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Preparation of α-aminophosphines on solid support: model studies and parallel synthesis

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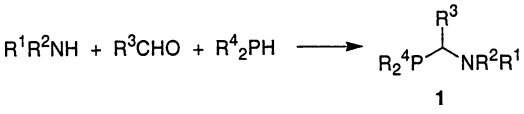
Abstract—On-resin assembly of phosphine ligands represents a formidable challenge. Following model solution studies, we developed two synthetic routes for α-aminophosphine synthesis on solid support. The ligands are prepared via the Mannich reaction of the resin-bound aldehyde, amine and diphenylphosphine with very good yield and purity. Alternatively, the amine can serve as the anchoring building block. The ligands were qualitatively and quantitatively analyzed using gel-phase ^{31}P and ^{13}C NMR techniques. The studies culminated in the parallel synthesis of a 40-member library of borane-protected α-aminophosphines.

1. Introduction

The combinatorial approach has been applied to catalysis research with increasing frequency over the last five years.[1] Arrays of ligands and catalysts have been tested using various high-throughput techniques. A significant number of these studies were based on parallel solid-phase synthesis of ligands. Solid-phase organic synthesis (SPOS), a vital tool of combinatorial research, experienced a dramatic revival over the last decade.[2] This technique can lead to the efficient and expeditious assembly of ligands on a solid support in a single or parallel format. Ligand libraries, prepared in this way, can be screened while still bound to the support, as has been demonstrated in recent years.[3] The majority of ligands assembled in a library format on solid supports are peptide or Schiff base ligands.[3b,4] No parallel assembly of phosphine ligands on solid support have ever been reported, except for the phosphine-containing peptides of Gilbertson.[5] One of the reasons for this fact is the general underdevelopment of solid-phase synthetic methods, especially those for the preparation of air-sensitive compounds. Thus, while the attachment of phosphine ligands, pre-synthesized in solution, to a reactive polymer through a remote functionality is well known,[6] the multi-step/multicomponent assembly of such ligands on resin has hardly been investigated and still represents a formidable challenge.[7]

We have become interested in the parallel assembly of phosphorus–nitrogen ligands on solid support and, particularly, those ligands with secondary nitrogen moieties. Recently, we reported an efficient route to resin-bound β-aminophosphines.[8] α-Aminophosphines represent an especially attractive target since they can be readily assembled by a multicomponent Mannich condensation (Eq. (1)). Multicomponent reactions are highly valuable for combinatorial synthesis since they introduce a number of diversity elements into the target molecule in one step.[9] Ligands with potential hemilabile chelating ability (like α-aminophosphines) were effective in a number of catalytic processes.[10] Numerous synthetic schemes, based on variations of the Mannich condensation, were used for the preparation of α-aminophosphines in solution.[11] While this work was in progress, solution-phase Mannich condensation of secondary phosphines, aldehydes and secondary amines was exploited for the preparation of a first library of soluble α-aminophosphines.[12] However, an analogous solid-phase route has never been explored.



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Herein we report our studies of α-aminophosphine assembly on solid support, an examination of anchoring building blocks and the synthesis and analysis of the first supported α-amiophosphine libraries. Some of these results have been published in a preliminary communication.[13]

2. Results and discussion

2.1. Model studies in solution

Our primary goals in this work were the development of

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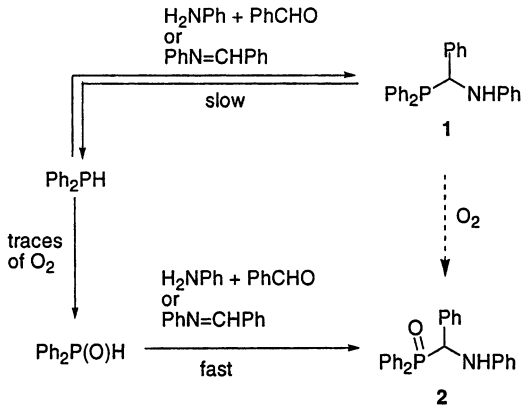
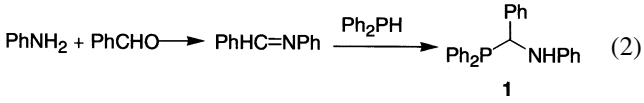


Scheme 1.

solid-phase synthetic routes to α-aminophosphine ligands (PCN) with secondary amino groups and the preparation of a diverse library of the ligands through parallel synthesis.

Initially, model studies in solution (ligand **1**) demonstrated that the stepwise approach (Eq. (2)) must be favored over the one-pot three-component reaction (Eq. (1), R^1=R^3=R^4=Ph, R^2=H) due to the formation of the double condensation by-product. In solution, traces of the imine and diphenylphosphine are always observed (by NMR) together with product **1**. This demonstrates the slight disassembly of **1** to its precursors since the reaction between the imine and the secondary phosphine is in fact an equilibrium process (Eq. (2a)).[14]



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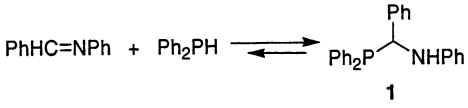
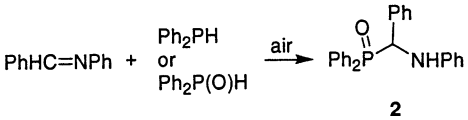


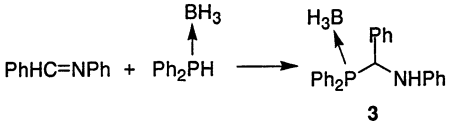
(2a)

The synthesis of ligand **1** suffers from its high sensitivity to oxygen, as was repeatedly observed. Without special precautions, some α-aminophosphine oxide **2** was always formed along with **1**. Benzylidene aniline reacts very quickly and irreversibly with diphenylphosphine oxide or diphenylphosphine under air, forming pure **2** (Eq. (3)). Thus, it is quite possible that the oxidation of **1** does not proceed directly but rather through the aforementioned equilibrium (Scheme 1).



(3)

The abovementioned observations led us to use a phosphine–borane adduct in the Mannich condensation (Eq. (4)), forming **3** irreversibly. Compound **3** can readily be converted to **1** by deprotection with amines.[15] The synthesis according to Eq. (4) was examined for a number of substituents and was recently published as a communication.[16]



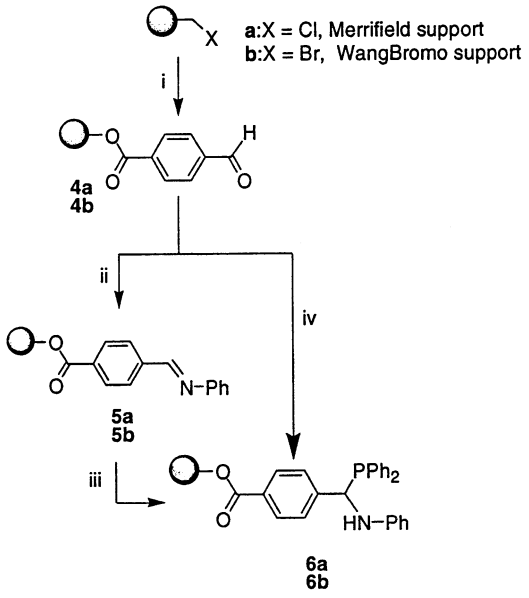
(4)

2.2. Method development on solid support

Following the model solution studies, one of the possible approaches on solid support was implemented. According to this approach, the aldehyde partner of the Mannich condensation carries out the anchoring function. The model ligand **6**, analogous to soluble compound **1**, was assembled on Merrifield or Wang Bromo support according to Scheme 2. Immobilization of 4-carboxy-benzaldehyde, via standard nucleophilic substitution,[17] was followed by the conversion of the aldehyde to the imine with aniline using a TMOF-based procedure.[18] The final step formed the α-aminophosphine **6** via Ph_2PH addition to the imine. Alternatively, the immobilized aldehyde could be converted into the product **6** in one step via a 3-component reaction. In the latter case, double condensation is unlikely, due to the pseudodilution principle.

In order to analyze the products along the synthetic pathways, we mainly used nucleophilic cleavage, followed by proton NMR of the cleaved mixture. Unfortunately, this method was not applicable for analyzing the final product which is unstable under the cleavage conditions. (Equilibrium (2a) is notably shifted to the left under basic conditions.[14]) Therefore, all phosphine-containing products were analyzed qualitatively and quantitatively using gel-phase ^{31}P NMR.[8]

The gel-phase ^{31}P NMR spectrum of **6b** (Fig. 1(a)) exhibits a single peak at 6.6 ppm (for comparison, **1** absorbs at



Scheme 2. (i) For **4a**: 4-formylbenzoic acid, Cs_2CO_3, KI (cat.), DMF, 80°C, 24 h. For **4b**: 4-formylbenzoic acid, DIPEA, CsI, DMF, rt, 18 h; (ii) $PhNH_2$, AcOH (cat.), DCM/TMOF, rt, 18 h; (iii) Ph_2PH, $CHCl_3$, rt, 18 h; (iv) $PhNH_2$, Ph_2PH, DCM/TMOF–$CHCl_3$, AcOH (cat.), rt, 18 h.

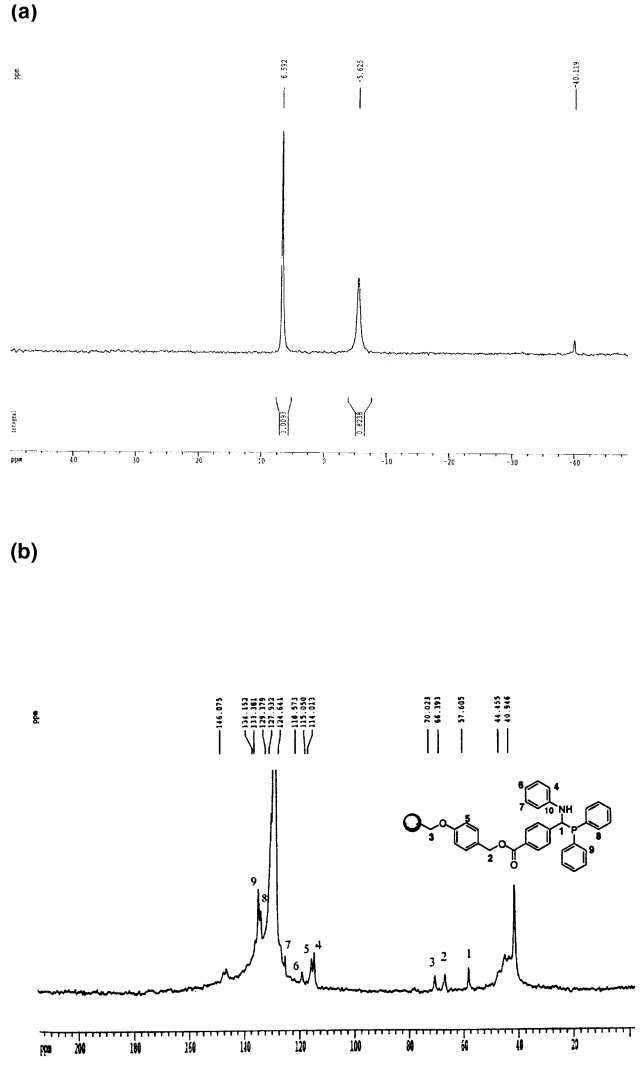


Figure 1. Gel-phase ^{31}P NMR (a) and ^{13}C NMR (b) of **6b**.

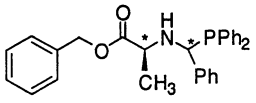
6.2 ppm), the signal of the resin-bound reference phosphine (−5.6 ppm), which helped determine the yield of **6b** (see Section 4.1), and traces of Ph_2PH at −40 ppm. The equilibrium (2a) is responsible for the generation of these traces of Ph_2PH and a resin-bound imine (although only in a minor amount) from **6** whenever it is incubated in a solvent (e.g. benzene-d_6 for the gel-phase measurements).

Due to the equilibrium, and in order to maximize the yield and purity of **6**, two adjustments of the synthetic scheme were made: (1) a large excess of diphenylphosphine was used for the preparation of **6** from the resin-bound imine or aldehyde; (2) minimal washing of the resin was performed at the end of the synthesis.

Quantification using the aforementioned reference resin demonstrated 85% yield, while ^{13}C gel-phase NMR (Fig. 1(b)) exhibited only peaks for the polymer and the ligand **6b**, indicating the high purity of the product.[19] Especially characteristic is the signal of the bridge methine carbon at 57.6 ppm.

We have also used the amine building block as an anchoring functionality in an alternative approach. For this task, *N*-protected amino acids were immobilized on support. While both aliphatic aminoacids (Ala, Gly) and aromatic aminoacid (4-aminobenzoic acid) were used (Schemes 3 and 4, respectively), only in the latter case was a good yield of α-aminophosphine observed.

For the model aliphatic amine (Ala, Scheme 3), both Merrifield/Boc and Wang/Fmoc chemistries led to resin-immobilized amine with high yield. This amine can easily be converted to imine with benzaldehyde (94% overall yield for the product on Wang resin). However, the conversion of the imine into α-aminophosphine never exceeded 30% yield. The aforementioned equilibrium (2a) is responsible for this effect (according to the literature, electron donating substituents destabilize the α-aminophosphines[14]). For resin-bound ligand **9b**, two diastereomers are formed, as determined from the gel-phase ^{31}P NMR spectrum (Fig. 2). The integration ratio of the signals of the diastereomeric ligands at 3.3 and 1.0 ppm indicates chiral 1,3-induction during the formation of the aminophosphine with de ≈60%. Interestingly, a similar de was observed for **10**, the soluble model of **9**. 1,3-asymmetric induction was recently reported for the formation of α-aminophosphine oxides and sulfides with de's within the same range.[20]



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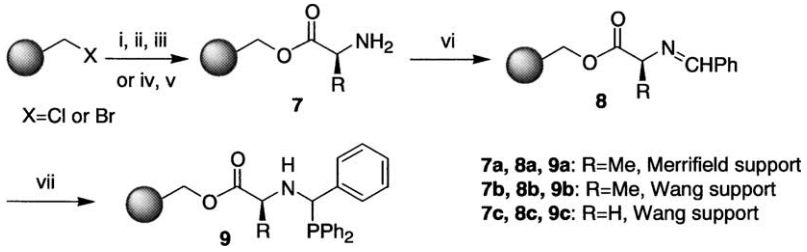
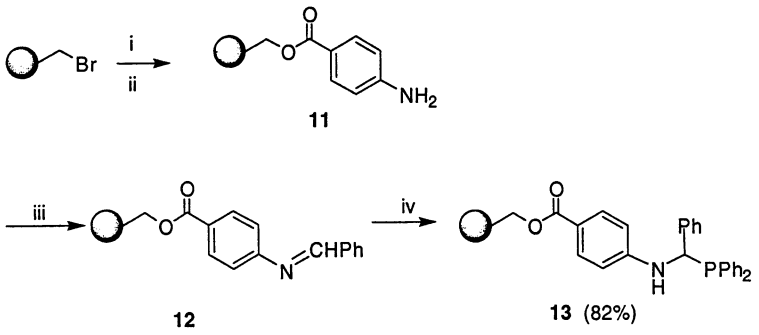
The aromatic amine **11** was initially generated on solid support through the immobilization of Fmoc-aminobenzoic acid, followed by deprotection of the amino group (Scheme 4). A large excess of benzaldehyde and a reduced amount of TMOF (as compared to the related procedure) was used for the efficient conversion of the amine into the imine in order



Scheme 3. X=Cl: (i)*t*-Boc-Ala-OH, Cs_2CO_3, KI (cat.), DMF, 80°C, 24 h; (ii) TFA–$CHCl_3$ (1:1 vol); (iii) DIPEA, THF; X=Br: (iv) Fmoc-Ala-OH, DIPEA, CsI, DMF, rt, 18 h; (v) 20% piperidine in DMF; (vi) PhCHO, TMOF/DCM, AcOH (cat.), rt 24 h; (vii) Ph_2PH, $CHCl_3$, rt, 18 h.



Scheme 4. (i) Fmoc-4-benzoic acid, DIPEA, CsI, DMF, rt, 18 h; (ii) piperidine, DMF; (iii) PhCHO, TMOF/DCM, AcOH (cat.), rt 24 h; (iv) Ph_2PH, $CHCl_3$, rt, 18 h.

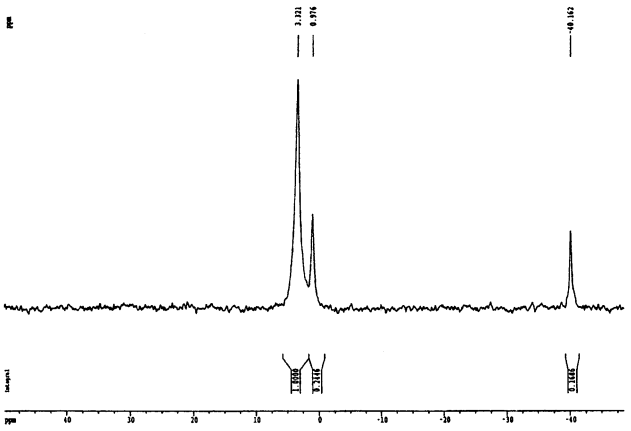
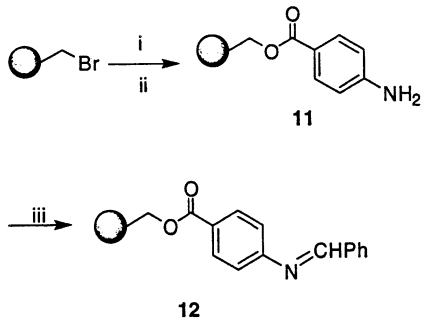
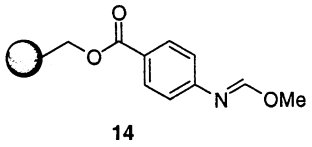


Figure 2. Gel-phase ^{31}P NMR of **9b**.

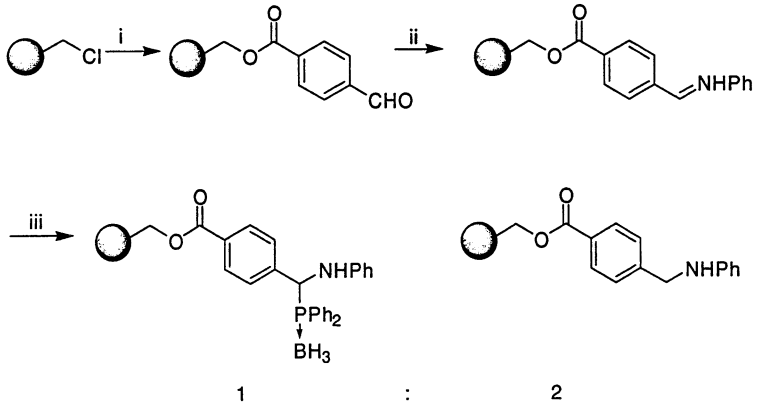


Scheme 5. (i) *p*-Nitrobenzoic acid, DIPEA, CsI, DMF, rt, 18 h; (ii) 2 M $SnCl_2 \cdot H_2O$, DMF, rt, 6 h; (iii) PhCHO, TMOF/DCM, AcOH (cat.), rt 24 h.

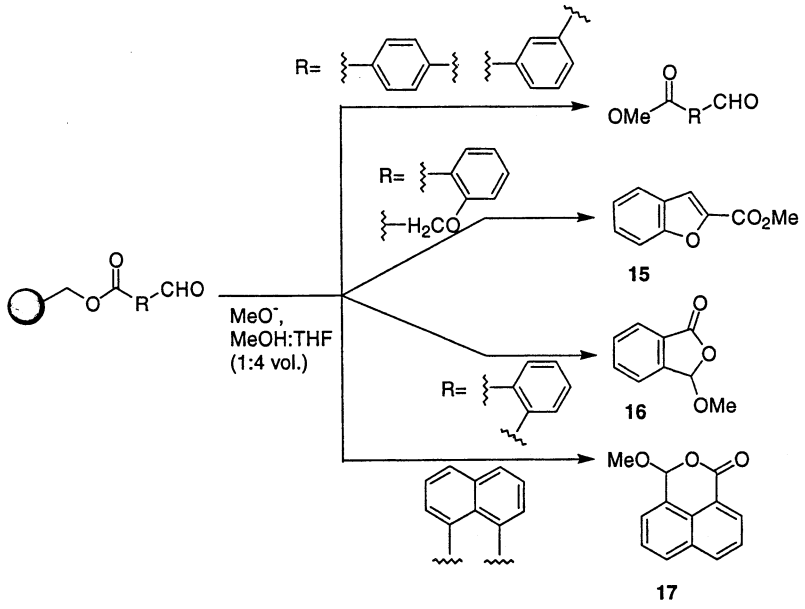
to reduce the amount of imidate byproduct **14**. Reaction of the imine with diphenylphosphine yields the ligand with 82% overall yield (as determined by gel-phase ^{31}P NMR). Since the number of easily accessible Fmoc-aminobenzoic acid building blocks is limited, an alternative simple path to immobilized anilines was explored (Scheme 5). According to this scheme, nitrobenzoic acid was immobilized on Wang Bromo resin and then reduced with stannous chloride. Such an approach is expected to benefit from the diversity of easily accessible nitroaromatic carboxylic acids.



Although polymer-supported ligands are less sensitive to oxidation than their solution analogues, an attempt was made to perform the reaction of an imine with the diphenylphosphine–borane adduct on solid support (Scheme 6)—an analogue of Eq. (4). Unfortunately, reduction of the imine, which is only a minor side reaction in solution, becomes a major process on the solid support. The excess of the phosphine–borane reagent, that must be used for solid-phase reaction, is the probable reason for this reaction outcome. Although the synthetic approach of Scheme 6 was abandoned, post-synthetic protection of the resin-bound ligand with BH_3 was later applied (vide infra).



Scheme 6. (i) 4-Formylbenzoic acid, DIPEA, CsI, DMF, rt, 18 h; (ii) $PhNH_2$, AcOH (cat.), DCM/TMOF, rt, 18 h; (iii) diphenylphosphineborane complex, $CHCl_3$, rt, 18 h.



Scheme 7.

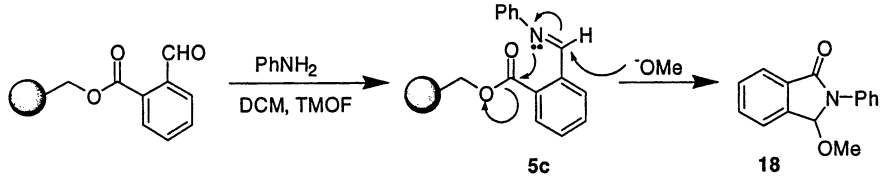
Following the preparation of model ligands on support, the method using the aldehyde as the anchoring building block was preferred for parallel synthesis. A number of aldehydocarboxylic acids were examined for this function. While some proved unsuitable for the chosen loading scheme (for instance, 5-formyl salicylic acid only exhibited loading efficiency of 10%), a reasonably high efficiency of immobilization was observed for others. Thus, in addition to 4-formylbenzoic acid demonstrating 98%-efficient loading, 3-formylbenzoic acid and 2-formylphenoxy acetic acid demonstrated 99- and 78%-yield loading respectively. The loading yield was determined via the nucleophilic cleavage method.

Interestingly, while for 3- and 4-formylbenzoic acids, the cleavage products are simply methyl esters (Scheme 7), for 2-formylphenoxyacetic acid the methyl ester of 2-benzofuran carboxylic acid (**15**, Scheme 7) is obtained. This is a product of aldol condensation, a secondary reaction in cleavage solution. It is likely that, due to the additional transformation, the measured loading efficiency, based on **15**, is in fact lower than the actual one. A similar situation was observed for 2-formylbenzoic acid. Thus, nucleophilic cleavage of the loaded carboxyaldehyde formed 3-methoxy-3*H*-isobenzofuran-1-one (**16**) with 30% yield (primary cleavage product or secondary product of intramolecular acetalization in solution). However, the cleavage following an attempted conversion of the resin bound aldehyde to imine **5c** formed 1*H*-3-methoxy-2-phenylisoindol-1-one (**18**) in 84% yield. Formation of **18** is likely to occur by the mechanism demonstrated in Scheme 8 and reported for a similar imino-ester in solution.[21] This result, as well as ^{13}C NMR measurements (showing aldehydic carbons at 188.5 and 191.2 ppm for 2-formylphenoxyacetic and 2-formylbenzoic acids respectively) indicate that both acids are bound to the resin as aldehydoesters. It is clear that the actual efficiency of loading for the 2-formylbenzoic acid is substantially higher than the obtained yield of **16**.

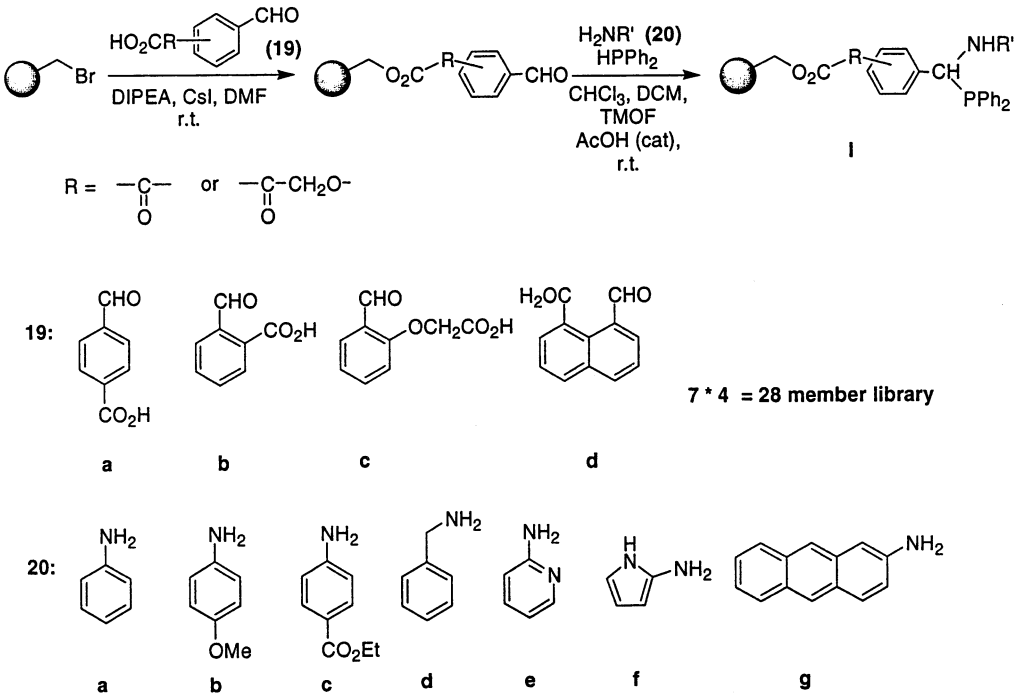
An additional aldehydic acid that was examined as a possible building block is 1,8-naphthalaldehydic acid. Similar to 2-formylbenzoic acid, an acetal ester, 3-methoxy-1*H*,3*H*-naphtho[1,8-*cd*]pyran-1-one (**17**) was obtained as a single product upon nucleophilic cleavage of the resin-bound acid (Scheme 7).

2.3. Parallel synthesis

Following these studies, an attempt to prepare the first library of resin-supported α-aminophosphines was accomplished. Four carboxy-aldehydes and seven amines were chosen for its construction (library **I**, Scheme 9). Our preliminary attempts to perform automated synthesis of α-aminophosphines according to Schemes 2 and 3 revealed substantial oxidation of the target ligands. In order to determine whether the oxidation occurred before analysis, an



Scheme 8.



Scheme 9.

additional step—boronation-protection—was applied to some of the wells during the synthetic scheme used for the generation of the first library. While in the wells where boronation was applied, pure α-aminophosphine borane was formed, in other wells, a variable amount of oxidation led to the mixture of α-aminophosphine and the corresponding α-aminophosphine oxide. The reduction of the already formed phosphine oxide during the boronation can be ruled out since it requires the presence of $CeCl_3$.[22] The results of this experiment clearly show that the oxidation occurs only after the completion of the automated synthesis and while the resin is handled outside the synthesizer.

The results of the analysis of this library are summarized in Table 1. Since it was established that the atmosphere in the synthesizer was kept inert throughout the synthesis and oxidation only occurred thereafter (during the NMR sample preparations), the yield given in the table combines the yields of both α-aminophosphine and its oxidized counterpart. The purities of the resin-bound compounds generally reflect the yields, since any functionalized site not occupied by the product is an impurity per se. However, with regard to our research, it was important to determine how pure are the library members from the phosphorus-containing by-products, which can interfere with the catalytic screening of the library in the future. This data was determined for all library members using ^{31}P NMR and is summarized in Table 1 (in parentheses). The 1,8-naphthalaldehydic acid building block that had a low loading efficiency in the preliminary results, proved unsuitable for parallel synthesis. The same is true using the 3-aminopyrazole (not a true amine, but rather an amidine) as a building block. Somewhat lower yields were obtained for 2-aminopyridine (again amidine) and benzylamine (aliphatic substituents destabilize α-aminophosphines according to the literature[14]). The majority of the members were pure from any phosphorus-containing byproducts.

An interesting observation was made when the ^{31}P chemical shifts of the library members were compared to a 6.6 ppm chemical shift of the model ligand **6** (Table 2). It seems that the substituent on the bridge strongly influences the chemical shift of the phosphorus atom. Thus, when 2-formylcarboxylic acid was used as the building block, the chemical shift of the phosphine moved ca. 4 ppm downfield. When 2-formylphenoxyacetic acid was employed as an aldehydic/anchoring building block, the chemical shift

Table 1. Yield and purity (in parenthesis) of library **I** members

Aldehyde	Amine						
	20a	**20b**	**20c**	**20d**	**20e**	**20f**	**20g**
19a	nd[a] (100)	97 (98)	27 (100)	45 (92)	56 (98)	Traces (–)	nd (95)
19b	50 (100)	nd (100)	60 (100)	0	28 (92)	0	66 (93)
19c	Traces (–)	80 (95)	nd (100)	20 (100)	nd (95)	18 (96)	89 (79)
19d	6 (–)	17 (–)	Traces (–)	0	0	0	Traces (–)

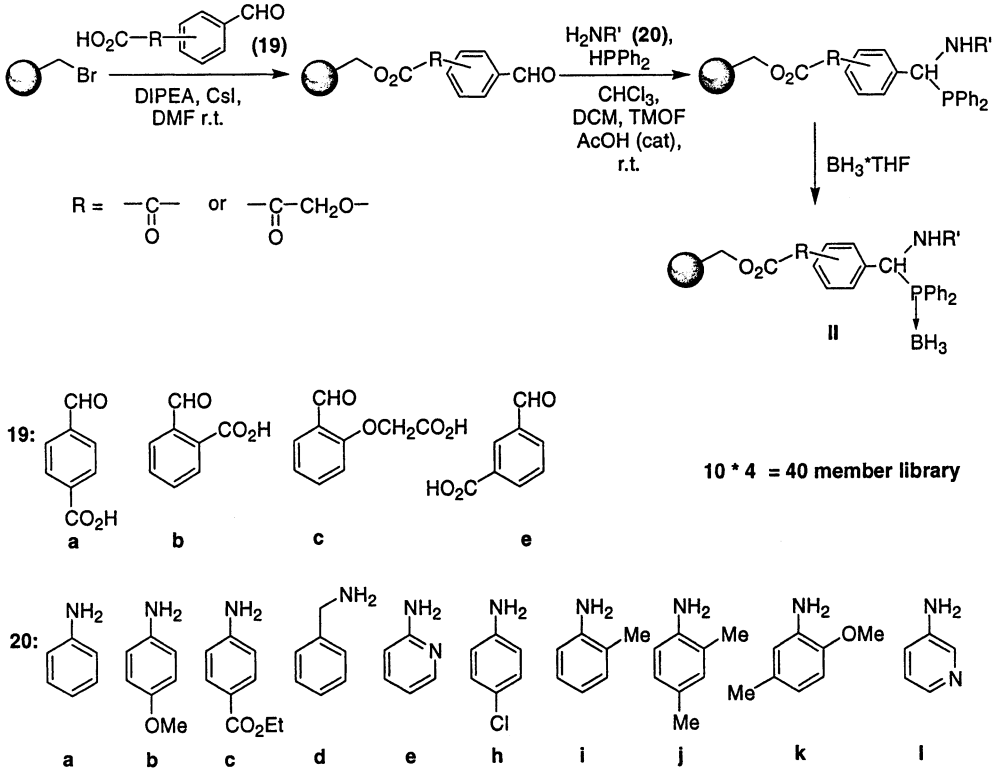
Yields as determined using referenced gel-phase ^{31}P NMR; purity: purity from phosphorus-containing byproducts.
[a] nd=not determined.

Table 2. ^{31}P Chemical shift of library **I** members

Library members formed from	δ (ppm)
19b/20a	10.6
19c/20a	2.8
19a/20b	6.1
19c/20b	2.9
19a/20c	5.8
19b/20c	10.1
19a/20d	2.7
19c/20d	0.6
19a/20e	4.4
19b/20e	8.9
19c/20e	3.6
19c/20f	−0.8
19b/20g	7.6
19c/20g	2.7

moved ca. 3 ppm in the opposite direction. The influence of the nitrogen substituent can also be seen from Table 2. Aliphatic substituents (Bn), as well as 2-pyridyl, shift the phosphine peak upfield by 2–3 ppm (see also the chemical shifts of **9**). The combined influence of the bridge and nitrogen substituents span the range of the ^{31}P chemical shifts of the library over 11 ppm and this difference in chemical shifts holds promise for the diverse activity of the libraries' members in the future.

Four carboxaldehydes and 10 amines were chosen for the construction of the improved, extended library (library **II**). Most building blocks of the previous sets were used (Scheme 10). Naphthalaldehydic acid, which was unsuitable for parallel synthesis, was replaced by 3-formylbenzoic acid. In addition to the first five amino building blocks, which demonstrated reasonable reactivity in the previous experiments, five new amino building blocks were chosen. These included electron-rich, electron-poor and sterically crowded aromatic amines. The formed α-aminophosphines were protected with borane (Scheme 10) in order to prevent oxidation during post-synthetic manipulations. Initial gel-phase ^{31}P NMR screening of the whole library demonstrated that all library members, except one (derived from **19b** and **20d**), were formed (Table 3). The same tests also demonstrated the excellent purity of the library members from phosphorus-containing byproducts (exceeding 90% for 95% of the library members) (Table 4).



Scheme 10.

Table 3. ^{31}P Chemical shifts, δ (ppm), of library **II** members

Aldehyde	Amine									
	20a	**20b**	**20c**	**20d**	**20e**	**20h**	**20i**	**20j**	**20k**	**20l**
19a	28.8	28.4	28.9	25.8	30.2	28.8	29.7	29.6	29.4	28.8
19b	29.7	29.4	29.9	–	31.4	29.7	30.6	30.3	30.3	29.8
19c	28.4	26.9	29.6	25.0	27.4	27.4	28.1	27.9	27.2	26.9
19e	28.5	28.2	28.7	25.8	30.3	28.6	29.6	29.4	29.1	28.3

Table 4. Yield and purity (in parenthesis) of library **II** members

Aldehyde	Amine									
	20a	**20b**	**20c**	**20d**	**20e**	**20h**	**20i**	**20j**	**20k**	**20l**
19a	85 (100)	97 (100)	nd[a] (100)	nd (100)	nd (99)	nd (100)	100 (99)	99 (100)	80 (100)	nd (100)
19b	67 (100)	49 (97)	60 (90)	Traces (–)	18 (87)	nd (84)	100 (100)	nd (100)	66 (100)	nd (90)
19c	nd (100)	70 (100)	67 (100)	37 (100)	19 (98)	nd (100)	nd (100)	nd (100)	nd (100)	nd (100)
19e	nd (100)	nd (100)	88 (100)	19 (95)	35 (91)	96 (93)	91 (100)	91 (100)	nd (100)	nd (100)

Yields as determined using referenced gel-phase ^{31}P NMR; purity: purity from phosphorus-containing byproducts.
[a] nd=not determined.

The yield was determined using the ^{31}P NMR method for 21 library members. 71% of the members were formed with yields exceeding 60%. As before, 2-amino-pyridine- and benzylamine-incorporating products were produced with lower efficiency (vide supra). Generally, lower yields were observed for products formed from *ortho*-substituted aldehydes (**19b** and **19c**). Surprisingly, sterically hindered amines (**20i**–**k**) form the aminophosphines with excellent yields.

The strikingly different influence of steric hindrance when associated with the aldehydic and amine partners, can be attributed to the fact that the steric interactions between the phosphine moiety and bridge substituent of the α-amino-phosphine must destabilize the molecule much more than the steric interactions between the phosphine moiety and the nitrogen substituent. Consequently, the equilibrium (2a) for bridge-hindered α-aminophosphines is less favorable.

As aforementioned, for the library of resin-bound compounds, the general purity reflects the yield. Additional analysis was applied in order to test the purity of the products. Twenty one library members were examined using gel-phase ^{13}C NMR. The spectra generally confirm our conclusions from the ^{31}P measurements. While all resins exhibited the peaks assigned to the products (Table 5), some of those derived from electron-poor or aliphatic amines, or hindered aldehydes, exhibited additional signals. For four members, an additional peak at 64–65 ppm reveals that benzylic alcohols, which were derived from unreacted aldehydes upon boronation, occupy the remaining sites of the resin.[23] For another four resins, additional peaks at 43–47 ppm reveal occupation of the remaining 'impurity' sites by aryl-benzyl secondary amines, formed by the reduction of unreacted imines during the boronation-protection step.[24]

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 due to the pseudodilution principle.

3. Conclusion

In conclusion, we developed synthetic routes for solid-phase α-aminophosphine synthesis. The methods are compatible with parallel synthesis, as demonstrated by the construction of the first libraries of α-aminophosphines. Difficulties in qualitative and quantitative analysis of the products were overcome by gel-phase NMR techniques. This research opens the way to parallel complexation and catalysis studies with α-aminoposphines.

Table 5. Partial gel-phase ^{13}C NMR data for library **II** members

Members formed from	δ (ppm)
19a,**20b**	139.2, 132.8, 132.2, 130.9, 114.4, 69.3, 65.9, 54.5
19a,**20c**	132.9, 131.1, 114.3, 73.5, 69.4, 63.5, 59.6, 13.7
19a,**20d**	145.1, 132.5, 114.3, 69.1, 70.0, 58.1, 50.8
19a,**20h**	145.9, 144.1, 132.8, 131.9, 114.4, 113.4, 69.2, 65.9, 54.2
19a,**20k**	145.3, 140.5, 132.9, 132.1, 130.8, 118.1, 114.2, 111.8, 109.5, 69.3, 65.9, 63.8, 45.7, 20.54
19a,**20l**	132.0, 114.3, 69.1, 65.9, 53.5
19b,**20a**	166.2, 145.6, 138.7, 132.6, 128.3, 117.9, 113.3, 69.2, 65.8, 47.4
19b,**20c**	165.4, 138.1, 132.6, 114.2, 69.3, 66.1, 59.3, 47.2, 13.7
19b,**20j**	154.1, 141.6, 132.7, 130.7, 122.4, 121.1, 114.3, 110.7, 69.3, 65.9, 46.5, 19.8, 16.8
19b,**20k**	149.5, 144.3, 142.0, 139.2, 132.8, 130.0, 117.5, 114.3, 69.3, 68.1, 62.8, 54.8, 47.5, 20.8
19c,**20b**	152.4, 132.7, 129.9, 114.4, 69.1, 63.8, 54.4, 46.9
19c,**20h**	154.0, 144.1, 132.6, 122.5, 121.9, 114.4, 110.7, 109.6, 69.3, 66.1, 63.9, 56.7
19c,**20i**	132.6, 114.1, 69.2, 63.8, 46.1, 16.8
19c,**20j**	167.2, 154.1, 141.5, 132.7, 130.7, 128.3, 122.5, 121.1, 114.3, 110.6, 109.5, 102.4, 69.3, 65.9, 63.9, 16.5, 19.8, 16.8
19c,**20k**	154.2, 145.1, 132.7, 130.1, 121.1, 117.4, 114.3, 111.5, 109.4, 104.1, 69.2, 65.9, 63.9, 56.0, 45.5, 20.7
19c,**20l**	154.3, 143.0, 136.6, 132.7, 122.4, 121.3, 114.4, 110.6, 69.1, 66.2, 64.5, 46.4
19e,**20a**	165.4, 145.1, 139.7, 135.5, 132.8, 132.0, 130.9, 118.4, 113.6, 69.2, 65.8, 53.7
19e,**20b**	165.3, 139.1, 135.9, 132.8, 138.8, 129.5, 114.4, 69.2, 67.0, 54.4
19e,**20h**	143.8, 132.8, 132.0, 131.1, 123.0, 114.6, 69.2, 65.9, 53.9
19e,**20i**	143.3, 135.5, 132.8, 131.9, 130.9, 122.5, 118.1, 114.2, 110.9, 106.1, 69.0, 65.7, 54.0, 16.6
19e,**20j**	165.9, 140.9, 135.9, 132.8, 131.9, 130.8, 129.4, 122.5, 114.3, 111.1, 108.3, 105.6, 102.4, 69.2, 65.7, 54.2, 19.8, 16.6
19e,**20k**	145.2, 135.1, 132.1, 130.7, 129.4, 118.0, 114.3, 111.9, 109.5, 69.2, 65.6, 54.7, 53.6, 20.5

4. Experimental

4.1. General

All reactions were conducted in oven-dried glassware. THF was dried over, and distilled from, sodium metal with benzophenone as the indicator. DCM and chloroform were dried over, and distilled from CaH_2. Anhydrous DMF was purchased from Sigma–Aldrich. Diphenylphosphine was purchased from Strem as a 10% solution in Hexanes. Resins were purchased from Novabiochem and all other reagents were purchased from Sigma–Aldrich. ^1H, ^{31}P and ^{13}C NMR were recorded using Brucker Avance-200, Avance-400 or ARX-500 instruments and referenced to TMS (^1H), solvent (^{13}C) or external 85% H_3PO_4 (^{31}P) standard signals. Chemical shifts are reported in ppm. The gel-phase samples were prepared in benzene-d_6. Since the polymeric matrix obscures some of the compounds signals, partial ^{13}C data is reported for most compounds. The library was prepared on an Advanced ChemTech Multiple Organic Synthesizers 440Ω. Yields were determined using nucleophilic cleavage (0.4 M NaOMe in MeOH–THF (1:4))[25] or ^{31}P NMR of the products with triphenylphosphine–polystyrene resin (Fluka, 100–200 mesh, 1.6 mmol/g) as a reference.

Reduction of nitro group and cleavage of protecting groups was performed according to literature procedures.[26,27]

4.2. Solution synthesis

4.2.1. *N*-Phenyl, α-phenyl aminomethyldiphenylphosphine (1).[20] A solution of diphenylphosphine (940 mg, 5 mmol, 1 equiv.) in dry toluene (10 ml), was slowly added under nitrogen atmosphere, to two-necked flask, equipped with a condenser, and preheated to 65°C, which contained a solution of aniline (1.8 ml, 20 mmol, 4 equiv.) and benzaldehyde (0.5 ml, 5 mmol, 1 equiv.) in dry toluene (20 ml). The solution was stirred overnight. After cooling, the suspension was filtered, the toluene was evaporated from the filtrate and the excess of aniline was distilled off under vacuum, yielding crude product (colorless solid).

Yield 880 mg (48%). ^1H NMR (500 MHz, $CDCl_3$): δ 7.44 (m, 1H, P–Ph), 7.37 (m, 2H, P–Ph), 7.32 (t, J=7.5 Hz, 2H, P–Ph), 7.03–7.30 (m, 12H, 5H P–Ph, 5H C–Ph, 2H N–Ph), 6.64 (t, J=8.0 Hz, 1H, N–Ph), 6.49 (d, J=7.5 Hz, 2H, N–Ph), 5.12 (d, J=3.4 Hz, 1H, CH), 4.25 (bs, 1H, NH). ^{13}C NMR (50.4 MHz, $CDCl_3$): δ 147.2, 140.1 (d, J=10.9 Hz), 135.4 (d, J=13.6 Hz), 135.2 (d, J=8.5 Hz), 133.7, 129.3, 128.7, 128.6, 128.4, 128.3, 127.7, 126.9, 126.0, 121.0, 117.9, 113.8, 57.5 (d, J=13.6 Hz). ^{31}P NMR (202.5 MHz, CDCl3): δ 6.2 (s).

4.3. *N*-Phenyl, α-phenyl aminomethyldiphenylphosphine (1)—stepwise procedure

In a glove box, a solution of diphenylphosphine (940 mg, 5 mmol, 1 equiv.) in dry chloroform (5 ml) was added to a 20 ml vial, which contained a solution of benzylideneaniline (905 mg, 5 mmol, 1 equiv.) in dry chloroform (5 ml). After 2 h, the solution was filtered and evaporated to give the pure ligand in 92% yield (1.69 g).

4.3.1. *N*-Phenyl, α-phenyl aminomethyldiphenylphosphine oxide (2). A solution of diphenylphosphine (940 mg, 5 mmol, 1 equiv.) in dry toluene (10 ml), was added to a dry flask, equipped with $CaCl_2$ tube, which contained a solution of aniline (1.8 ml, 20 mmol, 4 equiv.) and benzaldehyde (0.5 ml, 5 mmol, 1 equiv.) in dry toluene (20 ml). After 4 h stirring at room temperature, the precipitate was filtered, washed with cold toluene and then dried under vacuum.

Yield 1.92 g (100%). Mp: 200°C. ^1H NMR (500 MHz, $CDCl_3$): δ 7.78 (dd, J=9.8, 5.8 Hz, 2H, P(O)–Ph), 7.48 (dt, J=7.5, 1.5 Hz, 1H, P(O)–Ph), 7.40 (dt, J=7.5, 3.0 Hz, 2H, P(O)–Ph), 7.31 (m, 3H, P(O)–Ph), 7.18 (dt, J=7.5, 3.0 Hz, 2H, P(O)–Ph), 7.04 (m, 5H, C–Ph), 6.99 (t, J=8.0 Hz, 2H, N–Ph), 6.58 (t, J=7.3 Hz, 1H, N–Ph), 6.51 (d, J=7.5 Hz, 2H, N–Ph), 5.06–5.12 (m, 2H, CH, NH). ^{13}C NMR (50.4 MHz, $CDCl_3$): δ 146.2, 135.3, 132.4, 131.9, 131.8, 131.5, 129.3, 129.1, 128.8, 128.5, 128.3, 128.2, 127.8, 118.6, 115.3, 114.1, 57.7 (d, J=75.6 Hz). ^{31}P NMR (202.5 MHz, $CDCl_3$): δ 33.6 (s). HRMS (FAB): found (m/z) 384.1528; cald for $C_{25}H_{23}NOP$ (MH^+) 384.1517.

4.3.2. *N*-Phenyl, α-phenyl aminomethyldiphenylphosphine borane (3). In a glove box, diphenylphosphine borane (400 mg, 2 mmol, 1 equiv.) and benzylideneaniline (726 mg, 4 mmol, 2 equiv.) were dissolved in 6 ml of dry toluene, in a pressure tube. The closed tube was heated to 60°C for 72 h. After cooling, the precipitate was filtered and dried under vacuum.

Yield 687 mg (90%). ^1H NMR (500 MHz, $CDCl_3$): δ 7.78 (t, J=4.4 Hz, 2H, P–Ph), 7.52 (t, J=6.8 Hz, 1H, P–Ph), 7.45 (dt, J=7.8, 2.3 Hz, 2H, P–Ph), 7.39 (dt, J=7.5, 1.5 Hz, 1H, P–Ph), 7.30 (t, J=8.0 Hz, 2H, P–Ph), 7.24 (dt, J=7.5, 2.5 Hz, 2H, P–Ph), 7.12–7.06 (bm, 5H, 3H C–Ph, 2H N–Ph), 7.01 (d, J=6.5 Hz, 2H, C–Ph), 6.68 (t, J=12.5 Hz, 1H, N–Ph), 6.56 (d, J=4.9 Hz, 2H, N–Ph), 5.38 (dd, J=16.0, 8.5 Hz, 1H, C*H*), 5.07 (t, J=8.0 Hz, 1H, NH), 0.87–1.27 (bm, 3H, BH_3). ^{13}C NMR (50.4 MHz, $CDCl_3$): δ 145.9 (d, J=4.4 Hz), 135.0, 133.4 (d, J=7.8 Hz), 132.6 (d, J=7.7 Hz), 131.6, 129.3, 129.1, 128.9, 128.8, 128.6, 128.4, 128.3, 127.9, 126.7 (d, J=17.5 Hz), 118.5, 113.9, 54.7 (d, J=39.9 Hz). ^{31}P NMR (202.5 MHz, $CDCl_3$): δ 27.9 (bs). Anal. Cald for $C_{25}H_{25}BNP$: C, 78.76; H, 6.61; N, 3.67. Found: C, 78.52; H, 6.64; N, 3.67.

4.4. Solid-phase synthesis

4.4.1. General procedure for acidic cleavage. Resin (50 mg) was stirred in $CDCl_3$–TFA solution (1:1 vol) for 1 h. The filtrate was collected into NMR tube. Yields were established using benzene as an internal reference (11 mM solution).

4.4.2. General procedure for the attachment of acids to Merrifield resin. The Merrifield resin (0.72 mmol/g, 1 equiv.) was swollen in a minimal volume of DMF. The acid (5 equiv.), Cs_2CO_3 (5 equiv.) and KI (1 equiv.) in DMF (10 ml/1 g resin) were added to the suspension. The mixture was gently stirred for 24 h at 80°C, cooled and filtered. The

resin was washed with DMF, DMF/THF (1:1), THF, THF/H_2O (1:1), H_2O, THF and DCM and dried under vacuum.

4.4.3. General procedure for the attachment of acids to Wang Bromo resin. The Wang Bromo resin (1.19 mmol/g, 1 equiv.) was swollen in a minimal volume of DMF. The acid (5 equiv.) DIPEA (5 equiv.) and CsI (0.5 equiv.) were dissolved in DMF (10 ml/g resin) and added to the resin suspension. The mixture was gently stirred for 18 h and then filtered. The resin was washed with DMF, DMF/THF (1:1), THF, THF/H_2O (1:1), H_2O, THF and DCM and dried under vacuum.

For the following acids the yield was determined by nucleophilic cleavage:

4-Formylbenzoic acid (**4b**): yield 98%. Partial gel phase ^{13}C NMR: δ 190.7, 165.4, 145.6, 139.4, 108.7, 70.0, 67.1.

4-Formylcinnamic acid: yield 34%. Partial gel phase ^{13}C NMR (128.5 MHz, $CDCl_3$): δ 190.6, 165.8, 145.7, 143.2, 124.6, 121.3, 70.0, 66.4.

5-Formylsalicylic acid: yield 7%.

3-Formylbenzoic acid: yield 99%.

2-Formylphenoxy acetic acid: yield 71%. Partial gel phase ^{13}C NMR (128.5 MHz, $CDCl_3$): δ 188.5, 160.2, 145.3, 135.2, 126.1, 123.9, 121.7, 112.8, 70.0, 66.7, 65.4.

2-Benzofuran carboxylic acid, methyl ester (**15**):[28] (product of the nucleophilic cleavage) ^1H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, J=7.9 Hz, 1H, Ar), 7.59 (d, J=8.5 Hz, 1H, Ar), 7.45 (t, J=7.8 Hz, 1H, Ar), 7.31 (t, J=7.5 Hz, 1H, Ar), 6.97 (s, 1H, CH=C), 3.98 (s, 3H, O–CH_3).

2-Formylbenzoic acid: yield 30%. Partial gel phase ^{13}C NMR (50.4 MHz, $CDCl_3$): δ 191.2, 168.8, 145.7, 137.7, 132.3, 130.7, 126.2, 124.6, 70.0, 67.3.

3-Methoxy-3*H*-isobenzofuran-1-one (**16**):[29] (product of the nucleophilic cleavage) ^1H NMR (200 MHz, $CDCl_3$): δ 7.90 (d, J=7.4 Hz, 1H, Ar), 7.76 (d, 7.2 Hz, 1H, Ar), 7.70 (t, J=8.0 Hz, 1H, Ar), 7.61 (t, J=7.6 Hz, 1H), 6.31 (s, 1H, CH), 3.64 (s, 3H, OMe).

1,8-Naphthaldehydic acid: yield 25%.

3-Methoxy-1*H*,3*H*-naphtho[1,8-*cd*]pyran-1-one (**17**):[30] (product of the nucleophilic cleavage) ^1H NMR (200 MHz, $CDCl_3$): δ 8.47 (d, J=7.8 Hz, 1H, Ar), 8.16 (d, J=8.0 Hz, 1H, Ar), 7.98 (t, J=7.4 Hz, 1H, Ar), 7.59–7.73 (m, 3H, Ar), 6.48 (s, 1H, CH–OMe), 3.74 (s, 3H, O–CH_3).

t-Boc-L-Ala-OH: yield 92%.

4-Nitrobenzoic acid: yield 94%.

For the following acids, yields were established by spectrophotomeric determination of Fmoc group.[31]

Fmoc-L-Ala-OH: yield 81%.

Fmoc-aminobenzoic acid: yield 87%.

4.4.4. Typical procedure for the preparation of imines from resin bound aldehydes. Under a nitrogen atmosphere, aniline (10 equiv.) and acetic acid (0.1 equiv.) were dissolved in DCM/trimethylorthoformate (1:1, 5 ml/g resin) and added to resin-aldehyde which was swollen in dry DCM (5 ml/g resin). The mixture was gently stirred overnight and then filtered. The polymer was washed with DCM and dried under vacuum.

For the following imines the yield (based on initial loading of the Merrifield or Wang resin) was determined by nucleophilic cleavage

5a, **b**: yield 85%.

5b: Partial gel-phase ^{13}C NMR: δ 165.7, 158.8, 152.2, 146.8, 128.0, 124.5, 121.4, 70.0, 66.9.

5c: yield 84%.

1*H*-2,3-Dihydro-3-methoxy-2-phenyisoindol-1-one (**18**):[32] (product of the nucleophilic cleavage): ^1H NMR (500 MHz, $CDCl_3$): δ 7.93 (d, J=7.5 Hz, 1H, Ar), 7.82 (d, J=8.0 Hz, 2H, N–Ph), 7.66 (t, J=7.4 Hz, 1H, Ar), 7.61 (t, J=7.5 Hz, 1H, Ar), 7.58 (d, J=6.3 Hz, 1H, Ar), 7.45 (t, J=7.8 Hz, 2H, N–Ph), 7.22 (t, J=7.5 Hz, 1H, N–Ph), 6.98 (s, 1H, CH), 2.88 (s, 3H, OCH_3). ^{13}C NMR (50.4 MHz, $CDCl_3$): δ 166.9, 140.0, 137.6, 133.1, 132.9, 130.5, 129.3, 129.2, 128.5, 125.7, 125.5, 124.1, 121.9, 87.6, 49.3.

4.4.5. General procedure for the reaction of resin-bound imines with diphenylphosphine. In a glove box, a solution of diphenylphosphine (10 equiv.) in chloroform (5 ml/g resin) was added to resin-bound imine (1 equiv.) which was swollen in chloroform (5 ml/g resin). The mixture was gently stirred overnight and then filtered. The resin was briefly washed (just once) with DCM and dried under vacuum.

Yield for **6a**: 85% (by gel-phase ^{31}P NMR); gel-phase ^{31}P NMR: δ 6.6 (s).

Yield for **6b**: 85% (by gel-phase ^{31}P NMR); gel-phase ^{31}P NMR: δ 6.6 (s). Partial gel-phase ^{13}C NMR: δ 146.0, 134.1, 133.4, 124.6, 118.6, 114.0, 70.0, 66.4, 57.6.

Yield for **9b**: 30%; gel phase ^{31}P NMR (202.5 MHz, benzene-d^6): δ 3.3 (s), 1.0 (s).

Yield for **13**: 82%; gel phase ^{31}P NMR (202.5 MHz, benzene-d^6): δ 5.1 (s).

4.5. General procedure for the multicomponent synthesis of 6

In a glove box, diphenylphosphine (10 equiv.) and aniline (10 equiv.), dissolved in a 2:2:1 mixture of DCM, $CHCl_3$ and trimethylorthoformate (5 ml/g resin), were added to aldehyde-bound resin which was swollen in the same solvent mixture (5 ml/g resin). The mixture was gently

stirred overnight and filtered. Brief washing with DCM and drying under vacuum yielded **6** with ca. 85% yield.

4.5.1. General procedure for the preparation of imines using amine resins. Under nitrogen atmosphere, benzaldehyde (20 equiv.) and AcOH (0.1 equiv.) dissolved in DCM/TMOF (3:1 vol) were added to a suspension of the swollen amine resin in the minimum volume of the same solvents. The suspension was gently stirred at room temperature, overnight and then washed with DCM and dried under vacuum.

For the following resin-bound imines the yield was determined by nucleophilic cleavage:

N-Benzylidene alanine (**7b**): yield 94%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.51 (s, 1H, CH═N), 8.14 (d, J=8.2 Hz, 2H, C–Ar), 7.90 (d, J=8.2 Hz, 2H, C–Ar), 7.38 (m, 2H, N–Ph), 7.25 (m, 3H, N–Ph), 3.95 (s, 3H, O–CH_3).

N-Benzylidene-4-carboxyaniline (**12**): yield 98%. Partial gel phase ^{13}C NMR (128.5 MHz, $CDCl_3$): δ 190.7, 165.4, 145.6, 139.4, 108.7, 70.0, 67.1.

N-Benzylidene (4-carbomethoxy) aniline (product of the nucleophilic cleavage): ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.44 (s, 1H, CH═N), 8.08 (d, J=8.6 Hz, 2H, N–Ar), 7.89–7.84 (m, 2H, C–Ph), 8.47–8.52 (m, 3H, C–Ph), 7.21 (d, J=8.4 Hz, 2H, N–Ar), 3.92 (s, 3H, O–CH_3).

By-product was obtained: *O*-methyl, *N*-(4-carbomethoxyphenyl)formimidate (product of the nucleophilic cleavage of **14**): ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.25 (s, 1H, CH═N), 8.01 (d, J=8.5 Hz, 2H, N–Ar), 7.11 (d, J=8.4 Hz, 2H, N–Ar), 3.91 (s, 3H, O–CH_3), 3.86 (s, 3H, O–CH_3).

4.5.2. Postsynthetic protection of 6. The resin **6** (200 mg, 0.192 mmol, 1 equiv.) was suspended in a 1 M solution of BH_3·THF in THF (6 ml, 40 equiv.) diluted with an additional 4 ml THF. The suspension was gently stirred for 2 h and then filtered. The resin was washed with THF, DCM and dried under vacuum.

Yield 100% (by gel-phase ^{31}P NMR); gel-phase ^{31}P NMR: δ 28.9 (bs). Partial gel-phase ^{13}C NMR: δ 159.8, 145.9, 133.7, 132.7, 119.2, 115.0, 70.0, 66.5, 55.0.

4.6. Parallel synthesis of the libraries (libraries I, II)

4.6.1. Aldehyde attachment. Under nitrogen atmosphere. Wang Bromo resin was distributed to the wells of the reaction block of the synthesizer (150 mg/well). DMF (1.5 ml) was added to each well and the block was shaken at 500 rpm for 20 min. A carboxyaldehyde (10 equiv.) solution in 1 ml of DMF was added to each well, followed by a DIPEA (10 equiv.) solution in 0.5 ml DMF and a CsI (1 equiv.) solution in 0.5 ml DMF. The block was shaken at 500 rpm for 17 h. The solution was removed and the resin in each well was washed with 3 ml portions of DMF, DMF/THF, THF, THF/H_2O (1:1), H_2O, THF and DCM. The resin was dried under a nitrogen stream for 1 h.

4.6.2. Synthesis of aminophosphine. Under argon atmosphere. $CHCl_3$ (1 ml) and DCM (0.5 ml) were distributed to each well of the block. The block was shaken at 500 rpm for 20 min. Trimethylorthoformate (1 ml) was added to each well followed by an amine (10 equiv.) solution in 1 ml DCM and 0.1 equiv. of AcOH. The block was shaken for 20 min and a Ph_2PH (20 equiv.) solution in 0.5 ml chloroform was added to each well. The block was shaken at 500 rpm for 18 h. The solution was removed and the resin in each well was washed with 3 ml of DCM. The resin was dried under an argon stream for 10 min.

4.6.3. Borane protection. Under nitrogen atmosphere. THF (2.5 ml) was added to each well, followed by 0.5 ml of a 1 M solution of BH_3·THF in THF. The block was shaken at 500 rpm for 6 h. The solvent was removed and the resin in each well was washed with THF (3×3 ml) and DCM (5×3 ml). The resin was dried under a nitrogen stream for 1 h and, after the contents of each well were transferred to a separate vial, dried again under vacuum.

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