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Letter

Enantioselective palladium-catalyzed allylic substitution with 1-diphenylphosphino-4-dialkylamino ligands

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Abstract

Various chiral 1-diphenylphosphino-4-dialkylamino ligands were easily prepared from tartaric acid. Palladium complexes of these ligands gave enantioselectivities up to 75% in the alkylation of 1,3-diphenylprop-2-enyl acetate with dimethyl malonate.

Keywords: Chiral aminophosphine; Palladium complex; Allylic substitution; Enantioselectivity

The palladium-catalyzed asymmetric allylic substitution reaction has been shown to be useful in the synthesis of various chiral molecules [1–7]. A large number of chiral ligands have been studied in this allylic substitution. The chiral ligands that produce high enantioselectivities could be divided into three families:

-ligand with a chiral side chain able to direct the attack of the nucleophile to preferentially one atom [8,9]

-ligand with a chiral environment constituting a chiral pocket [10,11]

-ligand exhibiting an electronic desymmetrization such as 'hetero-chelates' [12–17].

In the last family, the most studied ligands are *N,P*-chelates such as (phosphinoaryl)-oxazoline ligands, which are generally very efficient in the palladium-catalyzed allylic substitution, giving very high activities as well as enantioselectivities. Surprisingly, only three papers concerning the use of chiral hetero-chelates containing a dialkylamino and a diphenylphosphino group appeared until now in the literature [18–22]. In most of the examples, the chirality was on the substituents of the nitrogen via a binaphtyl unit.

In a programme concerning the synthesis and application of chiral ligands bearing a sp^3-nitrogen and a diphenylphosphino group, we evaluated the potential utilities of a number of these chiral ligands for enantioselective palladium-catalyzed allylic substitution. We report in this Letter the synthesis of a number of these

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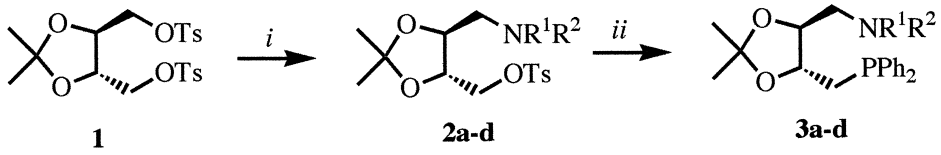


1 **2a-d** **3a-d**

i: $LiNR^1R^2$ *ii:* $LiPPh_2$

a : $R^1 = R^2 = C_6H_5$; **b** : $R^1 = C_6H_5$, $R^2 = CH_3$; **c** : $R^1 = C_6H_4$-*p*-OCH_3, $R^2 = CH_3$
d : $R^1 = C_6H_5$, $R^2 = \alpha$-naphtyl

Scheme 1.

ligands and their applications in the enantioselective palladium allylic substitution of 1,3-diphenylprop-2-enyl acetate with dimethylmalonate.

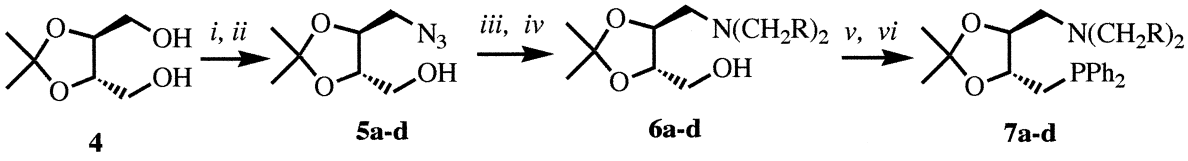
The ligands **3a–d** were prepared from the commercial bistosylate **1**. Reaction of **1** at 0°C for 4 h with lithium arylalkylamine or phenylarylamine, obtained by treatment of the corresponding amine with lithium diisopropylamine at −78°C for 1 h, gave the aminotosylate **2a–d**. Treatment of **2a–d** with lithium diphenylphosphine at room temperature in THF afforded ligands **3a–d** (see Scheme 1).

Monotosylation of diol **4** followed by reaction with sodium azide in DMF at reflux gave the azido compounds **5a–d**. Reduction of the azido function with molecular hydrogen in the presence of Pd/C, followed by alkylation of the resulting amino alcohol with various benzylic bromides in the presence of sodium carbonate afforded the dibenzylamino alcohols **6a–d**. Subsequent tosylation of compounds **6a–d** gave the corresponding aminotosylates, whose treatment with lithium diphenylphosphine at room temperature gave the corresponding aminophosphines **7a–d** (see Scheme 2).

The diaminoligand **8** (see Fig. 1) was also obtained by reaction of the ditosylate **1** with lithium diphenylamide.

We tested the ability of these new ligands in the palladium-catalyzed allylic substitution of racemic *(E)*-1,3-diphenylprop-2-enyl acetate with dimethyl malonate using an in situ catalyst prepared from $Pd_2(dba)_3$ and the chiral ligand in THF. The results are summarized in Table 1.

The ligands **DIOP** and **8**, having a C_2 symmetry, exhibited no enantioselectivity in this reaction (entries 1–2). When the reaction was performed using NaH as the base, enantioselectivities of 50, 68, 63, and 69% were obtained with ligands **3a**, **3b**, **3c**, and **3d**, respectively (entries 3–6). It seemed that the presence of two different substituents on the nitrogen gave higher enantioselectivities.

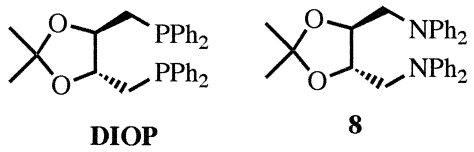


4 **5a-d** **6a-d** **7a-d**

i: TsCl, C_5H_5N; *ii:* NaN_3; *iii* : H_2, Pd/C; *iv* : RCH_2Br, Na_2CO_3; *v* : TsCl, C_5H_5N; *vi* : $LiPPh_2$

a : $R = C_6H_5$; **b** : $R = C_6H_2$-2,4,6-*tri*CH_3; **c** : R = α-naphtyl; **d** : $R^1 = C_6H_4$-*o*-C_6H_5

Scheme 2.



DIOP **8**

Fig. 1.

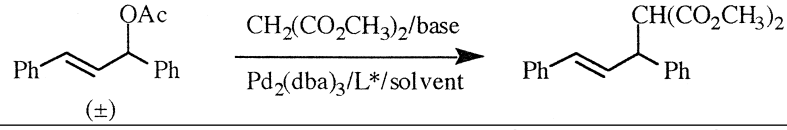
In the case of ligand **3d**, the use of BSA as the base in the presence of KOAc in THF gave lower conversion and enantioselectivity (entry 7). However, performing the alkylation in CH_2Cl_2 as the solvent, in the presence of NaH or BSA/KOAc as the base, gave a very active catalyst with enantioselectivity up to 68% (entries 8–9).

The palladium complex generated from $Pd_2(dba)_3$ and ligand **7** was also an effective catalyst for the asymmetric allylic alkylation of (*E*)-1,3-diphenylprop-2-enyl acetate with the sodium salt of dimethyl malonate, enantiomeric excess up to 75% being obtained (entries 10–13). However, it seems that the presence of a too bulky group at the ortho position lowered the enantioselectivity of the alkylation reaction (compare entries 10 and 13).

Preliminary experiments concerning the use of ligands **3d** and **7c** associated with $[Rh(\mu\text{-}OMe)(COD)]_2$ in the hydroformylation of styrene at 65°C and 30 atm gave enantioselectivities up to 18 and 15%, respectively, with a *iso*/*n* ratio of 91/9 and 91/10, respectively [26]; these results are quite promising, since performing the same reaction using Diop as the ligand gave lower regio- and enantioselectivity.

In summary, we have shown that asymmetric palladium-catalyzed allylic alkylation occurred with good enantioselectivities using easily accessible 1-diphenylphosphino-4-dialkylamino ligands derived from tartaric acid. The influence of the introduction of a chirality on the substituents of the nitrogen atom, as well as molecular modelling experiments of the π-allyl intermediate in the way to increase the enantioselectivities are currently under way.

Table 1
Allylic alkylation of (±)-(*E*)-1,3-diphenylprop-2-enyl acetate with dimethyl malonate catalyzed by palladium complexes[a]



(±)

Entry	Ligand	Solvent	Conversion (%)[b]	ee (%)[b] (configuration)[c]
1	**DIOP**	THF	95	0
2	**8**	THF	90	0
3	**3a**	THF	97	50 (*S*)
4	**3b**	THF	94	68 (*S*)
5	**3c**	THF	96	63 (*S*)
6	**3d**	THF	93	69 (*S*)
7	**3d**	THF[d]	47	30 (*S*)
8	**3d**	CH_2Cl_2	94	67 (*S*)
9	**3d**	CH_2Cl_2[d]	95	68 (*S*)
10	**7a**	THF	94	61 (*S*)
11	**7b**	THF	97	75 (*S*)
12	**7c**	THF	99	57 (*S*)
13	**7d**	THF	88	47 (*S*)

[a] [acetate]/[malonate]/[NaH]/[$Pd_2(dba)_3$]/[ligand] = 50/150/150/1/2; solvent: THF; 25°C; 24 h.
[b] Determined by HPLC analysis with chiral stationary column Daicel Chiralcel OD-H (hexane/2-propanol = 98/2).
[c] Determination based on the sign of the specific rotation of the alkylated product [23–25].
[d] *N*,*O*-bis[(trimethylsilyl)acetamide] (or BSA) and KOAc were used instead of NaH.

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