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Journal of Molecular Catalysis A: Chemical 212 (2004) 61–64
JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL
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Enantioselective palladium catalyzed allylic substitution with a new phosphite ligand issued from (2*S*,5*S*)-hexanediol

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Received 20 June 2003; received in revised form 8 October 2003; accepted 28 October 2003

Abstract

The synthesis of a new phosphite ligand **4** was achieved and assessed in the enantioselective palladium catalyzed allylic substitution of 1,3-diphenyl-2-propenyl acetate **1** with enantioselectivities up to 66% e.e.

Keywords: Enantioselective; Palladium; Phosphite ligand

1. Introduction

In the last few years, there was a great interest in asymmetric variants of palladium catalyzed allylic reactions [1–11]. In this context, the design of new highly efficient chiral ligands has been investigated. Among them, C_2 symmetric diphosphines [12–14] and P,N-oxazolines [15–17] have been thoroughly described. However, monophosphines or more generally ligands with one phosphorus, linked to one or several heteroatoms, may also be useful. Thus, the field of chiral monophosphines has not been widely studied even if literature indicates that greater attention should be devoted to this family of compounds [18–21]. On the basis of such considerations, the synthesis of a new chiral monophosphite ligand and its ability to control enantioselective Pd-catalyzed allylic substitution has been investigated (Scheme 1).

We decided to prepare a new chiral phosphite ligand **4** from (−)-menthol and (2*S*,5*S*)-hexanediol readily available through baker's yeast reduction of acetonylacetone [22]. Synthesis of ligand **4** was achieved by reaction of PCl_3 with (1*R*,2*S*,5*S*)-menthol in THF at room temperature for 1 h followed by addition of one equivalent of (2*S*,5*S*)-hexanediol in the presence of NEt_3. The reaction was monitored by ^{31}P NMR spectroscopy and after 1 h, the solvent was removed under vacuum. The product was purified by column chromatography affording the expected ligand **4** as a clear air- and moisture-stable oil in 72% chemical yield (Scheme 2) [23].

We have investigated the catalytic properties of the palladium complexes formed in situ from this ligand and $[Pd(allyl)Cl]_2$ in an allylic alkylation of 1, 3-diphenylprop-3-en-1-yl acetate (**1**) by the nucleophile generated from dimethylmalonate with *N*,O-bis(trimethylsilyl)acetamide (BSA) and a catalytic amount of an acetate salt (Table 1).

Thus, we have examined the use of ligand **4** in a variety of solvents, temperature conditions and ratios ligand palladium in allylic alkylation (Table 1). Dichloromethane appears to be the best solvent (entry 3, 35% e.e.). The observed decrease in enantioselectivity by changing to the more coordinating solvent DMF suggests that the ligand may be displaced by the solvent (entry 4, 2% e.e.). Lowering the temperature from 25 to −20 °C does not improve the enantioselectivity (entries 6, 28% e.e.). Increasing the ratio of **4**/Pd from 1/1 to 1/4 improved the e.e. (20% e.e. versus 35% e.e.). Moreover, the influence of the acetate salt added has been studied and the best result was achieved using potassium acetate (entry 3, 35% e.e.) whereas sodium and silver acetate salts led to lower enantiomeric excesses (entries 7 and 8, 29 and 0% e.e., respectively).

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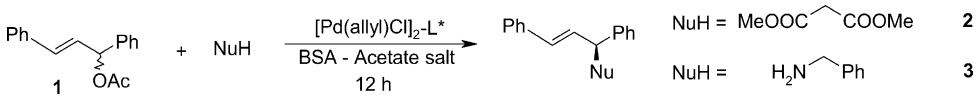
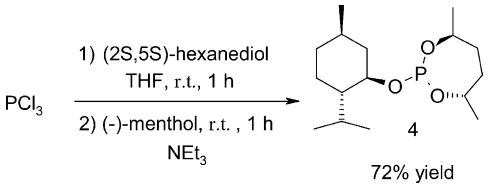
doi:10.1016/j.molcata.2003.10.031



Scheme 1.



Scheme 2.

It is well known that the substrate leaving group or the counterion of the catalyst complex may influence the enantioselectivity of the reaction (for a detailed investigation and interpretation of this particular aspect, see [24]). Thus, we decided to investigate the effect excerpted by different anions on the enantioselectivity using various additive salts (Table 2).

Spectacular decreases or increases in the enantiomeric excesses have been observed depending on the nature of the counterion associated to the ammonium species. As depicted in Table 2, an important decrease of the enantioselectivity has been noted using Br^-, or BF_4^- anions whereas the presence of Cl^-or I^- counterions improve slightly the enantiomeric excesses up to 66% e.e. (entry 3). On the other hand, the nature of the cation of the considered ammonium salt has an important effect on the outcome of the reaction in terms of enantioselectivity. Thus, the presence of a butyl, propyl or ethyl group improved the enantioselectivity (entries 3, 6 and 10; 66, 54 and 47% e.e., respectively) whereas a methyl, pentyl and benzyltrimethyl group led to an important decrease of the enantiomeric excess (entries 7, 8 and 13; 28, 22 and 0% e.e., respectively).

Table 2
Catalytic allylic alkylation of **1** in the presence of various ammonium salts

Entry[a]	Additive	Yield (%)[b]	e.e. (%)[c]
1	$[NBu_4]Br$	98	3 (*R*)
2	$[NBu_4]BF_4$	98	30 (*R*)
3	$[NBu_4]Cl$	99	66 (*R*)
4	$[NBu_4]F$	98	50 (*R*)
5	$[NBu_4]ClO_4$	93	37 (*R*)
6	$[N(propyl)_4]Br$	90	54 (*R*)
7	$N(pentyl)_4]Br$	95	28 (*R*)
8	[N(benzyltrimethyl]Br	3	0
9	[N(hexadecyltrimethyl]Br	98	42 (*R*)
10	$[NEt_4]I$	96	47 (*R*)
11	$[NEt_4]Br$	91	36 (*R*)
12	$[NEt_4]Cl$	94	22 (*R*)
13	$[NMe_4]Br$	93	22 (*R*)
14	$[NMe_4]I$	99	20 (*R*)

[a] Experiments performed in CH_2Cl_2 on a 0.39 mmol scale during 12 h using 2 mol% of $[\{(\eta^3\text{-}C_3H_5)PdCl\}_2]$ and 0.78 mmol of ammonium salt.
[b] Isolated yield.
[c] e.e. measured on a Daicel Chiralcel OD-H column at $\lambda = 254$ nm; flow rate 1 ml min^{-1}; eluent: hexane/*i*-PrOH 200/1, $t_R = 19.57$ min,$t_S = 18.18$ min.

As an extension of this study, asymmetric allylic amination of 1, 3-diphenylprop-3-en-1-yl acetate with benzylamine was carried out with palladium-ligand **4** complex catalyst (Table 3).

Contrary to that has been already observed in the asymmetric allylic alkylation, the best experimental conditions have been encountered in toluene at −20 °C (entry 4, 38% e.e.). It is noteworthy that the variation of the ratio **4**/Pd has

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

Entry[a]	Solvent	Temperature (°C)	Ratio **4**/Pd	Acetate salt	Yield (%)[b]	e.e. (%)[c]
1	THF	25	4/1	AcOK	36	0
2	Toluene	25	4/1	AcOK	20	0
3	CH_2Cl_2	25	4/1	AcOK	92	35 (*R*)
4	DMF	25	4/1	AcOK	54	2 (*R*)
5	CCl_4	25	4/1	AcOK	3	0
6	CH_2Cl_2	−20	4/1	AcOK	98	28 (*R*)
7	CH_2Cl_2	25	4/1	AcONa	95	29 (*R*)
8	CH_2Cl_2	25	4/1	AcOAg	10	0
9[d]	CH_2Cl_2	25	4/1	AcOK	49	12 (*R*)
10	CH_2Cl_2	25	1/1	AcOK	80	20 (*R*)
11	CH_2Cl_2	25	2/1	AcOK	87	30 (*R*)
12	CH_2Cl_2	25	3/1	AcOK	91	33 (*R*)

[a] Experiments performed in CH_2Cl_2 on a 0.39 mmol scale during 12 h using 2 mol% of $[\{(\eta^3\text{-}C_3H_5)PdCl\}_2]$.
[b] Isolated yield.
[c] e.e. measured on a Daicel Chiralcel OD-H column at $\lambda = 254$ nm; flow rate 1 ml min^{-1}; eluent: hexane/*i*-PrOH 200/1,$t_R = 19.57$ min, $t_S = 18.18$ min.
[d] Experiment performed using 2 mol% of $Pd(dba)_2$ instead of $[\{(\eta^3\text{-}C_3H_5)PdCl\}_2]$.

Table 3
Enantioselective allylic amination of **1** with benzylamine

Entry[a]	Solvent	Temperature (°C)	Ratio **4**/Pd	Yield (%)[b]	e.e. (%)[c]
1	THF	25	4/1	95	0
2	Toluene	25	4/1	90	37 (*S*)
3	CH_2Cl_2	25	4/1	92	27 (*S*)
4	Toluene	−20	4/1	95	38 (*S*)
5	Toluene	−20	2/1	95	30 (*S*)
6	Toluene	−20	3/1	92	31 (*S*)

[a] Experiments performed in CH_2Cl_2 on a 0.39 mmol scale during 12 h using 2 mol% of $[\{(\eta^3\text{-}C_3H_5)PdCl\}_2]$.
[b] Isolated yield.
[c] e.e. measured on a Daicel Chiralcel OD-H column at $\lambda = 254$ nm; flow rate 1 ml min^{-1}; eluent: hexane/*i*-PrOH 200/1, $t_R = 19.70$ min, $t_S = 21.70$ min.

not a significant effect on the enantioselectivity (entries 4–6; 38, 30 and 31% e.e., respectively).

2. Experimental

Tetrahydrofuran (THF) and toluene were distilled from sodium/benzophenone ketyl immediately prior to use. Dichloromethane was distilled over P_2O_5. Ethylacetate and petroleum ether (35–60 °C) were purchased from SDS and used without any previous purification. Column chromatography were performed on SDS silica gel (70–230 mesh). ^1H, ^{13}C and ^{31}P NMR spectra were recorded in $CDCl_3$ solution on a Bruker AC300 instrument (the usual abbreviations are used: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet). The positive chemical shift values are given in ppm from TMS, the coupling constants in Hertz.

2.1. General procedure for the synthesis of ligand **4**

A solution of phosphorous trichloride (2.5 g, 19 mmol) in dry THF (10 ml) was added dropwise under an argon atmosphere to a solution of (1*R*,2*S*,5*R*)-(−)-menthol (3 g, 19 mmol) in THF (10 ml). The mixture was stirred at room temperature for 1 h, then (2*S*,5*S*)-hexanediol (2.2 g, 19 mmol) diluted in THF (10 ml) and NEt_3 (5.7 g, 57 mmol) were added under argon at room temperature. After the addition was complete, the mixture was stirred for 1 h, filtered over Celite and purified by flash chromatography on a silicagel column (eluent: ethyl acetate). Ligand **4** was obtained as a clear oil stable to air and moisture.

Yield 72%; ^{31}P NMR: $\delta = 130.8$; ^1H NMR: $\delta = 4.59$–4.66 (m, 1H), 4.05–4.13 (m, 1H), 3.79 (m, 1H), 2.03–2.20 (m, 3H), 0.76–1.70 (m, 25H); ^{13}C: $\delta = 74.41$(d, $J = 22.5$ Hz), 68.76 (d, $J = 6.0$ Hz), 68.60 (d, $J = 6.0$ Hz), 48.31 (d, $J = 4.5$ Hz), 44.10 (d, $J = 3.7$ Hz), 37.10, 36.01, 34.28, 31.67, 25.16, 23.82 (d, $J = 6.0$ Hz), 23.24, 22.93, 22.06, 21.00, 15.76; $C_{16}H_{31}O_3P$ (302.40): calculated. C 63.5, H 10.3, O 15.8, P 10.2; found C 63.1, H 10.8, P 10.1.

2.2. General procedure for catalyzed allylic alkylation (Table 1, entry 3)

A mixture of $[Pd(allyl)Cl]_2$ (3 mg, 8.2×10^{-3} mmol (2 mol %)) and the ligand **4** (10 mg, 33×10^{-3} mmol) in anhydrous CH_2Cl_2 was stirred at room temperature for 15 min. A solution of 1,3-diphenylprop-3-en-1-yl acetate (100 mg, 0.396 mmol) was added and stirring was maintained for 5 min. Dimethylmalonate (157 mg, 1.18 mmol), *n*,L-bis(trimethylsilyl)acetamide (BSA, 241 mmol, 1.18 mmol) and a catalytic amount of potassium acetate (KOAc) were subsequently added. The resulting solution was stirred at 25 °C for 12 h. The solution was diluted with Et_2O (3'10 ml). The combined organic phases were dried over $MgSO_4$ and filtered. The solvent was removed in vacuo to afford a pale yellow oil that solidified on standing. The enantiomeric excesses can be determined on the crude mixture by HPLC analysis on a Daicel Chiralcel OD-H column ($\lambda = 254$ nm; flow rate 1 ml min^{-1}; eluent: hexane/*i*-PrOH 200/1, $t_S = 18.18$ min $t_R = 19.57$ min.

2.3. General procedure for palladium catalyzed allylic amination (Table 3, entry 3)

A mixture of $[Pd(allyl)Cl]_2$ (3 mg, 8.2×10^{-3} mmol (2 mol %)) and the ligand **4** (10 mg, 33×10^{-3} mmol) in anhydrous CH_2Cl_2 was stirred at room temperature for 15 min. A solution of 1,3-diphenylprop-3-en-1-yl acetate (100 mg, 0.396 mmol) was added and stirring was maintained for 5 min. Benzylamine (126 mg, 1.18 mmol) was subsequently added. The resulting solution was stirred at 25 °C for 12 h. The solution was diluted with Et_2O (3'10 ml). The combined organic phases were dried over $MgSO_4$ and filtered. The solvent was removed in vacuo to afford a pale yellow oil. The enantiomeric excesses can be determined on the crude mixture by HPLC analysis on a Daicel Chiralcel OD-H column ($\lambda = 254$ nm; flow rate 1 ml min^{-1}; eluent: hexane *i*-PrOH 200/1, $t_R = 19.7$ min, $t_S = 21.70$ min).

3. Conclusion

In conclusion, we have shown that readily accessible chiral monophosphite compound is an efficient ligand for palladium catalyzed allylic substitutions. Further studies including the design of the ligands replacing the menthol moiety and mechanistic aspects are in progress and will be published elsewhere.

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