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Chiral 2-(2-Diphenylphosphinophenyl)-oxazolines: Synthesis and Use in Pd-Catalyzed Asymmetric Allylic Alkylation

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The synthesis of 2-(2-diphenylphosphinophenyl)-oxazolines from o-fluorobenzonitrile and (–)-norephedrine or (+)-endo-2-hydroxy-endo-3-aminobornane is described. The Pd-catalyzed alkylation of (E)-1,3-diphenylallyl acetate with the sodium salt of dimethylmalonate using these chiral ligands occurs with an 82–87% yield and 88–93% ee.

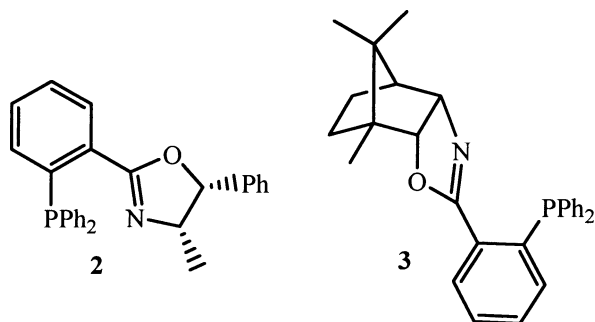
Keywords η^3 -allylpalladium; allylic alkylation; asymmetry; catalysis; oxazolines

Over the last 20 years, we have been strongly involved in the enantioselective protonation of prochiral enolic species produced either photochemically¹ or from Pd catalysis.² The chiral protic sources were ephedrine-type compounds, (+)-endo-2-hydroxy-endo-3-aminobornane (**1**),³ and its *N*-alkylated derivatives. Being also interested in Tsuji–Trost reactions,⁴ we have prepared oxazolines **2** and **3** from (–)-norephedrine and **1**, respectively, (Scheme 1) to test them for the Pd-catalyzed asymmetric alkylation of (*E*)-1,3-diphenylallyl acetate (**4**). Indeed, homochiral phosphinoaryloxazolines are a class of ligands commonly used in metal-catalyzed enantioselective reactions, in particular

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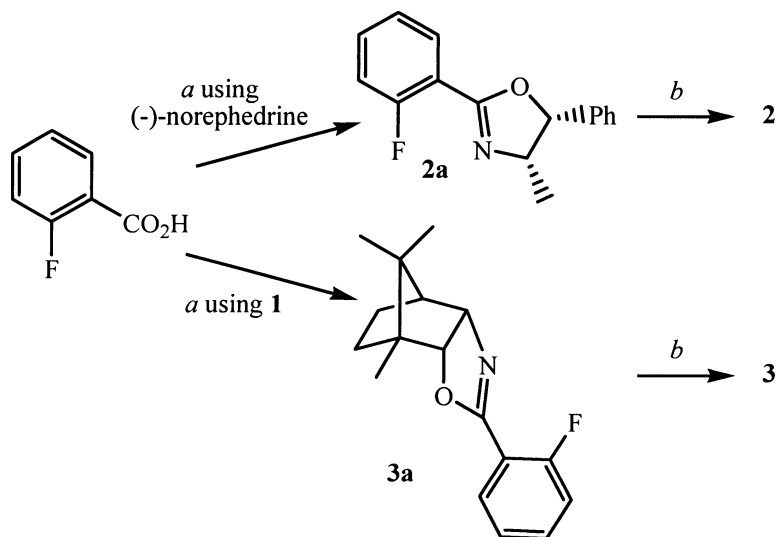
Address correspondence to Jacques Muzart, Unité Mixte de Recherche “Réactions Sélectives et Applications,” UMR 1039, CNRS–Université de Reims, Champagne–Ardenne, B.P. 1039, Reims, cedex 2, 51687 France. E-mail: jacques.muzart@univ-reims.fr



SCHEME 1

in the Pd-catalyzed allylic alkylation of **4**.^{5–7} Oxazoline **2** already has been used with **4** to synthesize the corresponding η^3 -allylpalladium complex,⁸ but its synthesis, analytical properties⁹ and use in catalysis have not been disclosed. Our results are here reported.

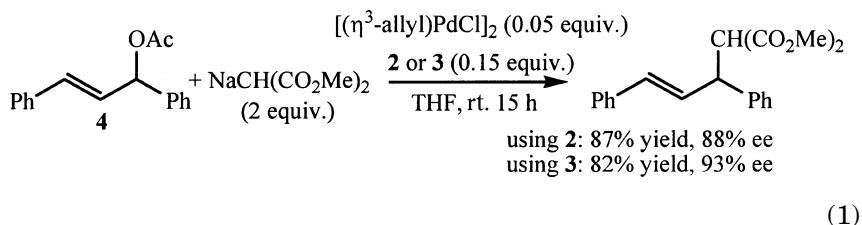
The synthesis of **2** and **3** was attempted via the synthesis of the corresponding 2-(2-fluorophenyl)-4,5-dihydrooxazoles **2a** and **3a**. Refluxing a mixture of *o*-fluorobenzonitrile, (–)-norephedrine and ZnCl₂ in chlorobenzene^{6,10} yielded 30% of **2a**. The yield was improved to 76% using *o*-fluorobenzoic acid¹⁰ under conditions depicted in Scheme 2. These experimental conditions using **1** instead of (–)-norephedrine



SCHEME 2 (a) **1**: PPh₃ (1 equiv.), CCl₄/MeCN (4:1), 0°C, 2.5 h; **2**: (–)-norephedrine or **1** (1 equiv.), NEt₃ (3.25 equiv.), r.t., 1 h; **3**: 0°C, PPh₃ (0.37 equiv.); **4**: r.t., 1 h (b) Ph₂PK (1.1 equiv.), THF, 0°C, 20–30 min.

afforded **3a** in a 94% yield. The treatment of **2a** and **3a** with potassium diphenylphosphide⁶ led to **2** and **3** in 86% and 71% yields, respectively.

The reaction of **4** with the sodium salt of dimethylmalonate in THF at r.t. using $[(\eta^3\text{-allyl})\text{PdCl}]_2/\mathbf{2}$ (or **3**) as the catalytic system led to dimethyl 2-((*E*)-1,3-diphenylallyl)malonate in an 82–87% yield with 88–93% ee (Eq.(1)).



In conclusion, we have synthesized two phosphorus-containing oxazolines that have been used for the first time as chiral ligands for efficient Pd-catalyzed Tsuji–Trost reactions.

EXPERIMENTAL

All reactions were carried out under an argon atmosphere using dry solvents. The Pd-catalyzed reactions were carried out according to a published procedure;⁶ the enantiomeric excesses were determined by HPLC using a Daicel Chiracel OD column and hexane/*i*-PrOH (99:1) as an eluent (254 nm, 0.5 mL/min). IR analyses were recorded on a Spectrafile IR-TF plus Midac. NMR spectra were recorded on Bruker spectrometers (¹H, 250 or 500 MHz; ¹³C, 62.9 or 125.8 MHz, ¹⁹F, 235.4 MHz, ³¹P, 120.2 MHz) and referenced to TMS, CFCl₃ and 85% H₃PO₄, respectively. MS analyses were performed on a Q-TOF micro (Micro-mass) with an electrospray source.

The Synthesis of **2a**

MeCN (8 mL) and CCl₄ (2 mL) were added to a round-bottom flask containing *o*-fluorobenzoic acid (560 mg, 4 mmol) and PPh₃ (1050 mg, 4 mmol) cooled at 0°C. After stirring for 2.5 h, a solution of (–)-norephedrine (605 mg, 4 mmol) and NEt₃ (1315 mg, 13 mmol) in MeCN (2 mL) was added. After stirring at r.t. for 1 h, the reaction was cooled at 0°C, and a supplementary portion of PPh₃ (393 mg, 1.5 mmol) was added. The mixture was stirred at r.t. for 1 h. The residue obtained after evaporation of the solvents under reduced pressure was dissolved in CH₂Cl₂ (20 mL). This was washed with 2M of aqueous NaOH,

evaporated, and then subjected to column chromatography to afford **2a** (775 mg, 76%).

IR (KBr, cm^{-1}): 699, 745, 766, 1455, 1497, 1584, 1613, 1649. ^1H NMR (CDCl_3 , δ ppm): 1.55 (d, 6.7 Hz, 3H), 4.22 (quint, 6.8 Hz, 1H), 5.08 (d, 7.9 Hz, 1H), 7.16 (m, 1H), 7.29 (m, 1H), 7.35 (m, 5H), 7.40 (m, 1H), 7.94 (dt, 1.7 and 7.4 Hz). ^{13}C NMR (CDCl_3 , δ ppm): 21.2, 71.0, 87.4, 115.9 (d, $J_{\text{CF}} = 10.3$ Hz), 116.6 (d, $J_{\text{CF}} = 21.9$ Hz), 123.8 (d, $J_{\text{CF}} = 3.8$ Hz), 125.4, 128.4, 128.6, 131.0 (d, $J_{\text{CF}} = 1.3$ Hz), 132.8 (d, $J_{\text{CF}} = 8.7$ Hz), 140.1, 159.2 (d, $J_{\text{CF}} = 5.7$ Hz), 161.1 (d, $J_{\text{CF}} = 258.5$ Hz). ^{19}F NMR (CDCl_3 , δ ppm): -108.9 .

The Synthesis of **2**

A 0.5-M Ph_2PK solution in THF (11 mL, 5.5 mmol) was added dropwise to a solution of **2a** (1275 mg, 5 mmol) in THF (10 mL) at 0°C . The mixture was stirred at 0°C until the color changed from red to yellow (20–30 min). After the addition of water (15 mL) and extraction of the aqueous phase with CH_2Cl_2 (3×10 mL), the organic phases were washed with brine and dried over MgSO_4 . Evaporation of the solvent followed by column chromatography led to **2** (1810 mg, 86%).

$[\alpha]_D^{20} = +73.2$ ($c = 0.7$, CH_2Cl_2). ^1H NMR (CDCl_3 , δ ppm): 1.26 (d, 6.6 Hz, 3H), 4.02 (quint., 7.7 Hz, 1H), 4.71 (d, 8.3 Hz, 1H), 6.88 (m, 1H), 7.13 (d, 5.9 Hz, 2H), 7.34 (m, 15H), 7.98 (m, 1H). ^{13}C NMR (CDCl_3 , δ ppm): 20.6, 70.8, 87.8, 125.8, 127.9, 128.0, 128.3 (d, $J_{\text{CP}} = 6.8$ Hz), 128.4 (d, $J_{\text{CP}} = 8$ Hz), 128.5, 128.7, 130.0 (d, $J_{\text{CP}} = 2.5$ Hz), 133.5 (d, $J_{\text{CP}} = 2.4$ Hz), 133.9 (d, $J_{\text{CP}} = 20.9$ Hz), 134.4 (d, $J_{\text{CP}} = 21.2$ Hz), 138.0 (d, $J_{\text{CP}} = 10.8$ Hz), 138.1 (d, $J_{\text{CP}} = 12.2$ Hz), 139.4 (d, $J_{\text{CP}} = 25.9$ Hz), 140.0, 162.3 (d, $J_{\text{CP}} = 3.5$ Hz). ^{31}P NMR (CDCl_3 , δ ppm): -4.4 . M. S. (E. S.): 422(M + 1).

The same procedures were used for the synthesis of **3a** and **3**.

3a (770 mg, 94%) from *o*-fluorobenzoic acid (420 mg, 3 mmol). IR (KBr, cm^{-1}): 764, 1457, 1497, 1612, 1643. ^1H NMR (CDCl_3 , δ ppm): 0.92 (s, 3H), 0.96 (s, 6H), 1.20 (m, 2H), 1.49 (m, 2H), 2.14 (wide s, 1H), 4.58 (d, 9.8 Hz, 1H), 4.72 (dd, 9.8 and 5.0 Hz, 1H), 7.14 (m, 2H), 7.37 (m, 1H), 7.83 (t, 7.4 Hz, 1H). ^{13}C NMR (CDCl_3 , δ ppm): 15.0, 18.4, 19.9, 20.6, 27.1, 49.1, 49.3, 49.5, 71.8, 88.6, 116.6 (d, $J_{\text{CF}} = 22$ Hz), 123.9 (d, $J_{\text{CF}} = 3.9$ Hz), 131.0, 132.5, 132.6, 160.2 (d, $J_{\text{CF}} = 6.0$ Hz), 161.2 (d, $J_{\text{CF}} = 273.8$ Hz). ^{19}F NMR (CDCl_3 , δ ppm): -109.7 .

3 (312 mg, 71%) from **3a** (723 mg, 2.65 mmol). $[\alpha]_D^{20} = +77.4$ ($c = 0.7$, CH_2Cl_2). ^1H NMR (CDCl_3 , δ ppm): 0.74 (s, 3H), 0.79 (s, 6H), 1.10 (m, 4H), 1.90 (t, 1.2 Hz, 1H), 4.28 (d, 9.9 Hz, 1H), 4.41 (dd, 4.9 and 9.9 Hz, 1H), 6.81 (m, 1H), 7.23 (m, 12H), 7.92 (m, 1H). ^{13}C NMR (CDCl_3 ,

δ ppm): 14.8, 18.3, 198.8, 20.3, 27.0, 49.1, 49.2, 49.2, 71.8, 88.6, 128.0, 128.2 (d, $J_{\text{CP}} = 7.3$ Hz), 128.3 (d, $J_{\text{CP}} = 4.6$ Hz), 129.9 (d, $J_{\text{CP}} = 2.9$ Hz), 130.2, 132.3 (d, $J_{\text{CP}} = 19.9$ Hz), 133.9, 134.0, 134.1, 138.1 (d, $J_{\text{CP}} = 37.9$ Hz), 138.4 (d, $J_{\text{CP}} = 39.2$ Hz), 138.8 (d, $J_{\text{CP}} = 25.6$ Hz), 163.4 (d, $J_{\text{CP}} = 2.5$ Hz). ^{31}P NMR (CDCl_3 , δ ppm): -5.7 . M. S. (E. S.): 440 ($M + 1$).

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