Pergamon

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Tetrahedron Letters 44 (2003) 2413–2415

TETRAHEDRON LETTERS

New enantiopure cyclic β-iminophosphine ligands: applications in Pd-catalyzed asymmetric allylic substitution

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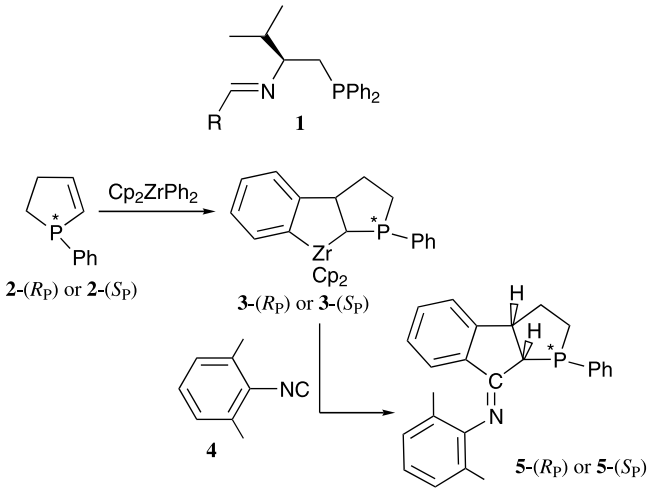
Received 12 December 2002; accepted 16 January 2003

Abstract—New enantiopure cyclic β-iminophosphines were applied as ligands in Pd-catalyzed asymmetric allylic substitution reactions.

Transition metal-catalyzed asymmetric reactions performed with phosphorus–nitrogen mixed donor bidentate ligands generally led to excellent levels of stereocontrol.[1] A large variety of phosphorus–nitrogen ligands was used but very few of them concern linear or cyclic iminophosphines.[2–4] Among them, chiral linear γ-iminophosphines **1** have shown a versatile behaviour in some catalytic asymmetric transformations such as for example palladium-catalyzed asymmetric allylic substitutions.[3] However to the best of our knowledge, no similar work has been conducted with cyclic iminophosphines. Electronically and sterically different chiral arrangements as well as variation in the ligand flexibility might induce better enantioselectivities. In this paper we report the synthesis of new enantiomerically pure cyclic β-iminophosphines, the crystal structure characterization of an enantiomer and preliminary results concerning the catalytic properties of Pd(0) complexes in asymmetric allylic alkylation and amination.

According to the procedure already published[5] we have prepared and separated the (*R*)- and (*S*)-phospholene enantiomers **2**-(R_P) and **2**-(S_P) (Scheme 1). Each of these enantiomeric forms was reacted first with diphenyl zirconocene—a precursor of zirconabenzyne—to give the tricyclic zirconaindanephospholanes **3**-(R_P) and **3**-(S_P), respectively.[6] Further treatment of **3**-(R_P) and **3**-(S_P) with the isocyanide **4** (R = 2,6-$Me_2C_6H_3$) afforded the β-iminophosphines **5**-(R_P) and **5**-(S_P) in pure enantiomeric form. These two enantiomers were characterized by ^1H, ^{13}C, ^{31}P NMR and by mass spectrometry analysis.[6] The enantiomeric purity of **5** was determined by either chiral HPLC[7] or ^1H NMR using the chiral shifting agent (+)-Eu(hfc)$_3$. The structure of the **5**-(R_P) enantiomer {$[\alpha]_D^{20} = -252$ (*c* 3.1, $CHCl_3$)} was solved by X-ray diffraction studies which confirm its absolute configuration at the level of the phosphorus atom.[8] Absolute configuration for carbons $C_8(S)$ and $C_{(11)}(S)$ was also established (see Fig. 1). NMR data of the **5**-(S_P) enantiomer {$[\alpha]_D^{20} = +254$ (*c* 2.3, $CHCl_3$)} were similar to that observed for **5**-(R_P).



Scheme 1. Synthesis of the enantiopure cyclic β-iminophosphines **5**.

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0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)00182-5

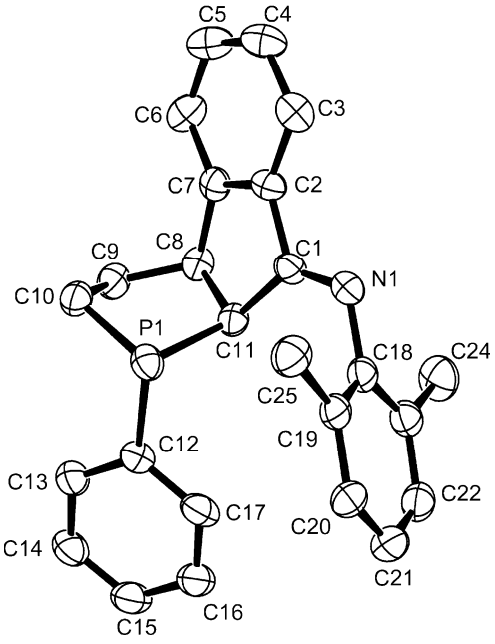
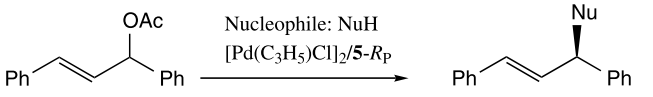


Figure 1. Molecular structure of **5**-(R_P) showing the atom numbering scheme. Selected bond distances (Å) and angles (°): P(1)–C(11) 1.880(4), P(1)–C(10) 1.837(4), C(11)–C(1) 1.521(5), C(8)–C(7) 1.502(5), C(1)–N(1) 1.272(5), N(1)–C(18) 1.426(5), C(10)–P(1)–C(11) 92.27(19), P(1)–C(11)–C(1) 112.7(3), C(11)–C(1)–N(1) 130.3(4), C(1)–N(1)–C(18) 118.9(3), C(11)–C(8)–C(7) 103.3(3), P(1)–C(10)–C(9) 107.4(3).

We shown that the ligand **5** is able to form five-membered ring chelates with both nitrogen and phosphorus atoms coordinated to Pd(II) in the (P–N)$PdCl_2$ complex.[9] The Pd–Cl bond lenghts are significantly different from one another, the chlorine atom *trans* to phosphorus displaying the expected longer distance (2.343 Å as compared to its partner *trans* to nitrogen (2.296 Å). This is the expression of the higher *trans* influence of the phosphine ligand. We have tested the catalytic properties of the palladium complexes formed in situ from this new ligand **5**-(R_P) and 2 mol% of [Pd-(allyl)Cl]$_2$ in an allylic alkylation of 1,3-diphenylprop-3-en-1-yl acetate **6** by the nucleophile generated from dimethylmalonate with *N*,*O*-bis(trimethylsilyl) acetamide (BSA) and a catalytic amount of potassium acetate in methylene dichloride solution at room temperature (Table 1). The (*S*)-alkylated product **7** was obtained in 95% yield and 57% e.e. with a ratio ligand/Pd = 2 (entry 1). The enantioselectivity decreases to 48% with a ratio ligand/Pd = 1 (entry 2). For the amination the reaction solvents influenced the enantioselectivity of the reaction and the best enantioselectivity e.e. = 64% was observed in CH_2Cl_2 as solvent (entries 3 and 4). Both Pd(0)-allylic substitution alkylation and amination led to the same relative configuration for the products **7** and **8** involving probably the same η^3-allylic diastereomer Pd-complex during the nucleophilic attacks. By using **5**-(S_P), **7**-(*R*) and **7**-(*S*) were obtained with practically the same enantioselectivity.

Although these preliminary results reveal a good yield but a moderate enantioselectivity of allylation products, the original strategy applied to synthesize these new enantiopure chiral ligands should allow to modulate electronic and steric effects for achieving higher enantioselectivity in the asymmetric catalysis. The investigation on the application of these ligands in other transition-metal-catalyzed asymmetric reactions is ongoing in our laboratories.

Table 1. Asymmetric Pd(0)-catalyzed substitution of racemic allylic substrate **6** with malonate and benzylamine as nucleophile



(+/-)-**6**

7 Nu : $CH_2(COOMe)_2$

8 Nu : $PhCH_2NH_2$

Entry	Nucleophile	Solvent[d]	Temp. (°C)	Time (h)	Yield (%)[e]	ee (%)[f,g]
1[a]	$CH_2(COOMe)_2$	CH_2Cl_2	20	16	95	57 (*S*)
2[b]	$CH_2(COOMe)_2$	CH_2Cl_2	20	16	90	48 (*S*)
3[c]	$PhCH_2NH_2$	Toluene	−10	24	96	57 (*R*)
4[c]	$PhCH_2NH_2$	CH_2Cl_2	−10	24	72	64.(*R*)

[a] $[Pd(C_3H_5)Cl]_2$:**5**:KOAc:**6**:BSA:malonate = 2:8:10:100:300:300. Ligand/Pd = 2.
[b] $[Pd(C_3H_5)Cl]_2$:**5**:KOAc:**6**:BSA:malonate = 2:4:10:100:300:300. Ligand/Pd = 1.
[c] $[Pd(C_3H_5)Cl]_2$:**5**:**6**:benzylamine = 2:8:100:300. Ligand/Pd = 2.
[d] 0.15 M of **6**.
[e] Isolated yield.
[f] For **7** the e.e. was determined by HPLC on a Chiralcel AD-H column at $\lambda = 254$ nm, eluent: hexane/isopropanol: 95/5; flow rate: 1 mL/min; $t_S = 14.34$ min; $t_R = 19.39$ min.
[g] For **8** the e.e. was determined by HPLC on a Chiracel OD-H column at $\lambda = 254$ nm, eluent: hexane/isopropanol: 99/1; flow rate: 0.5 mL/min; $t_S = 20.98$ min; $t_R = 22.53$ min.

Acknowledgements

This work was performed with the support of the Laboratoire Européen Associé (LEA) financed by CNRS (France) and the Polish Committee for Scientific Research (KBN grant 3TO9A03619).

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6. NMR data are identical to that observed for the analogous racemic compound. See: Cadierno, V.; Zablocka, M.; Donnadieu, B.; Igau, A.; Majoral, J.-P.; Skowronska, A. *J. Am. Chem. Soc.* **1999**, *121*, 11086.
7. HPLC conditions for the determination of the e.e. of **5**: Chiralcel OD-H column [0.46×25 cm] at $\lambda = 254$ nm, eluent: hexane/isopropanol: 90/10; flow rate: 1 mL/min; $t_S = 4.32$ min; $t_R = 7.11$ min.
8. *X-Ray analysis of $C_{25}H_{24}NP$*: Data collection were collected at low temperature T (160 K) on a Stoe imaging-plate diffraction system (IPDS), equipped with an Oxford Cryosystems cryostream cooler device and using graphite-monochromated Mo Kα radiation. $C_{25}H_{24}NP$, $F_w = 369.42$, crystal dimensions: 0.25×0.20×0.07, colourless, platelet, orthorhombic, $P2_12_12_1$, $a = 9.3523(9)$, $b = 11.7112(9)$, $c = 18.3888(13)$ Å, 2014.1(3) Å^3, $D_{calcd} = 1.218$ mg m^{-3}, $\mu = 0.145$ mm^{-1}, number of reflections collected/unique 12960/3190 ($R_{int} = 0.1124$). Structure was solved by means of direct-methods using the program SIR-92, and refined using the program SHELXL-97 included in the package WINGX, $R_1 = 0.0470$, $wR_2 = 0.0526$ for [$I > 2\sigma(I)$], $R_1 = 0.1067$, $wR_2 = 0.0641$ for all data, GOF = 0.859, absolute structure parameter $x = 0.04(15)$ All hydrogen atoms were located on a difference Fourier map, but introduced in the refinement as fixed contributors by using a riding model and with an isotropic thermal parameter fixed at 20% higher than those of the carbon atoms to which they are connected, excepted concerning the hydrogen atoms H(8) and H(11) which were isotropically refined. All non-hydrogen atoms were anisotropically refined, and in the last cycles of refinement weighting schemes have been used. Drawings of molecules are performed by using the program ORTEP-32 with 50% probability displacement ellipsoids for non-hydrogen atoms. Crystallographic data (excluding structure factors) for the structure in this paper, have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC.195494. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
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