Palladium catalysed enantioselective phosphination reactions using secondary phosphine-boranes and aryl iodide†

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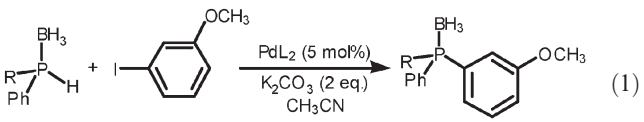
Preliminary results dealing with the enantioselective version of the C–P cross-coupling reaction between dissymmetric secondary phosphine-borane complexes and aryl iodide derivatives are presented. To gain information on the enantiodiscriminating step, direct observation of an intermediate involved in the catalytic cycle has been achieved by ^{31}P NMR spectroscopy.

Since several decades, phosphines have played a key role in the development of asymmetric catalysis. Among these, P-chirogenic ligands have been less studied, mainly because of the difficulties encountered in their synthesis. They are mainly prepared by resolution processes or by using a stoichiometric amount of a chiral auxiliary.[1] Recently, in a remarkable work, Glueck has demonstrated that P-chirogenic phosphines could also be prepared by asymmetric catalysis using a catalytic amount of a chiral auxiliary.[2] Thus, an enantioenriched tertiary phosphine was obtained with enantiomeric excesses varying from 53 to 78% *via* phosphination of a phenyl halide using a racemic bulky secondary phosphine [*i.e.* methyl(triisopropylphenyl)phosphine] as precursor, in conjunction with $NaOSiMe_3$ as base and a chiral palladium catalyst. Then, Helmchen successfully applied this kind of methodology to the synthesis of a family of enantioenriched triarylphosphines (ee between 25 and 93%) involving coupling phenyl(*o*-biphenyl)phosphine with an *ortho*-substituted aryl iodide.[3]

Our group has recently been involved in the C–P bond forming reactions by using either the hydrophosphination reaction[4] or the metal catalysed C–P cross-coupling reaction. In the latter case, we began our investigation by examining the catalytic cycle of the Pd(0) mediated cross-coupling reaction between an aryl iodide and diphenylphosphine-borane.[5] Herein we report our preliminary results on the enantioselective version of this reaction using simple unhindered racemic secondary phosphine-borane precursors **1** and **2** and chiral catalysts.

We first examined the racemic version of the reaction in order to determine conditions allowing the separation of the 2 enantiomers of the cross-coupling product. Preliminary coupling conditions tested were based on those reported for the coupling of diphenylphosphine-borane.[5] Thus, we reacted respectively, for 24 hours, *tert*-butylphenylphosphine-borane **1** and *o*-anisylphenylphosphine-borane **2** with *m*-iodoanisole in CH_3CN at room temperature in the presence of $dpppPdCl_2$ (5 mol%) and two equivalents of K_2CO_3 [eqn. (1)]. Under these conditions, the conversion was completed with **2**, however with **1**, the reaction was sluggish (6% conv.). Even at 60 °C, the reaction with **1** was sluggish (35% conv.). Since we had previously observed that the rate-limiting step was the reductive elimination,[5] we selected a ligand having a greater bite angle, which should favour the reductive elimination. Thus, using racemic BINAP and a palladium source [Pd_2dba_3 or $Pd(OAc)_2$], a complete transformation of the precursor **1** into the expected arylation product **3** was observed after 48 hours. Although both palladium sources are effective precatalysts, $Pd(OAc)_2$ was preferred since the use of Pd_2dba_3 resulted in the formation of a side product which was identified as the hydrophosphination adduct of dba.

After purification of the coupling products (**3** and **4**) by silica gel chromatography in air, conditions for the separation of the two enantiomers of each coupling product were defined by HPLC.[6]



(1)

1 R = *t*-Bu
2 R = *o*-An

3 R = *t*-Bu
4 R = *o*-An

We then investigated the C–P cross-coupling reaction between racemic phosphine **1** and *m*-iodoanisole mediated by various enantiopure ligands, using $Pd(OAc)_2$, K_2CO_3 and CH_3CN as previously stated. The reaction was monitored by ^{31}P NMR spectroscopy. Whatever the identity of the ligand, the reaction was sluggish at room temperature and heating at 40 °C proved more convenient. The reactions were stopped before reaching 50% conversion by quenching with an aqueous solution and each ee was measured by HPLC after purification by silica gel chromatography.‡ Selected results are reported below. With phosphine **1** and (*R*)-BINAP (**L1**), (*S*)-PHANEPHOS (**L2**), the bisoxazoline[7] **L3**, or (*R*)-(*S*)-PPFA (**L4**), racemic **3** was obtained. Even, (*R*,*R*)-Me-DuPHOS (**L5**), the ligand of choice used by Glueck,[2] gave racemic product in our reaction. Nevertheless, four ligands gave promising enantioselectivities: (*S*,*S*)-BDPP (**L6**) (17%), (*R*,*R*)-Et-FerroTANE[8] (**L7**) (12%), the bisthiazoline[9] **L8** (13%) and the phosphine-oxazoline[10] **L9** (27%). All results are summarized in Fig. 1.

Screening of other parameters (base and solvent) with the ligand giving the best results (*e.g.* phosphine-oxazoline **L9**) was then performed. With a more polar solvent (DMSO), a similar enantioselectivity was obtained. However using less polar solvents (CH_2Cl_2, THF or toluene) was always detrimental to the ee. Replacing K_2CO_3 by Cs_2CO_3 in CH_3CN showed no improvement.

† Electronic supplementary information (ESI) available: HPLC chromatogram for **3** and crystallographic data for **7b**. See http://www.rsc.org/suppdata/cc/b5/b501078k/

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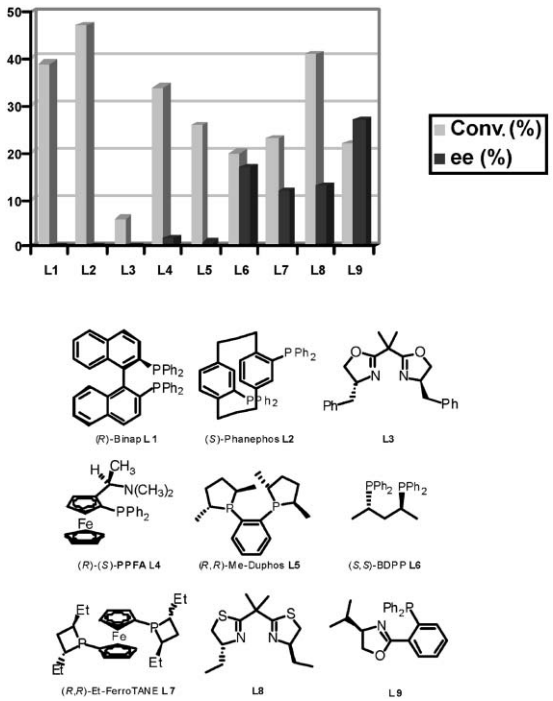


Fig. 1 Conversions and enantioselectivities in the C–P cross-coupling between **1** and *m*-iodoanisole using various chiral ligands (**L1–L9**).

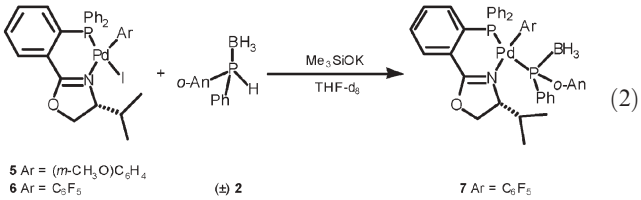
Using the best defined conditions [**L9**, $Pd(OAc)_2$, CH_3CN and K_2CO_3], the influence of temperature on ee was studied. Upon lowering the temperature from 40 °C to room temperature (20 °C), we were pleased to measure a satisfactory enantiomeric excess of 45%. Using a lower temperature (0 °C) resulted in an extremely slow reaction (2% conversion after 3 weeks).

We then turned our attention to *o*-anisylphenylphosphine-borane **2** in order to obtain information on the influence of the substituents on the ee. Using the conditions defined for **1** [**L9**, $Pd(OAc)_2$, CH_3CN, K_2CO_3, 40 °C], low enantioselectivity was obtained with **2** (3% compared to the 27% measured with phosphine **1**). Surprisingly, by lowering the temperature to rt, the ee was not improved.

To gain understanding of this result, we undertook a study of the catalytic cycle, following the preliminary work done using the racemic version.[5] Thus, one equivalent of complex **5** (previously prepared according to a method reported by Brown[11] for similar structures) and an excess of racemic phosphine-borane **2** (3 equivalents) were treated with a base (Me_3SiOK) in THF-d_8 at −70 °C [eqn. (2)].

Low temperature ^{31}P NMR monitoring of the reaction showed a complex mixture from which transmetallation intermediates were too ill-defined to be characterized. The mixture was then allowed to reach rt slowly and ^{31}P NMR revealed a clear formation at 0 °C of the coupling product **4**, indicating that reductive elimination had occurred.

To characterize the transmetallation adducts, the rate of the reductive elimination was decreased using iodopentafluoroben-zene. Thus complex **6**, prepared as previously, was reacted with an excess of **2** [eqn. (2)] and Me_3SiOK at −70 °C. Monitoring of the reaction by low temperature ^{31}P NMR spectroscopy showed, this time, the clean disappearance of the precursor signals and the quantitative formation of the transmetallation adduct at −70 °C.



(2)

The distinctive ^{31}P NMR spectrum, shown in Fig. 2, reveals the *trans* relationship of the two phosphorus atoms and is consistent with the proposed structure **7**. The transmetallation adduct was obtained as an equimolar amount of the two expected diastereomers (**7a** and **7b**) indicating no kinetic resolution in the reaction between the phospha-anion intermediate and complex **6**. The mixture was then allowed to reach rt slowly (5 h) and ^{31}P NMR spectra were recorded regularly. No variation of the diastereomeric ratio (50:50) was observed during the warming. To promote the reductive elimination, the mixture was gently heated in the NMR probe at 55 °C. Even at this temperature, complex **7** proved to be stable and did not produce the cross-coupling product or any decomposition product. Interestingly, during the heating, a modification of the diastereomeric ratio was observed by ^{31}P NMR, leading to a final ratio of 23:77. Only a thermodynamic equilibrium between the 2 diastereomers can account for the observed ratio modification. This result seems to indicate that, for this example, the stereoselectivity of the reaction is governed more by thermodynamic factors than by kinetic ones.

Since complex **7** was stable at rt, we were able to separate the two diastereomers **7a** and **7b** by flash chromatography using CH_2Cl_2 as eluant. A single crystal of the major diastereomer was grown from slow evaporation of a CH_2Cl_2–heptane solution allowing the confirmation of the structure of the transmetallation adduct **7** (Fig. 3) and establishing the absolute configuration of the phosphido-borane P centre which is (*S*) for the main diastereomer (**7b**).

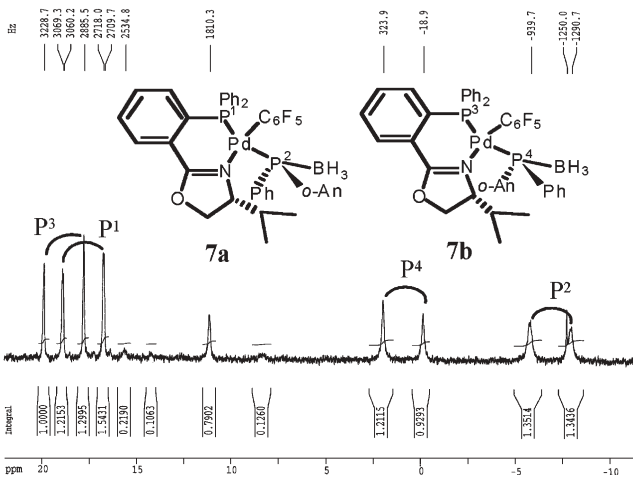


Fig. 2 ^{31}P NMR spectrum of transmetallation adducts **7a** and **7b** in THF-d_8 at −70 °C; assignments: δ ppm −6.8 (d, J = 351 Hz, P^2), 0.9 (d, J = 343 Hz, P^4), 17.9 (d, J = 351 Hz, P^1), 18.9 (d, J = 343 Hz, P^3).

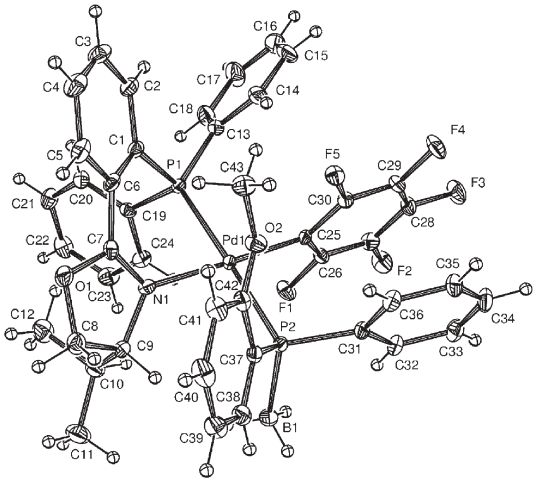


Fig. 3 X-Ray structure of the complex **7b**.§ Selected bond lengths (Å) and angles (°): Pd(1)–C(25), 2.010(3); Pd(1)–N(1), 2.107(3); Pd(1)–P(1), 2.3005(10); Pd(1)–P(2), 2.3504(10); C(25)–Pd(1)–N(1), 178.32(13); C(25)–Pd(1)–P(1), 93.37(10); N(1)–Pd(1)–P(1), 86.02(9); C(25)–Pd(1)–P(2), 88.71(10); N(1)–Pd(1)–P(2), 91.88(9); P(1)–Pd(1)–P(2), 177.87(4).

To confirm this result, the reaction was performed again under the same conditions but using strictly stoichiometric amounts of phosphine-borane **2** and complex **6** (1 to 1 equivalent). Under these conditions, the results obtained were exactly the same as those obtained previously (a 50:50 ratio and a 23:73 ratio were measured for the two diastereomers respectively at −70 °C and +55 °C) confirming the thermodynamic equilibrium. These results indicate that there is a temperature required for the equilibration between the two transmetallation adducts. Below this temperature the cross-coupling product is obtained with a low ee, assuming that P–C bond formation by reductive elimination proceeds with retention of configuration.[12]

In summary, conditions allowing the C–P cross-coupling between a racemic secondary phosphine-borane and an aryl iodide have been examined. A great difference between 2 simple phosphine precursors, an alkyl-aryl derivative (*tert*-butylphenylphosphine-borane **1**) and a diaryl derivative (*o*-anisylphenylphosphine-borane **2**), has been observed. Under the conditions defined [CH_3CN, K_2CO_3, rt, $Pd(OAc)_2$ and ligand **L9**], phosphine **1** was coupled with a satisfactory ee of 45% while phosphine **2** gave under the same conditions a racemic coupling product. A mechanistic investigation suggests that, at least for the diaryl derivative, the enantiodiscrimination could arise from thermodynamic control. Extensive exploration of this reaction to obtain more mechanistic details of the enantioselective C–P cross coupling reaction will be reported in due course.

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Notes and references

‡ *Representative procedure for enantioselective C–P cross-coupling reactions.* In a Schlenk tube, the ligand (0.022 mmol) and palladium acetate (2 mg, 8.9 10^{-3} mmol) were stirred for 15 min at room temperature in 1 mL of acetonitrile. To this solution were added *m*-iodoanisole (23 μL, 0.2 mmol), potassium carbonate (54 mg, 0.39 mmol) and phosphine-borane **1** or **2** (0.2 mmol). The mixture was heated for a time "*t*" at the desired temperature *T*. The reaction was followed by ^{31}P NMR and stopped before reaching 50% conversion by quenching with an aqueous solution. The product **3** or **4** was extracted with diethyl ether and the organic layer dried over magnesium sulfate. The solvent was removed under reduced pressure and the crude product purified by silica gel chromatography using toluene as eluant. Ee was measured by HPLC.

§ The following crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 227137. See http://www.rsc.org/suppdata/cc/b5/b501078k/ for crystallographic data in CIF or other electronic format. *Crystal data for* **7b**: $PdP_2C_{43}H_{39}BF_5NO_2{\cdot}C_5H_{12}$, M_r = 948.05, trigonal, $P3_2$, a = 11.9662(3), c = 26.4783(5) Å, V = 3283.5(1) Å^3, Z = 3, D_x = 1.438 mg m^{-3}, λ(MoKα) = 0.71073Å, μ = 5.58 cm^{-1}, F(000) = 1464, T = 120 K. The sample (0.35 × 0.32 × 0.32 mm) is studied on a NONIUS Kappa CCD with graphite monochromatized MoKα radiation. Structure refined with SHELXL97[13]: 541 variables and 6578 observations with $I > 2.0\sigma(I)$; R = 0.031, R_w = 0.075 and S_w = 1.071 , $\Delta\rho < 1.0$ *e* Å^{-3}. Absolute configuration determined with the Flack parameter: −0.05(2). Atomic scattering factors from International Tables for X-ray Crystallography.[14] Ortep views realized with PLATON98.[15]

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