/1 , t_R = 23.04 min, t_S = 21.25 min.

We first examined the use of ligand **1** in a variety of solvents, temperature and ratio of ligand to palladium. Toluene appears to be the best solvent (entry 11). The lowering in enantioselectivity observed in changing to the more coordinating solvent DMF suggests that the ligand may be being displaced by the solvent. A decrease in temperature from room temperature to -10°C led to improved enantioselectivity (75% ee *versus* 85% respectively). Increasing the ratio of **1**/Pd from 1/1 to 1/4 improved also the ee (50% ee *versus* 63% ee). Moreover, the influence of the acetate salt added has been studied and the best result was achieved using potassium acetate (entry 7).

Under the best conditions (entry 11, Table 1), ligands **2** and **3** provided level of enantioselectivity comparable to that obtained with ligand **1**. Furthermore, the use of $Pd(dba)_2$ as well as the dimethylsodiomalonate as the incoming nucleophile have no significant influences (entry 7 and 8 respectively) (Table 2).

Table 2 : Enantioselective allylic alkylation of 1,3-diphenyl-substituted substrates **4a** and **4b**.



4a X = OAc — **5** — **6**

4b X = OCOOEt

Entry	Substrate	Ligand	Conversion (%)[d]	ee (%)[e]
1	**4a**[a]	**1**	100	85 (*R*)
2	**4b**[a]	**1**	100	87 (*R*)
3	**4a**[a]	**2**	100	87 (*R*)
4	**4b**[a]	**2**	98	83 (*R*)
5	**4a**[a]	**3**	85	76 (*R*)
6	**4b**[a]	**3**	97	78 (*R*)
7	**4a**[b]	**1**	100	80 (*R*)
8	**4a**[a,c]	**1**	100	71 (*R*)

[a] Experiments performed on a 0.5 mmole scale during 16 hours using 2 mol% of $[\{(\eta^3\text{-}C_3H_5)PdCl\}_2]$. [b] Experiment performed using 2 mol% of $Pd(dba)_2$ as palladium source. [c] Experiment performed using $NaCH(CO_2Me)_2$ in place of $MeO_2CCH_2CO_2Me$ and BSA with catalytic KOAc as the nucleophilic component. [d] Determined by HPLC analysis. [e] Ee measured on a Daicel Chiralcel OD-H column at λ = 254 nm ; flow rate 0.5 mL/Min ; eluent : hexane/*i*-PrOH 200/1 , t_R = 23.04 min, t_S = 21.25 min.

In conclusion, we have shown that readily accessible pyridine-phosphine compounds are efficient ligands for palladium catalyzed allylic substitutions. Further studies including modification to ligands design and mechanistic aspects are in progress.

References.

(1) e-mail : buono@spi-chim.u-3mrs.fr ; fax : 04-91-02-77-76

(2) For general reviews on palladium catalyzed allylic substitution, see : (a) Godleski, S. A. in Comprehensive Organic Synthesis, Eds Trost, B. M. ; Fleming, I. ; Pergamon Press, Oxford, **1991**, *4*, 585. (b) Consiglio, G. ; Waymouth, R. *Chem. Rev.* **1989**, *89*, 257-270. (c) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1173-1180. (d) Reiser, O. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 547. (e) Dawson, G. J. ; Williams, J. M. J. ; Coote, S. J. *Tetrahedron Asymmetry* **1995**, 2535-2546 and références therein. (f) Trost, B. M. ; van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395-422.

(3) For example : (a) Trost, B. M. ; Organ, M. G. ; O'doherty, G. A. *J. Am. Chem. Soc.* **1995**, *117*, 9662-9670. (b) Bolm, C. ; Kaufmann, D. ; Gessler, S. ; Harms, K. *J. Organomet. Chem.* **1995**, *502*, 47-52. (c) Seebach, D. ; Devaquet, E. ; Ernst, A. ; Hayakawa, M. ; Kühnle, F. N. M. ; Schweizer, W. B. ; Weber, B. *Helv. Chim. Acta* **1995**, *78*, 1636-1650.

(4) (a) von Matt, P. ; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 566-569. (b) Sprinz, J. ; Helmchen, G. *Tetrahedron Lett.* **1993**, *34*, 1769-1773. (c) Dawson, G. J. ; Frost, C. G. ; Williams, J. M. J. ; Coote, S. J. *Tetrahedron Lett.* **1993**, *34*, 3149-3150.

(5) Akermark, B. ; Hansson, S. ; Krakenberger, B. ; Vitagliano, A. ; Zetterberg, K. *Organometallics* **1984**, *3*, 679-682. (b) Akermark, B. ; Krakenberger, B. ; Hansson, S. ; Vitagliano, A. *Organometallics* **1987**, *6*, 620-628. (c) Peña-cabrera, E. ; Norrby, P. ; Sjögren, M. ; Vitagliano, A. ; De Felice, V. ; Oslob, J. ; Ishii, S. ; O'Neill, D. ; Akermark, B. ; Helquist, P. *J. Am. Chem. Soc.* **1996**, *118*, 4299-4313.

(6) For reviews dealing with the stereocontrol of palladium catalyzed allylic substitution reactions, see : (a) Frost, C. G. ; Williams, J. M. J. *Tetrahedron Asymmetry* **1992**, *3*, 1089-1122. (b) Hayashi, T. in Catalytic Asymmetric Synthesis, VCH, Weinheim, Ed. Ojima, I., **1993**. (c) Williams, J. M. J. *Synlett* **1996**, 705-710.

(7) Chelucci, G. ; Cabras, M. A. ; Botteghi, C. ; Marchetti, M. *Tetrahedron Asymmetry* **1996**, *7*, 885-889.

(8) **1** was prepared by exchange reaction at 110°C in 20 mL of anhydrous toluene between 163 mg of tris(dimethylamino)phosphine (1 mmole) and 176 mg of (*S*)-(+)-2-anilinomethylpyrrolidine (1 mmole) for 2 hours, followed by subsequent addition of 136 mg of hydroxyquinoleine (1 mmole). Purification by flash chromatography using ethylacetate as eluent afforded ligand **1** in 72% chemical yield as a white solid stable to air and moisture. Similar procedure was used in order to prepare ligands **2** and **3**.

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