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Synthesis of a diverse set of phosphorus ligands on solid support and their screening in the Heck reaction

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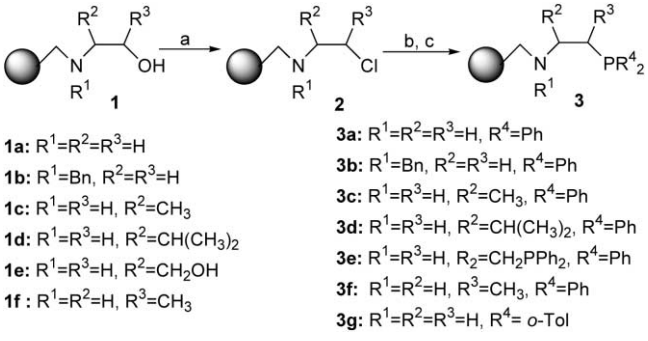
Abstract—Representative members from five different families of supported phosphine and phosphinite ligands have been prepared from common templates—polymer-bound aminoalcohols. These include β-aminophosphines, *N*,β-diphosphinoamines, α,β-diphosphinoamines, β-aminophosphinites and *N*-phosphino-β-aminophosphinites. Representatives of each family of ligands were complexed with $Pd(OAc)_2$ and screened in the Heck reaction of iodo- and bromobenzene. While the reaction of iodoarenes is ligand-independent, the reaction of bromoarenes is ligand-sensitive. The rationale for this behavior is suggested. Lead ligands for the reaction of bromoarenes were determined.

Multistep solid-phase synthesis of phosphorus ligands has rarely been applied in supported catalysis.[1] Most frequently, phosphorus ligands are prepared in solution and only thereafter attached to a reactive polymer via a remote functional group.[2] Alternatively, phosphorus ligands, containing a polymerizable unit, are prepared in solution and are copolymerized with other monomers to form polymer-supported catalyst precursors.[3] Yet, stepwise on-resin assembly is a more flexible approach that benefits from the well known advantages of solid-phase synthesis.[4]

Recently, we reported procedures for solid-phase synthesis of two types of phosphines: α- and β-aminophosphines.[5] In the latter case, the template used for the on-resin assembly of the ligand was a resin-bound aminoalcohol. Herein we report a number of additional families of phosphine and phosphinite ligands, formed on solid support from the same aminoalcohol template. Some families are formed directly, while others are synthesized through the β-aminophosphine intermediate.

Firstly, we would like to mention that the relatively drastic procedure previously reported for chlorodehydroxylation ($SOCl_2$) was replaced by a milder, but equally efficient one (PPh_3/C_2Cl_6).[6] Based on the improved procedure, a range of β-aminophosphines were prepared. These include a phosphine **3f** derived from the secondary alcohol **1f** and a β-aminobisphosphine ligand **3e** derived from L-serinol (Scheme 1). Both ligands were obtained with excellent yield and purity.[7] The fact that two different products are formed from **1c** and **1f**,[8] proves that aziridine intermediates are not involved in the synthesis.

In an attempt to diversify further the ligands attainable from the aminoalcohol templates, we reacted the β-



Scheme 1. *Reagents*: (a) PPh_3, C_2Cl_6, THF; (b) $^iPr_2NEt$, THF; (c) $LiPR^4_2$, THF.

Scheme 2. *Reagents*: (a) $ClPPh_2$, NEt_3, benzene.

Keywords: solid-phase synthesis; supported catalysts; Heck reactions; phosphorus ligands.

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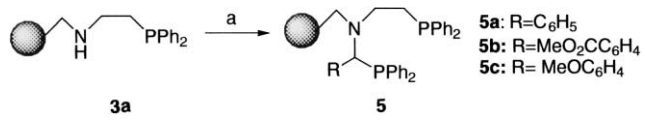


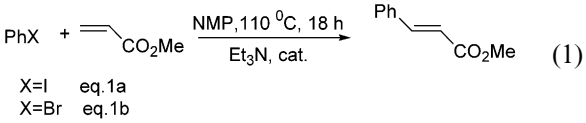
Scheme 3. *Reagents*: (a) $HPPh_2$, PhCHO, $CHCl_3$, DCM, TMOF.

aminophosphines that contained a secondary amino moiety with chlorodiphenylphosphine (Scheme 2). In this way, biphosphine ligands **4** incorporating two electronically different phosphorus coordinating sites were prepared.[9]

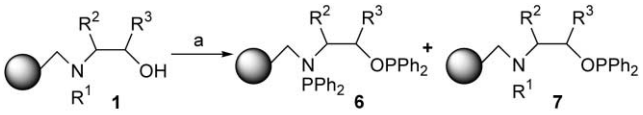
According to an additional scheme, leading to desymmetrized bisphosphine ligands, the resin-bound β-aminophosphine was used as an amino partner in a Mannich condensation leading to α,β-diphosphinoamine **5** generation (Scheme 3).[10] Due to the known problems associated with such synthesis only moderate yields of the ligands were obtained.[5b,11]

We later demonstrated that the amino alcohol templates can be converted into phosphinito ligands (Scheme 4).[12–14] The reaction of the polymer-immobilized β-aminoalcohols with chlorodiphenylphosphines can potentially produce two products **6** and **7** resulting from the substitution of both heteroatoms or *O*-substitution only. The extent of the reaction depends on the exact aminoalcohol structure and the reaction time. Obviously, for tertiary amines, only the *O*-substitution product is obtained. However, the same outcome is observed when a secondary amino moiety, substituted with a bulky substituent at the α-carbon, is reacted.[15] On the other hand, prolonged reaction times, for aminoalcohols without sterically congested nitrogen substituents, result mainly in the disubstituted product. Surprisingly, L-serinol forms only *O*-substitution products.

In order to demonstrate screening of the catalytic ability of the sets of ligands prepared, we chose the Heck reaction known as the 'sharpening stone of palladium catalysis'.[16] Although numerous homogeneous catalytic systems have been applied to a variety of targets in this reaction, the success with immobilized catalysts has been much more limited. Thus, in the Heck reaction using a soluble catalyst, aryl iodides, bromides and even chlorides can be used as substrates. Supported catalysts, on the other hand, work almost exclusively on iodides or electron-poor bromides, while non-activated bromides are generally unreactive.[17,18] Moreover, while in solution, phosphines are the most popular ligands for Heck catalysis, on solid support, only few phosphorus-based systems have been reported.[19] Most of the reported phosphorus ligand-based systems were active only with iodoarenes, and only in a fundamental study by Hallberg and co-workers was the activation of bromobenzene explored.[20]



(1)



6a, 7a: $R^1=R^2=R^3=H$ (ratio 9:1)
6b, 7b: $R^1=R^3=H$, $R^2=Me$(ratio 3:1)
6c, 7c: $R^1=R^2=H$, $R^3=Me$ (ratio 9:1)
6d, 7d: $R^1=R^3=H$, $R^2=Bn$ (ratio 1.5:1)
7e: $R^1=R^3=H$, $R^2=CH(CH_3)_2$
6f, 7f: $R^1=R^3=H$, $R^2=Ph$ (ratio 1:6)
7g: $R^1=Bn$, $R^2=R^3=H$
7h: R^1-$R^2=CH_2CH_2CH_2$, $R^3=H$

Scheme 4. *Reagents*: $ClPPh_2$, NEt_3, benzene.

Table 1. Results of Eq. (1b)[a]

Ligand	Conversion (%)	Yield (%)[b]
3a	18	11
3b	34	20
3e	63	56
4a	60	42
5a	26	19
6a	33	13
6d	8	1
6f	20	13
No ligand[c]	16	7

[a] Bromobenzene (0.56 mmol), methyl acrylate (0.67 mmol), triethylamine (0.73 mmol), resin-bound ligand precomplexed with $Pd(OAc)_2$ (0.02 mmol Pd) in 1 ml NMP, 110°C, 18 h.
[b] HPLC yield.
[c] Wang resin incubated with $Pd(OAc)_2$.

Initially, we tested the aforementioned ligands in the Heck reaction of iodobenzene (Eq. (1a)), following their complexation with $Pd(OAc)_2$.[21,22] While the conversion and yields were high (ca. 90%), they were equally high for all ligands (all results fall within experimental error margins). Moreover, when $Pd(OAc)_2$ was adsorbed on the phosphine-free Wang resin and the resin was used as a catalyst, the obtained yield was slightly higher. However, when the reaction of bromobenzene was investigated, clear differences in the activity of the various ligands were observed (Eq. (1b), Table 1).[23]

These results can be understood in light of the earlier work, comparing iodo- and bromoarene reactivity patterns with supported and soluble Pd complexes,[20,24] and later studies on Heck catalysis with metal Pd. Heating the immobilized Pd(II) complexes under the reaction conditions results very quickly in the reduction, coagulation and precipitation of black Pd particles in the polymer matrix. These particles, either directly or as the source for the solvated 'naked Pd^0', are the most active catalyst for iodoarenes in the described system.[17c–f] The reactivity of the ligand-coordinated species is much lower and, thus, catalysis of Eq. (1a) is practically ligand-independent. On the other hand, Pd^0 metal particles, or soluble 'naked' species derived from them, are not sufficiently reactive to promote the activation of

bromoarenes and only P-ligated Pd complexes can participate in the catalytic cycle. The Pd metal 'bypass' is blocked and, accordingly, the reaction is ligand-sensitive.

In addition to these interesting observations, another conclusion can be drawn from the fast screening summarized in Table 1 above. Ligands **3e** and **4a** gave the best yields and selectivity. There is a clear advantage to the use of phosphine over phosphinite ligands and bidentate over monodentate phosphines. The first point must reflect the requirement of high electron density on the metal for successful oxidative addition of aryl bromides.[25] The better performances of diphosphines in our system, although contradicting the results obtained with one of the rare supported phosphine-based systems,[19b] can be understood in the context of Hallberg's results.[20] It seems logical that Pd^0 complexes of P,P-chelates **3e** and **4a** are more stable than those of the monodentate phosphines and, thus, the number of phosphine-coordinated Pd complexes on these resins is higher.

In addition to the complex stability factor, the degree of cross-linking of the polymer may play a role. According to our studies, complexes of type $L_2Pd(OAc)_2$ (L = P-moiety) are predominantly formed on the resin. Formation of these moieties on most of our resins must lead to cross-linking, affecting the swelling properties and impeding the transport of reagents inside the polymer matrix. However, with bisphosphine 6-membered chelates (ligands **3e** and **4a**), such cross-linking is practically absent. Moreover, the chelate effect can also increase the activity of the catalyst itself and, thus, lead to a better catalytic system.[25,26]

In conclusion, we have prepared samples from a number of polystyrene-immobilized phosphine and phosphinite ligand families using resin-bound aminoalcohol templates. Fast screening of the Pd complexes of these ligands led to the demonstration of an interesting difference in reactivity of iodo- and bromoarenes and identification of two lead ligands for future studies.

Acknowledgements

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6. **2a**: Triphenyphosphine (0.45 g, 1.71 mmol, 5.5 equiv.) and hexachloroethane (0.41 g, 1.71 mmol, 5.5 equiv.) were added to a suspension of **1a** (ca. 0.31 mmol) in a minimal amount of THF. The suspension was stirred overnight. The resin was filtered off and washed with THF (×3) and DCM (×3) and dried in vacuo. Yield 95% to quantitative. Partial gel-phase ^{13}C NMR (100 MHz, C_6D_6): δ 60.9, 53.4, 50.9.
7. For methods of resin-bound ligand analysis and the spectral data of **3** see Ref. 5c.
8. **3c**: Gel-phase ^{31}P NMR: δ −19.9; **3f**: Gel-phase ^{31}P NMR: δ −5.3.
9. **4a**: Chlorodiphenylphosphine (0.25 ml, 1.4 mmol, 5 equiv.) in 3.4 ml benzene was added dropwise to a suspension of **3a** (ca. 0.28 mmol) in a minimal amount of benzene and triethylamine (0.2 ml, 1.4 mmol, 5 equiv.) at 0°C. After 30 min of stirring, the temperature was raised to room temperature and the suspension stirred for 48 hours. The resin was filtered off and washed with benzene (×3), THF (×3) and DCM (×3) and dried in vacuo. Yield 86%. Gel-phase ^{31}P NMR (400 MHz, C_6D_6): δ 65.1, −20.1. Partial gel-phase ^{13}C NMR (100 MHz, C_6D_6): 52.1, 27.2.
10. **5a**: Under a nitrogen atmosphere, diphenylphosphine (2.8 mmol, 10 equiv.) in chloroform was added to resin **3a** (ca. 0.28 mmol) which was swollen in a 3:2:1 mixture of $CHCl_3$, DCM, trimethylorthoformate and benzaldehyde (0.28 ml, 2.8 ml, 10 equiv.). The mixture was gently stirred overnight. The resin was filtered off and washed with DCM and dried in vacuo. Yield 75%. Gel-phase ^{31}P NMR (400 MHz, C_6D_6): δ −15.3, −20.3. Partial gel-phase ^{13}C NMR (100 MHz, C_6D_6): 66.4, 56.9, 54.7, 27.0.
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21. The complexation efficiency was determined using gel-phase ^{31}P NMR.
22. **Typical complexation and catalysis procedure**: Palladium acetate (0.5 equiv.) was added to a suspension of **3a** (1 equiv.) in NMP. After 2 hours of stirring the resin **8a** was filtered off and washed with NMP. Complexation efficiency: 100%. Iodobenzene (0.06 ml, 0.56 mmol, 1 equiv.), methyl acrylate (0.06 ml, 0.67 mmol, 1.2 equiv.) and triethylamine (0.1 ml, 0.73 mmol, 1.3 equiv.) were added to the suspension of **8a** (0.035 equiv. of Pd, two phosphines per Pd assumed) in 1 ml of NMP. The mixture was stirred overnight at 110°C. The suspension was filtered and washed with acetonitrile. The filtrate was diluted with acetonitrile and HPLC analyzed.
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