Pallado-catalysed hydrophosphination of alkynes: access to enantio-enriched P-stereogenic vinyl phosphine–boranes†

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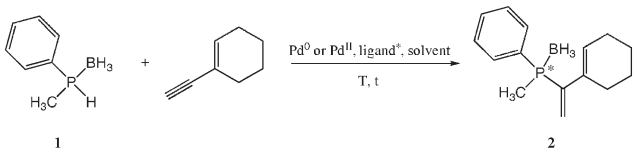
Preliminary results dealing with the synthesis of non-racemic P-stereogenic vinylphosphine–boranes by hydrophosphination of alkynes in the presence of a chiral catalyst are reported.

Phosphines are the main ligands in homogeneous catalysis.[1] Although many chiral phosphines are found in the literature, only few among them are P-stereogenic, *i.e.* with the chirality centre at the phosphorus atom. This low availability can be explained by the difficulties encountered in their synthesis. P-stereogenic phosphines are mainly prepared by resolution processes or *via* asymmetric synthesis using stoichiometric amounts of chiral auxiliaries.[2–6] A more elegant approach relies on the use of asymmetric catalysis. However, only few examples have been reported until now.[7–13]

In our group, we are interested in the formation of C–P bonds by the metallo-catalysed C–P cross coupling reactions[10,14] or by the atom economical hydrophosphination reactions.[15–18] Dealing with hydrophosphination reactions, our work is mainly focused on the less studied addition of phosphines to unactivated unsaturated compounds[19] *i.e.* alkenes and alkynes. With alkynes, we developed two procedures allowing to prepare the anti-Markovnikov adducts by addition of a secondary phosphine–borane to an alkyne under thermal conditions and the Markovnikov derivatives by using a metallo-catalysed activation.[17] We thus reasoned that the reaction between a racemic secondary phosphine–borane and a chiral palladium catalyst should give an access to P-stereogenic phosphines assuming a transfer of chirality from the catalyst to the product. We report here our preliminary results on the synthesis of tertiary vinylphosphine derivatives by palladium catalysed asymmetric hydrophosphination of alkynes. To the best of our knowledge, there is no example of catalyzed asymmetric hydrophosphination providing P-stereogenic vinylphosphines in the literature.

The reaction between methylphenylphosphine–borane **1**, a representative alkylarylphosphine and 1-ethynylcyclohexene was chosen as a model case (Scheme 1). The reactions were performed under kinetic resolution conditions, *i.e.* with 0.5 equiv. of alkyne for 1 equiv. of phosphine **1**.

First sets of experiments were performed under the conditions optimized for the racemic version ($Pd(OAc)_2$, diphosphine, toluene).[17] A range of chiral ligands having various steric and electronic properties such as ferrocenylbisphosphine (L1), ferrocenylphosphine-amine (L2), phosphine-oxazoline (L3), thiazoline amine (L4), bisphosphine with central (L5, L6, L7, L10, L11), planar (L8) or axial chirality (L9) were first tested (Fig. 1).



Scheme 1 Hydrophosphination of 1-ethynylcyclohexene.

The procedure was quite simple.‡ The ligand L and palladium acetate were mixed together in toluene and stirred 15 mn prior to introduction of **1** and alkyne. The mixture was then heated at 35 °C

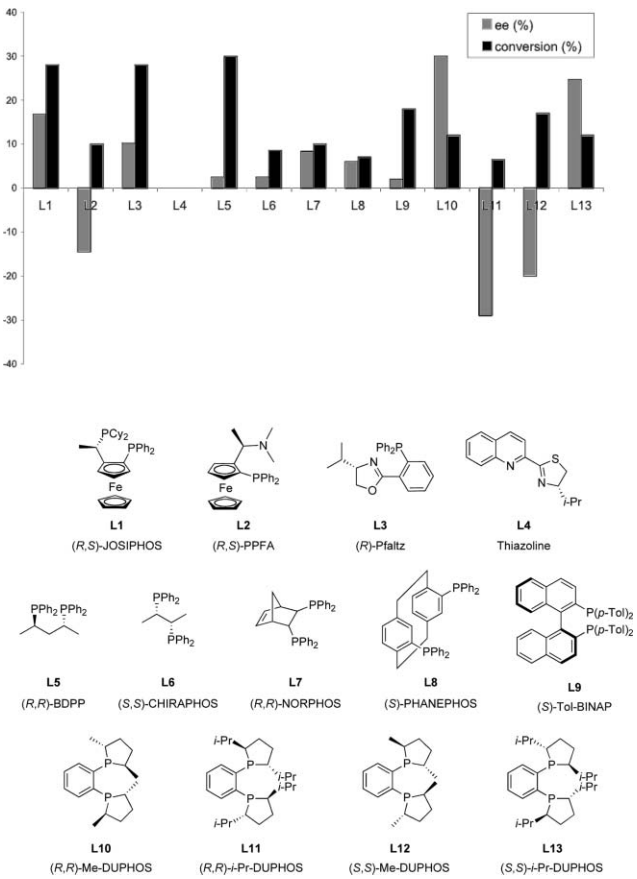


Fig. 1 Conversion of **1** into **2** and ee using enantiopure ligands.

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† Electronic supplementary information (ESI) available: ^{1}H, ^{11}B, ^{13}C and ^{31}P NMR spectra of **2**, HPLC chromatogram of enantio-enriched **2**. See DOI: 10.1039/b607434k

and the conversion was followed by ^{31}P NMR. After 17 h, the product was purified on silica gel chromatography under air and conditions for the separation of the two enantiomers were defined by HPLC. It should be pointed out that purification was made easier by the presence of the borane, which protects the phosphine from oxidation.[20] Important ligand effects in catalytic activity and in enantioselectivity were revealed by this screening (Fig. 1). A reasonable conversion of 30% (50% max. due to kinetic resolution conditions) was obtained with ferrocenyl ligand (L1), phosphine oxazoline (L3) and bisphosphine (L5). Other ligands afforded a rather low conversion ($\leqslant$10%) except BINAP (L9), for which a conversion of 20% was measured. With thiazoline (L4), no conversion was observed.[21] Low enantiomeric excesses (<10%) were obtained with all the electron poor bisarylphosphines whatever the kind of chirality involved: central (L5, L6, L7), axial (L9) and planar (L8) ones. With arylphosphine-amine ligands L2 and L3, ee slightly higher than 10% were obtained. Mixed alkyl-aryl bisphosphine (L1) showed promising ee (close to 20%). These preliminary results indicate that electron rich substituents on the phosphorus atom play a determining role in the enantioselection step. To validate this assumption, a rigid and electron rich ligand, the bis-phospholane (*R*,*R*)-MeDUPHOS (L10), was tested. A rather low conversion of 12% was obtained. Nevertheless, a promising ee of 30% was measured by HPLC. We thought that increasing the steric hindrance by using (*R*,*R*)-*i*-PrDUPHOS (L11) could favour the enantiodiscrimination even if the conversion could suffer. As expected a lower conversion was observed (8%) but without any benefit to the ee. Enantiomers of L10 and L11, respectively (*S*,*S*)-MeDuphos (L12) and (*S*,*S*)-*i*-PrDuphos (L13) gave the other enantiomer with similar ee.

Since low ee could result from autocatalysis (phosphine–boranes **1** and **2** playing the role of an achiral ligand),[22] compounds **1** and racemic **2** were both tested as ligands with $Pd(OAc)_2$. Almost no conversion was observed (<3%) indicating that autocatalysis may be disregarded under these conditions.

In order to improve the catalytic activity and the selectivity of the reaction, influence of other parameters such as palladium source, ligand/metal ratio, solvent and temperature were studied. (*R*,*R*)-MeDUPHOS, which gave the best ee, was used in these tests. Given that palladium acetate required first to be reduced to generate the active species, a palladium(0) source ($Pd_2(dba)_3$) was used. After 17 h at 35 °C in toluene, a conversion of 16% and a lower enantioselectivity of 19% were measured. Moreover, a by-product was detected ($\delta(^{31}P)$ = 19 ppm). The NMR signals of the by-product are consistent with the hydrophosphination adduct of dibenzylidene acetone (dba). To avoid this side-reaction, $Pd(OAc)_2$ was preferred.

Influence of the metal/ligand ratio on the enantioselectivity was then studied. The first set of tests was performed with a 1 : 1.5 metal : ligand ratio. Increase of the amount of ligand to 2 equiv. (10 mol%) led to similar conversion and selectivity, while a decrease to 1 equiv. (5 mol%) induced a considerable drop of selectivity (17 *vs.* 30% ee with 1.5 equiv.). These results could be explained by the fact that part of the ligand is used to reduce the Pd(II) into the catalytically active Pd(0) species.

The preliminary enantioselective hydrophosphination reactions were performed in toluene. Solubility of the palladium precatalyst being rather low in this solvent, we thought that the poor conversion could result from this low solubility. We thus decided

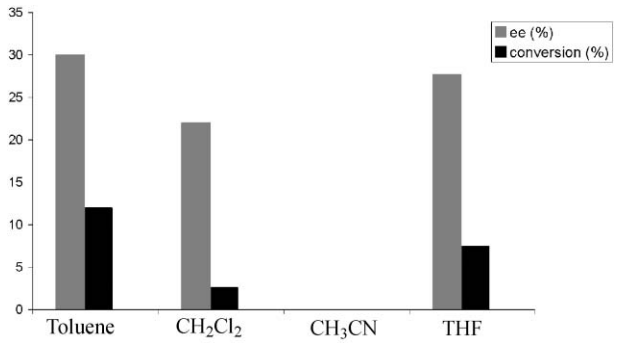

Fig. 2 Conversion of **1** into **2** and ee using different solvents.

to test more polar solvents (Fig. 2). Dichloromethane proved to be detrimental both for the activity and the selectivity even if the solubility of the precatalyst was good. In a more polar solvent such as acetonitrile, a high solubility of the precatalyst was observed, but no conversion was obtained. An explanation can arise from the high coordinating ability of acetonitrile, which is able to compete with the alkyne in the catalytic cycle. With these results in hand, we selected a less coordinating polar solvent (tetrahydrofuran) than acetonitrile. As expected, a high solubility of the catalyst was observed. However, the conversion and the selectivity were slightly lower than those obtained in toluene. Consequently toluene was retained to carry on the study.

Influence of the temperature on the activity and the enantioselectivity was then evaluated (Fig. 3). This set of tests was carried out in toluene and the reactions were stopped after 17 h.

At temperature lower than 35 °C, the conversion was too low to allow isolation and purification of the product, precluding measurement of the ee. At higher temperature (50 °C), the conversion increased dramatically (35 *vs.* 12% at 35 °C), presumably because of a better solubility of the precatalyst in this solvent. Furthermore a slight increase of enantioselectivity was observed (42 *vs.* 30% at 35 °C). Increasing further on the temperature (60 and 65 °C) proved to be detrimental for both activity and enantioselectivity. This drop of activity and selectivity can be attributed to the decomplexation of phosphine–borane **1** leading to the corresponding free phosphine, which is less reactive than **1** and can furthermore compete with the ligand for palladium

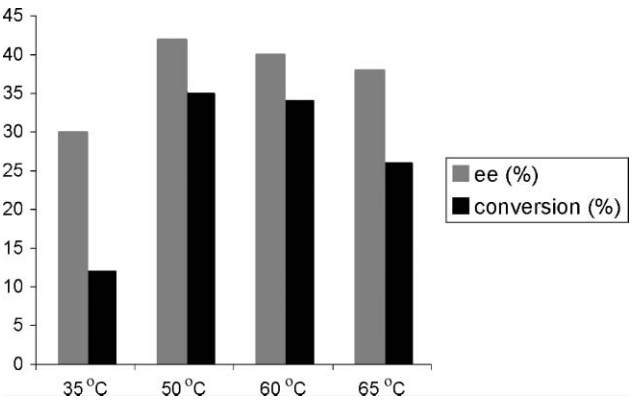

Fig. 3 Conversion of **1** into **2** and ee using different temperatures.

complexation. Monitoring of the reaction by ^{31}P NMR of crude samples confirmed the partial decomplexation of phosphine–borane **1** when heated at these temperatures.

Influence of the amount of alkyne was finally tested. The reaction was conducted under the best conditions previously defined [$(Pd(OAc)_2$, (*R*,*R*)-MeDuphos, toluene, 50 °C, 17 h] on using 1.2 equiv. of alkyne instead of 0.5 equiv. As expected, a strong increase in conversion was obtained (70%) for a similar ee.

In conclusion, we have reported the first palladium catalysed asymmetric hydrophosphination of non-activated alkynes. High conversion (70%) and enantiomeric excess up to 42% were obtained. Mechanistic investigations are currently under progress in order to gain information on the enantiodiscriminating step and will be reported in due course.

Notes and references

‡ *Typical procedure* for metallocatalysed hydrophosphination reaction: In a Schlenk tube, flamed under vacuum and flushed with nitrogen, $Pd(OAc)_2$ (1.25×10^{-5} mol, 3 mg, 5 mol%) and (*R*,*R*)-MeDUPHOS (1.9×10^{-4} mol, 6 mg, 7.5 mol%) were introduced. After three vacuum/N_2 cycles, 200 μL of toluene were added and the mixture was stirred at 50 °C during 20 min. Then methylphenylphosphine–borane **1** (2.5×10^{-4} mol., 35 μL), ethynylcyclohexene (3×10^{-4} mol, 33.5 μL, 1.2 equiv.) and toluene (50 μL) were added to the solution. The mixture was stirred for 17 h at 50 °C and then directly purified by silica gel chromatography (AcOEt–heptane–toluene, 2 : 6 : 2, $R_f = 0.6$) affording pure hydrophosphination product **2**. Ee values were measured by HPLC using an AD-RH column (H_2O–MeCN, 63 : 37, flow 1 mL min^{-1}, $t_1 = 61$ min, $t_2 = 66$ min) at 25 °C.

^{31}P NMR (161 MHz, $CDCl_3$): δ 11.61 (dm, $^1J_{PB} = 65.3$ Hz); ^1H NMR (400 MHz, $CDCl_3$): δ 7.75–7.60 (m, 2H); 7.55–7.40 (m, 3H); 5.92 (d, $^3J_{HP\textit{trans}} = 36.2$ Hz, 1H); 5.82 (d, $^3J_{HP\textit{cis}} = 18.1$ Hz, 1H); 5.77–5.71 (m, 1H); 2.10–1.85 (m, 4H); 1.69 (d, $^2J_{HP} = 9.8$ Hz, 3H); 1.65–1.52 (m, 2H); 1.52–1.43 (m, 2H); 0.95 (qm, $^1J_{HB} = 95.3$ Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 143.35 (d, $^1J_{CP} = 45.1$ Hz); 134.72 (d, $^2J_{CP} = 6.2$ Hz); 131.81 (d, $^2J_{CP} = 9.5$ Hz); 131.28 (d, $^4J_{CP} = 2.2$ Hz); 131.00 (d, $^1J_{CP} = 55.0$ Hz); 130.16 (d, $^3J_{CP} = 5.8$ Hz); 129.06 (d, $^3J_{CP} = 10.0$ Hz); 126.57 (d, $^2J_{CP} = 10.7$ Hz); 28.53 (d, $^3J_{CP} = 3.0$ Hz); 25.91 (s); 22.99 (s); 22.05 (s); 12.15 (d, $^1J_{CP} = 40.7$ Hz). ^{11}B NMR (128 MHz, $CDCl_3$): δ −33.53 (dq, $^1J_{BP} = 65.3$ Hz, $^1J_{BH} = 95.3$ Hz). HMRS calc. for $C_{15}H_{19}P$ ($[M - BH_3]^{+\bullet}$: 230.1227, found: 230.1224).

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