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First study on the enantioselective palladium-catalyzed C-P cross-coupling reaction between an alkenyltriflate and a phosphine-borane

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ABSTRACT

In this article, we report the first example of a palladium-catalyzed asymmetric C-P cross-coupling reaction between a racemic secondary phosphine-borane, methylphenylphosphine-borane **1**, and an achiral triflate. The influence of various parameters such as the structure of the chiral ligand, the temperature and the nature of the solvent on the activity and the selectivity of the reaction is reported. Enantiomeric ratios up to 78:22 were obtained using (*S,S*)-Me-DUPHOSPdCl$_2$ as catalyst. A kinetic resolution process is proposed to account for this selectivity.

RÉSUMÉ

Dans cet article, nous décrivons le premier exemple de couplage C-P asymétrique catalysé au palladium entre une phosphine-borane secondaire racémique, la méthylphénylphosphine-borane **1** et un triflate achiral. L'influence de différents paramètres tels que la structure du ligand chiral, la température, la nature du solvant et de la base, sur l'activité et la sélectivité de la réaction a été étudiée. Un rapport énantiomérique de 78:22 a été obtenu lorsque le catalyseur (*S,S*)-Me-DUPHOSPdCl$_2$ est utilisé. Un processus de dédoublement cinétique est proposé pour justifier cette sélectivité.

1. Introduction

Alkenylphosphines are a class of compounds that undergo numerous useful synthetic transformations due to the carbon-carbon double bond, which is directly linked to the phosphorus atom [1–3]. For example, a large variety of nucleophiles can add to the double bond to provide bifunctional or polyfunctional adducts (polyphosphines, dendrimers, polymers). Alkenylphosphines can also be used as dienophiles in cycloaddition reactions [4,5]. Due to the presence of both phosphorus and carbon-carbon double bond, they are also of great interest in coordination chemistry. Recently, they were successfully used as ligands in homogeneous catalysis. Various synthetic methods for accessing alkenylphosphine derivatives have been developed. The main methodologies are related to the preparation of racemic or achiral alkenylphosphines. They involve reaction between halophosphines and vinylic organometallic species, hydrophosphination of alkynes or C-P cross-coupling reactions [2]. Contrarily, enantiopure or enantioenriched derivatives are rare. If a few C-stereogenic derivatives have been prepared by C-P cross-coupling of enantiopure alkenyl-triflates [6–8] or halides [9], P-stereogenic derivatives are neglected and their synthesis requires resolution processes [5,10]. A more appealing route to P-chirogenic phosphines relies on the use of asymmetric catalysis. To the best of our knowledge, the only example dealing with the synthesis of an enantioenriched

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alkenylphosphine derivative by asymmetric catalysis was reported recently by some of us [11] in the course of our studies on the hydrophosphination reaction [12–16]. We report here the preliminary results dealing with the enantioselective coupling between an achiral alkenyltriflate and a racemic secondary phosphine-borane. Indeed, although examples of enantioselective Pd-catalyzed C-P cross-coupling reaction between an arylhalide and a secondary phosphine have recently appeared in the literature [17,18], no enantioselective variant of the coupling reaction involving alkenyl derivatives has ever been reported.

2. Experimental

2.1. General comments

All reactions were carried out under nitrogen atmosphere. All glassware was flamed before use. Cyclohex-1-en-1-yltrifluoromethanesulfonate, commercially available, was distilled under reduced pressure (Kugelröhr) before use. Methylphenylphosphine-borane was prepared according to literature procedure [19]. All commercially available ligands were used as purchased.

Dimethylsulfoxide (DMSO) was distilled from calcium hydride and degassed before use. DMF was stored on molecular sieves, freshly distilled and degassed before use. Toluene and THF were purified by an innovative technology Pure Solv. device (activated alumina column containing a copper catalyst and molecular sieves). Pentane was distilled from calcium hydride before use.

Column chromatography was performed on Merck silica gel Si 60 (40–63 μm). Solvents were used as purchased. Thin layer chromatography (TLC) was performed on silica gel 60 F-254 plates (0.1 mm) with iodine or UV detection.

^{1}H, ^{13}C, ^{19}F and ^{31}P NMR spectra were obtained on BRUKER DPX 250 or AC 400 spectrometers, ^{11}B NMR spectra were recorded on a BRUKER AC 400 spectrometer. ^{1}H and ^{13}C NMR chemical shifts are reported relative to Me_4Si used as an internal standard. ^{31}P, ^{19}F and ^{11}B NMR chemical shifts are reported relative to respectively H_3PO_4 (85%), $CFCl_3$ and $BF_3.Et_2O$ used as external references. Coupling constants are reported in Hertz (Hz).

Abbreviations are used as follows: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintuplet, sept = septuplet, oct = octuplet, m = multiplet and br = broad.

Mass spectroscopy was performed on a QTOF Micro WATERS.

High performance liquid chromatography (HPLC) separations were achieved using the following components:

- For flow up to 0.5 mL/min, the components are: a Waters 600 pump, a Waters 996 photodiode array detector (190–250 nm) and Millenium Software;
- For flow below 0.5 mL/min, the components are: a Waters Alliance 2695 pump, a Waters 2996 photodiode array detector (190–250 nm) and Empower Software.

Enantiomeric excess of compound **2** was measured by HPLC using two possible different conditions:

- Conditions A: Daicel Chiralpack OJ-H (250 × 4.6 mm, L × ID) column (*n*-heptane/isopropanol 90:10, 1 mL/min, $tR_1 = 9.34$ min, $tR_2 = 10.95$ min) at 20 °C;
- Conditions B: Daicel Chiralpack AD-H (250 × 4.6 mm, L × ID) column (*n*-heptane/(MeOH/EtOH 50:50) 98:2, 0.2 mL/min, $tR_1 = 36.41$ min, $tR_2 = 40.13$ min) at 12 °C.

Given enantiomeric excesses of compound **2** are average of at least two experiments.

2.2. General procedures

Enantiopure catalytic systems, (*R*)-Tol-BINAPPdCl_2 [20], (*R*,*R*)-BDPPPdCl_2 [21], (*R*)-*i*-Pr-PHOXPdCl_2 [22] and (*S*,*S*)-Me-DUPHOSPdCl_2 [23] were synthesized according to modified literature procedures [24].

2.2.1. General procedure for the preparation of L_2PdCl_2

In a two-necked round bottomed flask, containing a solution of $(CH_3CN)_2PdCl_2$ (0.077 M, 1 equiv.) in toluene, a solution of ligand L_2 (0.077 M, 1 equiv.) in toluene is added. The mixture is stirred overnight at room temperature. The obtained precipitate is filtered, washed with freshly distilled pentane and dried under vacuum to give quantitatively the desired complex.

2.2.2. Typical procedure for palladium-catalyzed asymmetric phosphination

In a schlenk tube, flushed under N_2, L_2PdCl_2 (0.01 mmol, 4.8 mol%) is dissolved into the solvent (0.3 mL). Cyclohex-1-en-1-yltrifluoromethanesulfonate (38 μL, 0.22 mmol, 1 equiv.), the base (0.26 mmol, 1.2 equiv.) and methylphenylphosphine-borane **1** (30 μL, 0.22 mmol, 1 equiv.) are then introduced. The mixture is stirred during a time *t* at the desired temperature *T*. The reaction is monitored by ^{31}P NMR spectroscopy. When the expected conversion is reached, the medium is hydrolyzed with degassed water (0.5 mL). The aqueous layer is extracted with diethyl ether (3 × 2 mL). The combined organic layers are dried over $MgSO_4$ and concentrated under reduced pressure. The crude product is then purified by silica-gel column chromatography with pentane/AcOEt (95/5, $R_f = 0.30$) as eluent affording pure coupling product **2** as a yellow oil. All attempts to crystallize the oily product failed. Er values are measured by HPLC using conditions A or B.

2.3. Experimental data

Coupling-product **2** [934338-23-5] [8]

Anal. calcd for $C_{13}H_{20}BP$ (218.1): C 71.60, H 9.24. Found: C 71.08, H 9.79. ^{31}P NMR (161.9 MHz, $CDCl_3$): δ 11.4 (q, $^{1}J_{PB} = 64.6$ Hz). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 7.70-7.62 (m, 2H), 7.52-7.43 (m, 3H), 6.57 (dm, 1H, $^{3}J_{HP} = 18.8$ Hz), 2.28-2.18 (m, 2H), 2.11-1.93 (m, 2H), 1.67-1.63 (m, 4H), 1.63 (d, 3H, $^{2}J_{HP} = 10.0$ Hz), 0.79 (q, 3H, $^{1}J_{HB} = 92.0$ Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 141.0 (d, $^{2}J_{CP} = 10.2$ Hz), 131.5 (d, $^{2}J_{CP} = 9.1$ Hz), 130.8 (d, $^{4}J_{CP} = 2.4$ Hz), 129.9 (d, $^{1}J_{CP} = 54.3$ Hz), 128.7 (d, $^{3}J_{CP} = 9.9$ Hz), 128.5 (d, $^{1}J_{CP} = 52.5$ Hz), 26.6 (d, $^{3}J_{CP} = 12.8$ Hz), 24.7 (d, $^{2}J_{CP} = 6.9$ Hz), 22.3 (d, $^{3}J_{CP} = 6.4$ Hz), 21.4 (d, $^{4}J_{CP} = 1.3$ Hz), 9.3 (d, $^{1}J_{CP} = 40.5$ Hz).