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Asymmetric Allylic Substitution Reactions with a Xylophos-Pd Catalyst

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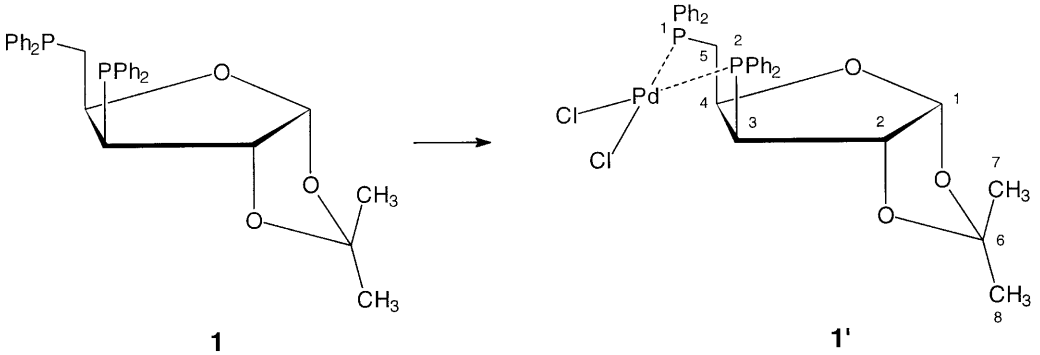
Summary. The chiral diphosphine ligand xylophos (**1**) was tested as an auxiliary in palladium catalyzed allylic substitution reactions. Whereas its activity was found to be generally good only in the case of 1,3-diphenylprop-2-en-1-yl acetate, a fair level of asymmetric induction was achieved with sodium dimethyl malonate (83% *ee*) and benzylamine (66% *ee*) as nucleophiles.

Keywords. Allylic substitution; Asymmetric catalysis; Allylic amination.

Introduction

Chiral auxiliaries derived from the chiral pool have attracted much attention, rendering tedious optical resolution procedures obsolete and being available in large amounts at reasonable prices. Particulary with phosphorus ligands containing a carbohydrate backbone impressive results have been obtained in various asymmetric transformations like hydrogenation, hydrocyanation, and hydroformylation [1].



1 **1'**

One of the more recently developed ligands belonging to this group is 1,2-O-isopropylidene-3,5-*bis*-diphenylphosphane-α-*D*-xylofuranose (xylophos, **1**), a diphosphino ligand accessible from xylofuranose in few steps [2] whose high efficiency in asymmetric hydrogenation [2a] and hydroformylation reactions has recently been demonstrated [2b]. The obtained results encouraged us to investigate its scope and

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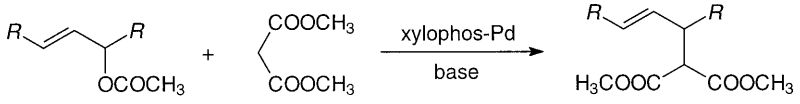
limitations also in Pd-catalyzed allylic substitution reactions and to compare reactivity and enantioselectivity to other ligands of similar structure [3]. The appropriate catalyst was either prepared *in situ* from **1** and $[Pd(allyl)Cl]_2$, $Pd(OAc)_2$, or $Pd_2(dba)_3$, or added to the reaction mixture as preformed xylophos-Pd(II) complex (**1′**). As test reactions, alkylations of linear and cyclic allyl acetates with the carbon nucleophile dimethyl malonate and four N-nucleophiles were investigated.

Results and Discussion

Allylic alkylation with dimethyl malonate

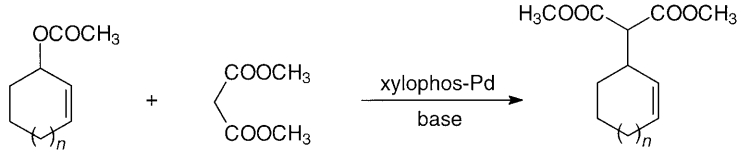
Typical test reactions (Scheme 1) with 1,3-disubstituted allylic substrates and dimethyl malonate under standard conditions were performed showing good enantioselectivity of up to 78% *ee* for substrate **2a**, but only 2–13% *ee* for aliphatic substrates (Table 1). In order to improve the asymmetric induction, optimization of the reaction conditions was attempted. Changing the solvent from *THF* to CH_3CN resulted in a heterogeneous reaction mixture, slow conversion, and side reactions. Even after three days only 27% of the desired product together with 24% of 1,3-diphenylpropenol was obtained, and 14% of unreacted starting material were recovered. In CH_2Cl_2 at room temperature the reaction was complete within 24 h, but with a lower level of asymmetric induction (61% *ee*). Neither variation of the Pd precursor nor of the ratio of ligand:Pd improved the enantioselectivity. The sharp drop in enantioselectivity with 1 mol% of ligand and the even more dramatic one upon application of the preformed xylophos-Pd(II) complex **1′** points to the presence of different catalytically active species coexisting under the reaction conditons applied; in the latter case, even a reversal of the absolute configuration was observed.

In order to detect presumably catalytically active intermediates, ^{31}P NMR experiments were performed. Recording the spectrum of a mixture of **1′** and **1** (2:1)



2a: R = Ph
3a: R = CH_3

2b: R = Ph
3b: R = CH_3



4a: n = 0
5a: n = 1
6a: n = 2

4b: n = 0
5b: n = 1
6b: n = 2

Scheme 1

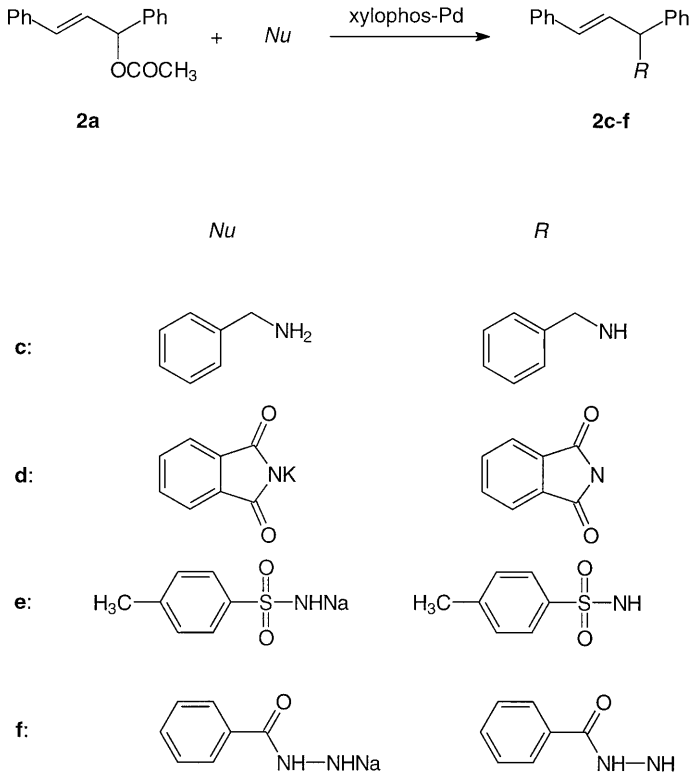
Table 1. Allylic alkylations with dimethyl malonate

Substrate	Yield/%	Configuration	*ee*/% (HPLC/GC)	Conditions
2a	86	(*S*)	78	
2a	79	(*S*)	38	+1 mol% xylophos
2a	79	(*R*)	2	+1 mol% **1′**
2a	78	(*R*)	53	+1 mol% **1′** +1 mol% xylophos
2a	87	(*R*)	35	+1 mol% **1′** +1 mol% xylophos +AgOAc (excess)
2a	78	(*S*)	55	$+Pd(OAc)_2$
2a	85	(*S*)	61	CH_2Cl_2
2a	27	(*S*)	79	CH_3CN, 72 h
2a	66	(*S*)	83	−10°C, 48 h
3a	85	(*S*)	13	
4a	87	(*R*)	2	
5a	89	(*R*)	8	
6a	93	(*R*)	3	

in CD_2Cl_2 gave neither any evidence for ligand exchange nor for the formation of other complexes in equilibrium ($\mathbf{1} + Pd(\mathbf{1})Cl_2 \rightleftharpoons Pd(\mathbf{1})_2Cl_2$). Upon addition of an excess of 1,3-diphenylprop-2-en-1-yl acetate the spectrum remained unchanged. Only after adding a small amount of sodium hydride the solution turned orange, the signals due to the free ligand **1** disappeared, the intensity of the resonances attributed to **1′** decreased, and several broad lines could be detected between 0 and 15 ppm. These observations are in agreement with the accepted mechanism which requires the formation of a Pd(0) intermediate to which the allylic substrate is added oxidatively to start the catalytic cycle. In the NMR experiment, the Pd(0) intermediate is assumed to be formed in two steps from **1′**. Upon reaction of **1′** with sodium hydride, a chloropalladium(II) hydride is generated, and from this HCl is (formally) reductively eliminated to give a Pd(0) species. For the catalytic reaction this means that only at this stage any free ligand being present in excess may take part in the reaction, changing eventually equilibria between competing catalytically active species. The influence of the Cl ligands was not further investigated, but the role of halide in facilitating *pseudo*-allyl rotation processes at palladium has been discussed in detail in the literature [4]. Lowering the temperature to −10°C resulted in a considerably slower reaction rate, but increased *ee* to 83%. The use of *BSA* (N,O-*bis*-(trimethylsilyl)-acetamide) instead of NaH gave irreproducible results (40–75% *ee* for **2a**) which can be attributed to partial cleavage of the ketal ring of xylophos caused by the presence of $(CH_3)_3Si$-OAc.

Allylic substitution of 1,3-diphenylpropenyl acetate (**2a**) *with N-nucleophiles*

With the more promising substrate **2a**, allylic substitution reactions with four N-nucleophiles were performed as well (Scheme 2); the results are given in Table 2. In



Scheme 2

Table 2. Allylic substitution of **2a** with N-nucleophiles

Nucleophile	Product	Yield/%	*ee*/%[1] (HPLC)
Benzylamine	**2c**	55	66
K-Phthalimide[2]	**2d**	11	59
Na-Tosylamide	**2e**	49	14
Na-Benzoylhydrazide	**2f**	41	33

[1] **2c**: Daicel-OD®, 0.20% Et_2NH / 0.25% 2-PrOH, 99.55% *n*-hexane; **2d**: Daicel-OD®, 2% 2-PrOH / 98% *n*-hexane; **2e**,**f**: Daicel-OJ®, 15% 2-PrOH / 85% *n*-hexane; [2] 56% of starting material were recovered

all cases the reactions proceeded slower compared with dimethyl malonate and afforded products **2c**–**f** in 11–55% yield with 14–66% *ee*.

Conclusions

It is demonstrated that the diphosphine ligand xylophos is suited as a chiral auxiliary in palladium catalyzed allylic substitution reactions. The degree of asymmetric induction was found to be moderate with a maximum of 83% *ee*. These results may be attributed to the medium conformative flexibility of both the six-membered chelate structure and the isopropylidene furanoside moiety, giving rise to

the coexistence of several catalytically active species in a labile equilibrium. From this point of view xylophos behaves according to expectations: its efficiency ranges between the excellent one of diphosphines forming five-membered chelates and the poor one of *diop* analogues involving seven-membered chelates [1g].

Experimental

General

NMR spectra were recorded on a Varian Gemini 300 NMR spectrometer at 300 (^{1}H), 75.4 (^{13}C), and 121.4 (^{31}P) MHz in CD_2Cl_2 in 5 mm sample tubes at 300 K. ^{1}H and ^{13}C spectra were referenced to internal *TMS*, ^{31}P chemical shifts are quoted relative to external 85% H_3PO_4. The numbering of carbon and phosphorus atoms refers to that given in the formula of **1′**; interchangeable assignments are marked by an asterisk.

[$PdCl_2$(xylophos)] (**1′**; $C_{32}H_{32}Cl_2O_3P_2Pd$)

55.0 mg (1.05 mmol) of xylophos were added to a solution of 38.3 mg (1 mmol) of [$PdCl_2(PhCN)_2$] in 2 cm^3 of CH_2Cl_2. After 10 min, the product was precipitated by addition of diethyl ether; filtration afforded 65 mg (91%) of **1′**.

^{1}H NMR: $\delta = 1.19$ (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 2.42 (ddd, 1H, H-5′, ^3J(H-5′, H-5) = 15.8 Hz, ^3J(H-5′, H-4) = 8.6 Hz, ^2J(H-5′, P-1) = 5.8 Hz), 2.80 (m, 1H, H-5), 2.91 (t, 1H, H-3, ^3J(H-3, H-4) = ^2J(H-3, P-2) = 6.9 Hz), 4.49 (m, 1H, H-4), 4.74 (dd, 1H, H-2, ^3J(H-2, H-1) = 4.1 Hz, ^3J(H-2, P-2) = 6.9 Hz), 5.60 (dd, 1H, H-1, ^3J(H-1, H-2) = 4.1 Hz, ^3J(H-1, P-1) = 2.1 Hz), 7.30–8.20 (m, 10H, CH =) ppm; ^{13}C NMR: $\delta = 26.1$ (C-7*), 26.3 (C-8*), 26.8 (dd, C-5, J(C-5, P-2) = 19.5 Hz, J(C-5, P-1) = 32.5 Hz), 45.2 (dd, C-3, J(C-3, P-2) = 23.9 Hz, J(C-3, P-1) = 10.8 Hz), 73.3 (d, C-4, J(C-4, P)[1] = 4.5 Hz), 82.4 (t, C-2, J(C-2, P-2) = 2.9 Hz), 103.6 (C-1), 111.8 (C-6), 124.3, 125.0, 125.2, 125.8 (C_{arom}), 127.4–135.3 (CH_{arom}) ppm; ^{31}P NMR: $\delta = 18.2$ (d, P-1, ^2J(P, P) = 7.4 Hz), 22.8 (d, P-2) ppm; calcd.: C 54.60, H 4.58; found: C 54.47, H 4.65.

Allylic alkylations with dimethyl malonate [5]

4 cm^3 of dry *THF* were degassed, [Pd(η^3-allyl)Cl]$_2$ (1.8 mg, 0.005 mmol, 1 mol% Pd), xylophos (10.5 mg, 0.02 mmol, 2 mol%), and 1 mmol of substrate were added in sequence, and the solution was stirred for 15 min. A solution of malonate anion was prepared by adding NaH dispersion (63 mg, 1.5 mmol) in portions to a degassed solution of dimethyl malonate (198 mg, 171 mm^3, 1.5 mmol) in 4 cm^3 of *THF*. After 30 min, the resulting turbid solution was added *via* a teflon tube to the ice-cooled solution containing allyl acetate **2a**–**6a** and the catalyst, and the mixture was stirred overnight at room temperature. The reaction was quenched by addition of a small amount of 2 *N* HCl, and the mixture was extracted with Et_2O (3×10 cm^3). The combined extracts were washed with brine until neutral and dried over Na_2SO_4. After removal of the solvent the crude products were purified by column chromatography (silica gel); the purity of the isolated products was checked by ^{1}H NMR spectroscopy.

2b: Column: 10×2.2 cm, *PE*:CH_2Cl_2 = 50:50; UV/Vis: $\lambda_{max} = 290$ nm; *ee*: chiral HPLC (Chiralcel OD-H®, 250×4.6 mm, 2% 2-PrOH / 98% *n*-hexane); specific rotation calculated for optically pure (*S*)-**2b**: $[\alpha]_D^{20} = -22.4$ ($c = 1.8$, $CHCl_3$) [6].

3b: Column: 25×2.5 cm, *PE*:Et_2O = 75:25; UV/Vis: $\lambda_{max} = 220$ nm; *ee*: enantioselective GC: (50% *octakis*-(6-O-methyl-2,3-di-O-pentyl)-γ-cyclodextrin, FS, 0.25×25 m, 0.5 atm H_2, 55°C); ^{1}H

[1] Coupling phosphorus atom not identified

NMR: shift of a doublet of one of the terminal CH_3 groups upon addition of Eu(*hfc*)$_3$; specific rotation calculated for optically pure (*S*)-**3b**: $[\alpha]_D^{20} = -31.9$ ($c = 1.1$, $CHCl_3$) [7].

4b: Column: 25×2.5 cm, *PE*:Et_2O = 75:25; UV/Vis: $\lambda_{max} = 220$ nm; *ee*: enantioselective GC: (50% 6T-2,3-diacetyl-β-cyclodextrin, FS, 0.25×25 m, 0.5 atm H_2, 90°C); specific rotation calculated for optically pure (*S*)-**4b**: $[\alpha]_D^{20} = -98.7$ ($c = 2.27$, $CHCl_3$) [8].

5b: Column: 25×2.5 cm, *PE*:Et_2O = 75:25; UV/Vis: $\lambda_{max} = 220$ nm; *ee*: enantioselective GC: (50% 6T-2,3-dimethyl-β-cyclodextrin, FS, 0.25×25 m, 0.5 atm H_2, 110°C); specific rotation calculated for optically pure (*S*)-**5b**: $[\alpha]_D^{20} = -46.1$ ($c = 2.86$, $CHCl_3$) [8].

6b: Column: 25×2.5 cm, *PE*:Et_2O = 75:25; UV/Vis: $\lambda_{max} = 220$ nm; *ee*: see **5b**; specific rotation calculated for optically pure (*S*)-**6b**: $[\alpha]_D^{20} = -7.8$ ($c = 3.04$, $CHCl_3$) [8].

Allylic substitution of **2a** *with N-nucleophiles*

2c [9]: The reaction was conducted in 3 cm^3 of dry CH_2Cl_2 at room temperature on a 1 mmol scale similar as described above for allylic alkylations with dimethyl malonate. As nucleophile, benzylamine (2 mmol, 214 mg) was added, and the solution was stirred for 48 h. After dilution with 20 cm^3 of Et_2O, 5 cm^3 of saturated NH_4Cl solution were added. The organic phase was separated, washed with NH_4Cl, dried over $MgSO_4$, and evaporated. After chromatography on silica gel (column 25×2 cm, *EE*:*PE* = 10:90) the pure product was obtained as a yellow oil.

2d: The reaction was run in *THF* on a 1 mmol scale. As nucleophile, K-phthalimide (2 mmol, 370 mg) was added as a solid at room temperature, and the mixture was stirred at 50°C for 72 h. For work-up, cf. **2c**.

2e,**f**: The reactions were performed exactly as described in Ref. [9] (nucleophiles: Na-tosylamide (**2e**), Na-benzoylhydrazide (**2f**)).

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