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Report

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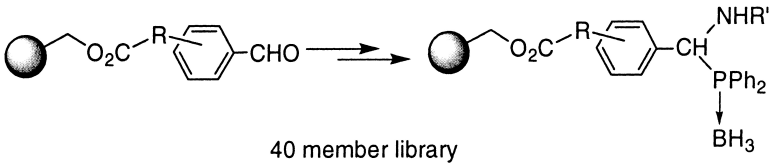

40 member library

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Solid-Phase Synthesis of an α-Aminophosphine Library

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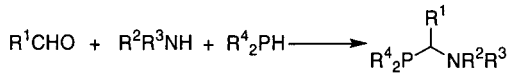
The combinatorial approach emerged during the past decade as a solution to biomedical challenges, but over the past five years, it has been applied with increasing frequency to catalysis research.[1] A significant part of these studies was based on parallel solid-phase synthesis of ligands. Ligand libraries, prepared in this way, can be screened while still bound to the support, as has been demonstrated in recent years.[2] Moreover, polymer-immobilized catalysts combine useful properties of both homogeneous and heterogeneous systems. The majority of ligands assembled in a library format on solid support are nitrogen ligands (e.g., peptides, Schiff bases).[2b,3] Except for the phosphine-containing peptides of Gilbertson,[4] no parallel assembly of phosphine ligands on solid support has ever been reported. While the attachment of phosphine ligands, presynthesized in solution, to a reactive polymer through a remote functionality is well-known,[5] a multistep−multicomponent assembly of such ligands on resin has hardly been investigated.[6]

We are interested in the parallel assembly on solid support of phosphorus−nitrogen ligands, particularly those with secondary nitrogen moieties. We recently reported an efficient route to resin-bound β-aminophosphines.[7] α-Aminophosphines are an especially attractive target because they can readily be assembled via a multicomponent Mannich condensation (eq 1). Aminomethylmono- and bisphosphines



(1)

have been applied in a variety of hydroformylation processes.[8] Structurally related 2-pyridylphosphines were involved in a number of catalytic applications, particularly alcoxycarbonylation of acetylenes.[9]

Numerous synthetic schemes, which are based on variations of the Mannich condensation and lead to α-aminophosphine preparation in solution, have been reported.[10] While this work was in progress, a solution-phase synthesis, which exploited Mannich condensation and resulted in the first library of soluble α-aminophosphines, was published.[11] However, an analogous solid-phase route has never been explored.

Herein we report the first synthesis of an α-aminophosphine library on solid support through multicomponent Mannich condensation of a secondary phosphine, aldehydes, and primary amines.

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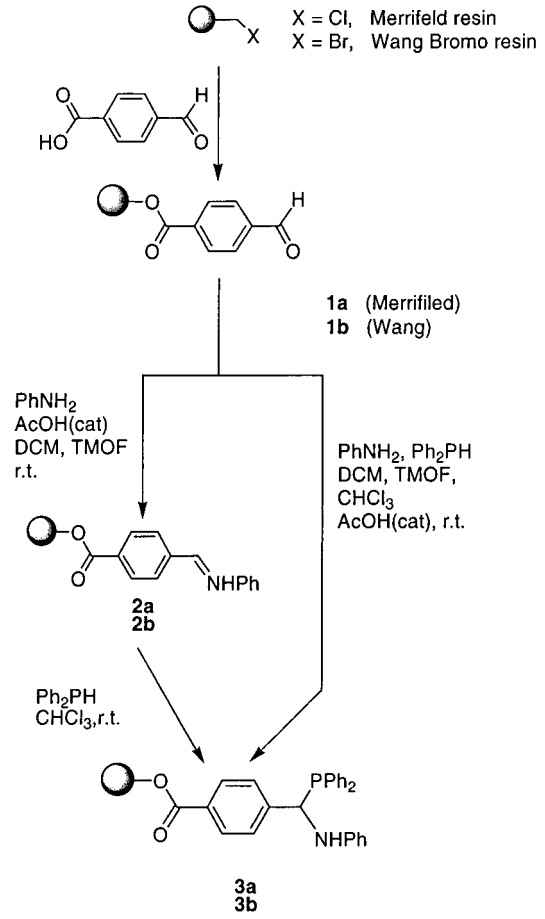
Scheme 1



As a result of the preliminary studies of the Mannich condensation in solution (eq 1), the decision to link the ligand to the support through the R^1 substituent was chosen. Because of the pseudodilution principle, this approach minimizes the chance of formation of the double-condensation byproduct of one-pot Mannich condensation.

According to the chosen strategy, a model synthesis with 4-carboxybenzaldehyde, aniline, and diphenylphosphine was investigated (Scheme 1). The synthesis was accomplished on both Merrifield and bromo Wang supports with a similar yield (85%). The standard immobilization of the aldehyde on the support was followed by imine formation. The imine was then reacted with diphenylphosphine, resulting in resin-bound ligand **3**. Alternatively, a multicomponent reaction of the polymer-immobilized aldehyde with the amine and phosphine led to the same product **3** with approximately the same yield and purity.

The synthetic steps were monitored using gel-phase ^{13}C NMR. Complete conversion of halomethyl resins into **1**, and of **1** into **2**, was confirmed by these measurements as well as methoxide-induced nucleophilic cleavage. While the latter method was not suitable for **3** (vide infra), the formation of the resin-bound ligand was confirmed by gel-phase ^{31}P and ^{13}C NMR (Figure 1). The ^{13}C NMR (Figure 1b) shows the peaks of the polymer along with the peaks assigned to **3**

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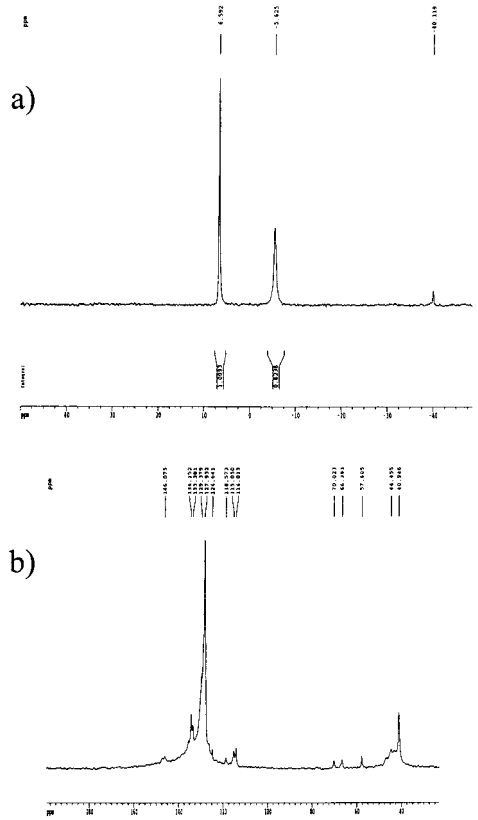
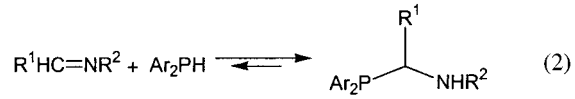


Figure 1. Gel-phase ^{31}P NMR (a) and ^{13}C NMR (b) of **3**.

(e.g., the characteristic peak of the bridge carbon at 57.6 ppm). ^{31}P NMR (Figure 1a) exhibits the ligand **3** peak (6.6 ppm), the signal of the resin-bound phosphine reference,[12] which helped determine the yield of **3** (−5.6 ppm), and traces of Ph_2PH at −40 ppm.

These traces are not the result of poor washing but rather a consequence of the fact that the formation of an N-monosubstituted α-aminophosphine from an imine and a secondary phosphine is a reversible process (eq 2). This



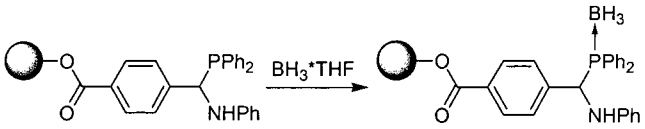
(2)

equilibrium, which was recently analyzed in detail in the literature,[13] is responsible for the generation of Ph_2PH and a resin-bound imine (although only in a minor amount) from **3** whenever it is incubated in a solvent (e.g., benzene-d_6 for the gel-phase measurements). The same equilibrium, which is significantly shifted to imine under basic conditions, is responsible for the decomposition of **3** under nucleophilic cleavage conditions.

Because of the equilibrium and in order to maximize the yield and purity of **3**, two adjustments of the synthetic scheme were made: (1) a large excess of diphenylphosphine was used for the preparation of **3** from the resin-bound imine or aldehyde; (2) minimal washing of the resin was performed at the end of the synthesis.

During the solution studies, extreme sensitivity of the α-aminophosphines to oxygen was observed. Although resin-bound α-aminophosphines are more resistant to oxidation, protection of the formed ligands was required for easy

Scheme 2



3 **4**

handling or prolonged storage. Boranes are well-known protecting groups that prevent phosphine oxidation.[14] Consequently, a direct solution synthesis of borane-protected α-aminophosphines from imines and diphenylphosphine-borane was developed.[15] Unfortunately, this technique is inapplicable to solid-phase synthesis, and therefore, postsynthetic protection (Scheme 2) was successfully tested for **3**. Deprotection can easily be achieved by washing the protected resin-bound ligand **4** with a solution of secondary amine.

Since the gel-phase NMR demonstrated good yield and purity for the model compound, a number of carboxyaldehydes and amines were tested using the optimized synthetic sequence. Four aldehydes and 10 amines were chosen for the synthesis of a library of borane-protected N-monosubstituted α-aminophosphines.

The synthesis was performed according to Scheme 3 on a robotic synthesizer, yielding a library of 40 protected α-aminophosphines (**5**). Initial gel-phase ^{31}P NMR screening of the whole library determined that all expected library members, except **5**{*2,4*}, were formed. Moreover, all resins exhibited a very clean ^{31}P NMR of the product **5**. The purity of **5** *from phosphorus-containing byproducts* (Table 1) exceeded 90% for all members except **5**{*2,5*−*6*} (i.e., for 95% of the library).

The yields were determined for 21 library members using gel-phase ^{31}P NMR and the aforementioned reference phosphine resin (Table 2). While most compounds were produced with fair to high yields, it is clear that benzylamine- and 2-aminopyridine-incorporating products are formed with low efficiency. In the case of the benzylamine, this fact is attributed to the markedly lower stability of the N-monosubstituted α-aminophosphines with an aliphatic substituent on the nitrogen.[16] 2-Aminopyridine is actually not an amine but rather an amidine, and therefore, its expected diminished nuclophilicity must be the reason for the lower yields. Generally, lower yields are observed for ortho-substituted aldehydes **6**{*2*−*3*} for steric reasons. Suprisingly, sterically hindered amines **7**{*7*−*9*} form the aminophosphines with excellent yield.

Since **5** is a library of resin-bound species, it is obvious that the general purity must reflect the yield. (The reactive sites of the resin not occupied by the ligand are, by definition, impurities.)

A total of 21 library resins were measured using gel-phase ^{13}C NMR, an alternative technique that tests the degree of purity of the library members. These spectra generally confirm our conclusions from the ^{31}P NMR. While all resins exhibited the peaks assigned to **5**, those derived from electron-poor or aliphatic amines, or from hindered aldehydes, exhibited an additional signal. For four members, an additional peak at 64−65 ppm reveals that the remaining sites of the resin are occupied by benzylic alcohols, which

Scheme 3

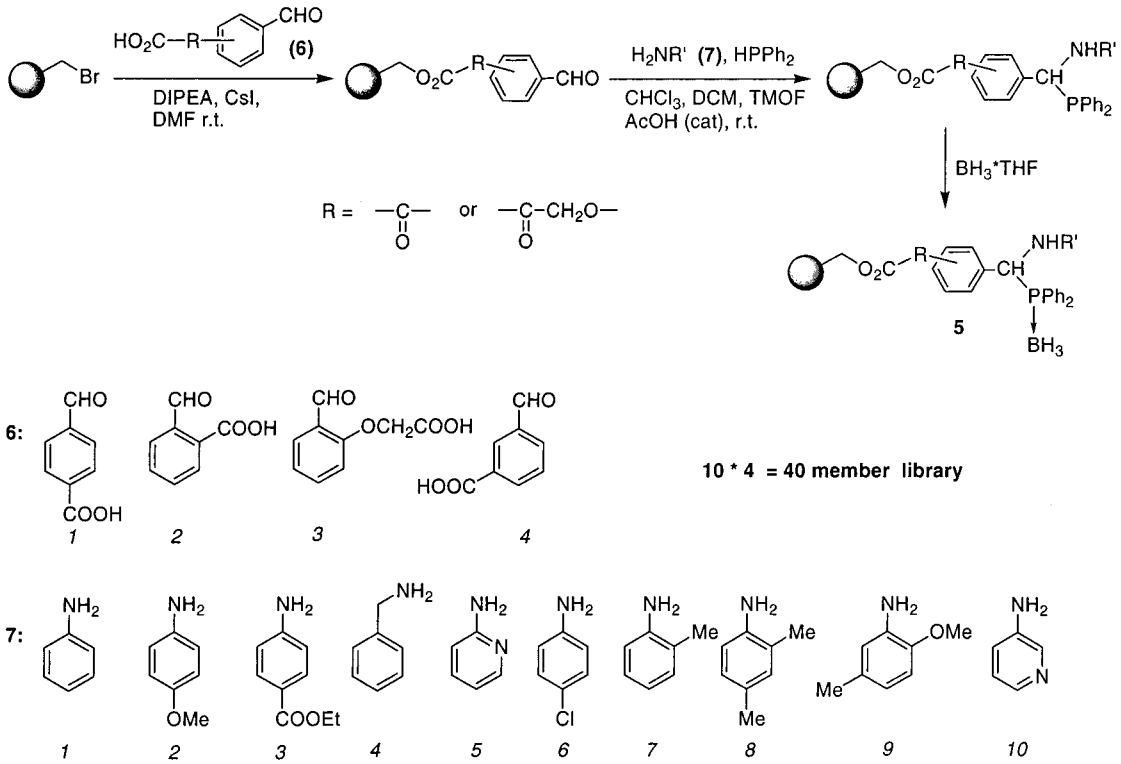


Table 1. Library Analysis Data: Purity from Phosphorus-Containing Byproducts (%)

	6			
7	*1*	*2*	*3*	*4*
1	100	100	100	100
2	100	97	100	100
3	100	90	100	100
4	100		100	95
5	99	87	98	91
6	100	84	100	93
7	99	100	100	100
8	100	100	100	100
9	100	100	100	100
10	100	90	100	100

Table 2. Library Analysis Data: Yields (%)

	6			
7	*1*	*2*	*3*	*4*
1	85	67		
2	97	49	70	
3		60	67	88
4		trace	37	19
5		18	19	35
6				96
7	100	100		91
8	99			91
9	80	66		
10				

were derived from unreacted aldehydes upon borination. For another four resins, an additional peak at 43−47 ppm reveals occupation of the remaining "impurity" sites by arylbenzyl secondary amines, formed by the reduction of unreacted imines during the borination−protection step.

The analysis performed on the library indicated that it can be used for complexation and catalysis studies. Even the members formed with low yield are present on the resin in amounts that allow meaningful evaluation (as demonstrated by the ^{31}P and ^{13}C NMR). Moreover, even for members containing resin-bound byproducts, the catalytic sites formed upon complexation, will be isolated from the byproducts because of the pseudodilution principle.

In conclusion, we have demonstrated, for the first time ever, the synthesis of a library of borane-protected N-monosubstituted α-aminophosphines accompanied by on-resin characterization. Solid-phase parallel assembly of phosphine ligands, diversified near phosphorus, is unprecedented. The borane-protected members are stable but can be readily "activated" by deborination. The extension of the methodology to additional libraries of α-aminophosphines and deprotection and metal complexation studies of these ligands in library format are underway.

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Supporting Information Available. Experimental Section and two tables listing ^{31}P and ^{13}C NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Purchased from Fluka, cross-linked with 1% divinylbenzene, particle size 100−200 mesh, 1.6 mmol g^{-1}.

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